DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

TOPIC :Properties of gastrointestinal tract ,tight junction complex .

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Properties of Gastrointestinal tract

The intestinal wall is composed of following layers

- ✓ Serosa
- ✓ Longitudinal muscle layer
- ✓ Circular muscle layer
- ✓ Submucosa
- ✓ Mucosa

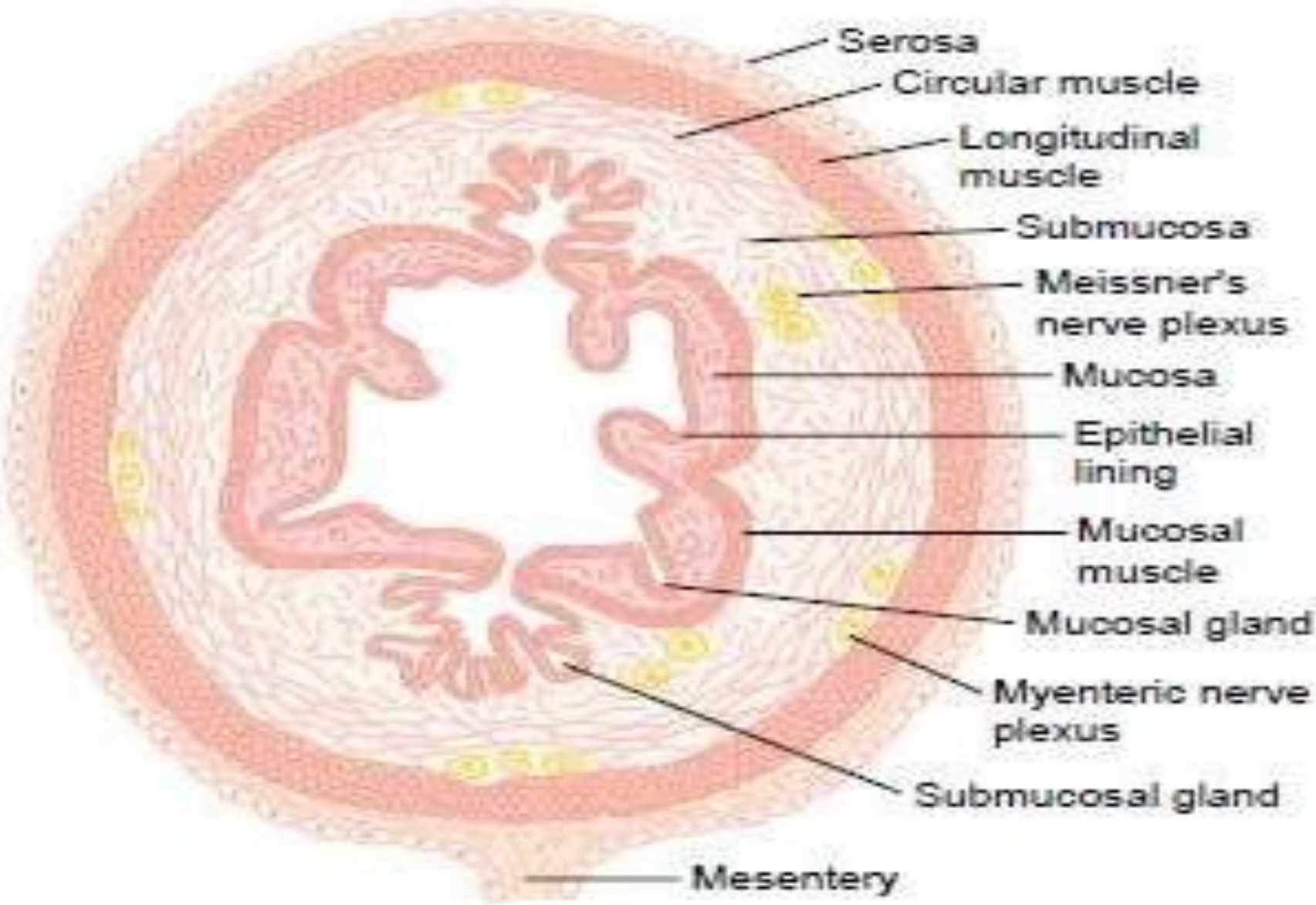


Figure 62–2

Typical cross section of the gut

1.Neural control of Gastrointestinal function

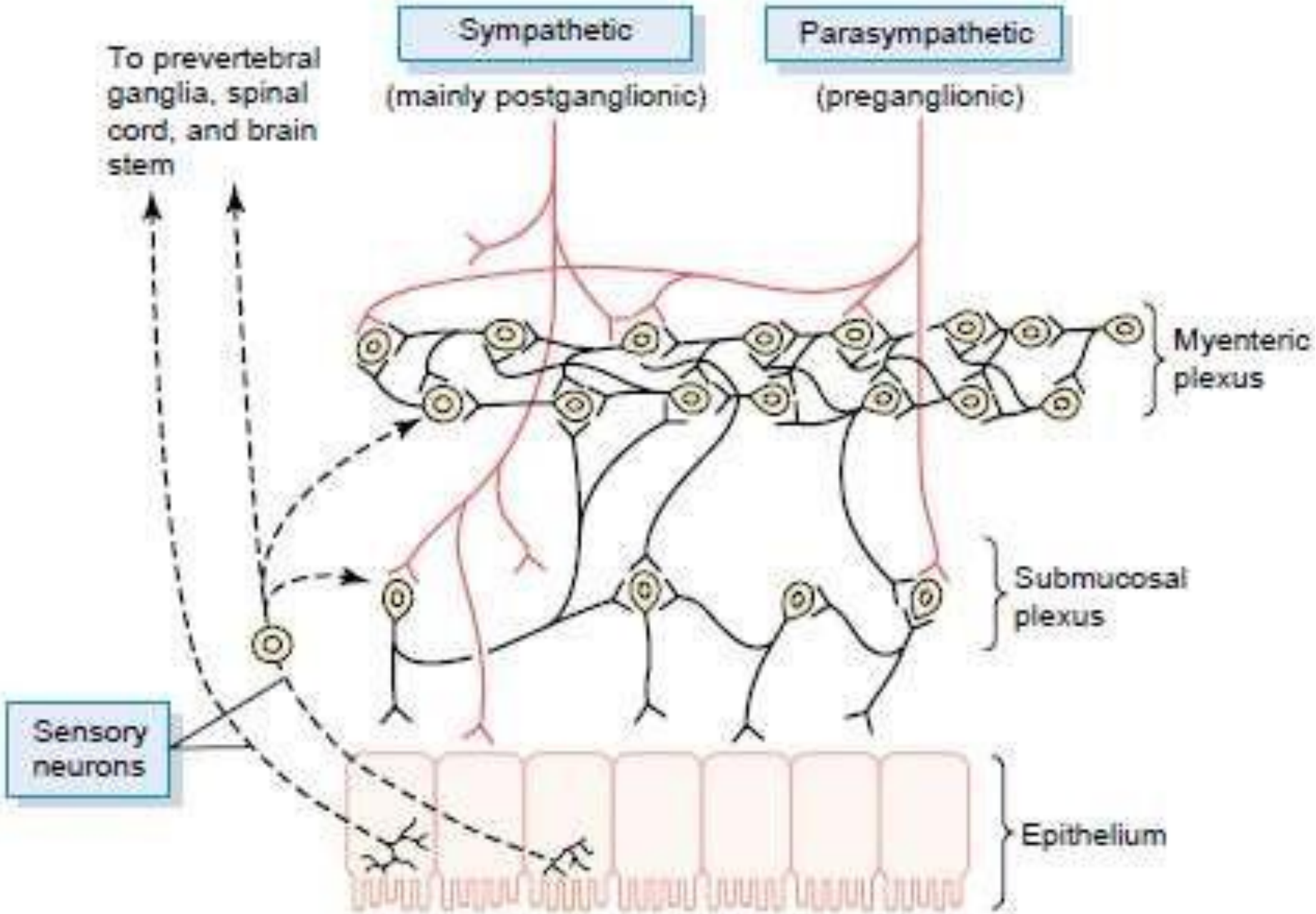
The gastrointestinal tract has its own nervous system, called the **Enteric nervous system.** It is composed of two plexuses

- ✓ The mysenteric plexus or Auerbach's plexus is an outer plexus located between the muscle layers.
- ✓ The submucosal plexus is an inner plexus that lies in the submucosa

Autonomic control of Gastrointestinal tract

The parasympathetic nervous system increases the activity of the enteric nervous system. The parasympathetic supply to the gut is made up of cranial and sacral divisions.

- ✓ The cranial parasympathetic innervate, by way of the vagus nerve, the esophagus, stomach, pancreas, and first half of the large intestine.
- ✓ The sacral parasympathetic innervate, by way of the pelvic nerves, the distal half of the large intestine.


Sympathetic
(mainly postganglionic)
Parasympathetic
(preganglionic)
To prevertebral ganglia, spinal cord, and brain stem
Myenteric plexus
Submucosal plexus
Sensory neurons
Epithelium

- The sympathetic nervous system usually inhibits the activity in the gastrointestinal tract, causing many effects opposite to those of the parasympathetic nervous system.

