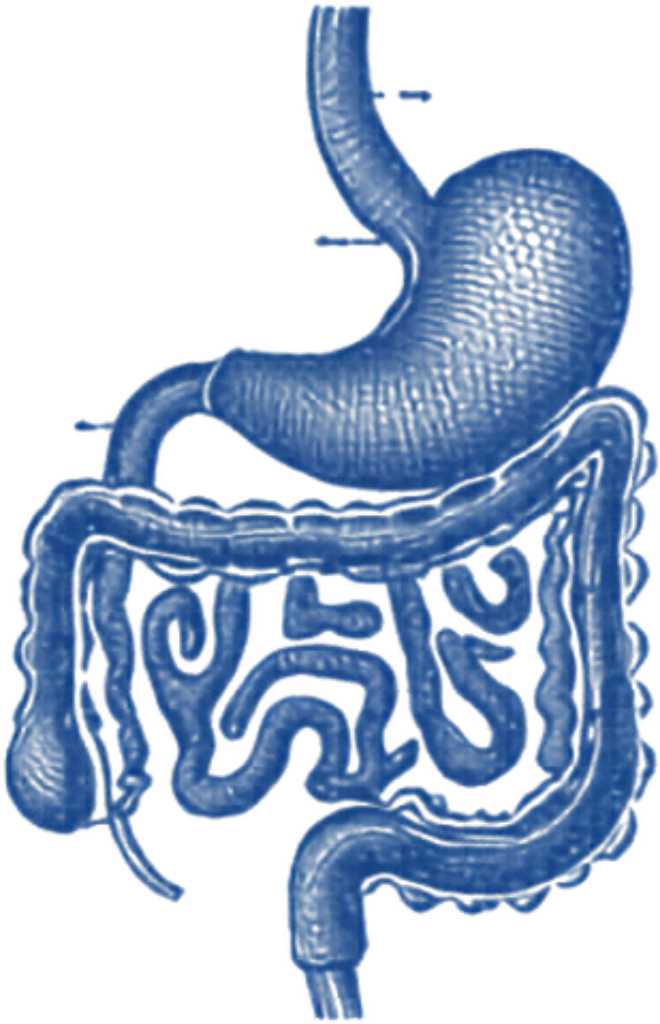
Physiology



Second Year Students
UJ-GIG GI Booklet

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The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Physiology

Introduction to GI physiology

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[Overview]

➔ In this lecture, we will cover:

1) **Introduction to the functions of the GI tract**
2) **Functional structures of the GI tract**
   - Brief review of the anatomy
   - Smooth muscle cells
   - Interstitial cells of Cajal
   - Secretory cells
   - Endocrine cells and hormones
3) **Innervation of the GI tract**
   - The Enteric Nervous System (ENS)
   - The Autonomic Nervous System (ANS)
4) **Blood flow to the GI tract**

[Introduction to the GI tract functions]

Four physiological processes take place along the gastrointestinal (GI) tract:

- **Motility** that propels the food from the mouth to the rectum
- **Secretions** from the alimentary tract and accessory organs that aid in digestion
- **Digesting** food into absorbable materials
- **Absorbing** nutrients from the GI lumen into the bloodstream

These 4 processes are controlled by:

1) **Neural control ➔** the autonomic nervous system supplying the GI tract controls its functions
2) **Hormonal control ➔** many different hormones act on the GI tract and control its function!
3) **Blood flow to the GI tract**

[Functional structures of the GI tract]

➔ Brief review of the anatomy of the GI tract:

The gastrointestinal system consists of:

- **Alimentary tract**: The hollow tube that carries food from the mouth to the anus.

  Starts with the mouth ➡️ esophagus ➡️ stomach ➡️ small intestines ➡️ large intestines ➡️ anus.

- **Accessory organs**: salivary glands, spleen, liver, gallbladder & pancreas.

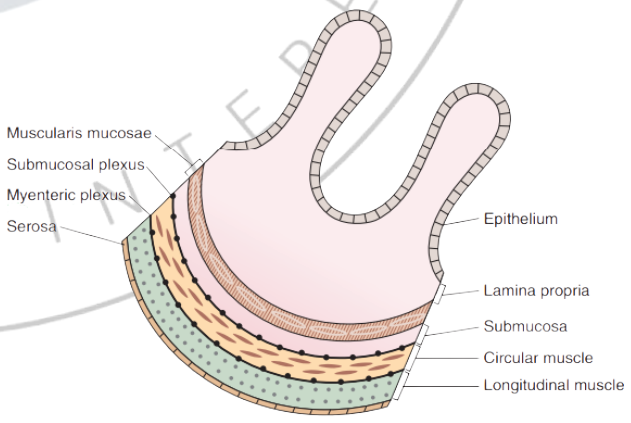
The layers of the GI tract are:

1) **Mucosa**: which consists of:
   - ***epithelial cells*** that are responsible for absorption
   - ***lamina propria*** (connective tissue), which contains blood vessels and lymphatics
   - ***muscularis mucosae***, which consists of contractile cells that change the shape and surface area of the epithelial cells. ➔ This layer is involved in the secretion from tubular glands and movement of mucosal folds.

2) **Submucosa**: connective tissue layer that contains collagen, elastin, blood vessels, and glands.

3) **Smooth muscle layers**: smooth muscle cells which allow for motility in the GI tract through contraction & relaxation. **It is made of 2 layers:**
   1- **Inner thick, *circular* layer**
   2- **Outer thin *longitudinal* layer**

4) **Serosa**: outermost layer of the GI tract, made of **mesothelium and connective tissue**, that reduces friction between organs. Serosa is present in intraperitoneal segments, while areas without peritoneal covering have **adventitia** instead.

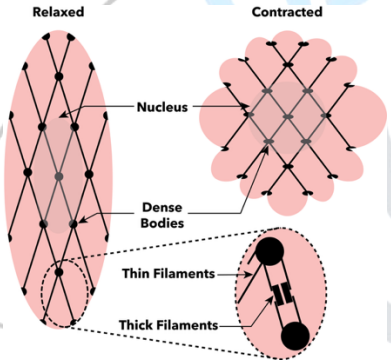


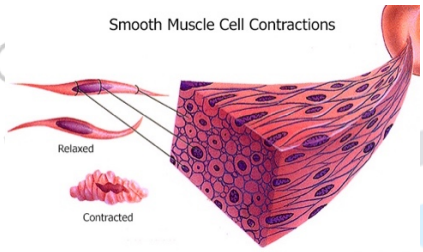
➔ Smooth muscle cells:

This is a special type of muscle cell that has its own characteristics, which may differ from skeletal muscles.

The organization of contractile proteins within the smooth muscle:

- The actin filaments are attached to a dense structure known as **dense bodies**.
- Midway between the dense bodies, a few myosin filaments overlap with actin filaments.



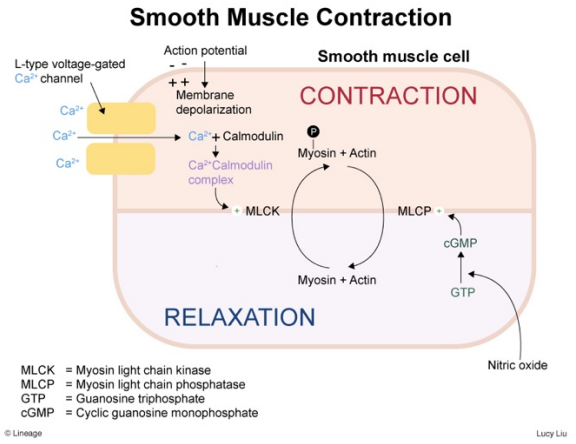


How smooth muscle contraction occurs:

1) Smooth muscle contraction depends on calcium from the sarcoplasmic reticulum **AND** extracellular fluid

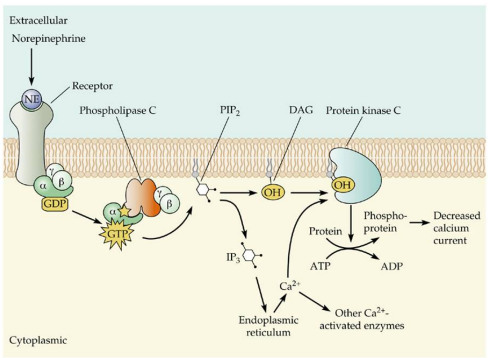
2) Calcium activates **myosin light chain kinase (MLCK)** → phosphorylates myosin → allows interaction with actin → contraction occurs (**notice:** For muscle contraction, the myosin head needs to be activated (phosphorylated) by an enzyme called myosin kinase. Then it can interact with the actin filaments.)

3) Relaxation happens when **myosin phosphatase** dephosphorylates myosin ➔ myosin detaches from actin (**Notice**: Relaxation of the muscle cells requires detachment of the myosin head, which is achieved by an enzyme called myosin phosphatase ➔ dephosphorylates the myosin head)



The role of Calcium in smooth muscle contraction

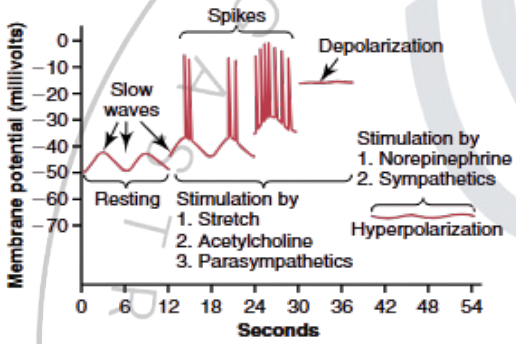
- **Calcium** is the main modulator of muscle contraction in the GI tract.
  1) A ligand (e.g., neurotransmitter or hormone) binds a **Gq-coupled receptor** on the smooth muscle cell.
  2) This activates **phospholipase C (PLC).**
  3) PLC cleaves a membrane phospholipid (PIP_2) ➔ into **IP_3 and DAG.**
  4) IP_3 travels to the sarcoplasmic reticulum and opens Ca^{2+} channels ➔ ↑ intracellular calcium.
  5) The released Ca^{2+} binds calmodulin ➔ activates MLCK ➔ myosin phosphorylation ➔ contraction.



Electrical activity of smooth muscle cells:

The smooth muscle cells of the gastrointestinal tract have two main forms of electrical activity:

1) **Slow waves**: baseline, rhythmic, almost continual slow intrinsic activity of the muscle cells, mediated by Na^+ channels. They're **not** true action potentials.
   The stomach has the lowest rate (3 waves/minute, while the duodenum has the highest (12 waves/minute).
2) **Spikes**: asre bursts of true action potentials (AP) that occur suddenly on top of the slow waves when the membrane's potential reaches higher than -40 mV. Mediated by Ca^{2+} channels.



- The *more positive* the membrane potential is (> -40 mV), the *more frequent* the spikes are.
- Increasing membrane potential (less negative) is referred to as depolarization, and it's stimulated by **stretching** of the muscle, **Acetylcholine** (parasympathetic system), and several **hormones**.
- Decreasing membrane potential (more negative) is referred to as hyperpolarization, and the **sympathetic** system stimulates it.

