

## Basic Notes in the Physiology of the Gastrointestinal Tract

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### Abstract

The gastrointestinal tract encounters many important clinical cases e.g., ulcers, gastritis (inflammation of the stomach), diarrhea, constipation, and tumors. The goal of the following notes is to provide the reader, mainly medical and veterinary students, with a basic background on the structures and functions of the gut.

### Introduction

Gastrointestinal physiology is divided into two parts, general and special. The general portion covers a definition, general anatomy, histology, and various control systems that orchestrate or organize the different functions of the gut e.g., motility, digestion, absorption, and secretion. The special part will discuss each of these functions in detail.

### General Gastrointestinal Physiology

#### Definition

The gastrointestinal tract is a tube-like structure

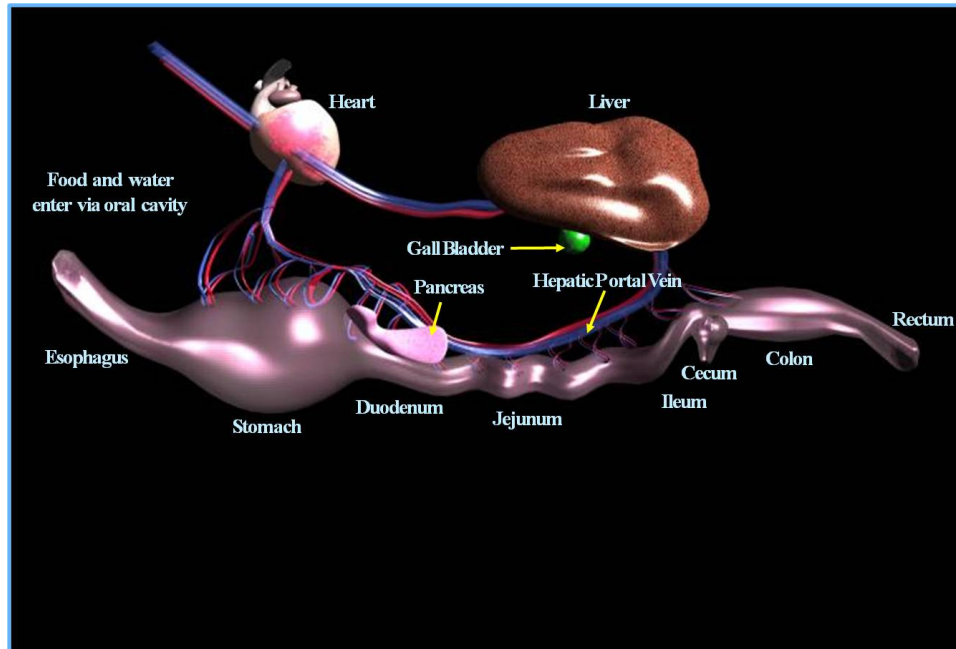
that extends from the mouth to the anus and supplies the body, including itself, with nutrients, water, and electrolytes by performing four functions, digestion, absorption, secretion, and motility. The gastrointestinal tract and the digestive system are two different terms. The gastrointestinal tract or the gut is the tube from the mouth to the anus. The digestive system is the tube, the liver, the gallbladder, and the pancreas. The liver, gallbladder, and pancreas are referred to as accessory digestive glands.

#### Anatomy of the Gastrointestinal Tract

Anatomically (Figure 1), the gut consists of the mouth, esophagus, stomach, small intestine (comprised of duodenum, jejunum, and ileum), and large intestine (con-

sists of cecum, colon, and rectum). The stomach can be a simple stomach, which consists of one compartment divided into two parts, glandular and non-glandular e.g., humans, horses, dogs, and a compound stomach, which con-

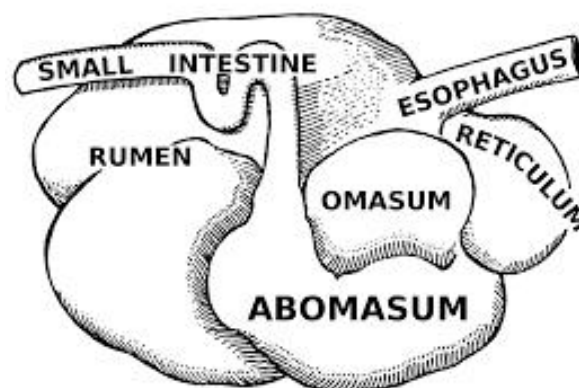
sists of multiple, distinct, compartments e.g., ruminants (Figure 2). The compartments of the ruminant stomach are rumen, reticulum, omasum, and abomasum. All these compartments are called stomach, one stomach.



dg

**Figure 1:** The Digestive System

The Digestive System consists of the gastrointestinal tract and the accessory digestive glands, liver, gallbladder, and pancreas. The gastrointestinal tract is a tube-like structure that extends from the mouth to the anus. It consists of the mouth, esophagus, stomach, small intestine, which consists of duodenum, jejunum and ileum, and large intestine, which consists of cecum, colon, and rectum.



**Figure 2:** Ruminant Stomach

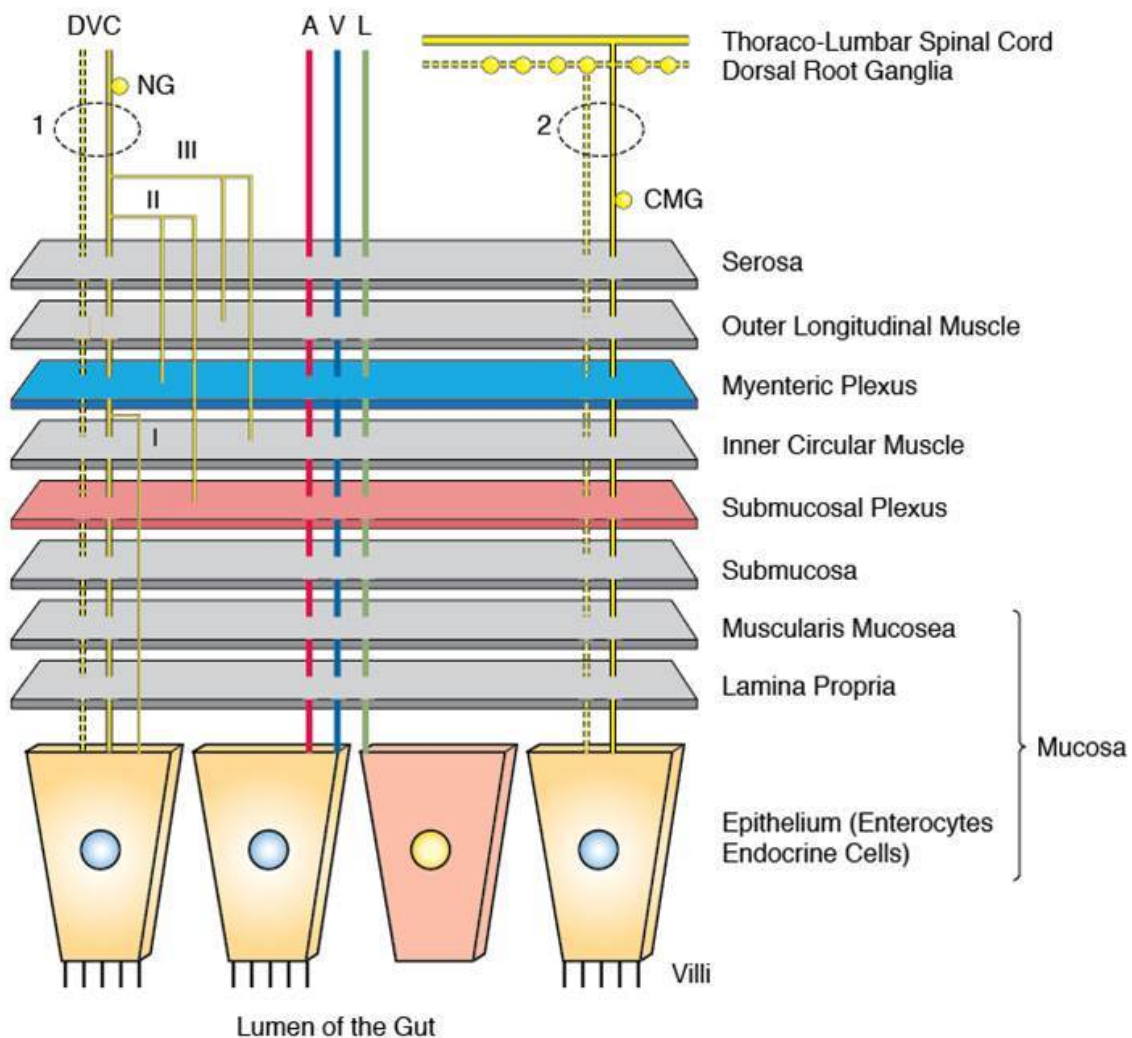
A ruminant stomach consists of four compartments, rumen, occupying the left side of the abdominal cavity, and reticulum, omasum, and abomasum, all of which reside in the right side of the abdominal cavity in ruminants.

## Histology of the Gastrointestinal Tract

Histologically, the gut consists of four layers (Figure 3), mucosa (the innermost layer or the one close to the

lumen of the gut, the layer that touches or in contact with the food), submucosa, muscularis, and serosa. The mucosa consists of an epithelial cell layer (comprised of enterocytes, enterochromaffin-like cells, and many other cell types), lamina propria, and muscularis mucosae. The muscle layer consists of two layers, an inner circular, thick, muscle layer (inner, located toward the lumen of the gut), and an outer longitudinal, thin, muscle layer underneath the serosa, the outer most layer. The muscle layers, circular and longitudinal,

along with the serosa can be severed (cut) during a myectomy procedure to relief pressure on a contracted part of the gut. For example, esophageal achalasia, an esophageal motility disorder manifested by failure of the muscles of the esophagus to relax and caused by loss of nerve cells, can be treated by myotomy (also known as Heller Myotomy) or cutting of the muscle of the lower esophageal sphincter to allow a better passage of food and liquids from the esophagus into the stomach.