2.Gastrointestinal reflexes

Three types of reflexes are essential for gastrointestinal control

- ✓ Reflexes that occur entirely within the enteric nervous system
- ✓ Reflexes from the gut to the sympathetic ganglia and back to the gut
- ✓ Reflexes from the gut to the spinal cord or brain stem and then back to the gut

3.Gastrointestinal Hormones

Four major hormones are

Secretin

- ✓ Secretin was the first gastrointestinal hormone discovered and is secreted by the “S” cells in the mucosa *of the duodenum in response to acidic gastric juice* emptying into the duodenum from the pylorus of the stomach.
- ✓ Secretin has a mild effect on motility of the gastrointestinal tract and acts to promote pancreatic secretion of bicarbonate which in turn helps to neutralize the acid in the small intestine.

Gastrin

The primary actions of gastrin are

- ✓ *stimulation of gastric acid secretion and*
- ✓ *stimulation of growth of the gastric mucosa.*

Cholecystokinin

- ✓ This hormone strongly contracts the gallbladder, expelling bile into the small intestine where the bile in turn plays important roles in emulsifying fatty substances, allowing them to be digested and absorbed.
- ✓ Cholecystokinin also inhibits stomach contraction moderately.

Gastric inhibitory peptide

- ✓ *Gastric inhibitory peptide is secreted by the mucosa of the upper small intestine, mainly in response to fatty* acids and amino acids but to a lesser extent in response to carbohydrate.
- ✓ It has a mild effect in decreasing motor activity of the stomach and therefore slows emptying of gastric contents into the duodenum when the upper small intestine is already overloaded with food products.

Functional movements in the Gastrointestinal tract

- ✓ Propulsive movements
- ✓ Mixing movements

4.Gastrointestinal blood flow

- ✓ The blood vessels of the gastrointestinal tract are a part of the Splanchnic circulation
- ✓ Parasympathetic stimulation increases the blood flow
- ✓ Sympathetic stimulation decreases blood flow.

5.Mastication

- Mastication (chewing) is the process for which teeth are especially designed. The anterior teeth (incisors) providing a strong cutting action and the posterior teeth (molars), a grinding action.
- Most of the muscles of chewing are innervated by the motor branch of the fifth cranial nerve (trigeminal nerve), and the chewing process is controlled by nuclei in the brain stem. Stimulation of specific reticular areas in the brain stem taste centers will cause rhythmical chewing movements. Also, stimulation of areas in the hypothalamus, amygdala, and even the cerebral cortex near the sensory areas for taste and smell can often cause chewing.

- The rate of digestion is absolutely dependent on the total surface area exposed to the digestive secretions.
- In addition, grinding the food to a very fine particulate consistency prevents damage to the gastrointestinal tract and increases the ease with which food is emptied from the stomach into the small intestine, then into all succeeding segments of the gut.

6.SWALLOWING

- **Swallowing**, known scientifically as deglutition, is the process in the human or animal body that makes food to pass from the mouth, to the pharynx, and into the esophagus, while shutting the epiglottis. If this fails and the object goes through the trachea, then choking or pulmonary aspiration can occur. In the human body it is controlled by the swallowing reflex.

Eating and swallowing are complex neuromuscular activities consisting essentially of three phases, an oral, pharyngeal and esophageal phase. Each phase is controlled by a different neurological mechanism.

Oral phase This is voluntary stage and includes

- ✓ **Moistening**
- ✓ **Mastication**
- ✓ **Trough formation**
- ✓ **Movement of the bolus posteriorly**

- **<u>Pharyngeal phase</u> :** This stage is involuntary and constitutes the passage of food from the pharynx to the esophagus. When the pharyngeal phase begins, other activities such as chewing, breathing, coughing and vomiting are concomitantly inhibited

Nervous regulation of Swallowing

- The most sensitive tactile areas of the posterior mouth and pharynx for initiating the pharyngeal stage of swallowing are the tonsillar pillars.
- Impulses are transmitted from these areas through the sensory portions of the trigeminal and glossopharyngeal nerves into the medulla oblongata, either into or closely associated with the *tractus solitarius*, which receives essentially all sensory impulses from the mouth.

