Organization of the gastrointestinal tract
Development of the Foregut, Midgut, and Hindgut
Development of the alimentary canal

It constitutes during the 4th week from 3 separate embryonic anlages (organs):

- The **stomodeum** (primitive mouth) – develops on the cephalic end of the embryo, is limited by 5 frominences (frontonasal, 2 maxillary, 2 mandibular) **ectoderm** oropharyngeal membrane.

- The **primitive gut** arises by incorporation of the dorsal part of the yolk sac into embryo during cephalocaudal and lateral folding of the embryo gut is connected to the yolk sac by means of the vitelline (omphalomesenteric) duct **endoderm** cloacal membrane

- The **proctodeum** (anal pit) - develops on the caudal end of the embryo between future bases of lower limbs - **ectoderm**
- While the **ectoderm** of the stomodeum and **proctodeum** as well as the **endoderm** of the gut differentiate into the epithelium of the alimentary canal,
- The muscular and fibrous elements + visceral peritoneum derive from the **splanchnic mesenchyma** that surrounds the lining of the primitive gut.

**Development of associated glands:**
- (Salivary glands, liver and pancreas) develop from the **endoderm (ectoderm)** that gives rise to specific cells (hepatocytes, exo- and endocrine cells of the pancreas (the parenchyma))
DERIVATIVES OF THE PRIMITIVE GUT

The foregut:
- the pharynx and branchiogenic organs
- the lower respiratory tract
- the esophagus
- the stomach
- the duodenum proximal to the opening of the bile duct
- the liver and pancreas + the biliary apparatus

The midgut:
- the small intestines, including the part of the duodenum distal to the opening of the bile duct
- the caecum and appendix
- the ascending colon
- the transverse colon

The hindgut:
- the descending colon
- the sigmoid colon
- the rectum
- the superior portion of the anal canal
- the epithelium of the urinary bladder and most of the urethra
Schematics showing stages in the embryonic development of the digestive system.

At 4 weeks:
- Stomach
- Dorsal pancreas
- Hepatic diverticulum
- Midgut
- Hindgut
- Proctodeum
- Cut edge of amnion
- Allantois
- Yolk stalk
- Yolk sac
- Body stalk
- Cut edge of amnion
- Liver (cut surface)
- Gallbladder
- Falciform ligament
- Cecum passing to right above coils of small intestine
- Yolk sac stalk
- Allantois
- Umbilical cord
- Genital tubercle
- Urogenital sinus
- Anus
- Ureter
- Rectum
- Urorectal septum
- Diaphragm
- Greater curvature of stomach rotated 90° to left
- Spleen within dorsal mesogastrium bulging to left to form omental bursa
- Pancreas within mesoduodenum
- Superior mesenteric artery within dorsal mesentery
- Mesocolon
- Colon
- Urinary bladder
- Arrow passing through right pleuro-peritoneal membrane
- Ventral mesentery (lesser omentum)
- Septum transversum
- Gallbladder
- Liver (cut surface)
- Ventral mesentery (falciform ligament)
- Yolk sac stalk
- Allantois
- Umbilical cord
- Proctodeum
- Cloacal membrane
- Cloaca

At 5 weeks:
- Esophagus
- Stomach
- Spleen
- Dorsal mesogastrium
- Celiac trunk
- Dorsal pancreas
- Mesoduodenum
- Common bile duct
- Duodenum
- Ventral pancreas
- Superior mesenteric artery
- Dorsal mesentery of midgut
- Inferior mesenteric artery
- Mesocolon of hindgut

At 8 weeks:
- Clinical manifestations of congenital megacolon. Abdominal distention showing hypertrophy of sigmoid and descending colon, moderate involvement of transverse colon, and constricted distal segment.
CLINICAL POINT

- A wide spectrum of **congenital disorders affecting different regions** of the gastrointestinal tract may result in significant complications, mostly in infants and children and less frequently in adults.

- **Congenital megacolon (Hirschsprung disease)**—the most common gut motility disorder **caused by failure of migration of neural crest cells** to the hindgut during weeks 5-12 of gestation leads to **partial or complete obstruction**, usually of the sigmoid colon and rectum, with aganglionic segments that lack Meissner and Auerbach plexuses.

- **Meckel diverticulum** the most prevalent developmental anomaly of the bowel is a small outpocketing (usually about 5 cm long) of the gastrointestinal tract caused by incomplete **obliteration** of the vitelline (yolk sac) stalk in the **seventh gestational week**. Usually **asymptomatic**, it may sometimes lead to **intestinal obstruction, perforation, and bleeding**.
- **Visceral:**
- **Parietal:**
- **Retroperitoneal:**
  - e.g., kidneys, pancreas, duodenum
- **Mesenteries:**
- **Greater omentum:**
  - connects greater curvature of the stomach to the transverse colon.
- **Lesser omentum:**
  - connects lesser curvature of the stomach and the proximal part of the duodenum to the liver and diaphragm

G. Hand in balloon explanation
The digestive system organs and the peritoneum

Mesenteries

- Mesenteries are layers of serous membranes that support portions of the digestive tract
  . Provides padding, protection, insulation, and energy reserves
Nervous regulation of the Digestive System

- **Local:** enteric nervous system
  - Types of neurons:
    - sensory, motor, interneurons
  - Coordinates peristalsis and regulates local reflexes
  - As stomach empties into small intestine, local reflex regulates rate of emptying

- **General:**
  - Coordination with the CNS.
    - May initiate reflexes because of sight, smell, or taste of food.
  - Parasympathetic primarily.
  - Sympathetic input inhibits muscle contraction, secretion, and decrease of blood flow to the digestive tract.
Pharynx
Pharynx

- Passes from mouth into pharynx (Common chamber of respiratory and digestive system)

- 3 parts
  - Nasopharynx
    - Functions only in respiration
  - Oropharynx
    - Digestive and respiratory functions
  - Laryngopharynx
    - Digestive and respiratory functions
Oropharynx

Nasopharynx, with a pseudostratified epithelium overlying a submucosa that contains prominent mucus-secreting glands.
Structure of Digestive system II: Esophagus and Gastrointestinal tract
Embryology

The notochord induces the formation of the foregut from endoderm.
- At about 21 days' gestation, septa arise from the lateral walls of the foregut, fuse, and divide the foregut into the esophagus and trachea. This process being completed by 5 to 6 weeks' gestation.
- Development of the gastrointestinal neuromuscular system begins at 4 weeks with neural crest cells entering the foregut and migrating rostrocaudally.
- At 6 weeks' gestation, the circular muscle layer develops, followed by the development of the longitudinal layer at approximately 9 weeks' gestation.
- Cajal appear at *9 week and become closely associated with the myenteric plexus).
- At approximately 10 weeks a single layer of columnar cells populates the proximal and distal ends of the esophagus.
- By 14 the week fetal gut has a mature appearance.
- At approximately 4 months' gestation, the esophageal cardiac-type glands form as a result of the downward growth of these columnar cells into the lamina propria, with subsequent proliferation and differentiation. They go distally as far as the oxyntic mucosa.

