Gastrointestinal Physiology
Structure and Innervation of the Gastrointestinal Tract
Structure of the gastrointestinal (GI) tract, Layers of the Gastrointestinal Tract

1. Mucosa: including
   ① A lining epithelium, including glandular tissue,
   ② an underlying layer of loose connective tissue called the lamina propria, which provides vascular support for the epithelium, and often contains mucosal glands. Products of digestion pass into these capillaries. Lymphoid follicles and plasma cells are also often found here.
   ③ Finally, a thin double layer of smooth muscle is often present; the muscularis mucosa for local movement of the mucosa.

2. Sub-mucosa:
   A loose connective tissue layer, with larger blood vessels, lymphatic vessels, nerves, and can contain mucous secreting glands.

3. Muscularis propria (externa):
   There are usually two smooth muscle layer;
   ① the inner layer is circular (contraction causes decrease diameter), and the
   ② outer layer is longitudinal (contraction causes shorting).

4. Adventitia layer (or serosa):
   Outermost layer of loose connective tissue; covered by the visceral peritoneum. Contains blood vessels, lymphatics and nerves.
Gastrointestinal Smooth Muscle Functions as a Syncytium.
The individual smooth muscle fibers in the gastrointestinal tract are 200 to 500 micrometers in length and 2 to 10 micrometers in diameter, and they are arranged in bundles of as many as 1000 parallel fibers. In the longitudinal muscle layer, the bundles extend longitudinally down the intestinal tract; in the circular muscle layer, they extend around the gut.

Within each bundle, the muscle fibers are electrically connected with one another through large numbers of gap junctions that allow low-resistance movement of ions from one muscle cell to the next. Therefore, electrical signals that initiate muscle contractions can travel readily from one fiber to the next within each bundle but more rapidly along the length of the bundle than sideways.

Each bundle of smooth muscle fibers is partly separated from the next by loose connective tissue, but the muscle bundles fuse with one another at many points, so in reality each muscle layer represents a branching latticework of smooth muscle bundles. Therefore, each muscle layer functions as a syncytium; that is, when an action potential is elicited anywhere within the muscle mass, it generally travels in all directions in the muscle. The distance that it travels depends on the excitability of the muscle; sometimes it stops after only a few millimeters, and at other times it travels many centimeters or even the entire length and breadth of the intestinal tract.

Also, because a few connections exist between the longitudinal and circular muscle layers, excitation of one of these layers often excites the other as well.

Digestive motility and secretion are carefully regulated to maximize digestion and absorption of ingested food. Four factors are involved in regulating digestive system function: (1) autonomous smooth-muscle function, (2) intrinsic nerve plexuses, (3) extrinsic nerves, and (4) gastrointestinal hormones.
Innervation of the GI tract

The autonomic nervous system (ANS) of the GI tract comprises both extrinsic and intrinsic nervous systems.

1. Extrinsic innervation (parasympathetic and sympathetic nervous systems)
   - Efferent fibers carry information from the brain stem and spinal cord to the GI tract.
   - Afferent fibers carry sensory information from chemo-receptors (activated by H+, proteins, and lipids in chyme), mechano-receptors (activated by distension of the digestive walls by food (bolus or chyme)) and osmo-receptors (activated by amino acids and glucose) in the GI tract to the brain stem and spinal cord.

a. Parasympathetic nervous system
   - is usually excitatory on the functions of the GI tract.
   - is carried via the vagus and pelvic nerves.
   - Pre-ganglionic parasympathetic fibers synapse in the enteric plexuses.
   - Cell bodies in the ganglia of the enteric plexuses then send information to the smooth muscle, secretory cells, and endocrine cells of the GI tract. All effects of vagal and pelvic efferent neurons are mediated via synapses on enteric neurons.
   1. The vagus nerve innervates the esophagus, stomach, pancreas, and upper large intestine.
   2. Reflexes in which both afferent and efferent pathways are contained in the vagus nerve are called vagovagal reflexes.

b. Sympathetic nervous system
   - is usually inhibitory on the functions of the GI tract.
   - Fibers originate in the spinal cord between T-8 and L-2.
   - Pre-ganglionic sympathetic cholinergic fibers synapse in the pre-vertebral ganglia.
   - Postganglionic sympathetic adrenergic fibers leave the pre-vertebral ganglia and synapse in
     a. the entéric plexuses. Cell bodies in the ganglia of the entéric plexuses then send information to the smooth muscle, secretory cells, and endocrine cells of the GI tract;
     b. End on post-ganglionic cholinergic neurons, where the nor-epinephrine they secret inhibits acetylcholine secretion.
     c. Direct postganglionic adrenergic innervation of blood vessels and some smooth muscle cells also occurs where they produce vasoconstriction.
• Extrinsic nerves functions:
The autonomic nerves influence digestive tract motility and secretion either by 1 modifying ongoing activity in the intrinsic plexuses, 2 altering the level of gastrointestinal hormone secretion, or, in some instances, 3 acting directly on the smooth muscle and glands. One of the major purposes of specific activation of extrinsic innervations is to coordinate activity between different regions of the digestive system.
The parasympathetic nerve fibers supplying the digestive tract, which arrive primarily by way of the vagus nerve, tend to increase smooth muscle motility and promote secretion of digestive enzymes and hormones. The sympathetic nervous system activation has an opposite effect.
The autonomic nerves, especially the vagus nerve, can be discretely activated to modify only digestive activity.

<table>
<thead>
<tr>
<th>Functions of ANS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sympathetic</strong></td>
</tr>
<tr>
<td>GIT</td>
</tr>
<tr>
<td>↓ motility</td>
</tr>
<tr>
<td>Sphincter contraction</td>
</tr>
<tr>
<td>Decreased secretions</td>
</tr>
</tbody>
</table>
In GIT the neurotransmitter are either major neurotransmitters (like (1) acetylcholine, (2) norepinephrine, (3) adenosine triphosphate, (4) serotonin, (5) dopamine, (6) cholecystokinin, (7) substance P, (8) vasoactive intestinal polypeptide, (9) somatostatin, (10) leu-enkephalin, (11) met-enkephalin, and (12) bombesin and (13) nitric oxide) or neuropeptides. Neuropeptides are short chains of amino acids; it may act as hormones or neurotransmitter. The primary criteria of neurotransmitter are:

1. the substance must be present within the presynaptic neuron
2. The substance must be released in response to presynaptic depolarization
3. Specific receptors for the substance must be present on the postsynaptic cell.

Acetylcholine most often excites gastrointestinal activity. Norepinephrine almost always inhibits gastrointestinal activity, as doe’s epinephrine, which reaches the gastrointestinal tract mainly by way of the blood after it is secreted by the adrenal medullae into the circulation.
2. Intrinsically innervated (enteric nervous system)

Enteric nervous system comprises submucosal plexus and myenteric plexus

Enteric nervous system lies entirely in the wall of the gut

Enteric nervous system beginning in the esophagus and extending all the way to the anus.

Enteric nervous system number of neurons is about 100 million, nearly equal to the number of neurons in the entire spinal cord.

Enteric nervous system integrates and coordinates the motility, secretory, and endocrine functions of the GI tract.

Enteric nervous system coordinates and relays information from the parasympathetic and sympathetic nervous systems to the GI tract.

The enteric nervous system uses local reflexes to relay information within the GI tract.