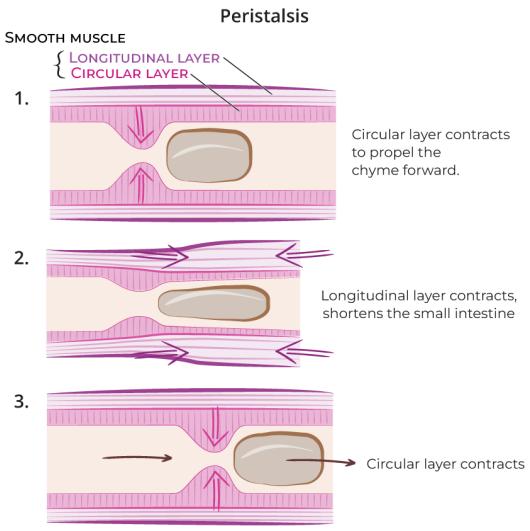
Nerve Action potential	Gastrointestinal Action Potential
Fast	Slower than nerve AP
Main ion is **sodium** (Na^+) – rapid channels	Main ion is **calcium** (Ca^{2+}) – slower channels

Tonic contractions of the gastrointestinal smooth muscle

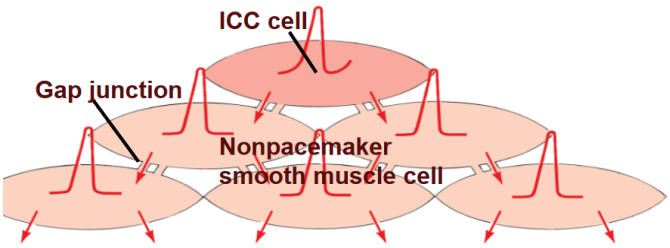
- Tonic contractions are **continuous contractions** that are not associated with the slow waves and can last up to several minutes or hours.
- They can be caused by:
  1) Repetitive spike potentials
  2) Hormones
  3) Continuous entry of Ca^{2+} that is not associated with changes in membrane potential.

The GI tract contains two muscular layers formed by smooth muscle cells, and they carry the motile function of the tract (called: Peristalsis):

1) **Circular layer**: inner layer (closer to the lumen). This layer is thick and highly innervated. Contraction of its cells leads to a decrease in the diameter of the GI tract.
2) **Longitudinal layer**: outer layer. This layer is thin and less innervated. Contraction of its cells leads to shortening of the GI tract



- The cells of these layers are arranged in bundles, and they're connected by many **gap junctions** that **allow easy and fast transmission of ions,** and, therefore, the cells act as one unit simultaneously. This is referred to as **"syncytium"**; when an electrical activity is initiated anywhere in the muscle mass, it travels in all directions in the muscle ➔



➔ The Interstitial Cells of Cajal (ICC):

A specialized type of cell that is interspersed between the smooth muscle cells in the GI tract. They have multiple characteristics:

- They have many **processes** that are connected by **gap junctions**. Through these processes, they communicate with each other and with smooth muscle cells.
- They undergo cyclic changes in membrane potential because they have special ion channels that open intermittently and generate an inward current. Hence, they're considered **pacemakers**.

These characteristics are believed to cause the slow waves in smooth muscle cells.

- They receive input from the **enteric nervous system** (autonomic nervous system of the GI tract), which contributes to mediating the activity of smooth muscle cells.

➔ Endocrine Cells and Hormones:

The functional processes in the GI tract are controlled by various hormones **secreted by the tract itself or the accessory organs**. This is a brief introduction, and they'll be discussed in more detail later, inshallah.

Hormone	Site of secretion	Stimuli	Function
Gastrin	**G cells** of antrum, duodenum, and jejunum	Protein, distention, nerve	Stimulates gastric acid secretion & mucosal growth
Cholecystokinin (The prefix: ***cholecys-*** usually refers to the gallbladder, which might help in remembering this hormone's function)	**I cells** of duodenum, jejunum, and ileum	Protein, fat, acid	Stimulates pancreatic enzymes & $HCO3^-$ secretion, gallbladder contraction, and exocrine pancreas growth
Secretin	**S cells** of duodenum, jejunum, and ileum	Fat, acid	Stimulates pepsin secretion, pancreatic & biliary $HCO3^-$ secretion, growth of exocrine pancreas
Gastric inhibitory peptide	**K cells** of duodenum and jejunum	Protein, fat, carbs	Stimulates insulin release & inhibits gastric acid secretion
Motilin	**M cells** of the duodenum and jejunum	Fat, acid, nerve	Stimulates gastric and intestinal motility

➔ Secretory cells:

These are specialized cells that line the digestive tract and secrete functional substances such as enzymes, hormones, factors, or mucus. Sometimes, they only secrete water and electrolytes (*serous secretion*).

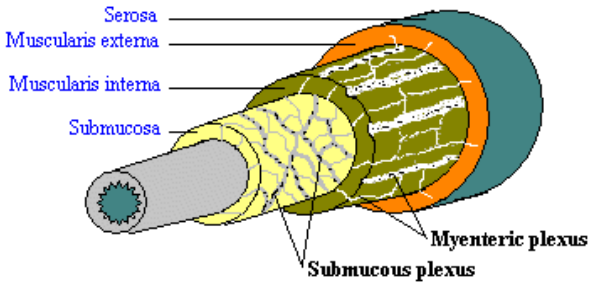
They can be:
1) Solitary (single cells)
2) Grouped as **Glands**

[Innervation of the GI tract]

➔ The Enteric Nervous System (ENS):

The gastrointestinal tract has its own specialized nervous system that controls movements and secretions along the tract. It's mainly divided into two sets of plexuses:
1. **Submucosal (Meissner's)**
2. **Myenteric (Auerbach's)**

Submucosal	Myenteric
Inner, Located between the submucosa and the circular muscle layer	**Outer**, Located between the circular and longitudinal muscle layers
Controls secretions, absorption, and blood flow	Controls movement along the GI tract



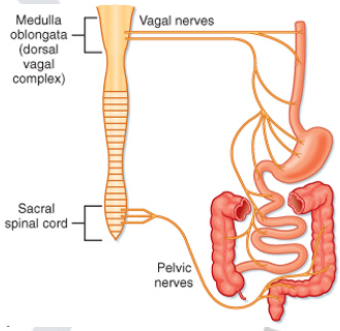
Other nerve fibers:
- Sympathetic and parasympathetic fibers also connect to these plexuses and activate or inhibit their function.
- Sensory nerve endings in the gut epithelium send signals to the enteric plexus, sympathetic nerves, the spinal cord, and the vagus nerve (nerve that provides parasympathetic supply to most of GI system)
1) Stimulated by irritation, distention, or specific chemical substances.
2) Their main function is to elicit local reflexes within the gut wall.

➔ Autonomic control of the GI tract:

[Parasympathetic system]

Source:
Preganglionic fibers come from 2 different CNS sources:
1) **Cranial division** (**the vagus nerve**)
   - supplies the esophagus, stomach, pancreas, small intestines, and the first half of the large intestines.
2) **Sacral division (pelvic nerves)**
   - supplies the second half of the large intestines all the way to the anus.

Postganglionic fibers ➔ in myenteric and submucosal plexuses.

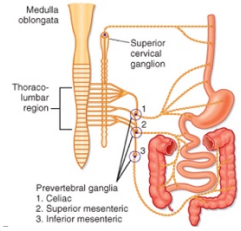


Neurotransmitter: Acetylcholine (ACh)

Function: Stimulation of the parasympathetic fibers causes an **increase in the activity of the ENS** and gastrointestinal functions e.g. secretion, motility etc.. (**remember** it's the **"rest & digest"** system).

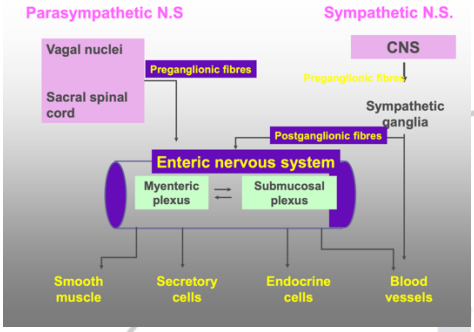
[Sympathetic system]

Source:
Preganglionic fibers ➔ segments T5-L2 in the spinal cord
Postganglionic fibers ➔ from the sympathetic chain (prevertebral ganglia) to the myenteric and submucosal plexuses



Neurotransmitter: Norepinephrine

Function: **Inhibit the activity of the GI tract** through direct inhibition of the smooth muscle cells or inhibition of the ENS.



[Gastrointestinal blood flow and splanchnic circulation]

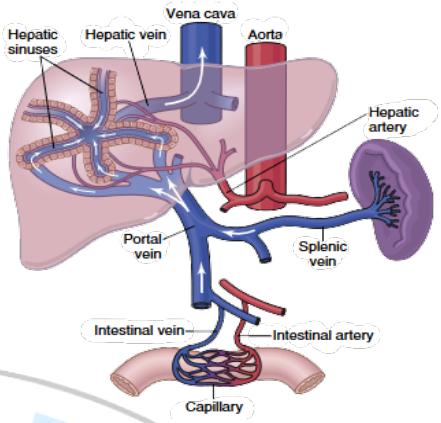
Splanchnic circulation = the extensive network of blood vessels that supply the gut, as well as the spleen, pancreas, and liver.

It's organized in a way that **all the blood from these organs eventually passes through the liver** via the **portal vein** ➔ then it leaves the liver through the hepatic vein and enters the inferior vena cava, where it enters systemic circulation.

The purpose of passing through the liver is:

1) Filter the blood from any bacteria or metabolic byproducts that might enter the bloodstream from the GI tract.
2) Temporarily store nonfat water-soluble nutrients like carbs and proteins.
3) Processing of most nutrients occurs in the liver.
4) Detoxification of any toxins that might enter the body from the GI tract

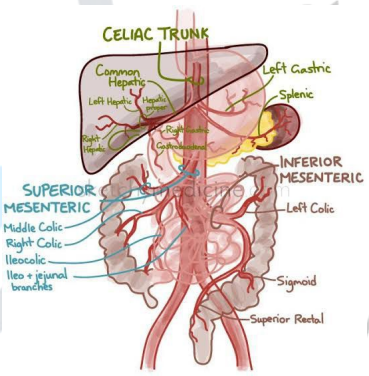
[VERY IMPORTANT NOTE: Fats bypass the liver and are absorbed into the lymphatics of the GI tract and reach the systemic circulation via the **thoracic duct** (we will talk about this more in later lectures)**]**



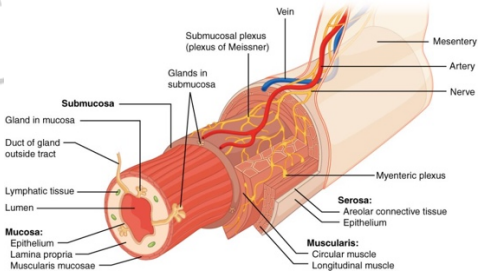
➔ Anatomy of the GI blood supply:

The gastrointestinal system organs are supplied by three main arteries:

1) **Celiac artery** ➔ supplies the lower third of the esophagus and the stomach
2) **Superior mesenteric artery** ➔ supplies the small intestines, and the large intestines up to the proximal two-thirds of the transverse colon.
3) **Inferior mesenteric artery** ➔ supplies the rest of the tract.