- At approximately 5 months' gestation, stratified squamous epithelium initially appears in the middle one-third of the esophagus and extends cephalad and caudally, replacing the ciliated epithelium, and

- Striated muscle gradually develops in the upper esophagus so that by 5 months.

- The submucosal glands develop after the appearance of the squamous epithelium and are likely derived from this squamous epithelial layer.
Fetal esophagus (late first trimester). Transverse section overview of the esophagus demonstrating inner mucosal layer, middle submucosal layer, and thin outer muscle layer. Note the vagus nerves lying over the esophagus.

Fetal esophagus (third trimester). The epithelial layer at this stage consists of stratified squamous epithelium with occasional ciliated cells on the surface. Note the individual smooth muscle cells of developing muscularis mucosae.
Overview of the esophagus and gastrointestinal tract

Wall of GI tract from lower esophagus to anal canal has same basic 4 layers

1- **Mucosa – inner lining**
   - Epithelium protection, secretion, absorption
   - Lamina propria – connective tissue with blood and lymphatic vessels and mucosa associated lymphatic tissue (MALT)
   - Muscularis mucosae – thin layer of smooth muscle making folds to increase surface area

2- **Submucosa**
   - Connective tissue binding mucosa to muscularis
   - Contains many blood and lymphatic vessels
   - Submucosal plexus
3. **Muscularis**
   - Voluntary skeletal muscle found in mouth, pharynx, upper 2/3 of esophagus, and anal sphincter
   - Involuntary smooth muscle elsewhere
     - Arranged in inner circular fibers and outer longitudinal fibers
     - Myenteric plexus between muscle layers

4. **Serosa**
   - Outermost covering of organs suspended in abdominopelvic cavity
   - Also called visceral peritoneum (*mesothelium*)
   - Esophagus lacks serosa – has adventitia
Overall histologic organization of the digestive tube
Basic mucosal types in the gastrointestinal tract.
(a) Squamous mucosa, H&E (MP) (b) Gastric type secretory mucosa, H&E (LP) (c) Intestinal type absorptive mucosa, H&E (MP) (d) Colorectal type absorptive/protective mucosa, H&E (MP)
Structure and function of the Esophagus
Features and Functions of the Esophagus

- A hollow muscular tube
- About 25 cm (10 in.) long and 2 cm (0.80 in.) wide.
- Propels food to stomach;
  - Bolus enters stomach through esophageal hiatus.
- Skeletal muscle (upper third for swallowing) and smooth muscle (lower third) for peristalsis
- Esophageal glands produce mucus to lubricate bolus
- Esophageal sphincter prevents backflow into oral cavity
- Cardiac sphincter prevents backflow into esophagus.
- Secretes mucous, transports food – no enzymes produced, no absorption
Histology of esophagus

**Mucosa:**
- Stratified squamous non-keratinized epithelium, protection against wear and tear.
- In the lamina propria of the region near the stomach are groups of glands, the esophageal cardiac glands, that also secrete mucus

**Submucosa** a group of small mucus-secreting glands, the esophageal glands, whose secretion facilitates the transport of foodstuffs and protects the mucosa

**Muscularis externa (muscularis propria):**
- At the distal end of the esophagus, consists of only smooth muscle cells that, close to the stomach, form the lower esophageal sphincter
- At mid portion, a mixture of striated and smooth muscle cells; and at the proximal end, only striated muscle cells.

**Serosa** covered only that portion of the esophagus that is in the peritoneal cavity.

**Adventitia** covered the rest of the esophagus, that blends into the surrounding tissue.
Photomicrograph of the esophagus. This low magnification photomicrograph shows an H&E–stained section of the esophagus with its characteristically folded wall, giving the lumen an irregular appearance. The mucosa consists of a relatively thick stratified squamous epithelium, a thin layer of lamina propria containing occasional lymphatic nodules, and muscularis mucosae. Mucous glands are present in the submucosa; their ducts, which empty into the lumen of the esophagus, are not evident in this section. External to the submucosa in this part of the esophagus is a thick muscularis externa made up of an inner layer of circularly arranged smooth muscle and an outer layer of longitudinally arranged smooth muscle. The adventitia is seen just external to the muscularis externa. 8.
Lamina propria

Muscularis mucosa

Submucosa

Non-keratinized stratified squamous epithelium

Sub-mucosal Mucus and Serous glands

Skeletal muscle,

Muscularis externa

If outer layer is not covered by mesothelium = adventitia

Perichondrium
Histology

- **Mucosa** consists of a nonkeratinizing, stratified squamous epithelium, lamina propria, and muscularis mucosae.

- **Epithelium** Consist of basal, prickle, and functional cell layers.
  - In addition, argyrophilic positive endocrine cells, melanocytes, Merkel cells, intraepithelial mononuclear cells (*Langerhans cells*) and Intraepithelial lymphocytes (term الخلايا المتمايلة squiggle cell) are CD3+/CD8+.
  - **Epithelial turnover** in the esophagus is slower than in the small bowel, is approximately 7 days.
  - **Stem cells** in the esophagus consist of a single layer of cells attached to the basement membrane that lie between the papillae (interpapillary basal cells).
Midesophagus. The basal cell layer of the esophageal epithelium shows lack of glycogen, allowing for ready distinction from the overlying glycogen-rich cells (PAS-D).