The enteric nervous system (ENS) generates and modulates many digestive functions especially motility and secretion without input from the central nervous system and has been described as the “little brain.”
The enteric nervous system consists of nerve cell bodies that are connected by their processes to form two major ganglionated plexi in the digestive tract:
a. Myenteric plexus (Auerbach's plexus)
The myenteric plexus consists mostly of a linear chain of many interconnecting neurons
The myenteric plexus extends the entire length of the gastrointestinal tract.
The myenteric plexus is located between the circular and longitudinal smooth muscle layers
The myenteric plexus primarily controls the motility of the GI smooth muscle.
Because the myenteric plexus extends all the way along the intestinal wall and lies between the longitudinal and circular layers of intestinal smooth muscle, it is concerned mainly with controlling muscle activity along the length of the gut. The myenteric plexus should not be considered entirely excitatory because some of its neurons are inhibitory; their fiber endings secrete an inhibitory transmitter, possibly vasoactive intestinal polypeptide or some other inhibitory peptide. The resulting inhibitory signals are especially useful for inhibiting some of the intestinal sphincter muscles that impede movement of food along successive segments of the gastrointestinal tract, such as the pyloric sphincter, which controls emptying of the stomach into the duodenum, and the sphincter of the ileocecal valve, which controls emptying from the small intestine into the cecum.
When the myenteric plexus is stimulated, its principal effects are
(1) increased tonic contraction, or "tone," of the gut wall;
(2) increased intensity of the rhythmical contractions;
(3) slightly increased rate of the rhythm of contraction; and
(4) increased velocity of conduction of excitatory waves along the gut wall, causing more rapid movement of the gut peristaltic waves.
b. Sub-mucosal plexus (Meissner’s plexus)
• is located between the inner layer of the circular muscle layer and the sub-mucosa
• Primarily controls secretion and blood flow.
The submucosal plexus, in contrast to the myenteric plexus, is mainly concerned with controlling function within the inner wall of each minute segment of the intestine. For instance, many sensory signals originate from the gastrointestinal epithelium and are then integrated in the sub-mucosal plexus to help control local intestinal secretion, local absorption, and local contraction of the sub-mucosal muscle that causes various degrees of folding of the gastrointestinal mucosa.
• receives sensory information from chemoreceptors and mechanoreceptors in the GI tract.
The enteric nervous system is very extensive, containing as many neurons as are present in the spinal cord.
The extrinsic sympathetic and parasympathetic fibers that connect to both the myenteric and submucosal plexuses. Although the enteric nervous system can function independently of these extrinsic nerves, stimulation by the parasympathetic and sympathetic systems can greatly enhance or inhibit gastrointestinal functions, as we discuss later.
The enteric nervous system contains:

1. Sensory or afferent neurons (sometimes called intrinsic primary afferent neurons [IYANs]) that sense the environment (e.g., intestinal pH, osmolarity, wall stretch),

2. Inter-neurons (the connectors), and

3. Secretomotor or efferent neurons that control many cell types to stimulate or inhibit motility, secretion, absorption, and immune function of the GI tract.
3. Interstitial cells of Cajal (Gastrointestinal action potential and Mechanical contraction):

- The interstitial cells of Cajal are specialized pacemaker cells located between the smooth muscle in the wall of the stomach, small intestine, and large intestine. These cells are connected to the smooth muscle and the myenteric plexus via gap junctions.

The functions of interstitial cells of Cajal are:

(a) Generation of electrical slow wave activity,

(b) Coordination of pacemaker activity and active propagation of slow waves,

(c) Transduction of motor neural inputs from the enteric nervous system, and

(d) Mechano-sensation to stretch of GI muscles.

These cells characterize by:

i. These cells are stellate mesenchymal (mesenchyme: the tissue from which all connective eventually arise) pacemaker cells with smooth muscle-like feature that send long multiply branched processes into the intestinal smooth muscle.

ii. In stomach and the small intestine, these cells are located in the outer circular muscle layer near the myenteric plexus; in the colon, they are at the sub-mucosal layer.

iii. In the stomach and small intestine, there is a descending gradient in pacemaker frequency, and as in the heart, the pacemaker with higher frequency usually dominate.

The cell membranes of the pacemaker cells undergo a rhythmic depolarization and re-polarization from -65mV to -45mV.

This rhythm of depolarization-repolarization of the cell membrane creates a slow wave (general name for spontaneous electrical rhythm) known as a BER (Basal or Basic electrical rhythm (BER) or electrical control activity (ECA): specific name of slow wave in GIT), and it is transmitted to the smooth muscle cells.
Slow waves are not action potentials and do not directly induce muscle contraction; they are rhythmic, wave-like fluctuations in membrane potential (between -65 and -45 mV) that cyclically bring the membrane closer to or farther from threshold potential. If these waves reach threshold at the peaks of depolarization (spike potential), a volley of action potentials is triggered at each peak, resulting in rhythmic cycles of muscle contraction.

Sheets of smooth muscle cells are connected by gap junctions through whom charge-carrying ions can flow. In this way, electrical activity initiated in a digestive-tract pacesetter cell spreads to the adjacent contractile smooth-muscle cells. The whole muscle sheet behaves like a functional syncytium, becoming excited and contracting as a unit when threshold is reached. If threshold is not achieved, the oscillating slow-wave electrical activity continues to sweep across the muscle sheet without being accompanied by contractile activity.

Threshold is reached depends on the effect of various mechanical, neural, and hormonal factors that influence the starting point around which the slow-wave rhythm oscillates. The rate of self-induced rhythmic digestive contractile activities depends on the inherent rate established by the involved pace-setter (or pace-maker) cells.
Slow waves
Slow wave are undulating متموج and regular change in resting membrane potential
Slow wave are produced by interstitial cell of cajal
Slow wave do not cause smooth muscle contraction unless slow wave reach a threshold
Slow wave when reach a threshold action potential appears (called spike potential).
Slow wave are not action potentials. Instead, they are slow, undulating changes in the resting membrane potential. Their intensity usually varies between 5 and 15 millivolts, and their frequency ranges in different parts of the human gastrointestinal tract from 3 to 12 per minute—about 3 in the body of the stomach, as much as 12 in the duodenum, and about 8 or 9 in the terminal ileum. Therefore, the rhythm of contraction of the body of the stomach, the duodenum, and the ileum is usually about 3 per minute, about 12 per minute, and 8 to 9 per minute, respectively.
The slow waves usually do not by themselves causes muscle contraction in most parts of the gastrointestinal tract, except perhaps in the stomach. Instead, they mainly excite the appearance of intermittent spike potentials, and the spike potentials in turn actually excite the muscle contraction.
Slow wave propagate along the GI tract due to gap junction between smooth muscles. Spike potential cause smooth muscle contraction.
GI smooth muscle have unstable resting membrane potential of (-50mV to -60mV). If the slow wave potential rise above (-40mV), spike potential (true action potential) appears superimposed on the slow wave.
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Slow waves propagate along the GI tract due to gap junction between smooth muscles. Spike potential cause smooth muscle contraction.

GI smooth muscle have unstable resting membrane potential of (-40mV to -50mV). If the slow wave potential rise above (-40mV), spike potential (true action potential) appears superimposed on the slow wave.
Important difference between the action potentials of the gastrointestinal smooth muscle and those of nerve fibers
1. The higher the amplitude of slow wave (i.e. the higher the slow wave rise), the higher the frequency of spike potential usually ranging between 1 and 10 spikes per second. The spike potentials last 10 to 40 times as long in gastrointestinal muscle as the action potentials in large nerve fibers, with each gastrointestinal spike lasting as long as 10 to 20 milliseconds.

2. Ionic bases of slow wave
Slow wave without spike potential: Depolarization: opening Fast Na channels, repolarization: opening of K channels
Slow wave with spike potential: Depolarization: opening Ca-Na channels, repolarization: opening of K channels

• Note:
  - opening Ca-Na channels allows large amount of calcium to enter and small amount of sodium to enter. These channels are much slower to open and close than are the rapid sodium channels of large nerve fibers. The slowness of opening and closing of the calcium-sodium channels accounts for the long duration of the action potentials.
  - spike potential last about 40 times longer duration than nerve action potential
  - spike potential allows L-type calcium channel to open which causes smooth muscle contraction
Among the principle factors that can increase the basal electrical rhythm of GI smooth muscle making them to be more excitable including and less negative (depolarization): stretch, acetylcholine, parasympathetic stimulation, some GI hormones. These factors increase the frequency of spikes (and contraction) as well as the force of contraction. The number of spikes in slow wave will determine the degree of contraction.