The blood vessels enter the GI tract wall from the site of attachment to the mesentery, and they branch into smaller arteries that reach the villi and the submucosa of the tract wall, where they contribute to the secretory and absorptive function of the gut.



➔ Regulation of gastrointestinal blood flow:

The blood flow to the gut is very well related to local activities ➔ After meal the increase in absorption, secretion and motor activities is accompanied by an increase in blood flow ➔ This increase continues during the next few hours after meal and return back over the next 2-4 hours.

Metabolites

1) Multiple vasoactive substances are released during the digestive process ➔ cholecystokinin, vasoactive intestinal peptide (VIP), gastrin, and secretin.
2) The GI glands release **kinins** (kallidin and bradykinin), which are **vasodilators**.
3) Low oxygen caused by increased metabolic activity stimulates the release of adenosine, another vasodilator.

Nervous control of blood flow

1) **Parasympathetic input:** increased blood flow ➔ an **indirect** effect through increasing glandular activity, which in turn increases blood flow.
2) **Sympathetic input:** decreased blood flow ➔ a **direct** effect through strong vasoconstriction of the arterioles along the entire tract.

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Gastrointestinal Motility

Written by: Rawan Fratekh

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[Overview]

➔ **In this lecture, we will cover:**

1) **Functional types of movements in the GI tract**
   a) Peristalsis
   b) Mixing movements
2) **Ingestion of food**
   a) Mastication
   b) Swallowing
3) **Motor functions of the stomach**
   a) Storage
   b) Mixing and propulsion of food
   c) Stomach emptying
   d) Regulation of stomach emptying
4) **Movements of the small intestines**
   a) Mixing contractions
   b) Propulsive movements
   c) Other movements
5) **Movements of the colon**
   a) Mixing contractions
   b) Propulsive movements
   c) Defecation

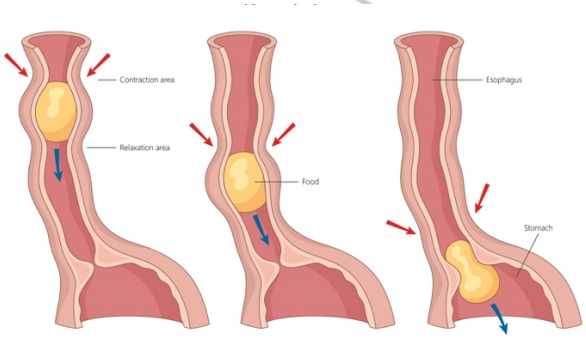
[Functional types of movement in the GI Tract]

➔ Peristalsis:

Peristalsis is a property of most smooth muscle tubes, manifesting as a contractile ring that appears around the gut and then moves forward ➔ **Goal:** to push food forward down the GI tract

- Main stimulus (trigger) is **distention** of the GI tract by food. But it can also occur due to **chemical or physical irritations** (e.g. infection) of the epithelial lining of the gut or **parasympathetic** stimulation.

(**Remember:** peristalsis is mediated by the myenteric (Auerbach's) plexus)

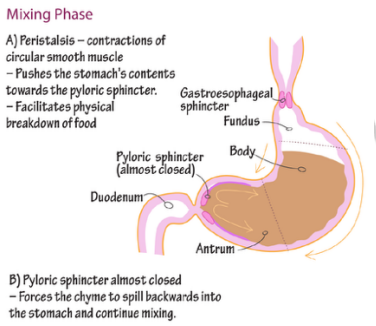


➔ Mixing movements:

The purpose of **Mixing Movements** is to mix the gut content of food with its secretions to aid in the digestion and absorption of nutrients. **It can occur in two ways:**

1) Peristalsis can lead to mixing ➔ **How?** if the intestinal content is blocked by a sphincter that prevents its forward movement (peristalsis normally pushes content forward, but when movement is blocked by a sphincter, the wave forces contents back and forth → resulting in mixing with digestive secretions instead of movement)

Example



2) Local constrictive movements that chop and turn the gut content around.

[Food journey inside the GI tract]

➔ **Food progresses through the GI tract via coordinated motility patterns that ensure digestion الهضم and absorption الامتصاص:**

#1 Ingestion (Mastication & Swallowing): Food is mechanically broken down by chewing and mixed with saliva, then propelled from the mouth ➔ pharynx ➔ esophagus via swallowing.

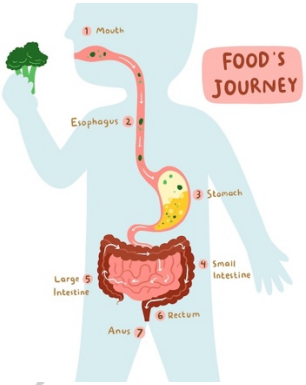
#2 Esophagus: Peristalsis moves the food into the stomach.

#3 Stomach: Stores and mixes food with gastric secretions, forming **chyme**, and gradually empties it into the small intestine.

#4 Small Intestine: Combines **mixing** and **peristalsis** to allow digestion and nutrient absorption.

#5 Colon: Absorbs water and electrolytes, leading to formation of **feces** البراز

#5 Defecation: Coordinated reflex leads to elimination of waste.



[Ingestion of food]

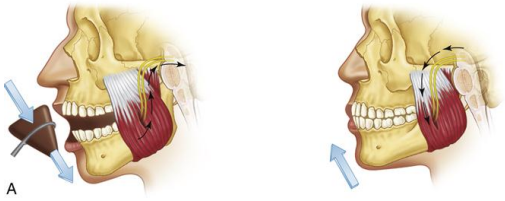
➔ Mastication (Chewing):

Mastication = the grinding (breakdown) of food into smaller particles by the action of teeth ➔ **Why is this important?** To breakdown food into smaller pieces that are easier to digest and absorb by the small intestine (smaller particles = more surface area for enzymes to work on = better digestion)

- It's controlled by the **brainstem**. Chewing jaw muscles are innervated by the **fifth (trigeminal) cranial nerve**.

- Stimuli include **taste and smell**, which send signals to the brain cortex and amygdala (structures found in the brain) to initiate the mastication process.

- **The chewing reflex:**
  - Initiated by **the presence of a food bolus** in the mouth.
  - This leads to inhibition of the jaw muscles and a drop of the lower jaw.
  - This drop initiates the stretch reflex, which leads to a **rebound contraction**.
  - This leads to pressing of the bolus against the lining of the mouth, which inhibits the jaw muscles, again causing the jaw to drop and repeat the cycle.



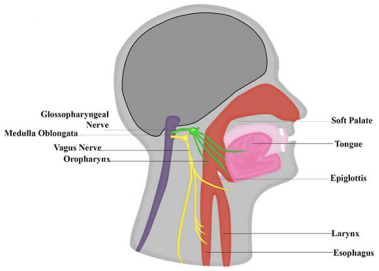
➔ Swallowing:

Swallowing البلع = a complex mechanism that starts at the **pharynx** and ends in the **esophagus**. It aims to propel (push) food from the mouth to the stomach without compromising the airways.

It's divided into 3 stages:

1) **Oral stage** – voluntary
2) **Pharyngeal stage** – involuntary (reflex)
3) **Esophageal stage** – involuntary (reflex)

- The reflex portion is mediated by the **swallowing center in the medulla** (part of the brainstem) ➔ The **Vagus** (cranial nerve X) and **Glossopharyngeal nerves** (cranial nerve IX) carry sensory information from the mouth to the brain to initiate the reflex



Important idea to understand:

- Voluntary: Movements under conscious control (you decide to start/stop them) ➔ Example: mastication (chewing), initiation of swallowing.

- Involuntary: Movements that occur automatically without conscious control, regulated by the autonomic nervous system and enteric nervous system ➔ Example: peristalsis, gastric mixing, intestinal segmentation, most of swallowing after initiation.

Oral (voluntary) stage

After chewing, when the food is ready to be swallowed, the tongue pushes the food bolus **upwards and backwards** against the palate, moving the food to the pharynx.

Pharyngeal (involuntary) stage

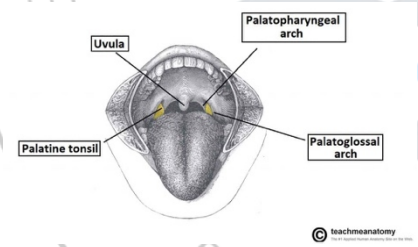
Sensory stimulus: the food bolus stimulates the epithelial swallowing receptors at the opening of the pharynx ➔ impulses are transmitted via the **vagus and glossopharyngeal nerves** to the swallowing center (found in the medulla)

Motor response: they're carried from the swallowing center to the pharynx and esophagus via the **fifth, ninth, tenth, and twelfth** cranial nerves.

Process:

1) The **soft palate** is pulled **upward** to *prevent food from entering the nasal cavity*.

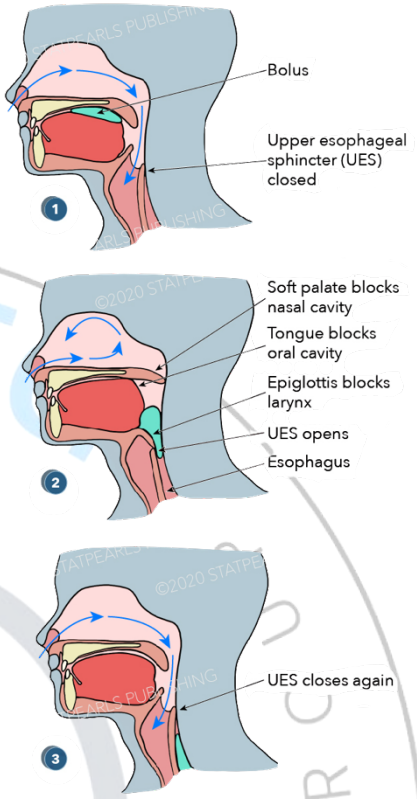
2) The **palatopharyngeal folds** are pulled **medially**, which forms a narrow passage that *prevents food that was chewed inadequately from passing to the esophagus*.



3) The **vocal cords** are approximated **medially**, and the **larynx** is pulled **upwards and anteriorly**, leading to swinging of the epiglottis over the opening of the larynx. This *prevents food from passing into the airways*. It also enlarges the opening of the esophagus. ➔

4) The **upper esophageal sphincter** (pharyngoesophageal sphincter) **relaxes**.