- The successive stages of the swallowing process are then automatically initiated in orderly sequence by neuronal areas of the medulla and lower portion of the pons. This area is known as Swallowing center.
- The motor impulses from the swallowing center to the pharynx and upper esophagus that cause swallowing are transmitted successively by the 5th, 9th, 10th, and 12th cranial nerves

Esophageal stage

Esophageal stage of swallowing: The esophagus normally exhibits two types of peristaltic movements

1. Primary peristalsis
2. Secondary peristalsis

- Primary peristalsis is simply continuation of the peristaltic wave that begins in the pharynx and spreads into the esophagus

- If the primary peristaltic wave fails to move into the stomach all the food that has entered the esophagus, *secondary peristaltic waves* result from distention of the esophagus itself by the retained food; these waves continue until all the food has emptied into the stomach.
- The secondary peristaltic waves are initiated partly by intrinsic neural circuits in the mysenteric nervous system and partly by reflexes that begin in the pharynx and are then transmitted upward through *vagal afferent fibers* to the medulla and back again to the esophagus through *glossopharyngeal* and *vagal efferent nerve fibers*.

Function of sphincter lower esophageal sphincter (gastroesophageal sphincter)

- At the lower end of esophagus, extending from about 2-5 cm above its juncture with the stomach, the esophageal circular muscle functions as lower esophageal sphincter or gastroesophageal sphincter.

7.Stomach

- The stomach is a small, 'J'-shaped pouch with walls made of thick, elastic muscles, which stores and helps break down food.
- Storage of large quantities of food until the food can be processed in the duodenum
- Mixing of this food with gastric secretions until it forms a semi fluid mixture called chyme
- Slow emptying of the food from the stomach into the small intestine at a rate suitable for proper digestion and absorption

Receptive relaxation of the stomach

- As the food bolus travels through the lower esophagus, the stomach reflexly begins to relax.
- This phenomenon allows the stomach to accept large amounts of food with minimal increase in gastric pressure; it also minimizes esophageal reflux.

Mixing and propulsion of food in the stomach

- As long as food is in the stomach, weak peristaltic *constrictor waves, called mixing waves, begin in the mid- to upper portions of* the stomach wall and move toward the antrum about once every 15 to 20 seconds. These waves are initiated by the gut wall *basic electrical rhythm.*

- **Chyme**
- After food in the stomach has become thoroughly mixed with the stomach secretions, the resulting mixture that passes down the gut is called *chyme.* The degree of fluidity of the chyme leaving the stomach depends on the relative amounts of food, water, and stomach secretions and on the degree of digestion that has occurred.The appearance of chyme is that of a murky semifluid or paste.

Phases of digestion

1. **Cephalic phase:** in cephalic phase the sight and even thought of food can stimulate gastric secretions
2. **Gastric phase:** In gastric phase, after eating has begun, the presence of food and distension it causes also stimulate gastric secretions

3- Intestinal Phase: In intestinal phase, the entry of gastric contents stimulate release of multiple factors, which then inhibit gastric activity.

8.Movements of the Small intestine

- Most Digestion & Absorption occurs in the small intestine
- No more digestion as food moves into large intestine, where a little absorption of salt & water does take place.

- The three segments of small intestine (which is more than 6 meters long) are the:
  - Duodenum, only few cms.
  - Jejunum, more than 2 meters
  - Ileum, more than 3 meters

MECHANISM: When small intestine filled with chyme, it is distended, mysenteric plexus stretched.

- Due to stimulation of mysenteric plexus, a **series of constrictions** occur throughout the length of small intestine. (Area of constriction is about 1cm),forming segmentation
- Segmentation consists of ring like contractions along the length of small intestine.

- Within seconds, contracted area relaxes & previously relaxed area contracts.
- This mixes the chyme.
- Rate of segmentation contractions in duodenum is around 7-12 / minute
- In terminal ileum it is 9 / minute
- Contents take 3-5 hours to move through the intestine

9.Movement of villi

- Villi present in jejunal mucosa.
- Increases surface area for absorption about 10 folds.

Peristalsis or Propulsive Movements

- Also called MMC (migrating motility complex)
- When most food is absorbed, segmentations cease
- migratory motility complex (propulsive movements) propels unabsorbed residue from small intestine to large intestine.
- meal motility consists of weak, repetitive, peristaltic waves, that move a short distance .

10.Peristaltic waves

- The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the chyme along the intestine; and this process intensifies as additional chyme enters the duodenum

Movements Caused by the Villi

- The *muscularis mucosae* can cause short folds to appear in the intestinal mucosa. In addition individual fibers from this muscle extend into the intestinal villi and cause them to contract.The mucosal folds increase the surface area exposed to the chyme, thereby increasing absorption. Also, contractions of the villi—shortening, elongating, and shortening again results into the increase in the flow of lymph freely from the villi into the lymphatic system.