Among the principle factors that can decrease the basal electrical rhythm of GI smooth muscle making them to be less excitable including and more negative (hyperpolarization): sympathetic stimulation, epinephrine and norepinephrine. These factors decrease the frequency of spikes (and contraction) as well as the force of contraction.

**Innervation of smooth muscle cells.**

Two mechanisms for neuronal innervation of gastrointestinal smooth muscle exist. Most innervation occurs through interstitial cells of Cajal. Neurons can also directly innervate intestinal smooth muscle cells.
Entry of Calcium Ions Causes Smooth Muscle Contraction
(The role of Calcium in smooth muscle contraction have been discussed previously)
The slow waves do not cause calcium ions to enter the smooth muscle fiber (they only cause entry of sodium ions). Therefore, the slow waves by themselves usually do not cause muscle contraction. Instead, it is during the spike potentials, generated at the peaks of the slow waves, that significant quantities of calcium ions enter the fibers and cause most of the contraction.

Tonic Contraction of Some Gastrointestinal Smooth Muscle.
Some smooth muscle of the gastrointestinal tract exhibits tonic contraction as well as, or instead of, rhythmical contractions.
Tonic contraction is continuous; it is not associated with the basic electrical rhythm of the slow waves but often lasts several minutes or even hours. The tonic contraction often increases or decreases in intensity but continues.
Tonic contraction is sometimes caused by
1. tonic contraction is due to continuous repetitive spike potentials—the greater the frequency, the greater the degree of contraction.
2. tonic contraction is caused by hormones or other factors that bring about continuous partial depolarization of the smooth muscle membrane without causing action potentials.
3. tonic contraction is due to continuous entry of calcium ions into the interior of the cell brought about in ways not associated with changes in membrane potential. The details of these mechanisms are still unclear.
Gastrointestinal Reflexes

The anatomical arrangement of the enteric nervous system and its connections with the sympathetic and parasympathetic systems support three types of gastrointestinal reflexes that are essential to gastrointestinal control:

1. Reflexes that are integrated entirely within the gut wall enteric nervous system. These reflexes include those that control much gastrointestinal secretion, peristalsis, mixing contractions, local inhibitory effects, and so forth.

2. Reflexes from the gut to the pre-vertebral sympathetic ganglia and then back to the gastrointestinal tract. These reflexes transmit signals long distances to other areas of the gastrointestinal tract, such as signals from the stomach to cause evacuation of the colon (the gastrocolic reflex), signals from the colon and small intestine to inhibit stomach motility and stomach secretion (the entero-gastric reflexes), and reflexes from the colon to inhibit emptying of ileal contents into the colon (the colono-ileal reflex).

3. Reflexes from the gut to the spinal cord or brain stem and then back to the gastrointestinal tract. These reflexes include especially (a) reflexes from the stomach and duodenum to the brain stem and back to the stomach—by way of the vagus nerves (vagus do have afferent sensory and efferent motor) to control gastric motor and secretory activity; (b) pain reflexes that cause general inhibition of the entire gastrointestinal tract; and (c) defecation reflexes that travel from the colon and rectum to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contractions required for defecation (the defecation reflexes).
Regulatory Substances in the Gastrointestinal Tract

GI hormone can be classified depending on structure to two families:

The gastrin family: the primary members of which are gastrin and cholecystokinin (CCK).

The secretin family: the primary members of which are secretin, glicentin, VIP (vaso-active intestinal peptide), and gastric inhibitory peptide (GIP).

GI hormone can be classified depending on function to

A. GI endocrine (hormones)

GI hormones are released from endocrine cells in the GI mucosa into the portal circulation, enter the general circulation, and have physiologic actions on target cells.

Four substances meet the requirements to be considered "official" GI hormones; others are considered "candidate" hormones. The four official GI hormones are gastrin, cholecystokinin (CCK), secretin, and glucose-dependent insulino-tropic peptide (GIP).
1. Gastrin

Gastrin is produced by cells called G cells in the lateral walls of glands in the antral portion of the gastric mucosa.

Gastrin found in other organs in addition to stomach, including pituitary gland, hypothalamus, medulla oblongata, vagus and sciatic nerve.

Gastrin contains 17 amino acids ("little gastrin"). Little gastrin is the form secreted in response to a meal.

"Big gastrin" contains 34 amino acids, although it is not a dimer of little gastrin.

All of the biologic activity of gastrin resides in the four C-terminal amino acids.

The different forms of gastrin suggest that different forms are tailored for different action.

\( G_{17} \) have half-life of 2 to 3 minutes in the circulation, whereas \( G_{34} \) has a half-life of 15 min.

a. Actions of gastrin

1. Stimulation of gastric acid and pepsin secretion.

2. Stimulation of growth of mucosa of the stomach, and small and large intestines (trophic action). Stimulates growth of gastric mucosa by stimulating the synthesis of RNA and new protein. Patients with gastrin-secreting tumors have hypertrophy (size of cells) and hyperplasia (number of cells) of the gastric mucosa.


4. Stimulation of insulin secretion; however, only after a protein meal, and not carbohydrate meal.
b. Stimuli for secretion of gastrin
1. Luminal: ① Small peptides and amino acids,  ② Distention of the stomach.
2. Neural: Vagal stimulation, mediated by gastrin-releasing peptide (GRP)
   Atropine does not block vagally mediated gastrin secretion because the mediator of the vagal effect is GRP, not acetylcholine (Ach).
3. Blood borne: ① Calcium (hypercalcemia), ② Epinephrine

c. Inhibition of gastrin secretion
1. Luminal: acid in the antrum inhibit secretion partly by direct action on G cells and partly by release of somatostatin. The effect of acid is biased on negative feed-back loop regulating gastrin secretion. This negative feedback control ensures that gastrin secretion is inhibited if the stomach contents are sufficiently acidified. This is why in pernicious anemia in which the acid-secreting cells of the stomach are damaged, gastrin secretion is chronically elevated.
2. Blood borne: Secretin, somatostatin, GIP (Gastric inhibitory polypeptide also known as the glucose-dependent insulin-tropic peptide), VIP (vasoactive intestinal peptide), glucagon
d. Zollinger-Ellison syndrome (gastrinoma)
   • occurs when gastrin is secreted by non-β-cell tumors of the pancreas.
2. CCK (chole-cysto Kinin) or Chole-cysto-kinin Pancero-zymin (CCK-PZ)

CCK half-life of circulating is about 5 minute.
CCK is secreted from I cells in duodenum and jejunum.
CCK In the brain, especially the cerebral cortex, may be involved in regulation of food intake
CCK appears to be related to the production of anxiety and analgesia.
CCK contains 33 amino acids.
CCK is homologous to gastrin. The five C-terminal amino acids are the same in CCK and gastrin.
• The biologic activity of CCK resides in the C-terminal heptapeptide (7). Thus, the heptapeptide contains
  the sequence that is homologous to gastrin and has gastrin activity as well as CCK activity.

a. Actions of CCK
(1) Stimulates contraction of the gallbladder and simultaneously causes relaxation of the sphincter of Oddi
for secretion of bile.
(2) Stimulates pancreatic enzyme secretion.
(3) Potentiates secretin-induced stimulation of pancreatic HCO3- secretion.
(4) Stimulates growth (trophic effect) of the exocrine pancreas.
(5) Inhibits gastric emptying. Thus, meals containing fat stimulate the secretion of CCK, which slows gastric emptying to allow more time for intestinal digestion and absorption. Number 1+5 to give adequate time for digestion of the fats in the upper intestinal tract.
(6) Increase the secretion of entero-kinase.
(7) Enhance the motility of the small intestine and colon.
(8) CCK and secretin augments the contraction of the pyloric sphincter.
(9) Gastrin and CCK stimulate glucagon secretion after protein meal.
(10) Inhibits appetite to prevent overeating during meals by stimulating sensory afferent nerve fibers in the duodenum; these fibers, in turn, send signals by way of the vagus nerve to inhibit feeding centers in the brain.

b. Stimuli for the release of CCK

1. Small peptides and amino acids
2. Fatty acids containing more than 10 carbon atoms and mono-glycerides
   • Triglycerides do not stimulate the release of CCK because they cannot cross intestinal cell membranes.