**Figure 3:** Histology of the gastrointestinal tract

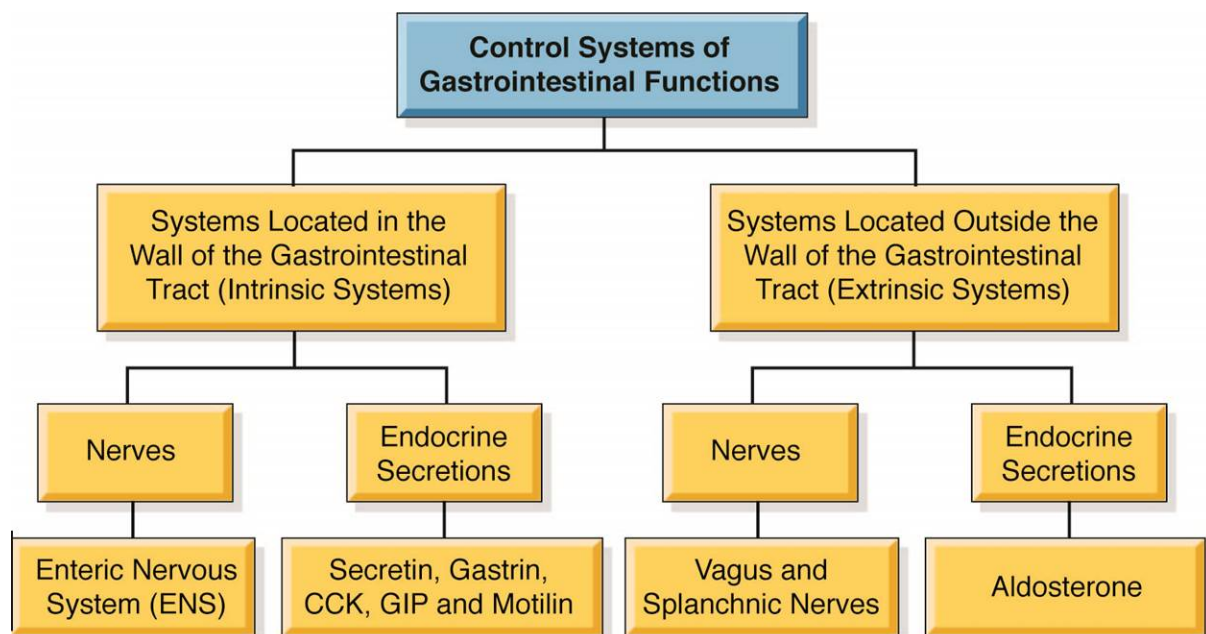
The gastrointestinal wall consists of four layers, mucosa, submucosa, muscularis, and serosa. The mucosa, the closest layer to the lumen of the gut, which is in direct contact with the food, consists of three layers, epithelium (enterocytes and endocrine cells), lamina propria, and muscularis mucosae. The mucosa is followed by the submucosa, then two muscle layers, an inner, thick, circular and an outer, thin, longitudinal, followed by the outer most layer the serosa. On the enterocytes of the mucosa there are villi i.e., sensors to sense the internal environment of the gut. Between the two muscle layers there are two nerve plexuses, myenteric and submucosal. The myenteric plexus is located between the two muscle layers and the submucosal is located above the submucosa. The two plexuses comprise what is known as the enteric nervous system or the intrinsic innervation of the gut. The gut is supplied by an artery (A), a vein (V) and a lymphatic (L) vessel. Also, the gut is supplied by extrinsic innervation, the vagus (1), a parasympathetic nerve, and the splanchnic (2), a sympathetic nerve. Each of these nerves con-

sists of a motor portion (efferent, sends orders from the central nervous system to the gut) and a sensory portion (afferent, receives information from the gut and sends them to the central nervous system). The cell bodies of the preganglionic motor part of the vagus are in the dorsal vagal complex (DVC) brainstem / hindbrain in a nucleus known as the motor nucleus of the vagus or DMV. The postganglionic cell bodies are located within or close to the myenteric ganglia. The cell bodies of the sensory portion of the vagus are in the nodose ganglia (NG). There are three vagal afferents, intravillus arbors (I), which sense the lumen of the gut, intraganglionic laminar endings (II), which communicate with the plexuses of the enteric nervous system, and intramuscular arrays (III), which sense muscle tension. The cell bodies of the preganglionic splanchnic nerve are in the thoraco-lumbar area of the spinal cord, and the postganglionic cell bodies are in the celiac-mesenteric ganglia (CMG). The cell bodies of the sensory portion of the splanchnic nerve are in the dorsal root ganglia (DRG).

## The Control Systems of the Gut

As mentioned earlier, the gut performs four major functions, digestion, secretion, absorption, and motility. There are systems (Figure 4) located inside and outside the wall of the gastrointestinal tract, which orchestrate, control, or organize the different functions of the gut. For example,

you do not want to eat and go to the bathroom at the same time. We call the systems that control the functions of the gut and located inside the gut wall intrinsic control systems. The systems that control the various functions of the gut and are located outside the gut wall are referred to as extrinsic control systems. Each of those systems, intrinsic and extrinsic, consists of nerves and endocrine secretions.



**Figure 4:** The systems that control of the gut

The systems that control the different functions of the gastrointestinal tract are divided into two categories, (1) intrinsic, located inside the wall of the gut and consists of nerves, the enteric nervous system or ENS, and endocrine secretions (gut hormones such as Secretin, gastrin, CCK, GIP, motilin), and (2) extrinsic, located outside the gastrointestinal tract and consist of nerves (vagus and splanchnic) and endocrine secretions (aldosterone).

## The Intrinsic Nerves of the Gut

### The Enteric Nervous System

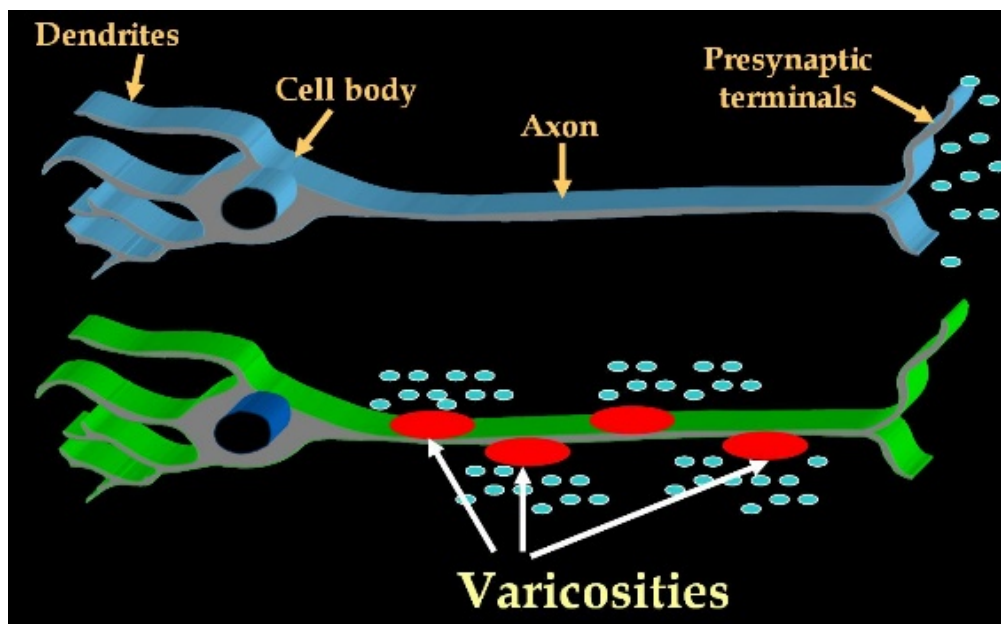
The nerves of the intrinsic control system of the gut are gathered in two ganglionated nerve plexuses, myenteric and submucosal. These two plexuses form what is known as the enteric nervous system or the ENS (Figure 3).

The ENS is located within the four layers of the gastrointestinal tract. The myenteric plexus resides between the inner circular and the outer longitudinal muscle layers of the gut wall. The submucosal plexus is located above (away from the lumen of the gut) the submucosa. The myenteric plexus controls the various types of motilities in the gut e.g., it increases tonic and rhythmic contractions, increases velocity of contractions, and it inhibits sphincters.

The submucosal plexus controls secretion and local blood flow.

There are some important differences between the enteric nerves and the other types of nerves in the body e.g., nerves that supply the muscles of the legs and the arms like the sciatic, radial, and ulnar nerves. First, the enteric neurons have bulges (swellings) along the length of their axons. These bulges are called varicosities (Figure 5), and they store and secrete neurotransmitters, unlike the regular nerves where they release neurotransmitters from their axo-

nal presynaptic terminals. Varicosities allow the enteric neurons to release neurotransmitters along the whole length of the axon rather than just a pointed area at the terminal. Second, the spike potentials of the enteric neurons are 10-40 times those of the other neurons – that means activation lasts for a longer duration, 10-20 millisecond for each spike. This is because the Na<sup>+</sup> ion channels of the enteric neurons are slow to open and close compared to the other neurons, therefore, the activation remains for a longer period in the enteric neuron.



**Figure 5:** Varicosities of Enteric Neurons

Difference between regular neuron (top picture) and enteric neuron (lower picture). Regular neurons secrete their neurotransmitters from their synaptic terminals. Enteric neurons secrete their neurotransmitters from bulges on their axons known as varicosities. Those structures allow the enteric neurons to spread their neurotransmitters over a longer and a wider area.

The number of enteric neurons is approximately one hundred million neurons, which is more than the number of neurons in the spinal cord. Thus, the enteric neurons are classified into three categories to simplify their study. The first category is based on the shape (morphology) of the cell bodies of the enteric neurons. The second category is based on the electro-physiological properties of the enteric neurons. The third category is based on the type of neurotransmitter(s) secreted by the enteric neuron, also known as chemical coding.

Based on the shape of the cell bodies of the enteric neurons, there are two major types, Dogiel type I and Do-

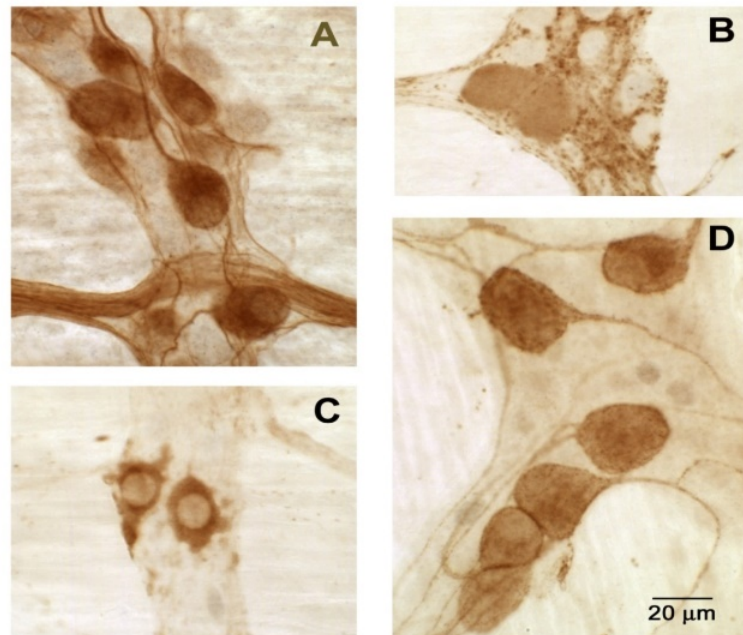
giel type II neurons (Figure 6). Dogiel type I neurons have small cell bodies with multiple short dendrites, while Dogiel type II neurons have large oval or circular cell bodies with one or two long dendrites. In general, Dogiel type I are motor neurons and Dogiel type II neurons are sensory neurons.