Numerous lymphocytes within the esophageal epithelium, some of which have a squiggle appearance (arrows).
**Basal layer** of esophagus immunostained with MIB-1.

**A.** The basal cell layer is relatively thin and unstimulated, consisting of only about 3 cell layers. Many of the cells in the basal layer are completely unstained, therefore representing likely stem cells, while the proliferating cells with black nuclei are in the cell layer immediately above.

**B.** In this biopsy, the basal layer is much thicker and therefore more proliferative, and there are fewer noncycling stem cells in the basal layer.

A model of the cellular organization in the esophageal epithelium. The **interpapillary basal layer (IBL)** cells (blue-grey) constitute the **epithelial stem cell compartment**. IBL cells proliferate infrequently and asymmetrically. Proliferating cells reside in the **epibasal (suprabasal)** layers (blue). **Papillary basal cells (PBL) (green)** are proliferative and intermediate in behavior between IBL and epibasal cells. Differentiated squamous cells are shown in orange.
Lamina Propria
- The lamina propria consists of areolar connective tissue and contains vascular structures, scattered inflammatory cells, and mucus-secreting glands.

Muscularis Mucosae
- The muscularis mucosae is composed of smooth muscle bundles oriented longitudinally.
Midesophagus. **A. Esophageal cardiac-type glands** are located within the lamina propria. The ducts are lined by gastric foveolar “like cells.**

**B.** The duct-lining cells may extend over the stratified squamous epithelium for variable distances (PASD).

**C, D.** The glands stained **PASD positive** and **alcian blue at pH 2.5 negative,** characteristic of **neutral mucins.**
**Submucosa**

- The **submucosa** consists of **dense irregular connective tissue** containing larger blood and lymphatic vessels, ganglion cells, nerve fibers (including Meissner's plexus), and submucosal glands.

Midesophagus. **A.** The **submucosal glands** are composed predominantly of mucus-secreting cells with a variable serous component. **B.** and **C.** The **submucosal glands** stained positive with **Periodic acid–Schiff–diastase (PAS-D)** and Alcian blue at pH 2.5, a characteristic of **acid mucins**.
**Submucosa**

**LM of a submucosal gland in the esophagus.** The secretory part of the gland contains groups of tightly packed mucus acini (MA) located in the submucosa (SM) and draining into ducts that penetrate the muscularis mucosae (MM). The duct at the left crosses the lamina propria and opens onto the surface (⁎). Epithelium lining the duct merges with stratified epithelium (Ep) on the mucosal surface. The submucosa is richly vascularized connective tissue with many lymphatic channels (Ly) and blood vessels (BV). A predominance of elastic fibers in this layer provides the esophageal wall with considerable distensibility. 140×. H&E.

**Higher magnification LM of a submucosal gland in the esophagus.** Mucous acini (MA) contain pale-stained secretory cells around a central lumen. Flattened nuclei of these cells are basally located. A duct, lined by stratified cuboidal epithelium, drains the acini and pierces the muscularis mucosae (MM) on its way to the mucosal surface. 270×. H&E.
Muscularis Propria (muscularis externa)

- The muscular coat of the esophagus consists of an outer longitudinal and inner circular layer.
  . Upper quarter to upper one-third of the proximal muscularis propria is composed of striated muscle;
  - Immediately distal to this, smooth and striated muscle intermix, whereas slightly more than 50% of the distal muscularis propria is composed solely of smooth muscle.
  . Despite the presence of these two different muscle types, they can function as a unit.

. Auerbach's plexus is found between the two muscle layers.
Proximal esophagus. A. The muscularis propria demonstrates a mixture of smooth and striated muscle bundles. B. This mix of smooth (weakly stained) and striated (strongly stained) muscle is demonstrated using a myoglobin antibody. C. Detail photomicrographs of myoglobin-stained section demonstrates peripherally located nuclei typical of striated muscle.
Muscularis externa of Esophagus
Serosa

- Only short segments of the thoracic and intra-abdominal esophagus are lined by serosa derived from the pleura and peritoneum, respectively.
- The majority of the esophagus is surrounded by fascia (adventitia).
Innervation of esophagus

- The esophagus receives both parasympathetic and sympathetic nerve supplies containing afferent and efferent fibers that innervate glands, blood vessels, and muscles of the esophagus.

- Intrinsic innervation system.
  - This consists of ganglion cells in the submucosa (Meissner's plexus) and between the circular and longitudinal muscle layers (Auerbach's plexus).
Innervation of esophagus

Three cell types are described in the plexuses.
- Type I neurons are multipolar and confined to Auerbach's plexus, and their axons establish synapses with type II cells.
- Type II neurons are more numerous, are multipolar, and are found in both Auerbach's and Meissner's plexuses.
  . These cells supply the muscularis propria and muscularis mucosae and stimulate secretory activity.
- Interstitial cells of Cajal (ICC) are widely distributed within the submucosal, intramuscular, and intermuscular layers associated with the terminal networks of sympathetic nerves.

- Regulatory peptides identified within nerve fibers and around smooth muscle bundles include vasoactive intestinal peptide (VIP), substance P, enkephalin, and neuropeptide Y (NPY).
  . Nerve fibers containing VIP and NPY are the most abundant types present in the esophagus, and the pattern of innervation by these peptide-containing neurons differs from that in the stomach and small intestine.
  - Cholecystokinin (CCK) receptors are found in both the mucosa and nerves of the cardia.
Immunolocalization of **interstitial cells of Cajal (ICC)** and adjacent fibroblasts. a, Immunohistochemistry for c-kit, digitized and colour-changed.