CCK receptors are (A and B), receptor CCK-A found in the periphery, and CCK-A and CCK-B receptors found in brain.
3. Secretin
The secretin contains 27 amino acids, synthesized by S cells, which are found in the mucosa of the duodenum and the jejunum of the gastrointestinal tract.

The secretin half-life is about 5 minutes. All of the amino acids are required for biologic activity.

The secretin is homologous to glucagon; 14 of the 27 amino acids in secretin are the same as those in glucagon.

a. Actions of secretin

• are coordinated to reduce the amount of H+ in the lumen of the small intestine.

(1) Secretin increase secretion of bicarbonate by the duct cells of the pancreas and biliary tract. Secretin thus causes the secretion of watery, alkaline pancreatic juice. Pancreatic HCO₃⁻ neutralizes H+ in the intestinal lumen.

(2) Secretin Stimulates HCO₃⁻ and H₂O secretion by the liver, and increases bile production.

(3) Secretin Inhibits H+ secretion by gastric parietal cells.

(4) Secretin increases growth of the exocrine pancreas.

(5) Secretin augments the action of CCK in producing pancreatic secretion of digestive enzyme.

(6) Secretin has a mild effect on motility of the gastrointestinal tract.

b. Stimuli for the release of secretin

• Secretin is released by the S cells of the duodenum in response to:

(1) H+ in the lumen of the duodenum

(2) Protein in the lumen of the duodenum
4. GIP (Glucose-dependent insulin-tropic peptide or Gastro-inhibitory peptide)

GIP contains 42 amino acids.

GIP is produced by K cells in the mucosa of the duodenum and jejunum.

GIP is homologous to secretin and glucagon.

a. Actions of GIP

(1) Stimulates insulin release. In the presence of an oral glucose load, GIP causes the release of insulin from the pancreas. Thus, oral glucose is more effective than intravenous glucose in causing insulin release and, therefore, glucose utilization.

(2) Large dose (not small dose) of this hormone inhibits gastric secretion (H+ secretion by gastric parietal cells) and motility this why this hormone named gastric inhibitory peptide

b. Stimuli for the release of GIP

- GIP is the only GI hormone that is released in response to fat, protein, but to a lesser extent in response carbohydrate.

- GIP secretion is stimulated by fatty acids, amino acids, and orally administered glucose.
5. Motilin
Motilin is secreted by the stomach and upper duodenum during fasting. Motilin only known function of this hormone is to increase gastrointestinal motility. Motilin secretion is inhibited after ingestion of food by mechanisms that are not fully understood. Motilin is released cyclically and stimulates waves of gastrointestinal motility called inter-digestive myoelectric complexes that move through the stomach and small intestine every 90 minutes in a person who has fasted. Inter-digestive myoelectric complexes is often divided into four consecutive phases:

1. Basal (Phase I) is a quiescent period with virtually no contractions lasts from 40–60 min
2. Pre-burst (Phase II) consists of intermittent, irregular low-amplitude contractions lasts for 40–60 min
3. Burst (Phase III) consists of intense short burst of regular high-amplitude contractions for short periods. Due to this contraction all the undigested material is swept out of the stomach down to the small intestine. This is also known as the housekeeper wave. Phase III contractions periodically occur every 90-120 minutes in humans.

Plasma motilin levels vary in a cyclic fashion and its peaks regularly occur every 90-100 minutes during the period of gastric phase III in humans.

Motilin administration causes gastric phase III contractions in humans.

(4) Phase IV represents a short transition period back to the quiescence of phase I.
B. GI Paracrines
- are released from endocrine cells in the GI mucosa.
- diffuse over short distances to act on target cells located in the GI tract.
- The GI paracrines are somatostatin and histamine.

1. Somatostatin
Somatostatin is secreted by cells throughout the GI tract in response to H+ in the lumen.
Somatostatin secretion is inhibited by vagal stimulation.
Somatostatin inhibits the release of all GI hormones.
Somatostatin inhibits pancreatic exocrine secretion; gastric acid secretion and motility; gallbladder contraction; and the absorption of glucose, amino acid, and triglycerides.

2. Histamine
- is secreted by mast cells of the gastric mucosa.
- increases gastric H+ secretion directly and by potentiating the effects of gastrin and vagal stimulation.

C. GI Neurocrines
- Neurocrines are synthesized in neurons of the GI tract, moved by axonal transport down the axon, and released by action potentials in the nerves; then diffuse across the synaptic cleft to a target cell.
- The GI neurocrines are vasoactive intestinal peptide (VIP), GRP (bombesin), and enkephalins.
1. Vasoactive intestinal peptide (VIP)
VIP contains 28 amino acids and is homologous to secretin. VIP is released from neurons in the mucosa, smooth muscle of the GI tract and blood (which it has a half-life of about 2 minutes).

Functions of VIP

1. Produces relaxation of GI smooth muscle, including the lower esophageal sphincter dilation of peripheral blood vessels
2. Stimulates pancreatic HCO$_3^-$ secretion and inhibits gastric H$^+$ secretion. In these actions, it resembles secretin.
3. VIP markedly stimulate intestinal secretion of electrolytes and hence of water.
4. VIP potentates the action of acetylcholine in salivary glands

However, VIP and acetylcholine do not coexist in neurons that innervate other parts of GIT.

2. GRP (Gastrin Releasing peptide or bombesin)

- is released from vagus nerves that innervate the G cells.
- stimulates gastrin release from G cells.

3. Enkephalins (met-enkephalin and leu-enkephalin)

- stimulate contraction of GI smooth muscle, particularly the lower esophageal, pyloric, and ileocecal sphincters.
- inhibit intestinal secretion of fluid and electrolytes. This action forms the basis for the usefulness of opiates in the treatment of diarrhea.
Gastrointestinal Motility

• Contractile tissue of the GI tract is almost exclusively unitary smooth muscle, with the exception of the ① pharynx, ② upper one-third of the esophagus, and ③ external anal sphincter, all of which are striated muscle.

Single-unit smooth muscle tissues: the autonomic nervous system innervates a single cell within a sheet or bundle and the action potential is propagated by gap junctions to neighboring cells such that the whole bundle or sheet contracts as a syncytium.

• Depolarization of circular muscle leads to contraction of a ring of smooth muscle and a decrease in diameter of that segment of the GI tract.
• Depolarization of longitudinal muscle leads to contraction in the longitudinal direction and a decrease in length of that segment of the GI tract.

• Phasic contractions: Phasic contraction is twitch-like shortening followed by relaxation.
  Phasic contraction occur in the ① esophagus, ② gastric antrum, and ③ small intestine, which contract and relax periodically.

• Tonic contractions: Tonic contractions is sustained contraction of a muscle without relaxation.
  Tonic contractions occur in the ① lower esophageal sphincter, ② orad stomach (fundus and superior part of the body), ③ ileo-cecal sphincters ④ internal anal sphincters.
Functional types of movements in GIT

Two types of movements occur in the gastrointestinal tract:

1. Propulsive movement (Peristalsis)

Propulsive movements, which cause food to move forward along the tract at an appropriate rate to accommodate digestion and absorption, (The basic propulsive movement of the gastrointestinal tract is peristalsis. A contractile ring appears around the gut and then moves forward; this mechanism is analogous to putting one’s fingers around a thin distended tube, then constricting the fingers and sliding them forward along the tube. Any material in front of the contractile ring is moved forward.