Based on the electro-physiological properties of the enteric neurons they are divided into an S (synaptic) type, and an AH (after-hyperpolarization) type. The S type has a short activity that lasts from 10 milliseconds to 0.5 second. The AH type has a long activity that lasts over 20 seconds.



Based on the neurotransmitter(s) secreted by enteric neurons, these neurons can be divided into two types, excitatory neurons, which secrete acetylcholine (ACh) and / or

substance P (Sub P), and inhibitory neurons, which secrete vasoactive intestinal peptide (VIP) and / or nitric oxide or NO.

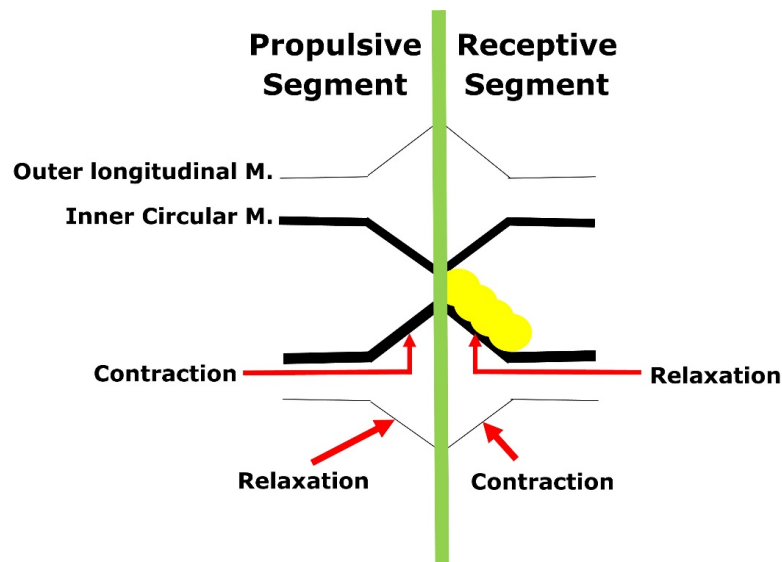


**Figure 6:** Morphology of the enteric neurons

The morphology of the enteric neurons can be divided into Dogiel type I neurons (C), which have small cell bodies, short one or two dendrites, and they are motor in function. Dogiel type II neurons (A, B, D), which have large cell bodies, long dendrites, and they are mostly sensory in function.

Three examples may illustrate the importance of this classification. First, research have shown that the gut hormone cholecystokinin (CCK), which reduces food intake and inhibits gastric emptying, in both animals and human activates NOS-containing, Dogiel type I enteric neurons in the myenteric plexus (NOS is a marker for inhibitory motor neurons) and calbindin- and calretinin-immunoreactive (markers for sensory enteric neurons), Dogiel type II neurons in the submucosal plexus. Second, enteric neurons supplying the sphincter of Oddi that guard the releasing of bile from the gallbladder to the duodenum are Dogiel type I, S type (inhibitory – meaning when you activate them, they relax [inhibit] the sphincter) and NOS-secreting. This means that activation of these neurons will relax the sphincter to release bile from the gallbladder to the duodenum. Third, for contraction and relaxation of the smooth muscles to take place at any point, the gut generates two segments, a propulsive segment before the bolus of food and a receptive segment to receive the bolus of food (Figure 7). The food

moves from the propulsive segment to the receptive segment. Therefore, to push the bolus of food from the oral (orad) to the anal (aborad) direction, mouth to anus, or anal to oral in cases of vomiting, the circular muscle of the propulsive segment must contract, and the longitudinal muscle of the same segment must relax. This means that in the propulsive segment enteric neurons that secrete ACh and Sub P activate the circular muscle to contract, while VIP and NO enteric neurons activate the longitudinal muscle to relax, because they are inhibitory neurotransmitters. The very opposite occurs in the muscles of the receptive segment. The circular muscle relaxes, using VIP and NO neurons for this inhibition, while the longitudinal muscle layer contracts, again using ACh and Sub P. In general, the previous sequence of contractions either fail or become compromised to a certain degree in cases of achalasia, intestinal pseudo-obstruction, gastroparesis, esophageal spasms, irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and paralytic ileus.



**Figure 7:** Small intestinal smooth muscle contraction

At any point, denoted by the vertical line, during small intestinal contraction the gut forms two segments, propulsive segment, and a receptive segment. Each of these segments has an inner circular muscle and an outer longitudinal muscle. For contraction to take place, so the food can move forward i.e., in front of the propulsive segment, the circular muscle in the propulsive segment must contract, using acetylcholine and substance P as the neurotransmitters, while the longitudinal muscle must relax, using vasoactive intestinal peptide and nitric oxide as their neurotransmitters. The opposite actions occur in the receptive segment. The circular muscle relaxes while the longitudinal muscle contracts.

Contraction of the smooth muscles of the gut requires not only enteric neurons but also another cell known as the interstitial cells of Cajal or ICCs. The ICC is a specialized cell which has a triangular cell body shape and multiple long dendrites or arms. These cells are the pacemakers of the gut. They can generate electrical activity on their own. Like the sinoatrial node and atrioventricular node of the heart, the ICC generates slow waves. Each slow wave consists of four phases, resting, rising (depolarization), plateau, and falling (repolarization). Contraction of the smooth muscles of the gut occurs only when [1] an action potential coming from an enteric nerve activates the smooth muscle cell and [2] a plateau phase of a slow wave generated by an ICC. One of these requirements will not result in contraction. On the other hand, there is one exception to this rule. In the stomach, slow waves can generate contractions.

With age, the ICCs decrease in number. This may explain gut motility problems in older individuals / animals. In addition, loss or malfunctioned ICCs can cause severe motility disorders such as dysrhythmias, gastroparesis, and slow intestinal transit comprising diabetic gastroenteropathy. Finally, ICC loss occurs following intestinal surgery. However, this is a transient loss that will recover in the post-

surgical period.

## The Extrinsic Nerves of the Gut

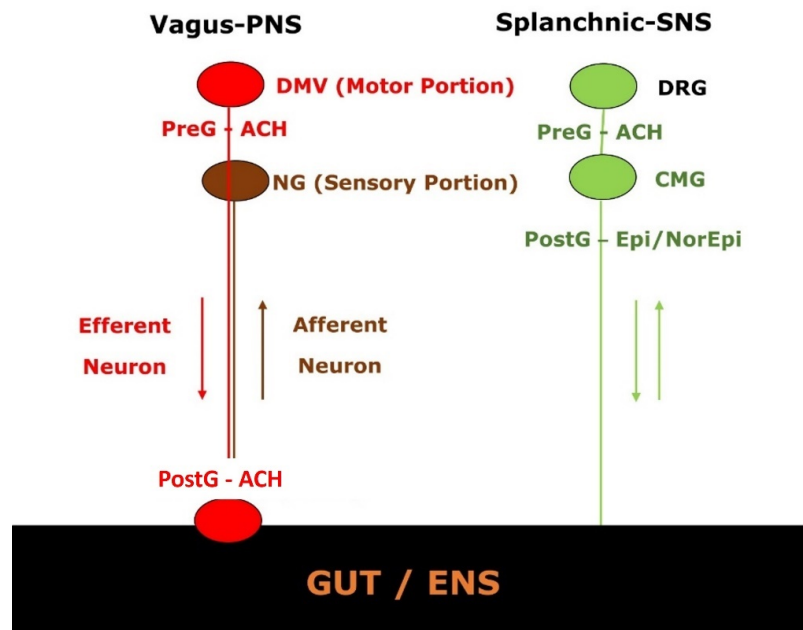
### Sympathetic and Parasympathetic Innervation of the Gut

The previous section discussed the intrinsic innervation of the gut, the ENS, or the nervous system that is located inside the gut wall and orchestrates the various functions of the gut such as motility, secretion, digestion, and absorption. This section discusses the extrinsic innervation of the gastrointestinal tract, or the nerves that are located outside the gut wall and control the various gastrointestinal functions.

The extrinsic innervation of the gut comprised of nerves that are parts of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) (Figure 8). Both systems are motor or efferent. Meaning they send orders from the central nervous system [CNS; brain and spinal cord] to the gut. The SNS functions when the individual is under tense conditions. That is why this system is the fight or flight system. As a result, activation of the SNS in-

hibits gut motility and secretions. On the other hand, the PNS works when the individual is in comfortable situations.

This is the rest and digests system, and activation of the PNS results in stimulation of gut motility and secretions.



**Figure 8:** Extrinsic Innervation of the gastrointestinal tract

Extrinsic innervation of the gut is provided by the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS and the PNS are motor systems. The splanchnic nerve is sympathetic innervation of the gut, while the vagus nerve is the parasympathetic innervation of the gut. In each of these nerves, there are two types of fibers, motor and sensory or efferent and afferent. The first sends orders from the central nervous system (CNS) to the gut and the second picks sensory information from the gut and sends them to the CNS. The PNS and the SNS is the efferent portion of each of the nerves. The vagus and the splanchnic, each as a unit, consists of two-neurons, preganglionic (PreG) and postganglionic (PostG). The cell bodies of the PreG sympathetic nerve are in the thoraco-lumbar area of the spinal cord. The cell bodies of the PostG sympathetic nerve are in the celiaco-mesenteric ganglia (CMG). The cell bodies of the sensory portion of the splanchnic nerve are in the dorsal root ganglia (DRG). The cell bodies of the PreG parasympathetic nerve are in the dorsal motor nucleus of the vagus (DMV) in the brainstem /hindbrain. The cell bodies of the PostG parasympathetic nerve are in or very close to the myenteric and submucosal plexuses of the enteric nervous system (ENS) in the gut. The cell bodies of the sensory portion of the vagus are in the nodose ganglia (NG). The PreG nerves of both the PNS and SNS secrete acetylcholine (ACH). The PostG nerve of the PNS continues to secrete ACH, while the PostG nerve of the SNS secretes epinephrine and norepinephrine (Epi/NorEpi).

The functional neuronal unit of the SNS and PNS that supplies the gastrointestinal tract consists of two nerves. Thus, this system is a two-neurons system, a preganglionic nerve, and a postganglionic neuron. The cell bodies of the preganglionic sympathetic nerve reside in the thoraco-lumbar area of the spinal cord, and they secrete Ach. The cell bodies of the preganglionic parasympathetic nerves reside in the hindbrain / brainstem, and they also secrete Ach. The cell bodies of the postganglionic sympathetic nerves that supplies the gastrointestinal tract reside in the celiaco-mesenteric ganglia, between the celiac and cranial mesenteric arteries that supply the gut, and they secrete epinephrine and norepinephrine (adrenaline and noradrenaline respectively). The cell bodies of the postganglionic

parasympathetic nerves reside in / or close to the enteric ganglia, or ENS, in the gut wall, and they secrete Ach. The sympathetic nerve that controls gut functions is the splanchnic nerve, while the parasympathetic nerve that controls gut functions is the vagus nerve.