**Cross section through circular muscle-submucosa interface of control dog colon.** A: a low-magnification micrograph shows a typical dense network of interstitial cells of Cajal (ICC) processes (arrows) and nerves (N) closely associated with innermost circular muscle layer (CM) present in dog colon. At low magnification, ICC are distinguished by a high concentration of mitochondria (m) and the branched character of their processes.
Interstitial cells of Cajal (ICC)

- Active propagation of slow waves in ICC network
- Spontaneous activation of pacemaker current
- Electrotonic conduction of slow waves via gap junctions
- Depolarization and activation of L-type Ca²⁺ channels in SMC
- Neural input to IM-ICC conditions responses of smooth muscles to slow waves
- IM-CCs and MY-CCs are electrically coupled to smooth muscle cells via gap junctions
CLINICAL POINT

- Esophageal varices abnormally dilated submucosal veins occur in the lower third of the esophagus.
  . When portal blood flow is obstructed, these veins serve as collateral vessels between portal and systemic circulations.
  . Varices often occur in patients with cirrhosis and portal hypertension.
- Alcoholic liver disease and viral hepatitis are leading causes.
  . The varices are prone to rupture and hemorrhage, which may be life threatening.
  - The mortality rate is 40%-70%.
- Increased endothelin.1 (a vasoconstrictor) and decreased nitric oxide (a vasodilator) have been implicated in pathogenesis of portal hypertension and esophageal varices.
  - Endoscopy is used for diagnosis and treatment.
- Inflammation of the esophagus with damage to the epithelium is called esophagitis.
  . Its most common cause is reflux of gastric contents into the lower esophagus, which impairs reparative capacity of esophageal mucosa.
- Gastroesophageal reflux disease, a common chronic condition, usually affects adults older than 40 years.
  . It often accompanies hiatal hernia or may occur with an incompetent lower esophageal sphincter.
  - Biopsy samples of affected mucosal areas show ballooned squamous epithelial cells, with irregular thickened regions (leukoplakia).
  . Elongated papillae with dilated capillaries and infiltration of eosinophils, neutrophils, and plasma cells mark the lamina propria.
CLINICAL POINT

- Of the different kinds of **cancers of the gastrointestinal tract**, incidence of **esophageal cancer continues to rise at alarming rates worldwide.**
- Two main clinical types occur in different regions;
  - both have poor prognosis after diagnosis is made because of the high metastatic potential of such tumors and their rapid invasion of the esophageal wall, which has a relatively rich lymphatic drainage and an outer, illdefined adventitia along most its length rather than a more circumscribed serosa.
- **Squamous cell carcinoma usually occurs in** the **mid-esophagus** arising from **stratified epithelium.**
- **Adenocarcinoma** most often occurs more distally and derives from glandular epithelium.
  - Diagnosis is via upper endoscopy, and tumor staging is done by endoscopic ultrasonography, biopsy and use of positron emission tomography and computed tomography.
Gastroesophageal Junction
Gastroesophageal Junction

The mucosal squamocolumnar junction, or Z line consists of small projections of red gastric epithelium, up to 5 mm long and 3 mm wide, extending upward into the squamous epithelium.
Esophagogastric junction

- Note that the esophagogastric junction is located approximately at the level of the diaphragm. Constrictions of the diaphragm create sphincter-like effects, preventing reflux of stomach acids and content. The esophagogastric junction is a functional, not anatomical, sphincter.

- Note the abrupt transition of epithelium at the esophagogastric junction, from the non-keratinized stratified squamous epithelium of the esophagus to the columnar gastric surface epithelium.

- Once again, there is no evident muscular sphincter at the junction.
lumen

simple columnar epithelium of the cardiac region of stomach

stratified squamous epithelium of the oesophagus

cardiac glands

lamina propria

muscularis mucosa

Slide 65 x 200
Structure and function of the Stomach
Stomach

The stomach; is a dilated segment of the digestive tract, that digest food and secrets hormone.

- lies beneath the diaphragm.
- It receives the bolus of macerated food from the esophagus.
- **Mixing and partial digestion** of the food in the stomach by its **gastric secretions** produces a pulpy fluid mix called **chyme**.
- The chyme then passes into the **small intestine** for further **digestion and absorption**
Functions of Stomach

- **Temporary storage** area for food and allows it to mix with gastric juice to produce chyme.
- Continue digestion of carbohydrates started in mouth
- Add **acidic fluid**
- Transform food **chyme** (mechanical & chemical breakdown)
- Promote initial digestion of **proteins** (via **pepsin**) and **triglycerides** (via **lipase**)
Stomach embryology and Postnatal Development

The stomach develops as a fusiform dilatation of the foregut caudal to the esophagus.
- The stomach is derived from endoderm.
- This occurs first when the embryo is 7 mm in length.
- Dorsal mesogastrium becomes the greater omentum and
- Ventral mesogastrium becomes the lesser omentum.
- Early glandular differentiation of the mucosal lining occurs first at the 80-mm stage of fetal development.
- Enzyme and acid production first occur at the 4 month of fetal life and are well established by the time of birth.
- The newborn stomach is fully developed and similar to that of the adult.
The stomach is divided histologically into three regions based on the type of gland that each contains.

- Gross anatomists subdivide the stomach into four regions:
  - The **cardia** surrounds the esophageal orifice - end under the heart;
  - The **fundus** lies above the level of a horizontal line drawn through the esophageal (cardiac) orifice - bulge above the esophageal opening;
  - The **body** lies below this line - largest region;
  - The **pyloric part** is the funnel-shaped region that leads into the **pylorus**, the distal, narrow sphincteric region between the stomach and duodenum.

- Histologists also subdivide the stomach, but into only three regions.
  - These subdivisions are based not on location but on the types of glands that occur in the gastric mucosa.

- The histologic regions are as follows:
  - **Cardiac region (cardia)**, the part near the esophageal orifice, which contains the **cardiac glands**
  - **Pyloric region (pylorus)**, the part proximal to the pyloric sphincter, which contains the **pyloric glands**
  - **Fundic region (fundus)**, the largest part of the stomach, which is situated between the cardia and pylorus and contains the **fundic** or **gastric glands**.
Distribution of Gastric Glands

Lesser curvature

Greater curvature

fundus

body or corpus

principal or corpus-fundic glands

cardiac glands

pyloric glands
The Inner surface of the stomach is irregular. There are: Rugae, Gastric mamillated area, and Gastric pits

Mucosal zones of the stomach. The cardiac mucosa (C) is present distal to the lower end of the esophagus (E). The pyloric mucosa (P) occupies a triangular zone proximal to the duodenum (D). Elsewhere, the fundic mucosa (F) shows prominent rugal folds.
Histology of the Stomach wall