Peristalsis is an inherent property of many syncytial smooth muscle tubes; stimulation at any point in the gut can cause a contractile ring to appear in the circular muscle, and this ring then spreads along the gut tube. (Peristalsis also occurs in the bile ducts, glandular ducts, ureters, and many other smooth muscle tubes of the body.)

The usual stimulus for intestinal peristalsis is

A. distention of the gut. That is, if a large amount of food collects at any point in the gut, the stretching of the gut wall stimulates the enteric nervous system to contract the gut wall 2 to 3 centimeters behind this point, and a contractile ring appears that initiates a peristaltic movement.

B. Other stimuli that can initiate peristalsis include 1. chemical or 2. strong parasympathetic nervous signals to the gut will elicit strong peristalsis

![Diagram of peristalsis](image-url)
Function of the Myenteric Plexus in Peristalsis.
Peristalsis occurs only weakly or not at all in any portion of the gastrointestinal tract has that had congenital absence of the myenteric plexus. Also, it is greatly depressed or completely blocked in the entire gut when a person is treated with atropine to paralyze the cholinergic nerve endings of the myenteric plexus. Therefore, effectual peristalsis requires an active myenteric plexus.

**Peristaltic waves move toward the anus with downstream receptive relaxation**


Peristalsis, theoretically, can occur in either direction from a stimulated point, but it normally dies out rapidly in the orad (toward the mouth) direction while continuing for a considerable distance toward the anus. The exact cause of this directional transmission of peristalsis has never been ascertained, although it probably results mainly from the fact that the myenteric plexus is “polarized” in the anal direction, which can be explained as follows.

When a segment of the intestinal tract is excited by distention and thereby initiates peristalsis, the contractile ring causing the peristalsis normally begins on the orad side of the distended segment and moves toward the distended segment, pushing the intestinal contents in the anal direction for 5 to 10 centimeters before dying out. At the same time, the gut sometimes relaxes several centimeters downstream toward the anus, which is called “receptive relaxation,” thus allowing the food to be propelled more easily toward the anus than toward the mouth.

This complex pattern does not occur in the absence of the myenteric plexus. Therefore, the complex is called the myenteric reflex or the peristaltic reflex.

The peristaltic reflex plus the anal direction of movement of the peristalsis is called the “law of the gut.”
Mixing movement:
Mixing movements, which keep the intestinal contents thoroughly mixed at all times. Mixing movements differ in different parts of the alimentary tract:

A. In some areas, the peristaltic contractions cause most of the mixing. This is especially true when forward progression of the intestinal contents is blocked by a sphincter so that a peristaltic wave can then only churn the intestinal contents, rather than propelling them forward.

B. At other times, local intermittent constrictive contractions occur every few centimeters in the gut wall. These constrictions usually last only 5 to 30 seconds; new constrictions then occur at other points in the gut, thus “chopping” and “shearing” the contents first here and then there.
Effect of GUT activity and metabolic factors on gastrointestinal blood flow

Under normal conditions, the blood flow in each area of the gastrointestinal tract, as well as in each layer of the gut wall, is directly related to the level of local activity. For instance,

1. during active absorption of nutrients, blood flow in the villi and adjacent regions of the submucosa increases as much as eightfold.
2. blood flow in the muscle layers of the intestinal wall increases with increased motor activity in the gut.
3. after a meal, the motor activity, secretory activity, and absorptive activity all increase; likewise, the blood flow increases greatly but then decreases back to the resting level over another 2 to 4 hours.

Possible causes of the increased blood flow during gastrointestinal activity.

Although the precise causes of the increased blood flow during increased gastrointestinal activity are still unclear, some facts are known.

First, several vasodilator substances are released from the mucosa of the intestinal tract during the digestive process. Most of these substances are peptide hormones, including cholecystokinin, vasoactive intestinal peptide, gastrin, and secretin. These same hormones control specific motor and secretory activities of the gut.
Second, some of the gastrointestinal glands also release into the gut wall two kinins, \( \text{kallidin} \) and \( \text{bradykinin} \), at the same time that they secrete other substances into the lumen. These kinins are powerful vasodilators that are believed to cause much of the increased mucosal vasodilation that occurs along with secretion.

Third, decreased oxygen concentration in the gut wall

A. decreased oxygen concentration in the gut wall can increase intestinal blood flow at least 50 to 100 percent; therefore, the increased mucosal and gut wall metabolic rate during gut activity probably lowers the oxygen concentration enough to cause much of the vasodilation.

B. decreased oxygen concentration in the gut wall can also lead to as much as a fourfold increase of adenosine, a well-known vasodilator that could be responsible for much of the increased flow.

Thus, the increased blood flow during increased gastrointestinal activity is probably a combination of many of the aforementioned factors plus still others yet undiscovered.
“Countercurrent” Blood Flow in the Villi.
The arterial flow into the villus and the venous flow out of the villus are in directions opposite to each other and that the vessels lie in close apposition to each other. Because of this vascular arrangement, much of the blood oxygen diffuses out of the arterioles directly into the adjacent venules without ever being carried in the blood to the tips of the villi. As much as 80 percent of the oxygen may take this short-circuit route and is therefore not available for local metabolic functions of the villi. Under normal conditions, this shunting of oxygen from the arterioles to the venules is not harmful to the villi, but in disease conditions in which blood flow to the gut becomes greatly curtailed, such as in circulatory shock, the oxygen deficit in the tips of the villi can become so great that the villus tip or even the whole villus undergoes ischemic death and disintegrates. For this reason and other reasons, in many gastrointestinal diseases the villi become seriously blunted, leading to greatly diminished intestinal absorptive capacity.
Nervous control of gastrointestinal blood flow

Stimulation of the parasympathetic nerves going to the stomach and lower colon increases local blood flow at the same time that it increases glandular secretion. This increased flow probably results secondarily from the increased glandular activity, not as a direct effect of the nervous stimulation.

Sympathetic stimulation, by contrast, has a direct effect on essentially all the gastrointestinal tract to cause intense vasoconstriction of the arterioles with greatly decreased blood flow. After a few minutes of this vasoconstriction, the flow often returns to near normal by means of a mechanism called “autoregulatory escape.” That is, the local metabolic vasodilator mechanisms that are elicited by ischemia override the sympathetic vasoconstriction, returning toward normal the necessary nutrient blood flow to the gastrointestinal glands and muscle.

Importance of nervous depression of gastrointestinal blood flow when other parts of the body need extra blood flow.

A major value of sympathetic vasoconstriction in the gut is that

1. It allows shutoff of gastrointestinal and other splanchnic blood flow for short periods during heavy exercise, when the skeletal muscle and heart need increased flow.

2. in circulatory shock, when all the body’s vital tissues are in danger of cellular death for lack of blood flow—especially the brain and the heart—sympathetic stimulation can decrease splanchnic blood flow to very little for many hours.
Sympathetic stimulation also causes strong vasoconstriction of the large-volume intestinal and mesenteric veins. This vasoconstriction decreases the volume of these veins, thereby displacing large amounts of blood into other parts of the circulation. In persons experiencing hemorrhagic shock or other states of low blood volume, this mechanism can provide as much as 200 to 400 milliliters of extra blood to sustain the general circulation.
Ingestion of food:
The amount of food that a person ingests is determined principally by an intrinsic desire for food called hunger. The type of food that a person preferentially seeks is determined by appetite.

Oral Cavity:
Mastication (chewing)
The teeth are admirably designed for chewing. The anterior teeth (incisors) provide a strong cutting action, and the posterior teeth (molars) provide a grinding action. All the jaw muscles working together can close the teeth with a force as great as 55 pounds on the incisors and 200 pounds on the molars. Most of the muscles of chewing are innervated by the motor branch of the fifth cranial nerve, and the chewing process is controlled by nuclei in the brain stem.