As mentioned above, the SNS and PNS are efferent or motor systems, i.e., they carry orders from the CNS to the gut. However, sensory afferent nerve fibers sense the environment of the gut and carry signals from the gut to the CNS. The afferent fibers run in the same nerves, splanchnic or vagus, along with the efferent motor fibers, but each one has a distinct function, one sends signals from the gut to the brain afferents and the other sends orders from the brain to



the gut efferents.

In the vagus nerve there are three afferents: intervillous arbors (IVA), intraganglionic laminar endings (IGLE) and inter muscular arrays (IMA) (Figure 3). As the names indicate, IVA picks signals from the villi. They sense changes in the lumen of the gut. The IGLE pick signals from the myenteric and sub mucosal plexuses. The IMA picks signals from the muscles of the gut and senses their stretch and tension. The afferent fibers in the splanchnic nerve are known as spinal afferents. The cell bodies of the vagal afferents reside in the nodose ganglia, and the cell bodies of the spinal afferents reside in the dorsal root ganglia.

Clinically, selective branch vagotomy, or severing branches of the vagus nerve, is one option to treat gastric ulcers due to hyperacidity. Similarly, sympathectomy or removal of the celiaco-mesenteric ganglia is one of the treatment options to decrease long term pain, and to increase blood flow to certain areas in the gut.

## The Intrinsic Secretions of the Gut

### Gastrointestinal Hormones

The previous sections discussed the intrinsic and the extrinsic nerves of the gastrointestinal tract that orchestrate the various functions of the gut, so no function can interfere or overlap with the other. This section discusses non-neuronal mechanisms that control those functions. Such mechanisms consist of gastrointestinal hormonal secretions.

Like the nerves, there are two types of secretions, intrinsic and extrinsic. The intrinsic secretions of the gut are those produced by gut cells and orchestrate the various functions of the gut e.g., motility, digestion, secretion, absorption. The extrinsic secretions of the gut are those produced by cells outside the gastrointestinal tract, but they control the functions of the gut.

The gut secretes five hormones in response to food from specialized cells, gastrin, CCK, secretin, gastric inhibitory peptide (GIP), and motilin. The hormone travels to the liver by the portal vein and between from liver by the vena

cava to the heart. Then, the hormone comes back to the gut through the two branches of the aorta, which supply the gut, the cranial mesenteric artery, and the celiac artery.

**There are criteria to consider a substance a gut hormone:** (1) the substance must be secreted in response to a certain food in the gut e.g., fat, protein, (2) secretion of the hormone should occur under neuronal control, thus, severing the nerve attenuates the secretion of the hormone, (3) it should be isolated from the body, (4) it should be synthesized and (5) the synthetic form should have the same effects as the natural substance that was isolated.

The small intestines, especially the duodenum, secrete all gut hormones. In addition to small intestines, the stomach also secretes Gastrin. The stomach and small intestine secrete gastrin in response to protein, while the duodenum secrete CCK in response to fat and protein, and GIP in response to all types of food. Secretin is nature's anti-acid, and motilin is important for gut motility. Gastrin stimulates gastric acid secretion, CCK stimulates gallbladder contraction and exocrine pancreatic secretions e.g., bicarbonate, secretin inhibits gastric acid secretion by inhibiting gastrin and increasing bicarbonate, GIP inhibits gastric acid secretion, and motilin stimulates gut motility. Finally, gastrin, CCK, and motilin stimulate gut motility, while secretin inhibits it.

**Gastrin:** The G cells of the stomach and the duodenum secrete gastrin. This hormone shares the CCK-2 (CCK-B) receptor with CCK, which has two receptors, CCK-1, or A (A for alimentary, the receptor was first discovered in the gut) and CCK-2 or B (B for brain, the receptor was first discovered in the brain). Therefore, blocking this receptor attenuates gastric acid secretion, while blocking the CCK-1 receptor attenuates gallbladder contractions, bicarbonate secretion, reduction of food intake and inhibition of gastric emptying.

Like blocking the CCK-2 receptor, branch vagotomy (cutting a branch of the vagus nerve that supplies the area of the stomach that has an ulcer or hyperacidity) also attenuates gastric acid secretion because it attenuates gastrin secretion. Gastric acid secretion can also be attenuated by blocking the histamine 2 receptor, which attenuates gastrin secretion. All three methods, separately or combined, are po-

tential treatments for ulcers / hyperacidity. High blood levels of gastrin, along with low levels of potassium, diarrhea, and fatty feces (steatorrhea), are good markers for gastrinoma or Zollinger-Allison Syndrome, a non-beta cell duodenal cancer.

**Cholecystokinin:** The I cells of the duodenum secrete CCK. This hormone stimulates gallbladder contraction, increases bicarbonate secretion, inhibits gastric emptying, and inhibits food intake (a potential anti-obesity hormone along with other gut peptides such as gastrin releasing peptide and glucagon like peptide 1).

**Secretin:** The S cells of the duodenum secrete secretin. It inhibits gastric acid secretion by inhibiting gastrin (except in cases of gastrinoma secretin stimulates gastrin secretion) and stimulating bicarbonate and water secretion. It is referred to as nature's anti-acid.

**Gastric inhibitory peptide:** The enteroendocrine K cells secrete GIP, which inhibits gastric acid and stimulates insulin secretion.

**Motilin:** The enteroendocrine Mo cells secrete motilin. This hormone is secreted every 90 minutes during fasting (a phase known as the interdigestive state when a person or an animal is not actively eating). This hormone is inhibited by food i.e., when a person starts eating the secretion of the hormone stops. Motilin is responsible for generating the interdigestive migrating motor complex (MMC). This type of contraction, especially in the small intestine consists electrically of three phases, phase one or the silent phase, phase two and phase three. Phase two and phase three together form what is known as the *activity front*. The activity front is the intestinal contraction that pushes food in the gut.

### Extrinsic Secretions of the Gut

**Aldosterone:** This steroid hormone is secreted by the adrenal cortex and causes sodium and water reabsorption from the gastrointestinal tract (causing water retention, high blood pressure, high sodium, and low potassium levels) and the salivary glands in exchange of potassium.

### Gastrointestinal Motility

The basic contractile tissue in the gut is the smooth muscle cells. These muscles are in all the gut except (1) the pharynx, after (2) oral third of the esophagus and (3) the external anal sphincter. In addition, in the large intestine there are three longitudinal muscle layers instead of two as in the rest of the gut. When these muscles contract, they form what is known as *tinea*. Furthermore, contraction of the circular muscles in the large intestine creates what is known as *haustra*. Both *tinea* and *haustra* are designed to increase the surface area for microbial digestion.

The smooth muscles are unitary type because they are organized as units. Each smooth muscle fiber contains gap-junctions. These junctions are called *nexus*. The *nexus* are designed to allow ions / contraction / activation / action potential to move freely between smooth muscle cells to reach wider / longer areas in the gut.

In the gastrointestinal tract, there are two types of contractions based on their duration or length of contraction, phasic and tonic. Phasic contraction lasts seconds and it occurs in the esophagus, small intestine, and gastric antrum. Tonic contraction lasts for minutes to hours, and it occurs in the lower esophagus, cardia, and internal anal sphincter.

As a reminder, for the gut to contract and ingesta to move either in the orad (toward the mouth) or the aborad (toward the anus) direction, and at any point along the entire length of the gut, two segments must be formed, propulsive and receptive (Figure 7). Each of these segments has an inner, thick, circular muscle layer and an outer, thin, longitudinal muscle layer. For food to move, the circular muscle layer of the propulsive segment must contract, whereas the longitudinal muscle layer must relax. This occurs by activation of the circular muscle by Ach/Sub P (so it will contract) and the longitudinal muscle by VIP/NO (so it will relax). In the receptive segment, and at the same time of the propulsive segment actions i.e., contraction of circular and relaxation of longitudinal muscles, the opposite thing happens. The circular muscle of the receptive segment relaxes while the longitudinal muscle contracts. Again, this occurs by activation of the circular muscle by VIP/NO and the longitudinal muscle by Ach/Sub P. This basic description of contraction and relaxation occurs throughout the gut (Fig-

ure 7).

Understanding the different motility patterns in the gastrointestinal tract requires dividing the gut into different sections, oral, esophageal, gastric, and intestinal. Each of these sections has a different motility pattern.

The oral phase is divided into two stages, an oral stage, and a pharyngeal stage. The motility pattern of the oral stage consists of mastication and chewing, and it is controlled by the mandibular / trigeminal nerves. The pharyngeal stage is designed for swallowing, and it is controlled by the vagus and glossopharyngeal nerves. Mastication and chewing are mechanical digestion that utilizes incisors to cut the food, and molars to grind it and increase its surface area to allow saliva to mix with it and lubricate it, and digestive enzymes to work on them more efficiently. During the pharyngeal stage, which is a pure motility stage, the respiratory center is inhibited to allow for swallowing. Failure of the oral phase occurs in cases of cerebrovascular injuries i.e., stroke.

The esophageal phase, a pure motility phase, characterized by relaxation of the stomach to receive the swallowed food. There is no digestion in this phase. In the esophagus there are two peristaltic movements, a primary and a secondary generated without slow waves i.e., the contractions are myogenic (muscle-generated) and controlled by the vagus nerve. This motility pattern of the esophagus can be measured by a manometer and can be viewed by an esophagogram. In esophagogram, irregular esophageal contractions occur in a case called diffuse esophageal spasms. The radiographic view of this case is referred to as a “rosary” or a “sheesh kabab” esophagus.

The stomach has two motility patterns, contraction, and relaxation. There are two types of contractions, a reservoir, and an antral pump. Relaxation of the stomach consists of gastric emptying.

A reservoir is a tonic contraction, continuous, and lasts for a long period of time. Antral pump is a phasic contraction, occurs as a single contraction and lasts for a short duration. These contractions are generated by slow waves, and they are under vagal control. A reservoir consists of three actions, (1) receptive, when the stomach expands to re-

ceive food, (2) adaptive, when the stomach stretches to accommodate all of the food received, and (3) feedback, when the stomach cannot take any more food, and a signal from the intestine is telling the stomach to stop receiving food from the esophagus and starts emptying what it has to the duodenum i.e., a feedback signal originates in the duodenum and arrives at the stomach to start emptying.

Gastric relaxation is referred to as gastric emptying, a protective mechanism where particles less than  $1\text{ mm}^3$  are allowed to leave from the stomach to the duodenum. This process is under the control of the ENS and gut hormones such as CCK. It takes between 15 minutes and 8 hours to completely empty the stomach. The emptying action is called sieving effect, which is a selective process where liquids leave the stomach before solids, isotonic solutions leave before hypo or hypertonic solutions, hypocaloric before hypercaloric and proteins, before carbohydrates, and fat.