5) Then, the **muscles of the pharynx contract** and initiate the peristaltic movement that pushes food into the esophagus,



End result: food passes from mouth ➔ pharynx ➔ esophagus WITHOUT entering the airway

- **NOTICE: In this stage respiration is interrupted** due to CLOSURE of the epiglottis & vocal cords

Esophageal (involuntary) stage

Propulsion (movement) of food along the esophagus to reach the stomach ➔ **carried by two types of contractions:**

1) **Primary peristalsis**: considered a continuation of the peristaltic wave that began in the pharynx. It spreads to the esophagus and reaches the stomach within seconds.
2) **Secondary peristalsis**: represented by intrinsic (within myenteric plexus) and extrinsic (through afferent and efferent vagus fibers) reflexes promoted by the distension of the esophagus by the retained food in esophagus **or** when the primary reflex fails to move bolus of food along esophagus.

Very important idea:

- The **upper third** of the esophagus is formed by **striated muscle**, and it's controlled by **the glossopharyngeal and vagus nerves**.
- **The lower two-thirds** are formed by **smooth muscle** that is innervated by **the vagus nerve ONLY** (no glossopharyngeal nerve).

Receptive relaxation of the gastroesophageal sphincter (GES) and the stomach

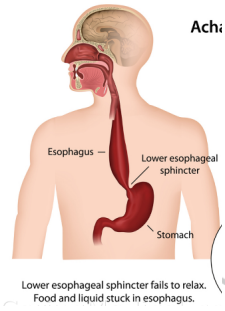
The **lower esophageal (gastroesophageal) sphincter** is tonically constricted under normal restingconditions. As a wave of peristalsis approaches, it begins to relax to allow passage of the swallowed food into the stomach. Similar changes happen in the stomach to prepare it to accommodate the food.

Reflux of stomach contents back into the esophagus can be prevented by two mechanisms:

1) The **tonic contraction** of the lower esophageal sphincter.
2) Formation of a **valve-like structure** because the esophagus extends slightly into the stomach.

Nice note:

- Failure of the Gastro-esophageal sphincter to relax causes a condition called **Achalasia** (so food becomes stuck in the esophagus and can't move to the stomach)



Lower esophageal sphincter fails to relax. Food and liquid stuck in esophagus.

- **Gastroesophageal Reflux Disease (GERD)** is a condition where stomach acid refluxes into the esophagus, causing symptoms like **heartburn** حرقة due to failure of normal anti-reflux mechanisms. This is mainly due to **inappropriate relaxation of the lower esophageal sphincter (LES),** which normally stays contracted to prevent backflow.

[Motor functions of the stomach]

The stomach has three major functions:

1) **Storage** of food **(MOST IMPORTANT FUNCTION)**
2) **Mixing** food into a mixture called **Chyme** (semi-liquid mixture of ingested food and gastric secretions formed in the stomach, which is gradually released into the small intestine for further digestion and absorption)
3) **Slow emptying** of the chyme into the small intestines.

➔ Storage function of the stomach:

As more food enters the stomach, stretching of its wall elicits a **vasovagal reflex** to the brainstem and back to the stomach that relaxes the wall muscles, increasing its capacity from 50 ml to approximately 1.8L, allowing it to accommodate greater quantities of food (**means**: vagus nerve senses the stretch ➔ vagus nerve gives motor supply to stomach and causes relaxation)

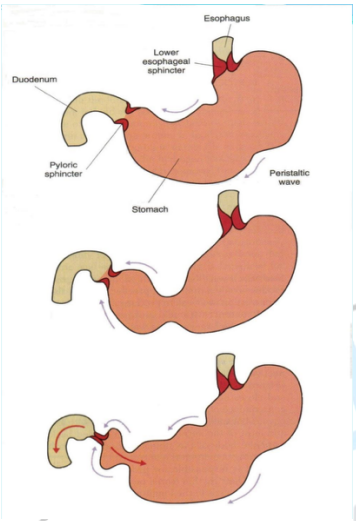
➔ Mixing and propulsion of food in the stomach:

The digestive juices of the stomach are secreted by the gastric glands, which are present throughout most of the stomach lining. As they mix with the food, they form a mixture called **Chyme** (a semi-fluid pasty mixture of ingested food and gastric secretions formed in the stomach. Its fluidity depends on the amount of food, water, and stomach secretions.)

If there's food in the stomach, low-level, slow constrictor waves occur, called **mixing waves**➔
These waves have several characteristics:

1) They begin in the mid-upper portion of the stomach and move distally towards the antrum (the most distal part of the stomach).
2) They're initiated by the gut wall's **basic electrical rhythm [BER - slow waves** (we discussed this in a previous lecture)
3) Their **intensity increases** as they approach the antrum.
4) As the peristaltic waves approach the **pylorus** (the junction between the stomach and small intestine), it contracts further, preventing emptying of the stomach. This leads to a backwards squeezing which causes food to move backward into the stomach action called **retropulsion**. This is

extremely important for the mixing of food in the stomach.



Note:

- **Propulsion =** Forward movement of chyme toward the pylorus, driven by strong peristaltic contractions of the stomach.

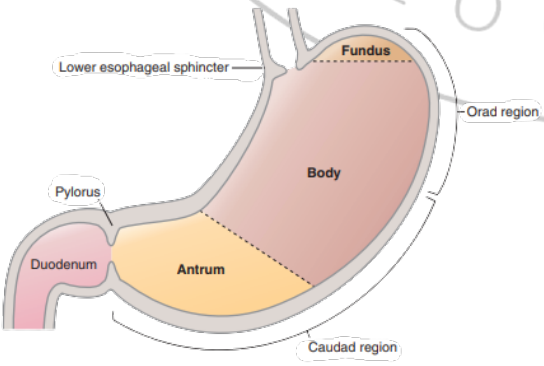
- **Retropulsion =** Backward movement of chyme when the pylorus is closed, mixing and breaking food into smaller particles for digestion.

Hunger Contractions ➔ This is a type of contraction that occurs when the stomach has been empty for several hours.

- These are considered strong, peristaltic contractions that occur in the body of the stomach.
- They often fuse to cause a continuous contraction that can last up to 2-3 minutes
- They're more intense in **young individuals** and **states of low blood sugar**.

- **ملاحظة لطيفة:**

تقلصات الجوع هي الإحساس اللي بتحسه بالمعدة لما تكون فاضية، زي القرقرة أو الخبطات الخفيفة.



➔ Stomach emptying:

The main driver for stomach emptying is **intense peristaltic contractions at the antrum**.

These contractions must overcome the tone of the pylorus (the contraction of the pylorus) ➔ The pylorus is the distal opening of the stomach, and, under normal conditions, it remains contracted, hence it's called the **pyloric sphincter**.

Emptying occurs in two ways:

1) Slow, minimal passage of fluids through the slight opening of the pylorus.
2) Intense contractions that overcome the tone of the pylorus and allow passage of several milliliters of chyme (~20% of the time). This is referred to as the **pyloric pump**.

➔ Regulation of stomach emptying

Multiple factors regulate stomach emptying to ensure it occurs at the rate at which the chyme can be absorbed effectively by the small intestines (we don't want large amounts to enter the intestine at the same time)

Gastric factors that promote gastric emptying

1) **Food volume**
   - **Effect:** increases emptying.
   - **Mechanism:** wall stretching elicits a local myenteric reflex that enhances the activity of the pyloric pump and inhibits the pylorus (so it is relaxed and allows emptying of food from the stomach to the intestine)

2) **Gastrin** (a hormone secreted by the stomach)
   - **Effect:** increases emptying.
   - **Mechanism:** stimulates the motor function in the body of the stomach and enhances the activity of the pyloric pump.

Duodenal factors that inhibit gastric emptying

1) **Enterogastric nervous reflexes:** a feedback mechanism where the small intestine signals the stomach to slow down its emptying when it's full or processing food, helping prevent overload and allowing proper digestion.

- **Triggers**: small intestine ➔ distention of the duodenum, chemical irritation, acidity of the chyme, and products of protein breakdown.

- **Effect:** decrease emptying

- **Mechanism:** inhibit the pyloric pump and increase the tone of the pylorus
  - Through the Enteric nervous system
  - Through prevertebral sympathetic ganglia (**remember**: the sympathetic system inhibits GI motility)
  - Through the vagus nerve, where it exhibits inhibitory signals

2) **Hormonal feedback**

- **Hormones**:
  - **Cholecystokinin:** hormone released in response to fat (slows gastric emptying because it signals that fat and protein are present in the small intestine, allowing more time for digestion and nutrient absorption)
  - **Secretin:** hormone released in response to acid (slows gastric emptying because it indicates acidic chyme has entered the duodenum, giving the intestine time to neutralize acid and protect its lining)
  - **Gastric inhibitory peptide GIP:** released in response to fat and carbs

- **Effect:** decreased emptying
- **Mechanism:** inhibit gastric motility

Note: The passage of chyme to the duodenum causes decrease pH (in duodenum) ➔ This initiates neural and hormonal reflexes to decrease gastric emptying

[Movements of the small intestines]

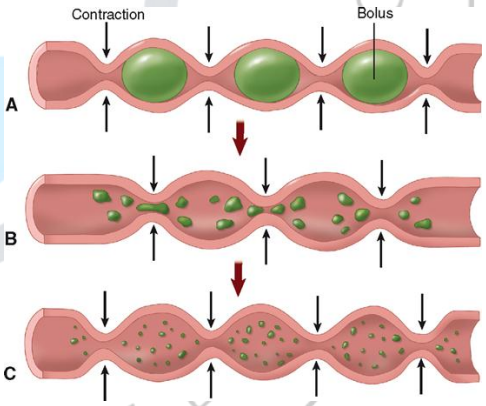
The intestine has 2 types of movement (similar to the general movements in the gastrointestinal tract):

1) **Mixing (segmentation) contractions**: mixing food particles with GI secretions
2) **Propulsive movement:** moves chyme forward at an appropriate rate.

➔ Mixing (segmentation) contractions:

The distention caused by the chyme as it enters the duodenum elicits localized **concentric** contractions along the tract.

- As one set of contractions (segments) relaxes, a new set appears at points between the previous contractions. This leads to effective chopping and mixing of the chyme with the secretions.
- The frequency of these contractions is determined by the **basic electrical rhythm (slow waves)**, The maximum frequency of contractions is about **12/minute in the upper part of intestine (duodenum and jejunum)** and **8/minute in the terminal ileum**
- The contractions caused by the slow waves alone are usually insufficient; they're typically enhanced by input from the Enteric Nervous System.
  - The medication "**Atropine**" which is a **muscarinic receptor antagonist** (blocks muscarinic acetylcholine receptors) blocks the ENS fibers, significantly weakening the contractions of the intestines.



➔ Propulsive movements:

Chyme is propelled through the small intestines by peristaltic waves. The rate of contractions is highest in the proximal intestines, and it slows down moving analwards (towards the anal canal).