Causing of chewing
1. Stimulation of specific reticular areas in the brain stem taste centers will cause rhythmical chewing movements.
2. Stimulation of areas in the hypothalamus, amygdala, and even the cerebral cortex near the sensory areas for taste and smell can cause chewing.
Much of the chewing process is caused by a chewing reflex: The presence of a bolus of food in the mouth at first initiates reflex inhibition of the muscles of mastication, which allows the lower jaw to drop.

This drop in turn initiates a stretch reflex of the jaw muscles that leads to rebound contraction. This action automatically raises the jaw to cause closure of the teeth, but it also compresses the bolus again against the linings of the mouth, which inhibits the jaw muscles once again, allowing the jaw to drop and rebound another time; this process is repeated again and again.

Chewing is important for digestion of all foods, but it is especially important for most fruits and raw vegetables because they have indigestible cellulose membranes around their nutrient portions that must be broken before the food can be digested.

Digestive enzymes act only on the surfaces of food particles; therefore, the rate of digestion is dependent on the total surface area exposed to the digestive secretions.

Grinding the food to a very fine particulate consistency and wetting by saliva prevents excoriation of the gastrointestinal tract; the wetting and homogenizing action (i.e. formation of bolus) aids swallowing and subsequent digestion.
Swallowing (Deglutition):

Swallowing is sequentially programmed all-or-none law:
Swallowing is initiated when a bolus, or ball of food, is voluntarily forced by the tongue to the rear of the mouth into the pharynx. The pressure of the bolus stimulates pharyngeal pressure receptors, which send afferent impulses to the swallowing center located in the medulla. The swallowing center then reflexly activates in the appropriate sequence the muscles that are involved in swallowing. Multiple highly coordinated responses are triggered in a specific all-or-none pattern over a period of time to accomplish the act of swallowing.

Swallowing is initiated voluntarily, but once begun it cannot be stopped.

In general, swallowing can be divided into:

1. Voluntary stage:
It is voluntarily squeezed or rolled posteriorly into the pharynx by pressure of the tongue upward and backward against the palate. From here on, swallowing become entirely automatic and ordinarily cannot be stopped.
• https://www.youtube.com/watch?v=wqMCzuIiPaM
2. Pharyngeal stage:
A. Associated actions with pharyngeal stage:
   i) The soft palate: it is pulled upward to close the posterior nares, in this way preventing reflex of food into the nasal cavities.
   ii) The palato-pharyngeal folds: it is found on each side of the pharynx are pulled medially to approximate each other forming a sagittal slit. This slit performs a selective action, allowing food that has been masticated sufficiently.
   iii) The vocal cords of the larynx: they are strongly approximated this action in addition to the action of epiglottis, both prevent passage of food into the trachea.
   iv) The upward movement of the larynx also pulls up and enlarges the opening of the esophagus. At the same time, the upper 3 to 4 centimeters of the esophageal muscular wall, an area called either the (upper esophageal sphincter or the pharyngeo-esophageal sphincter) relaxes, thus allowing food to move easily and freely from pharynx to esophagus.
B. Neural control of pharyngeal stage:
The pharyngeal swallowing is a reflex act with the following parts:
i) Receptors: epithelial swallowing receptor area all around the opening of the pharynx.
ii) Afferent nerve: the sensory portion of the trigeminal and glosso-pharyngeal nerve.
iii) Center: swallowing center in the medulla and lower portion of pons.
iv) Efferent nerve: 5th, 9th, 10th, and 12th cranial nerve.
v) Affecter organ: contraction of pharyngeal muscles.

Pharyngeal stage and respiration:
The entire pharyngeal stage of swallowing occurs in less than 2 seconds, thereby interrupting respiration for only a fraction of a usual respiratory cycle; this because the swallowing center inhibits the respiratory center of the medulla.

3. Esophageal stage (or esophageal motility):
The esophagus propels the swallowed food into the stomach. Sphincters at either end of the esophagus prevent air from entering the upper esophagus and gastric acid from entering the lower esophagus. Because the esophagus is located in the thorax, intra-esophageal pressure equals thoracic pressure, which is lower than atmospheric pressure. In fact, a balloon catheter placed in the esophagus can be used to measure intra-thoracic pressure.
The following sequence of events occurs as food moves into and down the esophagus:

a. As part of the swallowing reflex, the upper esophageal sphincter relaxes to permit swallowed food to enter the esophagus.

b. The upper esophageal sphincter then contracts so that food will not reflux into the pharynx.

The esophageal stage of the swallow now begins. The term peristalsis refers to ring like contractions of the circular smooth muscle that move progressively forward, pushing the bolus into a relaxed area ahead of the contraction. The types of esophageal peristalsis are:

c. Primary peristalsis:
A primary peristaltic is simply a continuation of the peristaltic wave that begins in the pharynx. A primary peristaltic takes its place with the aid of gravity. A primary peristaltic contraction creates an area of high pressure behind the food bolus. The peristaltic contraction moves down the esophagus and propels the food bolus.

The swallowing center triggers a primary peristaltic wave that sweeps from the beginning to the end of the esophagus, forcing the bolus ahead of it through the esophagus to the stomach. The peristaltic wave takes about 8 to 10 seconds to reach the lower end of the esophagus.
Secondary peristalsis:

Secondary peristalsis is caused by the distention of the esophagus with food. Secondary peristaltic contraction clears the esophagus of any remaining food. Secondary peristalsis is initiated

A. partly by intrinsic neural circuits in the myenteric nervous system and
B. partly by reflexes

Receptor: that begin in the pharynx
Afferent: vagal afferent fibers
Center: the medulla
Efferent: esophagus through glosso-pharyngeal and vagal efferent nerve.

When the vagus nerve to the esophagus is sectioned, the myenteric nerve plexus of the esophagus becomes excitable enough after several days to cause secondary peristaltic waves even without support from the vagal reflexes.

Distension of the esophagus also reflexly increases salivary secretion

Receptive relaxation of the stomach:
Preparation the stomach to receive food.
• The orad region of the stomach includes the fundus and the proximal body.
This region contains oxyntic glands and is responsible for receiving the ingested meal.
As the esophageal peristaltic wave passes toward the stomach, a wave of relaxation, transmitted through myenteric inhibitory neurons, precedes the peristalsis causes relaxation of the stomach.
• The orad region of the stomach relaxes without increase intra-gastric pressure to accommodate the ingested meal.
• is a vagovagal reflex that is initiated by distention of the stomach and is abolished by vagotomy.
• CCK participates in "receptive relaxation" by increasing the distensibility of the orad stomach.
Lower esophageal sphincter:
- The musculature of the gastro-esophageal junction (lower esophageal sphincter: LES) is tonically active but relaxes upon swallowing.
- The tonic activity of the LES between meals prevents reflex of gastric contents into the esophagus.
- The LSE is made up of three components:
  a) Intrinsic sphincter: The esophageal smooth muscle is more prominent at the junction with the stomach.
  b) Extrinsic sphincter: Fibers of the crural portion of the diaphragm, a skeletal muscle, surround the esophagus at this point. It exerts a pinchcock-like action on the esophagus.
  c) Oblique or sling fiber of the stomach wall: It creates a flap valve that closes off the esophago-gastric junction and prevents regurgitation when intra-gastric pressure rises.
The tone of the LES is under neural:

a) Release of acetylcholine from vagal endings causes the intrinsic sphincter to contract, and release of NO and VIP from inter-neurons innervated by other vagal fibers causes it to relax.

b) Contraction of the crural portion of the diaphragm, which is innervated by the phrenic nerve, is coordinated with respiration and contraction of chest and muscle.

The intrinsic and extrinsic sphincters operate together to permit orderly flow of food into the stomach and to prevent reflux of gastric contents into the esophagus.