Gastric ulcers slow gastric emptying, whereas duodenal ulcers accelerate it. In addition, mild vomiting causes metabolic alkalosis due to the loss of bicarbonate, while severe cases of vomiting cause metabolic acidosis due to loss of gastric acid.

Motility in the small intestine depends on the state of the gut. If the individual is actively involved in eating the gut is in a digestive state. If the individual is not actively eating, i.e., resting between meals, then the gut is in an interdigestive state. During the digestive state there is minimum secretion of the gut hormone motilin, and there is no MMC because there is food being consumed. In the interdigestive state the hormone motilin is being secreted and there is MMC because there is no food being consumed. The already existing food needs to be digested, absorbed, and then moved to be expelled. During this state, the MMC is the main motility pattern along with segmentation and power propulsion. All of which are being controlled by both the intrinsic and extrinsic nerves of the gut i.e., ENS, vagus, and splanchnic. In the digestive state, the MMC is replaced by mixing, segmentation, and bi-directional short-distant peristalsis. In cases of small intestinal diarrhea acidosis and hypokalemia may occur.

Motility of the large intestine is like that of the

small intestine but with different intensity, and with certain considerations due to the presence of taeniae and haustra. The patterns include segmentation, and propulsive contraction followed by defecation. Defecation is guarded by the tonic contraction of the external anal sphincter and under partial voluntary control by the pudendal nerve. Prior to defecation there is a massive colon contraction that moves the contents to the rectum. This event is followed by relaxation of the internal and external anal sphincter, then contraction of the external anal sphincter.

There are few cases that affect the intestine, both small and large. In the colon, a congenital defect manifested by loss of the ENS is referred to as Hirschsprung disease. The same case in adults is called megacolon. Also, there are two common cases named inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). If IBD occurs in the small intestine it is called Crohn's disease. If it occurs in the colon or rectum, it is called ulcerative colitis. Both Crohn's disease and ulcerative colitis are manifested by inflammation and the presence of lesions in the affected part of the gut. The case of IBS occurs in any part of the intestine, small or large, but there are no lesions associated with it. The clinical signs in IBS flare without prior indication for those signs to appear.

### Motility Patterns in Ruminants

Anatomy of the ruminant stomach is required to understand the motility patterns of this species. The ruminant stomach consists of four compartments, (1) rumen, which occupies the left side of the abdominal cavity, and (2) reticulum, (3) omasum, and (4) abomasum, which all occupy the right side of the abdominal cavity. Structurally each of these compartments is designed to perform a certain physiological function. The rumen contains numerous villi and microvilli which makes it suitable for microbial digestion. The villi are present to increase the surface area. The reticulum traps large particles because it has honey-comb shape structures. The omasum consists of leaves which grind the food and absorb all bicarbonate and volatile fatty acids (VFA) before they reach the duodenum. The abomasum is the location for enzymatic or glandular digestion.

An open view of the rumen (Figure 9), the largest of all four compartments, shows that it is divided into sacs e.g., dorsal sac, ventral sac, caudal sac (dorsal and ventral), and cranial sac by structures known as pillars. The pillars are longitudinal, cranial, caudal, ventral, caudoventral, dorsal and ventral coronary. These pillars function as (A) stretch receptors and (B) chemoreceptors. During eating, when the rumen is being filled the stretch receptors sense the amount of food coming and distend the rumen by increasing motility. Now, if the rumen has excessive amount of food, the pillars inhibit motility. The chemoreceptors sense the pH of the rumen. If the pH drops (below 7.4), they inhibit motility and stimulate absorption of the VFA.

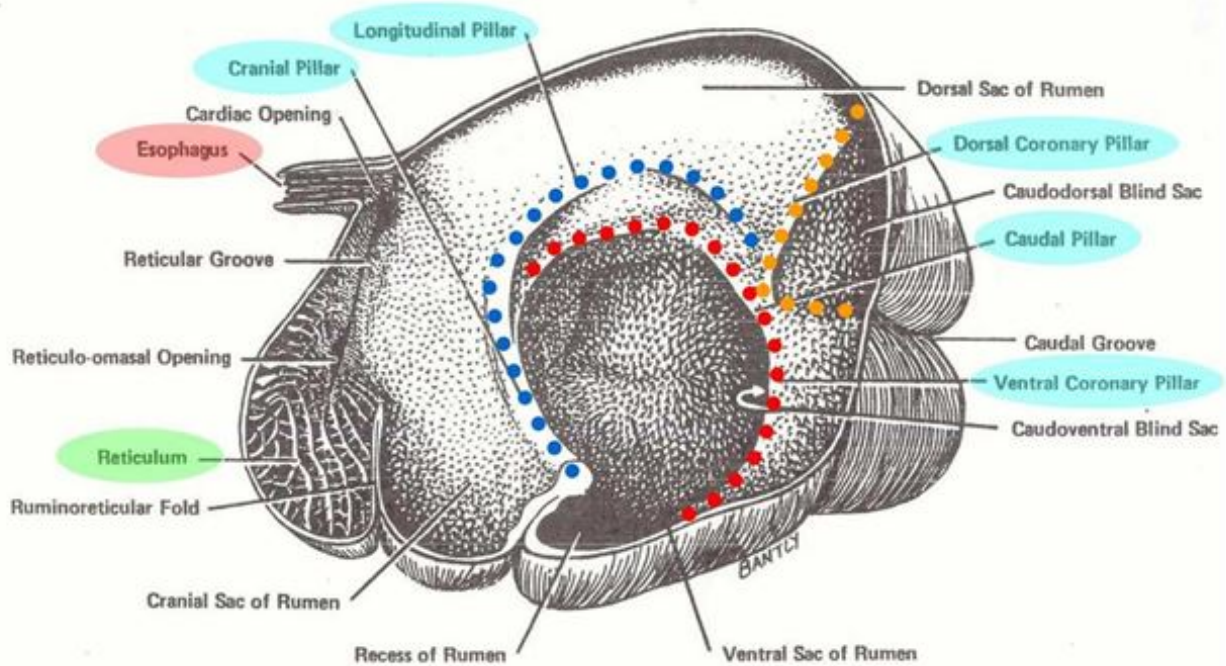
In ruminants, unlike other mammals, food travels in two cycles. The first cycle starts in the mouth, then esophagus, then rumen, then reticulum. The second cycle starts in the reticulum, then mouth again, then omasum and finally abomasum. The two cycles are connected and continuous. During the first cycle food is reduced in size significantly and altered by the microorganisms in the rumen. The second cycle refines the food and reduces it to millimeter size particles to be able to move to the omasum and abomasum.

The oral and esophageal stages / phases in ruminants are like those discussed in other animals.

Stomach motility is divided into two cycles, (1) rumen-reticulum, and (2) omasum-abomasum. The rumen-reticulum cycle is divided into two motility patterns, primary or mixing and secondary or eructation. The first pattern separates the ingesta by size or zones. The second pattern separates ingesta by gravity forcing CO<sub>2</sub> and CH<sub>4</sub> to enter the esophagus and liquids to go down in the rumen.

The primary (mixing) contraction starts by contraction of the reticulum, caudal contraction of the dorsal sac of the rumen, followed by caudal contraction of the ventral sac of the rumen, followed by cranial contraction of the dorsal sac and cranial contraction of the ventral sac. These contractions create two food zones, zone of potential escape, containing small food particles, and slurry zone, containing large food particles. Gravity separates the contents of the rumen into gas, solid, ejection, and liquid contents.





**Figure 9:** Anatomy of the Rumen

An open view of a ruminant stomach showing two of its compartments, the reticulum, and the rumen with all its sacs, and pillars.

The secondary or eructation contraction takes place by the following steps: cranial contraction of the dorsal sac, ventral relaxation of the ventral sac, dorsal elevation of the cranial pillar, cardia relaxes, lung expansion, glottis closed, and retro-peristalsis. The slurry zone enters the esophagus. The contents of this zone start to be re-chewed in the mouth. The tongue expresses the contents. Water is swallowed, re-mastication starts, and particles are separated by size. The large ones go back to the slurry zone in the rumen. The small particles reach the zone of potential escape, or the zone that will soon leave the rumen to go to the reticulum (that is why it is called a zone of potential escape because it will leave the reticulum to the omasum). This whole process is called rumination. It occurs all the time, except when the animal is sleeping. In addition, solid food enhances rumination whereas liquid, grains, and finely ground food slows it down. Finally, failure of rumination allows accumulation of gases, especially methane, and VFA, which both are toxic to the animal.

Reticular contraction that took place in the primary or mixing contraction above, allows the omasal orifice to dilate and permits the food zone of potential escape to enter the omasum, where the sieving effect takes place. When

the orifice contracts it pushes the contents of this zone between the leaves of the omasum. This process allows those leaves to absorb all VFA and bicarbonate from the contents of this zone, because if they escaped to the abomasum VFA and bicarbonates will neutralize the pH of the abomasum, which is highly acidic, and this will slow down or inhibit the process of enzymatic digestion, or conversion of pepsinogen to pepsin by hydrochloric acid, which is essential for protein digestion in the glandular stomach, or the abomasum.

### Gastrointestinal Secretions

The sources of secretions in the gut are epithelial cells, salivary glands, stomach, pancreas, and liver.

Epithelial cell secretions include water and electrolytes, mucus, and special molecules. Water and electrolytes are secreted throughout the gut to dissolve and liquifies, to provide a good reaction medium, and to provide hydrogen ion and bicarbonate sources. Mucus lubricates and protects. Special molecules are reserved for digestion and absorption.

Salivary secretions are utilized for digestion, lubrication, and protection. Digestion by saliva occurs by two en-



zymes, amylase, which digests carbohydrates and lipase which digests lipids. The amount of amylase and lipase from the salivary glands is insignificant compared to their pancreatic source. Therefore, losing a salivary gland will not affect digestion of carbohydrates or lipids. Lubrication by saliva also takes place by their mucus component. Protection by saliva occurs by the bactericidal (killers of bacteria) effect of lysozymes and lactoferrins. Furthermore, in saliva there is a substance called kallikrein which converts a plasma protein to bradykinin, a vasodilator.

Salivary secretions are controlled by a center in the hindbrain which can be activated by physiological factors such as food and smell and can be inhibited by fear and fatigue. Activation or inhibition occurs by two cranial nerves IX and XII, the glossopharyngeal and hypoglossal respectively.

Gastric secretions include HCl or hydrochloric acid, pepsinogen, mucus, and an intrinsic factor. In the stomach, acid has two functions. It converts pepsinogen to pepsin, the active form of the stomach enzyme that digests protein, and it has a bacteriostatic function. It stops bacterial growth but does not kill bacteria. Pepsin digests protein. Mucus protects, lubricates, and acts as a barrier in the stomach. The intrinsic factor is essential to bind vitamin B12. Therefore, lacking this factor will lead to a case of pernicious anemia. Gastric secretions come from acid-producing parietal cells, pepsinogen and intrinsic factor-chief producing cells, G-cells producing gastrin, and mucus cells.