- Distention of the gut wall elicits a reflex that causes contraction proximal to the distention and relaxation distal to it **(receptive relaxation)**

- The peristaltic reflex utilizes both muscles of the gut wall. The circular muscle forms the contractile ring, and with the elongation and shortening of the longitudinal muscle, it pushes the chyme forward. These successive changes are known as **"Law of the Gut."**

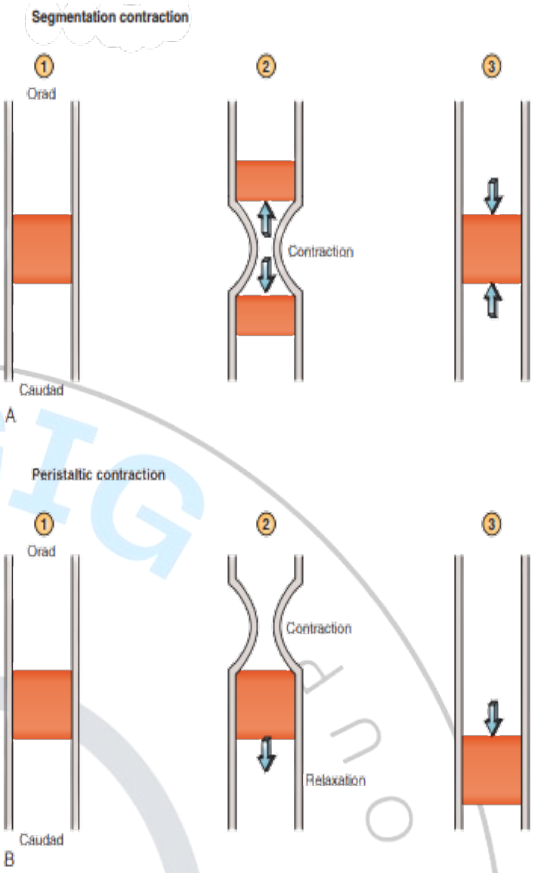
Role of the ENS in peristalsis ➔ The fibers of the ENS are organized in such a way that proximal (Orad – towards the mouth) fibers are excitatory, and distal (caudad – towards the anus) fibers are inhibitory ➔ This organization of the network plays a huge role in the peristaltic reflex

(**Note:** Congenital absence or decrease in the activity of the ENS leads to ineffective peristalsis.)

Control of peristalsis in the small intestines:
MANY factors affect peristalsis in the small intestine (either inhibit it or activate it)

1) **Wall stretch** (distention of the wall by the food induces a contractile ring above the distended part and relaxation of the part of the GI tube down to the distention leading to food movement forward)
2) **Gastroenteric reflex ➔** distention of the stomach leads to activation of peristalsis in the intestine
3) **Autonomic nervous system ➔** parasympathetic system activates peristalsis and sympathetic system inhibits it
4) **Hormones**:
   - **Gastrin, CCK, insulin, motilin, and serotonin enhance** intestinal motility
   - **Secretin and glucagon inhibit** intestinal motility.

- After the chyme reaches the **ileocecal valve** (the junction between the ileum which is the last part of the small intestine and the cecum which is the forst part of the colon) ➔ it stays there until the person has the next meal, which initiates another reflex (the **gastroileal reflex**) that intensifies peristalsis and pushes the remaining chyme across the valve.



➔ Other types of contractions that occur in the intestines:

Peristaltic rush ➔ This concept refers to strong and rapid peristalsis that is initiated by the ANS, ENS, and the brainstem in **response to intense irritation** of the intestinal wall, such as in cases of infectious diarrhea.
These waves sweep the small intestines and move the irritative material to the colon.

Migrating motor complexes ➔This is a type of motor activity that starts in the stomach and travels down to the intestines. It is believed to be controlled by **Motilin** (hormone produced in the small intestine during fasting). Contractions occur at 3 phases:

1) Phase 1 ➔ Slow waves (basic electrical activity) without contractions
2) Phase 2 ➔ Some slow waves are followed by contractions
3) Phase 3 ➔ All slow waves are followed by contractions

- These movements sweep the intestinal content between meals.

Movements caused by the muscularis mucosa
➔ The contractions of the muscularis mucosa result in lengthening and shortening of the mucosal folds, which affects the absorptive function of the gut wall.

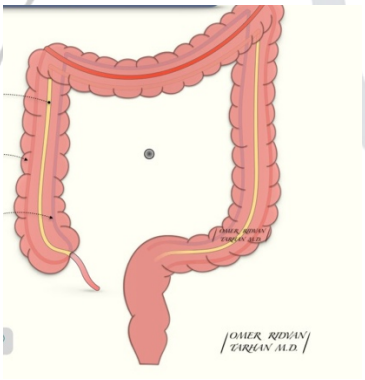
[Movements of the colon]

The main functions of the colon are:

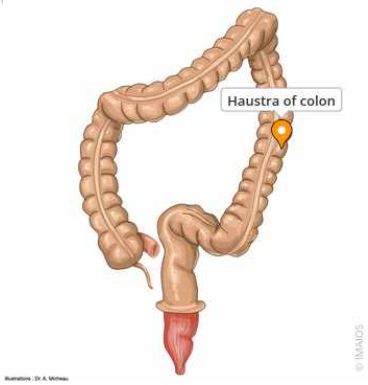
1) Absorption of water and electrolytes [proximal half of the colon]
2) Storage of fecal matter until it can be expelled [distal half of the colon]

➔ Mixing movements (Haustrations):

In the colon, the longitudinal muscle aggregates into three strips called "**Tenia coli**."



Contractions of the Tenia coli, combined with the intermittent constrictions of the circular muscle, lead to the formation of **Haustrations**, which are small bag-like bulges in the unstimulated area of the colon.



These contractions last 30-60 seconds and mainly move colonic content into the transverse colon. They:

1) **aid in the absorption of water and electrolytes** by spreading the colonic material along the surface of the colon.
2) **provide minimal forward propulsion** of the colonic content.

➔ Propulsive movements (mass movement):

These movements occur **one to three times daily**, mostly in the first hour after breakfast.
It's considered a modified type of peristalsis that occurs in the following sequence:

1) **Formation of a constriction ring** in response to distention or irritation of the colonic wall
2) A **segment of the colon distal to the constriction ring loses its haustrations** and contracts as one unit, propelling the fecal material forward *en masse* (as a block).

- Each contraction lasts for 30 seconds, followed by 2-3 minutes of relaxation, and then another contraction wave begins.

- These contractions are initiated by the **Gastrocolic** (Stretching of the stomach after eating stimulates colonic motility, creating the urge to defecate) **and Duodenocolic reflexes** (Presence of chyme in the duodenum increases colonic activity, helping move contents toward the rectum)

- Irritation to the colonic wall can initiate intense mass movements, as in a person with **Ulcerative colitis**, a condition that causes inflammation in the colon wall.

➔ Defecation:

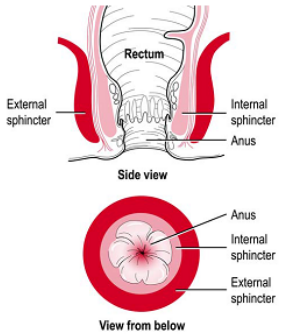
The rectum is usually empty of feces and has high resistance because:

1) It has a weak functional sphincter located at the junction of the sigmoid and rectum.
2) There's a sharp angulation between the sigmoid and the rectum, which provides additional resistance.

When mass movements force fecal matter into the rectum, desire for defection occurs, leading to **contraction of the rectum** and **relaxation of the anal sphincters**.

Continual dribbling of fecal matter through the anus is prevented in two ways:

1) Tonic contraction of the internal anal sphincter – **involuntary**.
2) Contraction of the external anal sphincter – **voluntary**



Defecation reflexes (BOTH ARE INVOLUNTARY)

The **intrinsic defecation** reflex: By the ENS. It's a weak reflex, fortified by the parasympathetic reflex.

- Stimulus: **distention** of the rectal wall when the feces enter the rectum.
- **Afferent (sensory) arm:** sensory fibers in the myenteric plexus
- **Center:** myenteric plexus
- **Efferent (motor) arm:** motor signals to smooth muscle cells
- **Response: peristaltic waves** forcing feces towards the rectum & **relaxation** of the internal anal sphincter

The **parasympathetic defecation** reflex

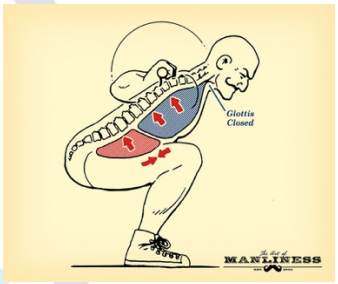
- **Stimulus: distention** of the rectal wall when the feces enter the rectum.
- **Afferent (sensory) arm**: stretch receptors in the rectal wall
- **Center**: **S2-S4** spinal cord segments
- **Efferent (motor) arm**: pelvic parasympathetic nerves
- **Response**: **peristaltic waves** forcing feces towards the rectum & **relaxation** of the internal anal sphincter

After all these reflexes, the defecation in normal people occurs only as a voluntary act by relaxing external sphincter (which is under voluntary control) and increasing abdominal pressure by closure of glottis and contractions of the abdominal wall which cause the pelvic floor to be pulled downward on the anal ring and relax to evacuate feces.

SO ➔ Defecation occurs when 3 things combine:

1) Combination of intrinsic and parasympathetic defecation reflexes

2) At convenience – Valsalva maneuver
- Closure of glottis
- Deep inspiration
- Abdominal contraction



3) Inhibition of the external anal sphincter **voluntarily** via the **pudendal nerve.**

REFLEXES SUMMARY

Reflex	Stimuli	Afferent	Center	Efferent	Response
Chewing reflex	Presence of a food bolus in the mouth				Inhibition of the jaw muscles allows it to drop. This activates the stretch reflex, which causes a rebound contraction.
Swallowing reflex	As the food enters the posterior mouth	Vagus and glossopharyngeal nerves	The swallowing center in the medulla	The fifth, ninth, tenth, and twelfth cranial nerves	Repositioning of the soft palate, palatopharyngeal folds, and vocal cords. Constriction of the pharyngeal muscles and relaxation of the esophageal sphincter
Enterogastric reflex	Duodenal distention, chemical irritation	ENS, prevertebral sympathetic ganglia, vagus nerve	Brainstem		Decrease the emptying of the stomach by inhibiting the excitatory signals sent to the stomach
Gastroenteric reflex	Distention of the stomach	Myenteric plexus			Increases peristaltic activity in the small intestines
Gastroileal reflex	Eating another meal				Intensifies peristalsis in the ileum and forces chyme across the ileocecal valve
Gastrocolic and Duodenocolic	Distention of the stomach and duodenum	ANS			Initiate mass movement in the colon
Intrinsic defecation reflex	Distention of the rectal wall	Myenteric plexus	Myenteric plexus	Myenteric plexus	Peristaltic waves force feces towards the rectum & relaxation of the internal anal sphincter
Parasympathetic defecation reflex		Stretch receptors in the rectal wall	S2-S4 segments in the spinal cord	ANS and pelvic nerves	