- **Stomach Mucosa** (epithelium, lamina propria, muscularis mucosae)
  - Thick muscle layers grind/mix food
  - Secretions of enzymes and acid begin digestion
  - Wall highly folded into ruga

- **Stomach Submucosa**
  - Dens connective tissue
  - Blood and lymphatic vessels
  - Lymphoid and mast cells
  - **Nerve fibers and ganglion cells (submucosal plexus)**

- **Stomach Muscularis Externa**
  - Internal oblique layer
  - Middle circular layer (forms pyloric sphincter)
  - Outer longitudinal layer
  - **Nerve fibers and ganglion cells (myenteric plexus)**

- **Serosa**
  - Thin layer of adventitia with covering of **Mesothelium**
Histology of the Stomach Wall

Three-dimensional view of layers of the stomach

- Lumen of stomach
- Gastric pits
- Simple columnar epithelium
- Lamina propria
- Gastric gland
- Lymphatic nodule
- Muscularis mucosae
- Lymphatic vessel
- Venules
- Arterioles
- Oblique layer of muscle
- Circular layer of muscle
- Myenteric plexus
- Longitudinal layer of muscle

Layers of the stomach:
- MUCOSA
- SUBMUCOSA
- MUSCULARIS
- SEROSA
Histology of the Stomach Wall

Longitudinal submucosal folds, rugae, allow the stomach to distend when filled.
- Examination of the inner surface of the empty stomach reveals a number of longitudinal folds or ridges called rugae.
- A view of the stomach’s surface with a hand lens shows that smaller regions of the mucosa are formed by grooves or shallow trenches that divide the stomach surface into bulging irregular areas called mamillated areas.
- At higher magnification, numerous openings can be observed in the mucosal surface.
  - These are the gastric pits, or foveolae.
  - The gastric glands open into the bottom of the gastric pits.
Wall of the stomach with rugae.
Mamillated areas of stomach

Histology of the Stomach Wall

Three-dimensional diagram of stomach wall (mamillated areas)
Gastric Mucosa

- Surface simple columnar epithelium invaginates to various extents into the lamina propria, forming gastric pits
- Gastric glands at base of pits
- Cardiac, gastric and pyloric glands differ
- Lamina propria of loose connective tissue with smooth muscle and lymphocytes
- Muscularis mucosa of inner circular and outer longitudinal smooth muscle.
Surface mucous cells

- Simple columnar epithelium of mucous Cells 20-40 µm high Oval nucleus basal, secrete an alkaline mucus.
  . Many mucous granules in apical cytoplasm
  . Mucous layer (The mucus forms an ~ 1 mm thick layer ) protects stomach epithelium from acid
  . Junctional complexes at apical surface
  . Renewed approximately every third day
  . Source of the new cells is the isthmus, i.e. the upper part of the neck
Gastric Mucosa

- Protective mucous lining of the stomach
- Gastric pit lined by mucous secreting surface epithelial cells
  - A simple columnar epithelium
- Parietal cells
**Mucosal surface of the stomach**

*Mucosal surface of the stomach. a.* Scanning electron micrograph showing the mucosal surface of the stomach. The gastric pits contain secretory material, mostly mucus (arrows). The surface mucus has been washed away to reveal the surface mucous cells. 1,000. *b.* Higher magnification showing the apical surface of the surface mucous cells that line the stomach and gastric pits. Note the elongate polygonal shape of the cells. 3,000.
Cardiac Region

- Narrow region 1.5-3 cm wide.
- Open shallow gastric pits.
- Tubular, somewhat tortuous, and occasionally branched with large lumen at terminus.
- Mostly mucous cells, a few parietal cells and enteroendocrine cells.
- Often has esophagus attached.
Distribution of Gastric Glands
Cardiac glands
Stomach, Fundocardiac junction, human, H&E.
Fundus/Body fill the whole propria mucosae
Fundic glands are composed of four functionally different cell types.

- **Gastric pits** narrow and shallow
- **Glands** long and straight at their ends, branched or coiled. Many parietal and chief cells:
  - **Neck of gland** has undifferentiated cells: oval nuclei basal, distinct nucleolus, mitotic, stem cells, surface cells survive 3-7 days and mucous cells: basal nuclei irregular, mucous granules.
  - **Base of glands** have parietal cells: upper half of glands, many mitochondria, eosinophilic, produce HCl, intracellular canaliculi, chief cells deeper in glands, basophilic, ribosomes, pepsinogen, serous and enteroendocrine cells.
Gastric pits and glands.
Mucous neck cells are localized in the neck region of the gland and are interspersed with parietal cells.

- As the name implies, the **mucous neck cells**.
- The mucous neck cells secrete a **soluble mucus** compared with the **insoluble** or **cloudy mucus** produced by the surface mucous cell.
- Release of mucinogen granules is **induced by vagal stimulation**.

Chief cells are located in the deeper part of the fundic glands.

- **Chief cells** are **typical protein-secreting cells**.
- Chief cells secrete **pepsinogen** and a **weak lipase**.
- On contact with the acid gastric juice, pepsinogen is converted to pepsin, a proteolytic enzyme.
**Gastric glands.**

**a.** This photomicrograph shows the fundic mucosa from an Alcian blue/PAS preparation to visualize mucus. Note that the surface epithelium invaginates to form the gastric pits. The surface mucous cells and the cells lining the gastric pits are readily identified in this preparation because the neutral mucus within these cells is stained intensely.

**b. Schematic diagram of a gastric gland, illustrating the relationship of the gland to the** gastric pit. Note that the isthmus region contains dividing cells and undifferentiated cells; the neck region contains mucous neck cells, parietal cells, and enteroendocrine cells, including amine precursor uptake and decarboxylation (APUD) cells. Parietal cells are large, pear-shaped acidophilic cells found throughout the gland. The fundus of the gland contains mainly chief cells, some parietal cells, and several types of enteroendocrine cells.
Gastric pits with surface mucous cells (simple columnar epithelium).
Mucous neck cells
- Located just below gastric pit.
- Are present in clusters or as single cells between parietal cells in the necks of gastric glands
- Columnar in shape
- Contain mucinogen granules in apical cytoplasm,
- while nuclei are basally situated basally.
- Produces soluble mucus
Gastric glands

1- Gastric Surface mucous cells secrets insoluble or cloudy mucus
2- Gastric Mucous Neck Cells: secrets a soluble mucus
Structure and function of Parietal cells
Parietal cells secrete HCl and intrinsic factor.