**Aero-phagia and intestinal gas:**

- **Aero-phagia:** is air that is un-avoidably swallowed in the process of eating and drinking.
- Some of the swallowed air is regurgitated (bleching), and some of the gases it contains are absorbed, but much of it passes on to the colon.

- **Intestinal gases:**
  - **Sources:**
    1. Aero-phagia
    2. Colonic bacteria forms hydrogen sulfate (which cause for the smell of the gases expelled: flatus), carbon dioxide, and hydrogen.
  - **Volume:** the volume of gas normally found in the human GIT is about 200 mL, and the daily production is 500 to 1500 mL.

The gastro-esophageal sphincter prevents reflux of gastric contents:

Except during swallowing, the gastro-esophageal sphincter stays contracted to keep a barrier between the stomach and esophagus, reducing the chance of reflux of acidic gastric contents into the esophagus. If gastric contents do flow backward despite the sphincter, the acidity of these contents irritates the esophagus, causing the esophageal discomfort known as heartburn.

The esophageal secretion is entirely protective:

Esophageal secretion is entirely mucus. In fact, mucus is secreted throughout the length of the digestive tract. By lubricating the passage of food, esophageal mucus lessens the likelihood that the esophagus will be damaged by any sharp edges in the newly entering food. The entire transit time in the pharynx and esophagus averages a mere 6 to 10 seconds.
Types of Alimentary Tract Glands

1. single-cell mucous glands called simply mucous cells or sometimes goblet cells
2. surface areas of the gastrointestinal tract are lined by pits that represent invaginations of the epithelium into the submucosa called crypts of Lieberkühn
3. in the stomach and upper duodenum; are large numbers of deep tubular glands
4. several complex glands (the salivary glands, pancreas, and liver)

The types of stimuli that activate GI glands are

A. Local epithelial stimulation
   (1) tactile stimulation,
   (2) chemical irritation, and
   (3) distention of the gut wall.

The resulting nervous reflexes stimulate both the mucous cells on the gut epithelial surface and the deep glands in the gut wall to increase their secretion

B. Neural stimulation
   (1) parasympathetic stimulation increase gland secretion
   (2) sympathetic stimulation can have a dual effect:
      (a) sympathetic stimulation alone usually slightly increases secretion and
      (b) if parasympathetic or hormonal stimulation is already causing copious secretion by the glands, superimposed sympathetic stimulation usually reduces the secretion, sometimes significantly so, mainly because of vasoconstrictive reduction of the blood supply.

C. Humoral:
   By different GI hormones
Main functions of mucous secretion

Mucus is a thick secretion composed mainly of water, electrolytes, and a mixture of several glycoproteins that are composed of large polysaccharides bound with much smaller quantities of protein.

Mucus is strongly resistant to digestion by the gastrointestinal enzymes (1) Protect the surface of GIT from injury (2) act as lubricant material (3) make fecal material to adhere to each other (4) are capable of buffering small amounts of either acids or alkalies (5) Antibacterial and antifungal activity by

- secretary immune globulin IgA
- lysozyme, which attacks bacteria
- Lacoferin, which bind iron and is bactero-static (stop replication)
- proline rich protein that protect tooth enamel and bind toxic tannins. Saliva contains mucins, glycoprotein that binds bacteria
Formation of saliva
Saliva is formed by three major glands—the parotid, sub-maxillary, and sublingual glands.
The structure of each gland is similar to a bunch of grapes.
The acinus (the blind end of each duct) is lined with acinar cells and secretes initial saliva.
A branching duct system is lined with columnar epithelial cells, which modify the initial saliva.
When saliva production is stimulated, myoepithelial cells, which line the acinus and initial ducts, contract and eject saliva into the mouth.
a. The acinus
The acinus produces initial saliva with a composition similar to plasma
This initial saliva is isotonic and has the same Na+, K+, Cl⁻, and HCO₃⁻ concentrations as plasma.
b. The ducts
-modify the initial saliva by the following processes:
(1) The ducts reabsorb Na⁺ and Cl⁻; therefore, the concentrations of these ions are lower than their plasma concentrations.
(2) The ducts secrete K and HCO₃⁻; therefore, the concentrations of these ions are higher than their plasma concentrations.
However, there is excess sodium reabsorption compared with potassium secretion, which creates electrical negativity of about $-70$ millivolts in the salivary ducts; this negativity in turn causes chloride ions to be reabsorbed passively. Therefore, the chloride ion concentration in the salivary fluid falls to a very low level, matching the ductal decrease in sodium ion concentration.

Second, bicarbonate ions are secreted by the ductal epithelium into the lumen of the duct. This secretion is at least partly caused by

1. the passive exchange of bicarbonate for chloride ions,
2. but it may also result partly from an active secretory process

**Composition of saliva**

**a. Saliva is characterized by:**

1. High volume (relative to the small size of the salivary glands)
2. High K and HCO$_3^-$ concentrations (than plasma)
3. Low Na$^+$ and Cl$^-$ concentrations (than plasma)
4. Hypotonicity (than plasma): Saliva becomes hypotonic in the ducts because the ducts are relatively impermeable to water. Because more solute than water is reabsorbed by the ducts, the saliva becomes dilute relative to plasma.
5. Presence of α-amylase, lingual lipase, and kallikrein
Salivary secretion
The salivary glands, secretary (zymogen) granule contain the salivary enzymes are discharged from

Functions of saliva
(1) Lubrication:
As a sero-mucous coating, saliva (1) lubricates and protects oral tissues (2) acting as a barrier against irritants (3) Aids speech by facilitating movements of the lips and tongue (4) facilitates swallowing (5) Keeps the mouth moist
(2) Salivary or oral clearance:
Saliva dilutes and removes substances (oral debris, noxious agents) from the oral cavity
(3) Buffering action and maintenance of tooth integrity
Facilitates the de-mineralization and re-mineralization process because the pH of saliva from resting gland is slightly less than 7.0, but during active secretion, it approaches 8.0.
(4) Taste:
Serves as a solvent for the molecules that stimulates the taste buds
(5) Digestion:
Saliva contains two digestive enzymes (1) lingual lipase, secreted by glands on the tongue (2) salivary α-amylase, secreted by salivary glands
(6) Protect the oral mucosa
Factors regulate salivary secretion:

1. Nervous regulation of salivary secretion:
   A. Salivary glands are controlled mainly by parasympathetic nervous signals all the way from the superior and inferior salivatory nuclei in the brain stem.
   Parasympathetic stimulation (cranial nerves VII and IX) causes profuse secretion of watery saliva with a relatively low content of organic material by increasing transport processes in the acinar and ductal cells and by causing vasodilatation which appears to be due to the release of VIP.
   Cholinergic receptors on acinar and ductal cells are muscarinic.
   The second messenger is inositol 1,4,5-triphosphate (IP3) and increased intracellular [Ca\(^{2+}\)].
   - Anti-cholinergic drugs (e.g., atropine) inhibit the production of saliva and cause dry mouth.

2. Taste: Many taste stimuli, especially the sour taste (caused by acids), elicit copious secretion of saliva—often 8 to 20 times the basal rate of secretion.
3. Tactile stimuli: Such as the presence of smooth objects in the mouth (e.g., a pebble), cause marked salivation, whereas rough objects cause less salivation and occasionally even inhibit salivation.
4. Higher centers of the central nervous system: As caused by smell or eat food.
5. Salivation also occurs in response to reflexes originating in the stomach and upper small intestines.

5. Nausea: Inhibited by
   1. Fear
   2. Sleep
   3. Anti-cholinergic drugs
B. Sympathetic stimulation can also increase salivation a slight amount—much less so than parasympathetic stimulation and the growth of salivary glands, although the effects are smaller than those of parasympathetic stimulation.

– Receptors on acinar and ductal cells are β-adrenergic.
– The second messenger is cyclic adenosine monophosphate (cAMP).