Gastric acid secretion depends on the state of the gut. If the person / animal is not actively engaged in eating, this is called non-parietal, interdigestive, state. Secretion during this stage is basal secretion and it consists of sodium chloride. If the person / animal is engaged in eating this is called parietal or digestive state during which the secretion is at a peak level, and it consists of hydrochloric acid. These two sources for gastric acid secretion are referred to as "The Two Component Theory."

Secretion of gastric acid occurs under the control of three phases, a cephalic phase, a gastric phase, and an intestinal phase. The cephalic phase of acid secretion is stimulated by hypoglycemia (low levels of glucose in the blood), and insulin, and this phase is vagally mediated. This means

cutting the vagus (vagotomy) will attenuate acid secretion by this phase. However, this phase controls only 30% of the total secretion of acid, which means that it is not a major contributor to this process. The gastric phase is the major phase that controls gastric acid secretion, it controls approximately 60% of the total. Gastrin is the major force in stimulating gastric acid by the gastric phase. Therefore, it is not affected by vagotomy but by blocking gastrin receptor, i.e., the CCK-B or CCK-2 receptor, or the histamine 2 receptor, H-2. The intestinal phase accounts for only 10% of gastric acid secretion, and it is stimulated by absorption of certain amino acids from the duodenum following protein digestion.

There are a few methods to decrease gastric acid secretion to treat hyperacidity or gastric ulcers. First, cutting a branch of the vagus nerve that supplies the area of the stomach that is problematic. Second, blocking gastrin secretion by blocking the CCK-2 or B receptor. Third, cutting the antrum of the stomach (antrectomy). Fourth, blocking histamine secretion by blocking the H2 receptor or the histamine-2 receptor, which is used in medicines such as ranitidine / cimetidine (Tagamet / Zantac).

Pepsin, the active enzyme that digests proteins by breaking their interior bonds, is secreted as the inactive pepsinogen (PG). Activation of PG takes place by the low pH (pH 2-3) of HCl in the stomach. Secretion of PG is stimulated by vagal stimulation and secretin. There are two groups of PGs, I and II. Pepsinogen I is secreted by the stomach, and PGII is secreted from the duodenum.

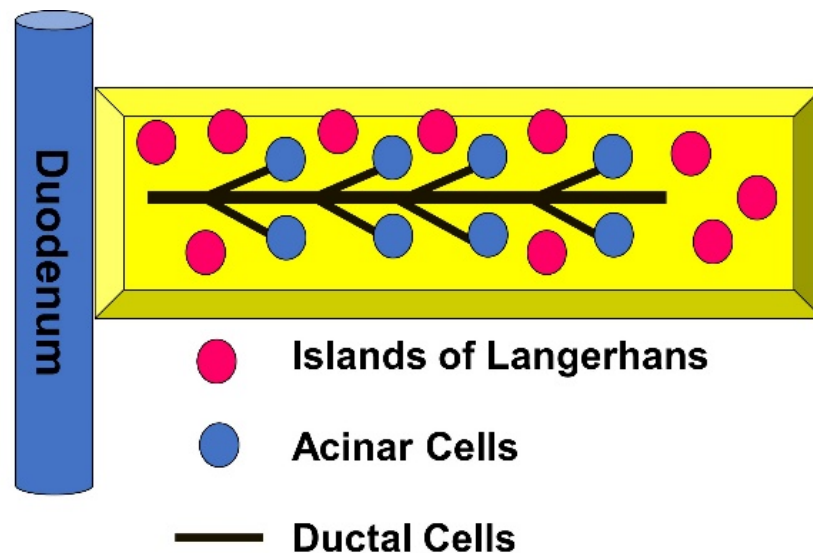
Mucus in stomach are two types, soluble and insoluble. Soluble mucus is secreted from the mucus neck cells, and its main function is lubrication. Secretion of this form of mucus is stimulated by vagal stimulation. Insoluble mucus is secreted by the surface mucus cells, and it acts as a physical barrier. This form of mucus is stimulated physically or chemically.

The intrinsic factor is secreted from the parietal cells, and it binds to vitamin B12 to facilitate its absorption. Absence of this factor leads to pernicious anemia.

Pancreatic secretions come from three types of tissues in the pancreas, islands of Langerhans, acinar cells, and

ductal cells (Figure 10). The islands of Langerhans secrete the hormones insulin and glucagon, the endocrine secretions of the pancreas or the hormones that are secreted directly into the blood stream. Ductal cells secrete ions such as NaCl and bicarbonate. Acinar cells secrete digestive enzymes such as amylase, lipase, and trypsinogen. Ductal and acinar secretions are referred to as exocrine secretions of

the pancreas because they are secreted in the duodenum, not the blood stream. The endocrine secretions of the pancreas, the hormones, form about 4% of the total pancreatic secretions, while the exocrine secretions of the pancreas form the remaining 96% of the total secretions, 6% ions (ductal secretions) and 90% digestive enzymes (acinar cell secretions).



**Figure 10:** Anatomy of the pancreas

The pancreas is an accessory gland of the digestive system located beside the duodenum, and consists of three types of tissues, Islands of Langerhans, which secrete the endocrine secretions of the pancreas including insulin and glucagon, acinar cells, which secrete an exocrine secretion of the pancreas, including digestive enzymes such as lipase, amylase and trypsinogen, and ductal cells, which also secrete an exocrine secretion including water and bicarbonates.

Insulin and glucagon regulate blood glucose. When glucose level is high insulin is secreted from the pancreas and reaches the liver and tissues to store the extra glucose as glycogen. If the level of blood glucose drops the pancreas secretes glucagon which activates the liver to turn glycogen into glucose and pump it to the blood to increase the level of glucose.

Ionic secretions of the pancreas consist of the ductal secretions of sodium chloride or NaCl (salt) and bicarbonate or  $\text{HCO}_3^-$ . At the low levels of pancreatic secretions salt is secreted. At the high levels of pancreatic secretions bicarbonate is secreted. This is called “The Two Component Theory” of secretion.

Enzymatic secretions of the pancreas are digestive enzymes that come from the acinar cells. Such enzymes are

secreted in two forms, active and inactive. The active enzymes that acinar cells secrete are lipase and amylase. The inactive enzyme that acinar cells of the pancreas secrete is trypsinogen, which is activated by enterokinases.

A very important question surfaces here and that is why pancreatic enzymes do not digest the pancreas and the other tissues? There are four answers to this question. First, pancreatic enzymes are secreted in an inactive form. Second, pancreatic enzymes face trypsin inhibitors which inactivate them. Third, these enzymes are bound to the membrane of the cells. They only become active when they leave the membrane. Fourth, there is a process of autodigestion by trypsin, which inactivates them.

Like gastric acid secretion, pancreatic secretion is also under the control of three phases, cephalic, gastric, and

intestinal. The cephalic phase accounts for 20% of the total pancreatic secretions, which are characterized by their low volume but high concentration, and it is vagally mediated. The gastric phase accounts for 5-10% of the total pancreatic secretions and it is also vagally mediated. The intestinal phase accounts for 70% of the total pancreatic secretions, and it is under a hormonal control e.g., CCK.

In pancreatitis, inflammation of the pancreas, bicarbonate level is low. In pancreatic cancer all enzymes / secretions decrease except amylase. Also, fatty feces or steatorrhea can be seen when there is 80% or more damage in the pancreas. In addition, diagnosing pancreatitis and pancreatic tumors is done by doing secretin and CCK tests. In a normal pancreas these hormones stimulate bicarbonate secretion, in a diseased pancreas they fail to do so.

Gallbladder secretions, bile secretions, are closely related to the liver and pancreas, and they are under vagal, and hormonal (mainly CCK) control. Bile assists in fat digestion, in a process known as emulsification, fat absorption, through forming a product known as micelle, elimination of products such as cholesterol, heavy metals, bile pigment, and drugs.

Bile consists of organic and inorganic components. The organic components are bile acids, make 50% of the total bile secretions, phospholipids, make 30-40% of the total secretions, cholesterol makes about 4% of the total secretions, and bile pigment makes 2% of those secretions. The inorganic components of bile consist of water, bicarbonate, and ions. The total amount of bile secretions is 2.5 gm, 600 mg of which are synthesized daily from cholesterol, and 90-95% are bound to plasma protein.

Bile acids, also called bile salts, are synthesized continuously by hepatocytes, or liver cells, secreted 30 min following a meal, and under vagal / hormonal (CCK) control. Bile acids are always conjugated, and only when there is a bacterial infection, do they become unconjugated. Half of bile acids are reabsorbed passively from the upper intestine while the rest are reabsorbed actively from the lower intestine. Only 5% of bile acids are lost in feces.

Phospholipids consist mainly of lecithin, which is an amphipathic molecule that has two sides, one is hy-

drophilic (water lover) and the other is lipophilic (fat lover). Phospholipids are important in micelle formation, the final product in lipid digestion, to solubilize cholesterol.

Cholesterol is important in bile secretions, and an excessive amount serves as a nidus for gallstones – most gallstones, 50-75%, are cholesterol based.

Bile pigment is mainly bilirubin, which comes from digested / damaged red blood cells (RBCs), especially in cases of liver damage where there is massive damage of RBCs e.g., cases of jaundice. Bile pigment is not found in the micelle like the other molecules. Like, cholesterol, bile pigment can serve as a nidus for gallstones.

### **Gastrointestinal Digestion and Absorption**

Digestion is decreasing the size of food particles to an acceptable size to allow tissues to utilize them. This takes place in all parts of the gut. On the other hand, absorption is passing these food particles from the gut to the tissues to use them. This process takes place mostly in the small intestine. There are few structures that allow the gut to perform functions, digestion, and absorption. The path of nutrients starts in the lumen of the gut. Then, they enter the cells of the mucosa of the gut, enterocytes. They leave the enterocytes to go to the blood / lymphatic vessels. Finally, the blood takes them to different tissues to use them. The methods for this movement between the gut and the tissues are simple diffusion, active transport, facilitated diffusion, or pinocytosis, for larger molecules. To facilitate digestion and absorption, the gut enjoys a well-developed circulation. It is supplied by an artery, branches of the cranial mesenteric artery, a vein, branches of the portal vein, and a lymphatic vessel or a lacteal that ends in the thoracic duct before it reaches the blood circulation. The small intestines are well equipped to absorb nutrients because they have folds and villi that increase the surface area of the gut. The cells of the upper portion of the villi, which are equipped for absorption, are more than the lower portion of the villi, which are considered for defense. There are age-related changes that affect those cells. With age, those cells decrease in number, and as a result this may affect the absorption ability of the gut in older individuals.