- **Parietal (oxyntic) cells** are found in the neck,
- parietal cells have an extensive **intracellular canalicular system** that communicates with the lumen of the gland.
- **Numerous microvilli project** from the surface of the canaliculi,
- An elaborate **tubulovesicular membrane system**.
- The membranes of the tubulovesicular system serve as a reservoir of plasma membrane containing active **proton pumps**.
- **Numerous mitochondria** with complex cristae and many matrix granules supply the high levels of energy necessary for acid secretion.
Oxyntic (Parietal) Cells
Gastric glands: parietal cells
Ultrastructure of parietal, chief, and enteroendocrine cells.
Diagram of a parietal cell. The cytoplasm of the parietal cell stains with eosin largely because of the extensive amount of membrane comprising the intracellular canaliculus, tubulovesicular system, mitochondria, and the relatively small number of ribosomes. This cell produces HCl and intrinsic factor.
Ultrastructural appearances of the parietal cell canaliculus (C). Note the fingerlike microvilli (MV) and the microtubular invaginations (MT). (Original magnifications: left, —9000; right, —41,000.)
Diagram of parietal cell HCl synthesis.

After parietal cell stimulation, several steps occur leading to the production of HCl. Carbon dioxide (CO2) from the blood diffuses across the basement membrane into the cell to form H2CO3. The H2CO3 dissociates into H+ and HCO3-.

The reaction is catalyzed by carbonic anhydrase, which leads to the production of H+ ions in the cytoplasm, which are then transported across the membrane to the lumen of the intracellular canaliculus by a H+/K+-ATPase proton pump. Simultaneously, K within the canaliculus is transported into the cell in exchange for the H+ ions. Cl- ions are also transported from the cytoplasm of the parietal cell into the lumen of the canaliculus by Cl- channels in the membrane. HCl is then formed from H+ and Cl-. The HCO3/Cl- anion channels maintain the normal concentration of both ions in the cell, as well as Na+/K+-ATPase on the basolateral cell membrane.
Control of Acid Secretion

- **Parietal cells** bear **receptors** for three stimulators of acid secretion, reflecting a triumverate of **neural, paracrine and endocrine control:**
  - Acetylcholine (**muscarinic type receptor**)
  - Gastrin
  - Histamine (**H2 type receptor**)

- **Prostaglandin E2** and several peptides **hormones**, including **Secretin, gastric inhibitory peptide, glucagon and somatostatin** may be **physiologic regulators**.

- **Somatostatin** inhibits secretion of **gastrin and histamine**, and appears to have a direct inhibitory effect on the **parietal cell**.
Structure and function of gastric chief cells
Chief or zymogenic cells:
- Located in the lower 1/3rd of gastric glands.
- Pyramidal cells with basal round nuclei
- Contain rough endoplasmic reticulum near the base (basophilic), secretory zymogen granules near their apex and a small golgi apparatus.

- Secrete:
  - **Pepsinogen** which is converted into pepsin in an acid environment.
  - **Rennin**
  - Little amount of **lipase**
Chief cells (basophilic)
Gastric Chief Cells: secrete pepsinogen and weak lipase, they have long lifespan (60-90d)
Ultrastructure of chief cell
EM 14
- Large granules of chief cell
- Granules of an argentaffin cell
- Lamina propria
- Nuclei
Enteroendocrine and APUD cells:
- Located in the basal portion of gastric glands
- Secretes serotonin, histamine and gastrin.
- These are endocrine cells which release their products into the blood vessels.
Enteroeendocrine Cells

- Are found in the neck and bases of gastric glands

- In the fundus of the stomach, **5-hydroxytryptamine** (serotonin) is one of the principal secretory products

- In the stomach the G–pylorus cells produces **Gastrin** that lead to the Stimulation of gastric acid secretion and Gastric mucosal growth
Pyloric Glands of the Gastric Mucosa

Pyloric gland cells are similar to surface mucous cells and help protect the pyloric mucosa.

- **Pyloric glands** are located in the **pyloric antrum**.
  - They are **branched, coiled, tubular glands**.
  - The **lumen is relatively wide**, and the **secretory cells**.
  - **Enteroendocrine cells** are found interspersed within the gland epithelium along with occasional parietal cells.
- The glands empty into **deep gastric pits** that occupy about **half** the thickness of the mucosa.
Pylorus:
- Deep and open gastric pits
- Glands are short, tortuous and branched
- Mucous cells
- Few parietal cells
- Gastrin cells, (increase HCl output), D cells, somatostatin
- Produce mucus and gastrin.
Section of the lining from a pylorus (Pyloric glands)

they are branched, tubular glands that are coiled. Secretory cells are very similar in appearance to the surface mucus cells, suggesting a relatively viscous secretion. APOD cells found interspersed within the gland epithelium along with occasional parietal cells.
PYLORIC GLANDS: CELL TYPES

CARDiac OR PYLORIC GLAND

- surface mucous cells
- surface epithelium
- gastric pit
- pit
- neck
- body
- base (fundus)
- cross section of a gland

- undifferentiated stem cell
- mucous neck cell
- mucous cell
- Mucus Lysozyme
- enteroendocrine cell
- Gastrin
Stomach regions: Mucosal glands
Pyloroduodenal junction stomach
Structure and function of Endocrine cells
Enteroendocrine cells secrete their products into either the lamina propria or underlying blood vessels.