The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Physiology

GI Secretions

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[Overview]

➔ **Outline of GI secretions will be:**

1) General principles of alimentary tract secretion
    a. Basic mechanisms of stimulation of the alimentary tract glands
2) Secretions of salivary glands
    a. Nervous regulation of salivary secretions
    b. Functions of saliva
3) Esophageal secretions
4) Gastric secretions
    a. Characteristics of gastric glands and their functions
    b. Regulation of gastric acid secretion
    c. Regulation of pepsinogen secretion
    d. Phases of gastric secretion
5) Secretions of the small intestines
    a. Secretion of mucus by Brunner's glands in the duodenum
    b. Secretion of intestinal digestive juices by the crypts of Lieberkühn
    c. Regulation of small intestinal secretions
6) Secretions of the large intestines
7) Pancreatic secretions
    a. Pancreatic digestive enzymes
    b. Secretion of bicarbonate ions
    c. Regulation of pancreatic secretions
    d. Phases of pancreatic secretions
8) Secretion of bile by the liver & functions of the biliary tree
    a. Physiological anatomy of biliary secretions
    b. Function of bile salts in fat digestion and absorption

[General principles of alimentary tract secretion]

Secretions along the digestive system appear as a response to the presence of food in the GI tract. The composition of secretions varies according to the type of food, and serves to:

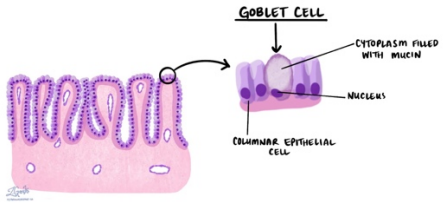
- Digest food.
- Lubricate and protect the mucosa.

The composition of secretion includes:

1) **Organic materials** (e.g. enzymes) ➔ secretory cells synthesize and store them in vesicles and then secreted upon stimulation.
2) **Water and electrolytes** ➔ these are taken from blood vessels and then secreted by secretory cells.

➔ Types of glands in GI tract:

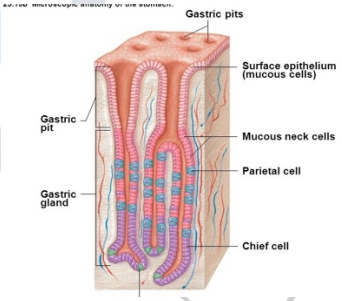
1) Single-cell mucus glands (also called **Goblet cells**) ➔ they mainly respond to irritation of the epithelial lining and secrete mucus that **acts as a lubricant** to the surface of the tract.



Very important note: Goblet cells are found in all GI tract EXCEPT esophagus (no goblet cells are present in the esophagus) ➔ Goblet cells increase as you go distally → few in small intestine → many in colon.

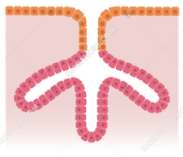
2) Pits ➔ invaginations of the epithelium into the submucosa, there is only 2 examples of this (we will discuss them in detail later):

1- **Gastric pits** in the stomach
2- **Crypts of Lieberkühn** in the small intestine.



3) Complex glands ➔ Tree-shaped glands specialized for secretion into a duct or surface, there is only 2 examples of this:

1- **Stomach tubular glands** ➔ secrete acid and pepsinogen
2- **Brunner's glands** in the Duodenum ➔ secrete alkaline mucus



4) Complex Organs ➔ these are located outside the tract (accessory organs) and contain multiple acini that produce secretions and transport them through a web of ducts to the tract. They provide secretions to **digest and emulsify** food particles. These include:

- Salivary glands
- Pancreas
- Liver

➔ Basic Mechanisms of stimulation of the alimentary tract glands:

#1: Contact of food with the surface of the epithelium ➔ The mechanical presence of food particles stimulates secretions in two main ways:

- Direct, local effect on the secretory glands, especially mucous-secreting cells.
- Activation of the enteric nervous system (ENS) leads to ⬆ secretions through:
  - Tactile stimulation (mechanical)
  - Chemical irritation
  - Distention of the gut wall

#2: Autonomic stimulation of secretions

- **Parasympathetic**
  Net effect: increase in secretions

  1) In the upper GI tract (esophagus/stomach) ➔ through the glossopharyngeal and vagus nerves.
  2) Distal portion of the large intestines ➔ through the pelvic parasympathetic nerves.
  3) In the small intestines and proximal portion of the large intestines ➔ secretions are mainly mediated by local enteric reflexes with minimal parasympathetic effect.

- **Sympathetic**
  Net effect: dual effect

  1) Direct sympathetic stimulation of glands ➔ increases secretions.
  2) Effect on blood vessels ➔ vasoconstriction reduces blood flow to the glands SO it decreases secretion.

#3: Hormones ➔ GI hormones are polypeptides or polypeptide derivatives released from the GI mucosa in response to the presence of food in the GI lumen. ➔ They are absorbed into the blood and carried to the glands, where they stimulate the release of their secretions.

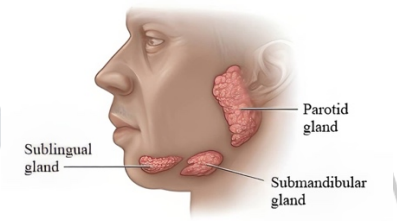
[Secretions of the salivary glands]

➔ Overview of salivary gland anatomy:

Salivary glands = exocrine glands located in and around the oral cavity that produce saliva ➔ divided into:

1) Major glands:
parotid gland → in front of ear
submandibular gland → under mandible
sublingual gland → floor of mouth

2) Minor glands:
Small glands scattered throughout oral mucosa (lips, cheeks, palate)



➔ Saliva:

Saliva = net secretion of water, electrolytes, and organic substances (enzymes and glycoproteins) into the lumen of the salivary ducts.

- Salivary secretion averages (1-1.5 L/day) and is produced mainly by the parotid, submandibular, and sublingual glands, with a smaller contribution from the minor glands.
- The secretion rate is less than 0.025 mL/min (during sleep) to about 0.5 mL/min (under basal conditions).
- The spontaneous secretion of saliva is maintained by a constant low level of parasympathetic stimulation.

There are two types of salivary secretions (each with a different function)**:**

1) **Serous**: secreted predominantly by the parotid glands, and to a lesser extent by the submandibular and sublingual glands. It is rich in **ptyalin (salivary amylase)** ➔ an enzyme that initiates the digestion of carbohydrates in the oral cavity.
2) **Mucus**: secreted mainly by the sublingual, submandibular, and minor salivary glands. It contains **mucin**, which provides lubrication and surface protection of the oral mucosa.

Reminder:

Serous secretion: watery, enzyme-rich, thin fluid

Mucous secretion: thick, viscous, mucus-rich due to the presence of the protein **MUCIN**

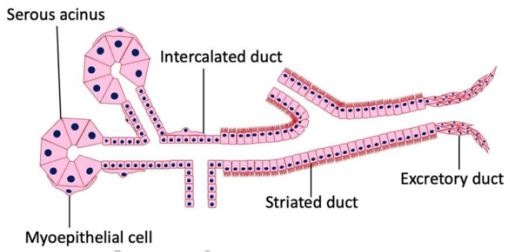
The amount of saliva secreted is not the same in all salivary glands, and the type of saliva also differs.

- The parotid glands secrete about 25% of total saliva, and the secretion is serous.
- The submandibular (submaxillary) glands secrete about 70% of saliva, and the secretion is mixed (predominantly serous).
- The sublingual glands secrete about 5% of saliva, and the secretion is mucous.

➔ Formation of Saliva:

Saliva is formed in two stages:

1- Salivary secretions ➔ produced by the acinar cells
2- Modification of the salivary secretion by the the salivary ductal cells.



#1: Role of acinar cells (primary secretion)

1) Acinar cells secrete a primary saliva that is isotonic (similar in electrolyte composition to extracellular fluid)
2) Water and electrolytes in the primary saliva originate from the extracellular fluid, which is supplied by a rich capillary plexus surrounding the acini.
3) Protein components of saliva, such as ptyalin, lingual lipase, and mucin, are synthesized in the rough endoplasmic reticulum of acinar cells.
4) These proteins are packaged into secretory vesicles within the acinar cells.
5) The proteins are released into the lumen by exocytosis.
6) Exocytosis is an energy-dependent process that requires ATP, which is supplied by the abundant mitochondria present in acinar cells.

#2: Role of ductal cells (modification of saliva)

As primary saliva passes through the ducts, its ionic composition is modified by the following transport processes:

1) Active **reabsorption** of Na^+ and active **secretion** of K^+ ➔ So sodium levels decrease and Potassium levels increase

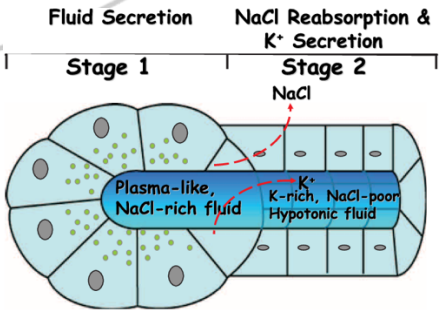
   - Sodium is reabsorbed at a much faster rate than potassium is secreted. As a result, **sodium levels in the ducts fall more rapidly than potassium levels rise, generating a negative electrical potential within the ducts** ➔ The electrical gradient drives chloride ion reabsorption

2) **Secretion** of bicarbonate HCO_3^- into the ducts by active transport mechanisms and passively in exchange for chloride ions Cl^- ➔ So bicarbonate levels increase and chloride levels decrease

   - **Important note:** The salivary ducts are **relatively impermeable to water**, so water does not follow these ionic movements.

Reminder:

the term "**reabsorption**" usually means movement of substances back to the plasma/systemic circulation, while "**secretion**" refers to movement of substances out of the circulation to a different system (lumens/ducts).



➔ **Net ionic composition of saliva**

1) Under resting (low flow) conditions, final saliva has:
   - **Low** Na^+ and Cl^- concentrations (approximately 1/7–1/10 of plasma levels)
   - **High** K^+ concentration (about 7 times plasma)
   - **High** HCO_3^- concentration (2–3 times plasma)

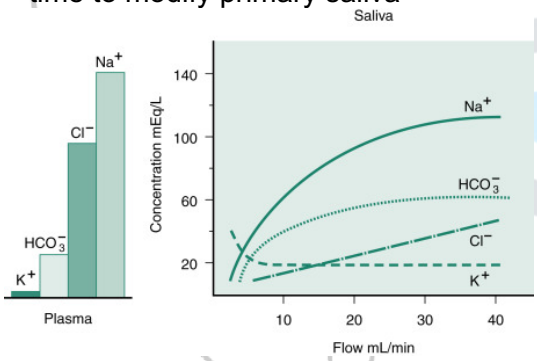
So, the final saliva is a hypotonic solution.