Digestion is two types, luminal or cavity, and mem-

brane or contact. Luminal digestion starts by digestive enzymes in the different cavities of the gastrointestinal tract e.g., mouth, stomach, intestine / pancreas. Digestion in the intestine is more significant than digestion in the stomach, and membrane digestion occurs by digestive enzymes at the level of the apical membrane of the enterocyte. Because digestion and absorption are connected to each other they will be discussed together.

Nutrients are three types, carbohydrates, proteins, and lipids. The first section will cover carbohydrate digestion and absorption. The end-products for carbohydrate digestion are glucose, galactose, and fructose. In the lumens of the mouth and the intestine amylase starts the process of carbohydrate digestion. At the level of the apical cell membrane of the enterocyte, many enzymes continue this process. Some of those enzymes are specific for certain sugars i.e., one-sugar-one enzyme, and some are not specific i.e., one enzyme digest multiple types of sugars. The specific enzymes ones are sucrase, lactase and trehalase. Sucrase digests sucrose to fructose and glucose. Lactase digests lactose to galactose and glucose, and trehalase digests trehalose to glucose. These three end-products, glucose, galactose, and fructose must first leave the intestinal lumen and enter the enterocytes of the intestinal mucosa. Then, they must be transferred from the inside of the enterocyte to the blood stream. Then, they must be transferred from the blood stream to the tissues, so they can use them. To do that, there are certain membrane bound carriers that will bind these sugars to transport them across the apical membrane of the enterocyte to the inside of the enterocyte. Transporter SGLT-1 transports glucose and galactose. Transporter GLUT-5 transports fructose. Now, glucose, galactose and fructose are inside the enterocytes. In this cell there is another transporter known as GLUT-2, which carries all three sugars, glucose, galactose, and fructose and transports them from the enterocyte to the blood vessel.

The end-product of protein digestion is amino acids. In the lumen of the stomach pepsin starts digesting the inside peptide (endopeptidase) bonds of proteins, and when protein moves to the intestinal lumen this same process, luminal or cavity digestion, continues by another very important endopeptidase called trypsin, following activation of the original inactive form of the enzyme trypsinogen

by the membrane-bound enzyme enterokinase i.e., enterokinase activates trypsinogen to become trypsin which in turn digests the inside peptide bonds of proteins. Still in the lumen of the intestine, protein digestion continues by enzymes that digest the outside peptide bonds of the protein. Those enzymes are called exopeptidases. Such enzymes may include for example carboxypeptidase A and B. By the end of digestion of proteins by both enzyme groups, endopeptidases and exopeptidases, amino acids are produced.

Amino acids are transported from the lumen of the intestine to the lumen of the enterocyte, then from the lumen of the enterocytes to the blood stream, by a simple diffusion method. Large proteins are transported by pinocytosis.

The end-products of lipid digestion are cholesterol, free fatty acids, monoglycerides and glycerol. Such products come from the original structure of lipids which are triglycerides, consist of three fatty acids and a glycerol, phospholipids, consist of two fatty acids and a glycerol, and cholesterol, consists of one fatty acid and a glycerol. These lipids form 12% of the caloric needs in the Asian diet, but 40% of the Western diet, which may be a clear cause for obesity in westerners. Fat is used to build bile, steroid hormones, and cell membranes.

Digestion of lipid starts in the mouth and the intestinal cavities by the enzyme lipase. In the lumen of the intestines, motility breaks fat and creates fat droplets. This formation allows hydrolysis of fat by enzymes to start. Three pancreatic enzymes start attacking the fat droplets in the lumen of the small intestine, lipase, phospholipase A2, which requires bile acids to work, and cholesterol ester hydrolase, which is less specific.

First, bile salts (bile acids) along with phospholipids start mixing with the fat droplets that were formed by gut motility and lipase in the intestinal lumen. Bile salts start attaching to these droplets. This process is called emulsification. The bile salts are simply adding an electrical charge to the fat droplets to make them more accessible to lipase and other lipid-digesting enzymes. The role of phospholipids, the portion of bile secreted by the gallbladder in response to the presence of fat in the small intestines, is to prevent aggregation of the fat droplets so lipase can work

more efficiently on them and hydrolyze them to the end.

When the final product of fat digestion becomes water soluble, the product is formed into a micelle. This process is called micelle formation. Micelles contain (A) bile acid, (B) cholesterol, (C) fatty acid, and (D) monoglyceride, and these four products are the final products of lipid digestion. The remaining final part of fat digestion is glycerol, but this molecule is not part of the micelle.

Now, micelles (Figure 11), located in the intestinal lumen, reach the apical membrane of the enterocytes. The contents of the micelle, cholesterol, fatty acid, and monog-

lyceride, need to leave the intestinal lumen, cross the apical membrane of the enterocytes, and enter the enterocyte to go from there to the lymphatic stream. Fat digestion products except glycerol must go from the enterocyte to the lacteal or the lymphatic vessel first then to the thoracic duct then they are transferred to the venous blood supply to go to the rest of the body. Only glycerol, which is not part of the micelle, goes from the lumen of the small intestine and enters the enterocyte, to leave to the blood vessel, by a simple diffusion. Glycerol does not enter the lacteal; only other lipid digestion products such as cholesterol, fatty acid, and monoglyceride, do.

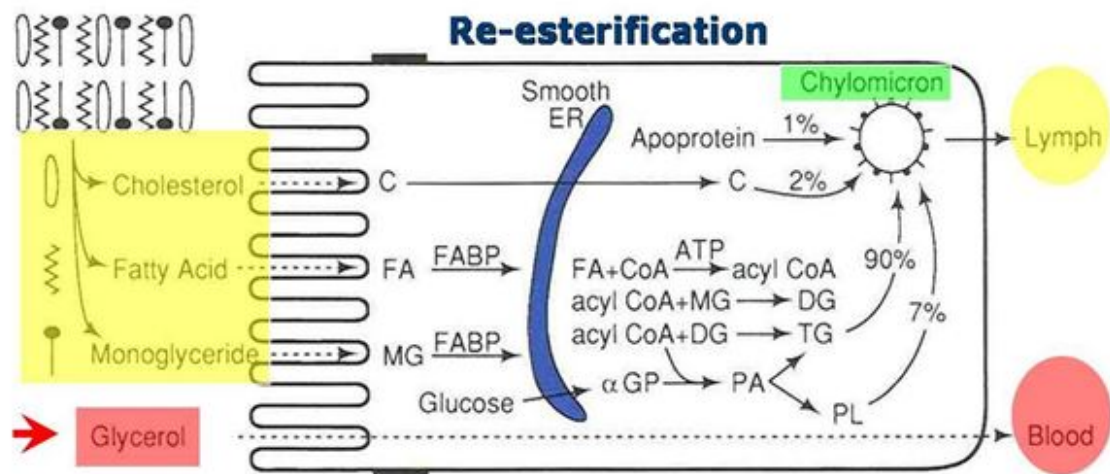


Figure 11: Fat absorption

Absorption of fat occurs when the end-products of fat digestion like cholesterol (C), fatty acid (FA), monoglyceride (MG) and glycerol, cross enter the enterocyte from the intestinal lumen and reach the blood stream or the lacteal or the lymphatic stream. Glycerol crosses by simple diffusion from the intestinal lumen to the lumen of the enterocyte, then from the enterocyte to the blood stream. Cholesterol also enters the enterocyte by simple diffusion. Fatty acids and MG require fatty acid binding proteins (FABP) to enter the enterocyte from the intestinal lumen. In the enterocyte, FA and MG convert into triglycerides (TG). Finally, cholesterol, TG, phospholipid (PL) along with a protein named apolipoprotein, through a re-esterification process, form a molecule called chylomicron. Chylomicron then enters the lymphatic vessel to end in the thoracic duct before it reaches the venous circulation.

Fatty acids and monoglycerides require carrier proteins known as fatty acids binding proteins or FABP to cross the apical membrane and enter the enterocyte. Cholesterol crosses the apical membrane into the enterocyte by simple diffusion. Bile acids are not part of fat digestion. They are only part of micelle formation. Therefore, they get reabsorbed to the liver to synthesize more bile for lipid digestion.

Inside the enterocyte, long fatty acids (short and medium fatty acids enter the enterocyte by simple diffusion,

and they enter the blood stream and not the lymphatic vessel or the lacteal like the long fatty acids), and monoglycerides, are re-synthesized to triglycerides. Now, the triglycerides, with the cholesterol that has already entered the cell, phospholipids, glucose, and a very important protein known as apolipoprotein, all these components are repackaged to a new molecule known as chylomicron. This chylomicron then enters the lacteal or the lymphatic vessel of the gut by exocytosis, not simple diffusion, to go to the thoracic duct, then to the venous supply of the body to reach



the general circulation.

In the blood vessels there are two types of lipid carrier proteins, low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The HDLs bind to cholesterol while LDLs do not bind to cholesterol. As a result, if an individual has high HDLs that means all the cholesterol in the blood will be removed and utilized, whereas an individual with high LDLs will have accumulated cholesterol in their blood vessels. This case is known as atherosclerosis. It may lead to blockage of the blood vessels and possible strokes.

## Fermentation

In most species digestion and absorption occur in the small intestine. However, in ruminants e.g., cows, sheep, goats, camels, llama, only 5-20% of digestion, and absorption occur in the small intestine. Most of the digestion and absorption in ruminants occur in the rumen, the largest component of the ruminant stomach. The process of digestion in ruminants is called fermentation, and this process occurs in the large intestine in all species.

Fermentation is an anaerobic (requires no oxygen) process that generates energy from a plant source and protein from dead organisms. Energy and protein are used for growth, maintenance, and production. Most energy (70% of all animal needs) produced by fermentation is absorbed from the rumen, and most of the protein (90% of all animal needs) produced from dead organisms and amino acids is absorbed from the small intestine.

Fermentation utilizes plants as a carbohydrate source to generate glucose and volatile fatty acids (VFA), and dead organisms as a protein source to produce peptides, and a nitrogen source to produce ammonia and urea. Although fermentation is slower than glandular digestion, it alters the substrate significantly more than regular, enzymatic digestion.

Fermentation occurs in the rumen, reticulum, and omasum of ruminants. It also occurs in the non-glandular portion of the stomach in horses and pigs, and in the large intestines, mainly cecum and colon, in all animals. Fermentation requires 20-50 billion bacteria, 200-500 thousand protozoa, and fungi. All these organisms live in a symbiotic rela-

tion. In addition, fermentation requires a plant substrate, a suitable pH (6-6.5), temperature (40°C, 100-108°F), 60-80 gallons ruminal capacity, and 10-45 gallons of saliva.