- **Enteroendocrine cells** are found at every level of the fundic gland, in the base.
- In general, **two types of enteroendocrine** known as enteroendocrine “closed” cells.
- Some, however, have a thin cytoplasmic extension **bearing microvilli** that are exposed to the gland lumen;
  . these are referred as **enteroendocrine “open” cells**.
  . It is now known that open cells serve as **primary chemoreceptors**.
    - The **taste receptors**, similar to those found in taste buds of the specialized oral mucosa, **detect sweet, bitter, and umami** been characterized on the free surface of the open enteroendocrine cells.
    - They belong to the T1R and T2R families of G protein–coupled receptors.
- The names given to the enteroendocrine cells in the older literature were based on their staining with salts of **silver and chromium** (i.e., **enterochromaffin cells, argentaffin cells, and argyrophil cells**).
- There are **more than 20 peptide and polypeptide hormones and hormone-like regulating agents** that they secrete at least **17 different types of enteroendocrine cells** have been described on the basis of **size, shape, and density of their secretory vesicles**.
Enteroendocrine cells

- The names given to the Enteroendocrine cells in the older literature were based on their staining with salts of silver and chromium, enterochromaffin cells, argentaffin cells, and argyrophil cells.
- Such cells are scattered, usually solitary.
  - They are part of the gastro entero pancreatic (GEP) endocrine system.
  - They are also described as constituting part of a diffuse neuroendocrine system.
  - Some enteroendocrine cells may be classifiable functionally as amino precursor uptake and decarboxylation (APUD) cells.
  - The best characterized endocrine cells in the gastric mucosa are gastrin-producing cells (G cells) and somatostatin-producing cells (D cells).

  - **G cells** are most frequent in the middle third of the glands.
  - **G cell** function is stimulated by nervous input, the distension of the stomach or secretagogues.

  - **D cells** are found mainly in glands of the pyloric antrum.
    - They inhibit G cells and thereby acid production.
    - **D cell** function is stimulated by acid in the lumen of the stomach and duodenum.

- Neurocrine hormones:
  - Bombesin, Enkephalins, and Vasoactive inhibitory peptide (VIP), these agents are released from nerve endings close to the target cells.
The enteroendocrine “open” extend to the epithelial surface. Microvilli on the apical surface of these cells possess taste receptors and are able to detect sweet, bitter, and umami sensations. These cells serve as chemoreceptor cells, which monitor an environment on the surface of the epithelium. They are involved in a regulation of gastrointestinal hormones secretion.
Enteroendocrine cells

Closed type

Open type
Enterocendocrine cells

enterocendocrine cell

chief cells
Pyloric Gastric Gland stained for Gastrin Cells
Somatostatin-positive cells of the pyloric mucosa: (A) control rat (B) 4 weeks old hypertensive rat, x 200.
An important source of ghrelin is the fundus region of the stomach. The oxyntic mucous contains entero endocrine cells of different types, of which **X/A cells** stain most positive for ghrelin. (b) The molecular composition of noctanoyl ghrelin. The octanoic acid tail is vital for receptor binding and thus for biological activity of ghrelin.
Ghrelin-positive X/A-like cells (arrows) are evenly distributed throughout the entire length of the gastric oxyntic glands.
Endocrine cells in gastric antral glands. The granules are located between the nucleus and the basement membrane (immunostain for chromogranin).
EM of an enteroendocrine cell in a gastric gland. This granulated cell lies between other cells of the gland. It has an elliptical, euchromatic nucleus and many small electron-dense secretory vesicles. The basal surface (arrows) touches the lamina propria. The cell does not reach the glandular lumen (*). Rather, other epithelial cells abut it. 9000×.

EM of part of an enteroendocrine cell in the stomach. Many membrane-bound, electron-dense secretory vesicles (arrows) lie in the basal part of the cytoplasm. Rough endoplasmic reticulum (RER) and mitochondria (Mi) are sparse. Hormones in the vesicles are released by exocytosis into the lamina propria (LP). 15,000×.
## Physiologic Actions of Gastric Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Site of Synthesis</th>
<th>Stimulates</th>
<th>Inhibits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrin</strong></td>
<td>G cells in stomach</td>
<td>Gastric acid secretion</td>
<td></td>
</tr>
<tr>
<td><strong>Ghrelin</strong></td>
<td>Gr cells in stomach</td>
<td>GH secretion</td>
<td>Lipid metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appetite and perception of hunger</td>
<td>Fat utilization in adipose tissue</td>
</tr>
<tr>
<td><strong>Paracrine hormones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D cells in mucosa throughout GI tract</td>
<td></td>
<td>Gastrin release</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastric acid secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Release of other GI hormones</td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
<td>Mucosa throughout GI tract</td>
<td>Gastric acid secretion</td>
<td></td>
</tr>
<tr>
<td><strong>Neurocrine hormones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bombesin</td>
<td>Stomach</td>
<td>Gastrin release</td>
<td>Intestinal secretion</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>Mucosa and smooth muscle throughout GI tract</td>
<td>Smooth muscle contraction</td>
<td></td>
</tr>
<tr>
<td>Vasoactive inhibitory peptide (VIP)</td>
<td>Mucosa and smooth muscle throughout GI tract</td>
<td>Pancreatic enzyme secretion</td>
<td>Smooth muscle contraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal secretion</td>
<td>Sphincter contraction</td>
</tr>
</tbody>
</table>
Epithelial Cell Renewal in the Stomach

Surface mucous cells are renewed approximately every 3 to 5 days.
- The relatively short lifespan of the surface mucous cells, 3 to 5 days, is accommodated by mitotic activity in the isthmus (the narrow segment that lies between the gastric pit and the fundic gland).
- The isthmus of the fundic gland contains a reservoir of tissue stem cells.

The cells of the fundic glands have a relatively long lifespan.
- The mucous neck cell, in contrast, has a much shorter lifespan, approximately 6 days.
- The parietal cells have the longest lifespan, approximately 150 to 200 days.
  - it has been hypothesized that parietal cells may have originated from a bacterium called Neurospora crassa that previously existed in a symbiotic relationship with the cells of the human stomach.
- The chief and enteroendocrine cells are estimated to live for about 60 to 90 days before they are replaced by new cells migrating downward from the isthmus.
Photomicrograph of a dividing cell in the isthmus of a pyloric gland. The gastric pits in this photomicrograph were sectioned in a plane that is oblique to the axis of the pit. Note that on this section, gastric pits (arrows) can be recognized as invaginations of surface epithelium that are surrounded by lamina propria. The lamina propria is highly cellular because of the presence of large numbers of lymphocytes. 240. Inset. This high magnification of the area indicated by the rectangle shows a dividing cell in the isthmus. 580.
CLINICAL POINT

- **Vitamin B12** is essential for production of erythrocytes in bone marrow and normal neurologic function.