II. Aldosterone acts on the ductal cells to increase the reabsorption of Na⁺ and the secretion of K⁺ (analogous to its actions on the renal distal tubule).

Blood supply to the salivary glands because secretion always requires adequate nutrients from the blood. The parasympathetic nerve signals that induce copious salivation also moderately dilate the blood vessels. In addition, salivation directly dilates the blood vessels, thus providing increased salivatory gland nutrition as needed by the secreting cells.

Part of this additional vasodilator effect is caused by kallikrein secreted by the activated salivary cells, which in turn acts as an enzyme to split one of the blood proteins, an alpha2-globulin, to form bradykinin, a strong vasodilator.
The effect of flow rate on saliva composition

It is explained by changes in the contact time available for re-absorption and secretion processes to occur in the ducts. Thus, at high flow rates, saliva is in contact with ductal epithelium for short time; saliva composition is most like the initial secretion from the acinus; it has the highest Na+ and Cl- concentrations and the lowest K+ concentration.

At low flow rates, saliva is least like the initial secretion from the acinus; it has the lowest Na+ and Cl- concentrations and the highest K+ concentration.

The only ion that does not "fit" this contact-time explanation is HCO3-; HCO3- is lowest at low flow rates and highest at high flow rate. This occurs because HCO3- secretion is selectively stimulated when saliva secretion is stimulated by vagus nerve. Thus as flow rate increase, HCO3- concentration increase.

Esophageal Secretion

Esophageal secretions are entirely mucous and mainly provide lubrication for swallowing.
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Gastro-esophageal reflux disease (GERD)

Definition:

Gastro-esophageal reflux disease (GERD) as troublesome symptoms and/or complications caused by refluxing the stomach content into the esophagus. When there is damage to the esophageal epithelium, it is known as reflex esophagitis.

Barrett’s esophagus is a complication of GERD characterized by replacement of the normal squamous epithelial lining of the esophagus by specialized columnar-type epithelium. Barrett’s esophagus is more likely to occur in patients with a long history (years) of symptomatic reflux and may be a risk factor for developing adenocarcinoma of the esophagus.
The retrograde movement of acid or other noxious substances from the stomach into the esophagus is a major factor in the development of GERD. Therapeutic regimens for GERD are designed to maximize normal mucosal defense mechanisms and attenuate these other factors that contributed to the disease.

A. Defective lower esophageal sphincter pressure or function
The lower esophageal sphincter is a manometrically (mano: pressure) defined zone of the distal esophagus with an elevated basal resting pressure. The sphincter is normally in a tonic, contracted state, preventing the reflux of gastric material from the stomach. The sphincter relaxes on swallowing to permit the free passage of food into the stomach.
Mechanisms by which defective lower esophageal sphincter pressure may cause gastro-esophageal reflux are three-fold:

First, and probably most important, reflux may occur after spontaneous transient lower esophageal sphincter relaxations that are not associated with swallowing. Esophageal distention, vomiting, belching, and retching can cause relaxation of the lower esophageal sphincter. These transient relaxations may play an important role in intermittent non-erosive reflux. Transient decreases in sphincter pressure are responsible for approximately 65% of the reflux episodes in patients with GERD.

Second, reflux may occur after transient increases in intra-abdominal pressure (stress reflux). An increase in intra-abdominal pressure such as that occurring during straining, bending over, coughing, eating, or a Valsalva maneuver may overcome a weak lower esophageal sphincter, and thus may lead to reflux.

Third, the lower esophageal sphincter may be atonic, thus permitting free reflux. Although transient relaxations are more likely to occur when there is normal lower esophageal sphincter pressure, the latter two mechanisms are more likely when the lower esophageal sphincter is weak. Smoking, ethanol, peppermint and medications may worsen esophageal reflux by decreasing lower esophageal sphincter pressure (include beta-agonists, alpha-adrenergic antagonists, nitrates, calcium channel blockers, anti-cholinergics) or by irritating the esophageal mucosa.
B. Problems with other normal mucosal defense mechanisms such as

1. Anatomic Factors
Disruption of the normal anatomic barriers by a hiatal hernia was once thought to be a primary etiology of gastro-esophageal reflux and esophagitis. Currently, the presence of hiatal hernia is generally considered a separate entity that may or not be associated with reflux.

2. Esophageal Clearance & salivary buffering
The esophagus is cleared by primary peristalsis in response to swallowing, or by secondary peristalsis in response to esophageal distention and gravitational effects. Swallowing contributes to esophageal clearance by increasing salivary flow. Saliva contains bicarbonate that buffers the residual gastric material on the surface of the esophagus. The production of saliva decreases with increasing age, making it more difficult to maintain a neutral intra-esophageal pH; Therefore, esophageal damage due to reflux occurs more often in the elderly and patients with Sjogren’s syndrome or xerostomia. Swallowing is also decreased during sleep, which contributes to nocturnal GERD in some patients.

Many patients with GERD produce normal amounts of acid, but the acid produced spends too much time in contact with the esophageal mucosa. The contact time is dependent on the rate at which the esophagus clears the noxious material, as well as the frequency of reflux.
3. Mucosal Resistance

The esophageal mucosa and sub-mucosa consist of mucus secreting glands that contain bicarbonate. Bicarbonate moving from the blood to the lumen can neutralize acidic refluxate in the esophagus. A decrease in this normal defense mechanism can potentially lead to erosions in the esophagus. When the mucosa is repeatedly exposed to the refluxate in GERD, or if there is a defect in the normal mucosal defenses, hydrogen ions diffuse into the mucosa, leading to the cellular acidification and necrosis that ultimately cause esophagitis.

4. Gastric Emptying

Gastric volume is related to the amount of material ingested, rate of gastric secretion, rate of gastric emptying, and amount and frequency of duodenal reflux into the stomach.

Delayed gastric emptying can lead to increased gastric volume and contribute to reflux.

Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with gastro-esophageal reflux. This partially explains the prevalence of postprandial gastro-esophageal reflux.
C. other factors associated with gastro-esophageal reflux

1. The composition of reflux into the esophagus includes:
   1. gastric acid,
   2. pepsin,
   3. bile acids,
   4. pancreatic enzymes.

2. pH

3. Volume of the refluxate are other factors associated with gastro-esophageal reflux.

Duodeno-gastric reflux esophagitis or “alkaline esophagitis” refers to esophagitis induced by the reflux of bilious and pancreatic fluid.

Although bile acids have both a direct irritant effect on the esophageal mucosa and an indirect effect of increasing hydrogen ion permeability of the mucosa, symptoms are more often related to acid reflux than to bile reflux.

The percentage of time that esophageal pH is below 4 is greater for patients with severe disease than for those with mild disease.

The pathophysiology of GERD is a complex process. It is difficult to determine which occurs first: gastro-esophageal reflux leading to defective peristalsis with delayed clearing, or an incompetent lower esophageal sphincter pressure leading to gastro-esophageal reflux. Understanding factors associated with the development of GERD is essential to providing effective treatment.
Clinical Presentation of GERD

A. Typical Symptoms
- Heartburn is the hallmark symptom of GERD and is generally described as a sub-sternal sensation of warmth or burning rising up from the abdomen that may radiate to the neck. It may be waxing and waning in character.
- Regurgitation is also very common.
- Symptoms may be worse after a ① fatty meal, ② when bending over, or ③ when lying in a recumbent position.
- Other symptoms include water brash (hyper-salivation) and belching.

B. Atypical Symptoms
- Atypical symptoms include non-allergic asthma, chronic cough, hoarseness, pharyngitis, chest pain, and dental erosions.
- In some cases, these extra-esophageal symptoms may be the only ones present, making it more difficult to recognize GERD as the cause, especially when endoscopic studies are normal.
- It is important to distinguish GERD symptoms from those of other diseases, especially when chest pain or pulmonary symptoms are present.