Energy is generated by an anaerobic oxidation-reduction process inside the organisms, bacteria, protozoa, and fungi. The process is called the Embden Meyerhof Parnas pathway, and it utilizes any hexose (six carbon sugars) in the plant to produce pyruvate. During this process two ATP molecules, not utilized by the host, and two NADPH molecules are generated. The end-product of this pathway are the VFAs acetate, propionate, and butyrate. These VFAs enter two metabolic pathways. Acetate and butyrate enter the methanogenic pathway, also known as acetic acid pathway, and propionate enters the randomized pathway. Through these processes acetate generates 8 ATP molecules, butyrate generates 5 ATP molecules, and propionate generates 4 ATP molecules. In addition, a direct reductive pathway produces 3 ATP molecules from propionate and acetate. All 20 ATP molecules produced by these two oxidative-reductive pathways are utilized by the host for growth, production, and maintenance.

The methanogenic pathway is important not only because it generates more energy for the host i.e., animal, but also because it produces a toxic gas called methane. A balance in the diet must be reached to minimize the production of methane because it is toxic. As such, high starch, high grain, finely grinded, and pelleted food cause high methane production, and should be controlled.

All the energy absorbed from the rumen to the blood stream reaches the liver for utilization by tissues or storage in the form of glycogen. Acetate is used for building muscles, fat, and milk (60%) and it comes mostly from roughages. Excessive amounts of acetate cause metabolic acidosis. Propionate is used for gluconeogenesis in the liver (20%), and it comes mostly from concentrates. It is the main source of lactate. Butyrate is the main builder of fat (20%) and less of milk. It provides energy to the rumen and excessive amounts of butyrate causes increased ketone bodies.

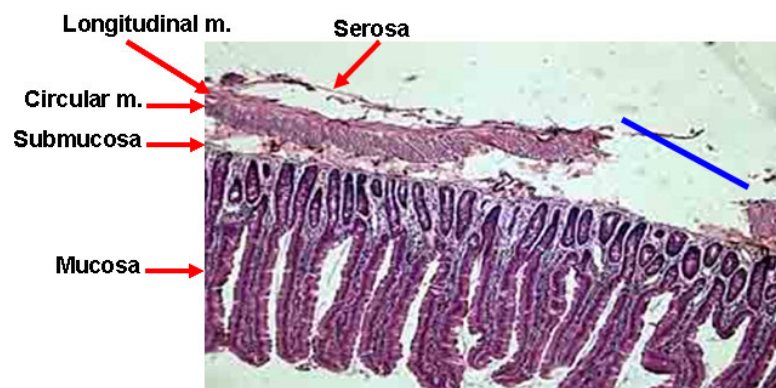
Proteins are generated mostly (60%) from dead organisms. Other sources of proteins include non-protein sources such as carbohydrates, nitrates, and urea – ammo-

nia. Dead organisms are washed from the rumen to the reticulum to the omasum to the abomasum and digested in the small intestine into amino acids by trypsin-like endopeptidases. The end-product is short chain peptides, which makes branched-VFA when water is added. For example, two molecules of water and the amino acid valine create isobutyrate, leucine with two molecules of water makes isovalerate and isoleucine with two molecules of water makes methylbutyrate. All these branch chained VFAs are utilized to build proteins for muscles and milk production e.g., leucine is the main source to muscles. All amino acids are absorbed by the various tissues to build proteins according to their physiological needs. Urea is absorbed from the rumen, detoxified in the liver to produce protein. The remain-

ing urea is secreted in the urine and the saliva.

## Conclusion

The work started by discussing the basic macro and microscopic structure of the gut. This system consists of four layers, mucosa, submucosa, two muscle layers, and a serosa. The submucosa is a holding layer in the gut, and it must be sutured and secured during surgery e.g., cases of enterotomy, enterectomy or myotomy / myectomy to prevent leaking of chyme (Figure 12). The serosa is part of the peritoneum. Therefore, there is a high risk of post-operative peritonitis / infection if this layer is not kept fully irrigated and clean during abdominal / intestinal surgery.



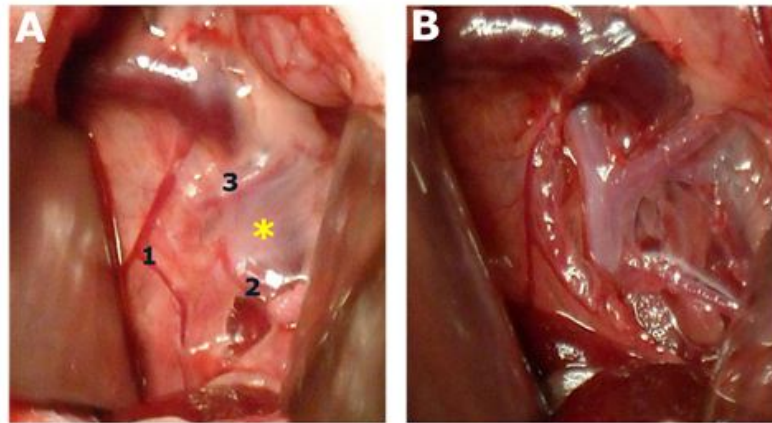
**Figure 12:** A photomicrograph of the small intestine following a myotomy / myectomy procedure (line) showing the severed and the intact layers of the gut. While the serosa and the two muscle layers are severed, the submucosa, the holding layer of the gut, is still intact. Any leakage through this layer may lead to peritonitis and severe post-operative complications. Therefore, the submucosal layer must be securely sutured. In addition, the serosa must also be kept clean and thoroughly irrigated during intestinal / abdominal surgery.

The article then outlined the intrinsic and the extrinsic nerves of the gut, which control the various functions of this system. Such nerves include the ENS and ICCs, the splanchnic nerve, and the vagus nerve. Irregular firing of these neurons / specialized cells is manifested clinically by diarrhea or constipation if the firing is in the aborad direction and vomiting if the firing is in the orad direction. Such cases may also result in metabolic acidosis, in the mild stage, or alkalosis in the more severe ones due to loss of gastric hydrochloric acid.

Absence of the ENS in neonates, also known as agenesis of the ENS, is considered a fatal disease, however, absence of the ENS from parts of the gut due to embryonic failure of these nerves to develop is called Hirschsprung dis-

ease or congenital aganglionic megacolon. On the other hand, absence of the ICCs, which are major players in gut contraction through the generation of slow waves, from the gut can cause gut diseases such as pseudo intestinal obstruction and stromal tumors. Diagnosing the loss of ICCs can be done by immunohistochemical detection of the protein c-Kit in the intestine.

The gut is also supplied by vagus and splanchnic nerves. As mentioned earlier, selective branch vagotomy is one of the treatment options for the treatment of certain cases of gastric ulcers. Sympathectomy or removal of sympathetic ganglia e.g., celiaco-mesenteric ganglionectomy (Figure 13) is a procedure done to increase blood supply to certain areas in the gut.

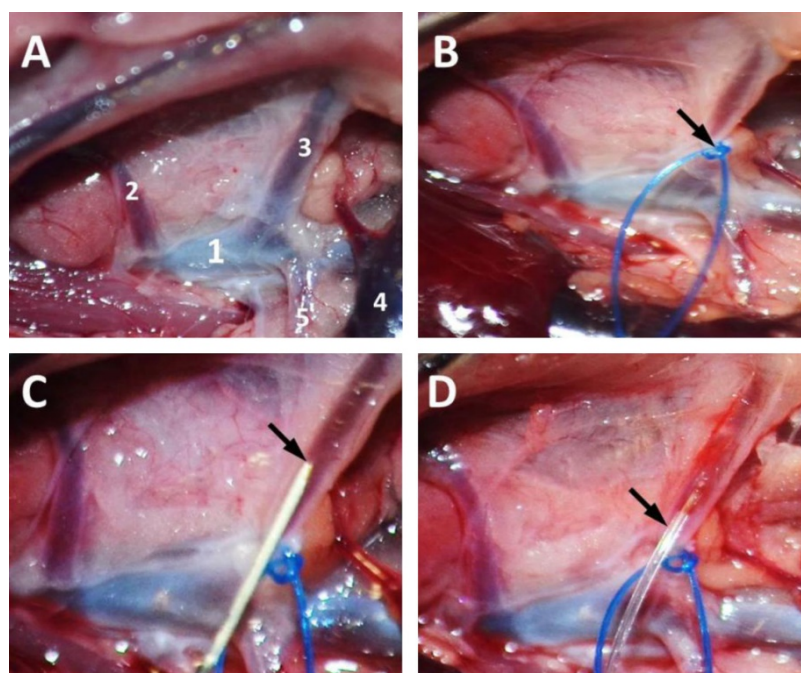


**Figure 13:** Celiaco-Mesenteric Ganglionectomy or removal of the celiaco-mesenteric ganglia, the sympathetic innervation of the gut. In A, the celiaco-mesenteric ganglia (denoted by the star) are located between the aorta (1), celiac artery (2) and the cranial mesenteric artery (3). In B, the ganglia have been removed.

This work then highlighted major points regarding the hormones that participate in the control of the various functions of the gut, gastrin, CCK, secretin, GIP, and motilin. For example, blocking the CCK-2 or CCK-B receptor alone or with severing a branch of the vagus nerve or blocking the histamine 2 receptor decreases gastric acid secretion. In addition, excessive gastrin secretion can be seen in cases of Zollinger Ellison syndrome, which is also accompanied by severe acidosis due to this acidity.

Cholecystokinin has been utilized as a potential weight reducing agent in combination with other gut peptides such as gastrin releasing peptide and glucagon like pep-

tide 1. All three agents were delivered in the cranial mesenteric artery (Figure 14) that supplied most of the gut, individually or in combination. It had been shown that combination of these hormones / peptides produced reduction of body weight more than each of them given individually. In addition, the hormones CCK and secretin along with the enzymes amylase and lipase carry a critical diagnostic value in cases of pancreatitis and pancreatic cancer. For example, in cases of pancreatitis increased CCK levels worsens the case, amylase increases rapidly, and stays elevated for five days, and lipase increases and remains increased for over two weeks.



**Figure 14: Intra-arterial catheterization**

This procedure has been developed to deliver very small amounts of combinations of gut hormones and peptides through external catheters to specific areas in the gastrointestinal tract. Such areas demonstrated that they contain sites of actions for those substances e.g., CCK, gastrin releasing peptide, glucagon like peptide 1. A depicts the normal anatomy of the vessels supplying the gastrointestinal tract, 1 aorta, 2 celiac artery which supplies the stomach and the upper duodenum, and 3 is the cranial mesenteric artery (CMA) which supplies most of the gut. 4 represent the renal artery. B depicts ligation of the CMA to control blood flow. C represents puncturing of the CMA. D represents placing a catheter in the CMA artery and loosening of the ligation.

This article summarized basic concepts related to the physiology of the gastrointestinal tract. It is intended as

a concise and a quick reference in gastrointestinal physiology. For more in-depth clinical and research information the reader is encouraged to find other sources.

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