Function of the Ileocecal Valve

- A principal function of the ileocecal valve is to prevent backflow of fecal contents from the colon into the small intestine.
- The ileocecal valve itself protrudes into the lumen of the cecum and therefore is forcefully closed when excess pressure builds up in the cecum and tries to push cecal contents backward against the valve lips.

- The wall of the ileum for several centimeters immediately upstream from the ileocecal valve has a thickened circular muscle called the *ileocecal sphincter*.This sphincter normally remains mildly constricted and slows emptying of ileal contents into the cecum.

- Resistance to emptying at the ileocecal valve prolongs the stay of chyme in the ileum and thereby facilitates absorption. Normally, only 1500 to 2000 milliliters of chyme empty into the cecum each day.

11.Movements of the Colon

- The principal functions of the colon are

(1)absorption of water and electrolytes from the chyme to form solid feces

(2)storage of fecal matter until it is expelled.

12.Haustrations

- **Mixing Movements—"Haustrations"**
- Large circular constrictions occur in the large intestine. At each of these constrictions, about 2.5 centimeters of the circular muscle contracts, sometimes constricting the lumen of the colon almost to occlusion.
- At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the *teniae coli*, contracts. These combined contractions of the circular and longitudinal strips of muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called *haustrations*.

- Each haustration usually reaches peak intensity in about 30 seconds and then disappears during the next 60 seconds.
- They also at times move slowly toward the anus during contraction, especially in the cecum and ascending colon, and thereby provide a minor amount of forward propulsion of the colonic contents.

13.Propulsive Movements—“Mass Movements.”

- **Propulsive Movements—“Mass Movements.”**
- Much of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions, requiring as many as 8 to 15 hours to move the chyme from the ileocecal valve through the colon, while the chyme itself becomes fecal in quality, a semisolid slush instead of semifluid.

- **Initiation of Mass Movements by Gastrocolic and Duodenocolic Reflexes.**
- Appearance of mass movements after meals is facilitated by *gastrocolic* and *duodenocolic reflexes*. These reflexes result from distention of the stomach and duodenum.
- The reflexes almost certainly are transmitted by way of the autonomic nervous system.

14.Defecation

- Most of the time, the rectum is empty of feces. This results partly from the fact that a weak functional sphincter exists about 20 centimeters from the anus at the juncture between the sigmoid colon and the rectum.
- There is also a sharp angulation which contributes additional resistance to filling of the rectum.

Defecation Reflexes

- Ordinarily, defecation is initiated by *defecation reflexes*.
- One of these reflexes is an *intrinsic reflex* mediated by the local enteric nervous system in the rectal wall. When faeces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the *mysenteric plexus* to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing faeces toward the anus.

- As the peristaltic wave approaches the anus, the *internal* anal sphincter is relaxed by inhibitory signals from the mysenteric plexus; if the *external* anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs.

WHAT EXACTLY IS A TIGHT JUNCTION

- ”A **tight junction**,which separates the cells into apical and basal compartments and is at one end of the spectrum.”
- “When two adjacent epithelial cells form a **TJ**, there is no extracellular space between them and the movement of substances through the extracellular space between the cells is blocked.”
- “The epithelia forms a protective barrier and has a selective permeability.”

EXAMPLES OF TIGHT JUNCTIONS FOUND IN HUMANS

- ***Intestinal Barrier***

- ***Blood Brain Barrier***

Intestinal Barrier

- The intestinal lining, the largest mucosal surface has three functions.

1. ”Serves as the vehicle or mechanism by which we obtain nutrients from the food we eat.”
2. “Blocks the entrance into the bloodstream of potentially harmful particles, chemicals, bacteria, and other organism that can pose a threat to the health.”
3. “Contains chemicals called immunoglobulins that bind to bacteria and foreign proteins to prevent them from attaching to the gut’s lining.”

- There are two pathways the body uses to absorb nutrients from the gut.

1. **Transcellular** pathway -nutrients move through the epithelial cells

2. **Paracellular pathway –** nutrients pass between the epithelial cells.

- the parameters of a leaky gut:
  - A “leaky gut” is caused by problems of the competency of these tight junctions, which is a intricate systems and highly regulated.
  - This tight junction measures 10 to 15 angstrom.
  - The problem with a “leaky gut” is the gut permeability is decreased, and the body is ineffective at allowing nutrients to pass.

Books

- Ganong's review of Medical Physiology, 23rd edition
- Biopharmaceutics and pharmacokinetics – by D.M.Brahmankar,Sunil B.Jaiswal