2) During maximal salivary stimulation, acinar secretion increases markedly (up to 20-fold), increasing the flow rate through the ducts. This reduces the time available for ductal modification, so saliva becomes less hypotonic compared with saliva secreted at low flow rates. with:
   - Higher Na^+ and Cl^-
   - Lower K^+

The **pH of saliva** is approximately **7.0 at rest** and approaches **8.0 during active secretion**, due to increased bicarbonate content.

So, in summary: the ionic composition of saliva differs according to the flow rate of saliva

- **Low flow rate** = ducts have a lot of time to modify primary saliva
- **High flow rate** = ducts don't have enough time to modify primary saliva



➔ Nervous regulation of salivary secretions:

Salivary glands are mainly under **parasympathetic control** (The main regulatory centers are the superior and inferior salivatory nuclei located in the brainstem)

Salivation can be stimulated by several mechanisms:

1) **Unconditioned salivary reflex:** Triggered by tactile, pressure, and chemical stimulation of chemoreceptors and mechanoreceptors in the oral cavity, such as during chewing or dental procedures, (however, very rough or painful stimuli may inhibit salivation) ➔ These transmit signals through afferent fibers to salivary centers in the brainstem, which transmit stimulatory signals through efferent fibers via extrinsic autonomic nerve fibers to increase salivation.

2) **Conditioned salivary reflex:** Triggered by signals from higher CNS centers, by thinking about, seeing, smelling, or hearing about pleasant food. This is known as (**Mouthwatering**) in anticipation of something delicious to eat. The conditioned response is learned and based on previous experience.

3) **Reflexes from the stomach and upper small intestines:** when the patient swallows irritating food or is nauseous due to some GI abnormality salivation increases ➔ Saliva washes away irritating particles.

4) **Parasympathetic stimulation:** causes vasodilation of blood vessels supplying glands, increasing delivery of water, electrolytes, and nutrients required for saliva synthesis ➔ result: increased salivary secretion

5) **Sympathetic stimulation:** through the superior cervical ganglia (minimal effect) ➔ However, strong sympathetic stimulation can reduce salivation by causing vasoconstriction and decreasing blood flow.

- **Note:** Both sympathetic and parasympathetic increase salivation, but by different mechanisms.

➔ Functions of saliva:

1) Begins the digestion of carbohydrates in the mouth through:
   - **Amylase:** an enzyme that breaks polysaccharides (starch) into maltose (disaccharide consisting of 2 glucose).

   - **NOTE:** the digestion of lipids and proteins starts in the STOMACH not the mouth (unlike carbohydrates)

2) Facilitates swallowing by:
   - Moistening the food particles.
   - Lubrication by mucus which protects the mucosa during swallowing and allowing easy slippage of solid food, which prevents physical damage to the mucosa.

3) Contains solvent molecules that stimulate taste buds.
4) Facilitates movement of the lips and tongue, which aids in speech.
5) Antibacterial properties, **HOW?**
   - The constant flow of saliva rinsing away materials (food residues, shed epithelial cells, and foreign particles) that may play an important role in oral hygiene and keeping mouth and teeth clean.
   - Contains antibacterial substances such as thiocyanate ions, **lysozyme**, and proteolytic enzymes.
   - Contains protein antibodies **(mainly IgA)** that destroy oral bacteria.

6) Bicarbonate neutralizes acids from food and bacterial metabolism, helping prevent dental caries.

Clinical Glimpse:
Sjögren's syndrome: a condition in which the body produces autoantibodies (autoimmune) attack against the lacrimal and salivary glands, destroying them ➔ Patients present with dry eyes, cracked lips, dry mouth, and dental caries.

[Esophageal secretions]

Esophageal secretions are **entirely mucous in nature** and function primarily in lubrication and protection of the esophageal mucosa during swallowing.

Two types of mucus-secreting glands are present:

1) **Simple mucous glands:** which line the body of the esophagus and secrete mucus that lubricates the esophageal surface and protects it from excoriation (injury) during the swallowing process.
2) **Compound mucous glands:** located near the lower ends of the esophagus, near the esophagogastric junction. These glands secrete alkaline mucus, which **protects the esophageal wall from gastric acid reflux and mechanical injury**.

[Gastric secretions]

➔ Characteristics of gastric glands and their functions:

Three types of glands line the stomach:

1) Mucus-secreting cells

- **Location:** line the entire surface of the stomach and
- **Function:** secrete a viscid, alkaline mucus ➔ this mucous
  1- Lubricates the gastric mucosa.
  2- Forms a protective barrier that prevents proteolytic enzymes from acting on the mucosa and damaging it
  3- Neutralizes hydrochloric acid HCL at the epithelial surface, protecting against chemical injury.

2) Oxyntic (gastric) glands:

- **Location:** in the fundus and body of the stomach
- **Function:** secrete the following
  - Hydrochloric acid (HCl)
  - Pepsinogen (an enzyme that degrades proteins)
  - Intrinsic factor. (a protein needed for vitamin B12 absorption)
  - Mucus

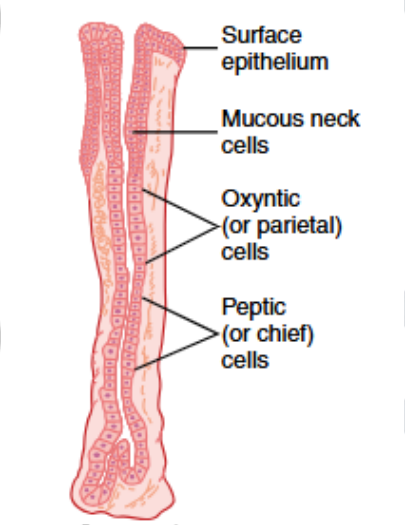
3) Pyloric glands:

- **Location**: antrum of the stomach
- **Function**: secrete Mucus + Gastrin (a hormone that plays a major role in regulating gastric acid secretion)

➔ Structure and function of oxyntic (gastric) glands:

Oxyntic glands line approximately 80% of the stomach surface and contain three main cell types:

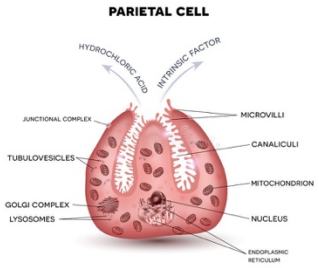
1. **Mucous neck cells**
   Secrete mucus and small amounts of pepsinogen
2. **Peptic (chief) cells**
   Secrete large amounts of **pepsinogen** (the inactive precursor of pepsin, which is an enzyme that breakdown protein)
3. **Parietal (oxyntic) cells**
   Secrete hydrochloric acid and intrinsic factor



[Basic mechanism of gastric acid secretion]

- Parietal cells secrete HCl with a very low pH (0.8–1) (extremely acidic). During its production, bicarbonate ions diffuse into the blood, making the gastric venous blood alkaline compared to arterial blood when the stomach is secreting acid, a phenomenon known as the **alkaline tide** ➔ meaning: for every HCL secreted into the stomach, 1 HCO3- is secreted to the blood

- The parietal cells contain intracellular branches called **canaliculi**, which greatly increase the surface area of the luminal membrane where acid secretion occurs.



- The primary driving force for HCl production is the **hydrogen-potassium pump (H^+- K^+ ATPase)** through an active process, located on the luminal membrane of parietal cells.

➔ Steps of gastric acid secretion:

1) Generation of hydrogen and bicarbonate ions

Inside the parietal cell, carbon dioxide (CO_2), derived from both cellular metabolism and the blood, combines with water (H_2O) under the action of the enzyme carbonic anhydrase.

$$H_2O + CO_2 \rightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

This reaction produces H_2CO_3 which rapidly dissociates providing continuous supply of hydrogen ions (H^+) for secretion into the gastric lumen and bicarbonate ions (HCO_3^-) for transport into the blood.

2) Active Secretion of Hydrogen Ions

Hydrogen ions (H^+) are actively transported across the apical (luminal) membrane of the parietal cell into the canaliculi. ➔ This process is mediated by the H^+/K^+ ATPase (proton pump), which exchanges intracellular H^+ for extracellular potassium ions (K^+).

Important note: This is a primary active transport process that requires ATP and represents the main driving force for gastric acid secretion.

3) Bicarbonate Exit and the Alkaline Tide

As H^+ ions are secreted into the lumen, the remaining bicarbonate ions (HCO_3^-) must be removed from the cell to maintain intracellular pH ➔ HCO_3^- is transported across the basolateral membrane into the blood in exchange for chloride ions (Cl^-) via the Cl^-/HCO_3^- exchanger.
The movement of bicarbonate into the gastric venous blood causes a transient rise in blood pH after a meal, known as the **alkaline tide.**

4) Chloride Secretion and Formation of Hydrochloric Acid

The chloride ions (Cl^-) that enter the parietal cell from the blood diffuse passively through chloride channels in the apical membrane into the canaliculus. ➔ In the canaliculus, Cl^- combines with the previously secreted H^+ to form hydrochloric acid (HCl).

5) Ion Recycling and Electrical Balance

To maintain continuous acid secretion and electrical stability:

- **Potassium Recycling:** Potassium ions (K^+) are pumped into the cell by the H^+/K^+ ATPase and the basolateral Na^+/K^+ ATPase ➔ so these K^+ don't accumulate inside the cell they recycle back into the canaliculus through potassium channels, so it can be reused for the next pump cycle.

- **Sodium Pump:** The Na^+/K^+ ATPase on the basolateral membrane maintains low intracellular sodium levels and supports secondary active transport processes.

6) Water Secretion (Osmosis)

The accumulation of hydrogen and chloride ions in the canaliculus creates a strong osmotic gradient. ➔ Water moves into the canaliculus by osmosis from the surrounding cells and interstitial fluid.

Net result: The canalicular secretion contains water and HCL, forming gastric juice that is approximately isotonic with plasma and has a very low pH (approximately 0.8).

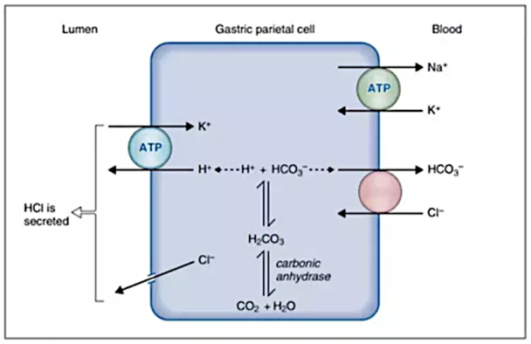


Fig. 8.17 Mechanism of HCl secretion by gastric parietal cells. *ATP*, Adenosine triphosphate.

[Physiological importance of gastric acid]

Gastric acid does not directly digest food, but it plays several essential roles:

- **Converts pepsinogen into pepsin** (the active form)
- Helps in the **decomposition of connective tissue found in food**
- Provides an important **antimicrobial defense** by killing ingested microorganisms

Clinical Glimpse:
The stomach has a strong gastric barrier formed by alkaline mucus that prevents direct contact of the highly acidic stomach acid with its mucosa. This barrier can be damaged by toxic substances (alcohol, tobacco, aspirin), causing mucosal damage, inflammation, and ulcers.