- **Pernicious anemia** a form of megaloblastic anemia is an autoimmune disease resulting in marked **atrophy of gastric mucosa**, destruction of parietal cells, and **failure to produce intrinsic factor**, which leads to vitamin B12 malabsorption. Symptoms include fatigue, asthenia, memory impairment, and peripheral neuropathy.

- The diagnosis is based on histologic findings of chronic atrophic gastritis and detection in serum of **antibodies to intrinsic factor** and the **proton pump (H\(^+\), K\(^+\)-ATPase)** of parietal cells.

- Patients respond favorably to early detection, continuing treatment via intramuscular injections of **cobalamin**, and a well-balanced diet rich in **folic acid** and **vitamin B12**.
The **lamina propria** of the stomach is relatively scant and restricted to the limited spaces surrounding the gastric pits and glands.

- The stroma is composed largely of **reticular fibers with associated fibroblasts and smooth muscle cells**.

- Other components include cells of the immune system, namely, **lymphocytes, plasma cells, macrophages, and some eosinophils**.

- **Occasional lymphatic nodules** are also present, usually intruding partially into the muscularis mucosae.

- The **muscularis mucosae** is composed of **two relatively thin layers**, usually arranged as an **inner circular and outer longitudinal layer**.
deep gastric pits

glandular region of the pyloric stomach mostly mucous secreting cells and enteroendocrine cells

muscularis mucosa

lymphatic nodule (MALT)
**Fundic stomach**

- **Mucosa**
- **Submucosa**
- **Antibody-producing plasma cells**
- **Gastric pits**

- Ganglion cells of the Auerbach's plexus regulate the muscularis externa
- Ganglion cells of the Meissner's plexus regulates muscularis mucosa
lymphoid tissue in the stomach

Diffuse lymphoid tissue
Gastric Muscularis Externa

- The **muscularis externa** consisting of an **outer longitudinal layer**, a **middle circular layer**, and a **inner oblique layer**.
- As with other hollow, spheroidal organs the smooth muscle of the **muscularis externa** of the **stomach** is somewhat **more randomly oriented** than the term **layer** implies.
  
  . the **longitudinal layer is absent** from much of the **anterior and posterior stomach** surfaces, and
  
  . the **circular layer is poorly developed** in the **periesophageal region**.
- The arrangement of the muscle layers is functionally important, as it relates to its role in mixing chyme during the digestive process as well as to its ability to force the partially digested contents into the small intestine.
- Groups of ganglion cells and bundles of unmyelinated nerve fibers are present between the muscle layers.
- Collectively, they represent the **myenteric (Auerbach’s) plexus**, which provides **innervation of the muscle layers**.
Gastric Serosa

- The **serosa** is continuous with the **parietal peritoneum** of the abdominal cavity via the **greater omentum** and with **visceral peritoneum** of the **liver** at the **lesser omentum**.
Musculosa of Fundus: 3 Layers
Inner oblique (IO), Middle Circular (MC) and Outer Longitudinal (OL).
Fundic stomach

Mucosa

Ganglion cells of the Auerbach's plexus regulate the muscularis externa

Ganglion cells of the Meissner's plexus regulates muscularis mucosa

Submucosa

Gastric pits
The **myenteric plexus** of Auerbach is found between the two layers of smooth muscle cells in the muscularis externa. The **ganglion cells are larger and more basophilic than the supportive cells.** Plexus like these are involved in controlling smooth muscle contractions as well as glandular secretions.
The MUSCULARIS EXTERNA and Serosa
Top left: LM of the stomach wall. 5x. H&E. Center: EM of the outer wall of the stomach. The serosa consists of one outer layer of flattened mesothelial cells and associated connective tissue. Smooth muscle cells in the muscularis externa sectioned longitudinally and transversely are seen. A blood vessel (BV) and part of a myenteric plexus with a ganglion cell are between the smooth muscle layers. 4800x.

Chronic peritonitis. This form, known as tuberculosis peritonitis, shows peritoneum studded with tubercles and congested; serofibrinous exudate; numerous adhesions between abdominal wall and viscera.
CLINICAL POINT

- **Peritonitis localized or diffuse inflammation of the peritoneum** is usually due to entry of bacteria into the peritoneal cavity via an internal perforation of the digestive tract or an external penetrating wound.
- Infecting bacteria are most commonly *Escherichia coli* and *Enterococcus faecalis*.
- Clinical features are severe abdominal pain and distention, nausea, vomiting, and diarrhea.
- Major causes are gastric (peptic) ulcer, appendicitis, diverticulitis, cholecystitis, and gangrenous obstruction of the small intestine.
- Peritonitis may also be a complication of abdominal surgery.
- A medical emergency, it can be life-threatening if untreated.
Blood Supply

- Five arteries supply blood to the stomach:
  . The left gastric artery arises directly from the celiac axis and supplies the cardiac region;
  . The right gastric artery (supplies the lesser curve);
  . The right gastroepiploic artery (supplies the greater curve) arise from the hepatic artery;
  . The left gastroepiploic and
  . The short gastric arteries arise from the splenic artery and also supply the greater curvature.

- All these vessels anastomose freely on the subserosal layer of the stomach and in the muscularis propria, with extensive true plexus formation present within the submucosa.

- This richness of blood supply explains why it is so unusual to see gastric infarcts.

- The mucosal arteries are derived from this submucosal plexus.
Lymphatics

- Lymphatic channels are present at all levels of the lamina propria immediately superficial to the muscularis mucosae.
- From there, referents penetrate the muscle and communicate with larger lymphatic channels running in the submucosa.
- The lymphatic trunks of the stomach generally follow the main arteries and veins.
- Four areas of drainage can be identified, each with its own group of nodes. Efferents from all four groups ultimately pass to celiac nodes.
Nerve Supply
- The sympathetic nerve supply to the stomach is derived from the celiac plexus via nerves.
- Branches are received from the left and right phrenic nerves.
- The parasympathetic supply is the vagus nerve.
- Nerve plexuses are concentrated in Meissner's plexus in the submucosa and Auerbach's plexus between the circular and longitudinal fibers of the muscularis propria.
THE END

Thank you