[Secretion and activation of pepsinogen]

Pepsinogen is secreted by **peptic (chief) cells** of the gastric glands as an inactive precursor, and it's activated and converted to pepsin as soon as it comes into contact with hydrochloric acid (HCl). ➔ Once activated, pepsin can also catalyze further activation of pepsinogen (autocatalysis).

Function of pepsin: a proteolytic enzyme (enzyme that breaks down proteins) that has optimal activity at an acidic pH.

Note: for enzymes, the suffix (gen) is linked to **inactive** molecules and dropped for **active** ones. Pepsinogen ➔ pepsin, trypsinogen ➔ trypsin... etc.

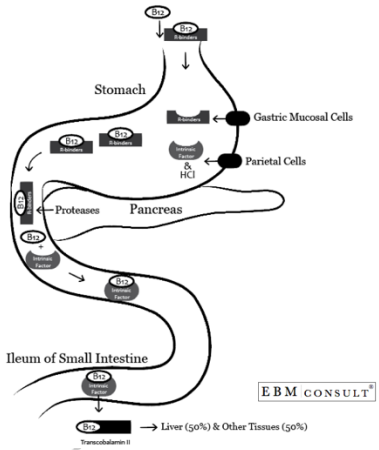
[Secretion of intrinsic factor]

Intrinsic factor is a protein secreted by **parietal (oxyntic)** cells along with HCl.

Function of intrinsic factor:

- Vitamin B_{12} absorption, steps of B12 absorption:
  1) Vitamin B_{12} binds to **R-binders** in the stomach
  2) The complex passes to the duodenum
  3) B_{12} is released from the R-binders and binds to **intrinsic factor**

4) The intrinsic factor–B_{12} complex travels to the ileum
5) Absorption occurs in the **ileum**



Clinical Glimpse:
Pernicious anemia: a condition in which the body develops antibodies against the intrinsic factor or parietal cells (autoimmune disorder), which leads to impaired vitamin B_{12} absorption. Patients may be present symptoms of B12 deficiency ➔ anemia symptoms (fatigue, pallor), and, in severe cases, neurological manifestations such as peripheral neuropathy.

➔ Structure and function of pyloric glands:

Pyloric glands have a similar structure to oxyntic glands, but they contain few peptic cells and almost no parietal cells.

- Location: located in the **antrum** of the stomach.

They contain 2 types of cells:
1) **Mucus-secreting cells**, which protect the antral mucosa by secreting mucous (same as mucous neck cells of oxyntic glands)
2) **G cells**, which secrete gastrin into the bloodstream

[Gastrin]

- Gastrin is released in response to: Gastric distension // Presence of proteins and peptides in chyme // Vagal stimulation (via GRP "gastrin releasing peptide")

- **Function:** acts on the body of the stomach to:
  - Increase HCL secretion.
  - Increase pepsinogen secretion.
  - Exert a trophic effect on the gastric mucosa (maintaining mucosal growth)

➔ Structure and function of surface mucus cells:

Surface mucus cells are simple epithelial cells that line the entire gastric mucosa and are interspersed between oxyntic and pyloric glands.
They secrete a viscid, alkaline mucus that forms a protective barrier against gastric acid and proteolytic enzymes, preventing damage to the mucosa.

➔ Regulation of gastric acid secretion:

Gastric acid (HCl) is secreted exclusively by parietal cells of the oxyntic glands only. Acid secretion is tightly regulated through neural, hormonal, and paracrine mechanisms, which act synergistically on parietal cells.

Parietal cells operate in conjunction with another type of cells called **Enterochromaffin-Like Cells (ECL)**, which **secrete histamine** and play a central role in acid regulation.

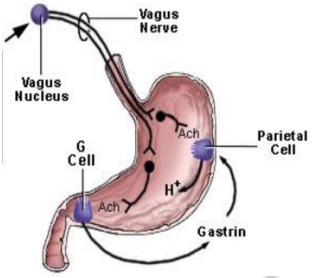
#1: Neural regulation

Main idea: Acetylcholine stimulate HCL secretion (source of Ach is both the ENS and ANS)

Enteric Nervous System (ENS):
- Directly stimulates parietal cells (HCl secretion) and chief cells (pepsinogen secretion).
- Mediated by acetylcholine (ACh) released from enteric neurons.

Parasympathetic (Vagal) Stimulation:
- Vagal activation stimulates HCL secretion, **HOW?**
  1) **Direct effect:** ACh stimulates parietal cells → ↑ HCl secretion.
  2) **Indirect effect via ECL cells:** ACh stimulates enterochromaffin-like (ECL) cells → histamine release → binds to H_2 receptors on parietal cells → further ↑ HCl.
  3) **Indirect effect via G cells:** Vagal fibers release Gastrin-Releasing Peptide (GRP)→ stimulates G cells

in the antrum → gastrin release → acts on parietal cells (direct) and ECL cells (indirect) to ↑ HCl secretion.



#2: Hormonal regulation (Gastrin)

Gastrin is secreted by G-cells and enters the bloodstream and reaches the oxyntic glands to act on parietal cells to stimulate HCL secretion, **HOW?**

1) Directly: Gastrin binds to CCK-B receptors on parietal cells, increasing intracellular Ca^{2+} and stimulating acid secretion.
2) Indirectly: by stimulating ECL cells to secrete histamine (histamine binds to H_2 receptors on parietal cells → stimulates ↑ HCl)

#3: Paracrine regulation (Histamine)

Histamine is secreted by ECL cells (these cells are found in the stomach)

- These cells are stimulated to secrete Histamine in response to:
  1) Vagal stimulation (acetylcholine)
  2) Gastrin
  3) Local chemical signals (inflammation).

- It diffuses locally and binds to H_2 receptors on parietal cells, increasing intracellular cAMP, which strongly stimulates HCL secretion.

Net effect of histamine: increased gastric acid secretion

#4: Inhibitory regulation (Somatostatin)

Somatostatin is a hormone released from paracrine cells in the gastric mucosa. It acts on somatostatin (SS) receptors on parietal cells, reducing intracellular cAMP and thereby inhibiting gastric acid secretion.

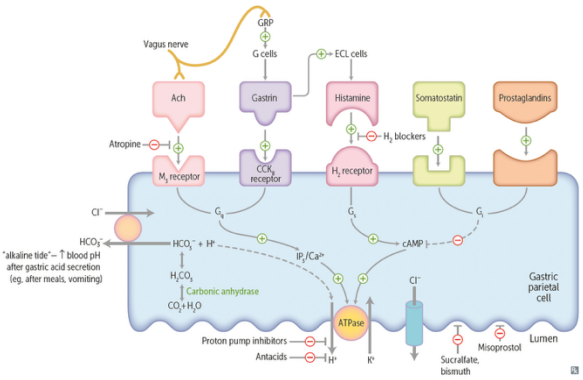
Net effect: decreased gastric acid secretion

****Note:** Excess gastric acid causes feedback inhibition of gastric secretions by:

- Reducing gastrin release
- Initiating inhibitory reflexes

Clinical Glimpse:
Many medications are used to decrease acid secretion to treat conditions where HCL is harmful (e.g. gastric ulcers, heartburn)

1) **H_2 receptor blockers** (e.g., cimetidine, famotidine) ➔ reduce acid secretion by blocking histamine action on parietal cells.
2) **Proton pump inhibitors** (PPIs) (e.g., omeprazole, lansoprazole)➔ inhibit the H^+/K^+ ATPase, producing a profound decrease in acid secretion.



➔ Regulation of pepsinogen secretion:

Pepsinogen is the precursor of pepsin, which is a crucial enzyme for protein digestion. Its secretion is regulated by:

1) Neural regulation

- Acetylcholine (ACh) released from the vagus nerve and the enteric nervous system stimulates peptic (chief) cells to secrete pepsinogen

2) Hormonal regulation

- Gastrin stimulates pepsinogen secretion directly and indirectly.

3) Role of gastric acid (HCl)

- HCl stimulates pepsinogen secretion indirectly by initiating enteric reflexes that increases peptic cell activity

➔ Phases of gastric secretions:

Gastric secretion of acid and other enzymes occurs in three phases:

1) **Cephalic phase**
   - Occurs before food enters the stomach.
   - Stimulated by sight, smell, taste, thought, chewing, and swallowing.
   - Signals originate in the brain and are transmitted via the vagus nerve.
   - This phase stimulates parietal cells and G cells.

2) **Gastric phase**
   - Begins when food enters the stomach and causes distension.
   - Mediated by local enteric reflexes, long vagovagal reflexes from the stomach to the brain and back, and gastrin release in response to proteins.
   - It is the phase that causes maximal stimulation of gastric secretions.
   - Alcohol and caffeine stimulate acid secretion even in the absence of food.

3) **Intestinal phase**
   - During the intestinal phase (when food enters intestine), the stomach continues to secrete small amounts of acid and hormones even after food enters the duodenum.
   - Intestinal chyme may have both stimulatory (during the early intestinal phase) and inhibitory effects on gastric secretion.

Excitatory (Stimulatory):

- Occur mainly in the early intestinal phase.
- Distension of the upper portion of the duodenum slightly stimulates gastric secretion.

Inhibitory (by post-stomach intestinal factors):

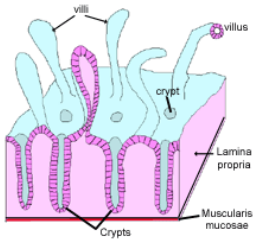
- The presence of chyme in intestine usually inhibits gastric secretions. The presence of food and acids in duodenum initiates neural reflexes (enterogastric reflex) and causes the release of hormones (GIP, CCK, secretin, enterogastrone). These hormones inhibit acid secretions.

[Small intestinal secretions]

➔ Types of intestinal glands and their functions:

1) Crypts of Lieberkühn (intestinal glands)

- **Location:** throughout the small intestine, at the base of villi
- **Function:** secrete intestinal juice (water, electrolytes, digestive enzymes) **AND** house stem cells for epithelial renewal



2) Brunner's glands

- **Location**: duodenum (submucosa)
- **Function**: secrete alkaline mucus to neutralize gastric acid and protect the duodenal lining from damage

➔ Secretion by Brunner's glands in the duodenum:

- **Brunner's glands** are compound mucus glands located in the first few centimeters of the **duodenum**.

- They secrete a large amount of alkaline mucus in response to:
  1) Tactile or irritating stimuli on the mucosa
  2) Vagal stimulation
  3) Gastrointestinal hormones (secretin)

- These glands are inhibited by sympathetic stimulation.

- The alkaline mucus protects the duodenal wall from digestion by acidic gastric juice and contains a high concentration of bicarbonate ions, which neutralize the HCl entering from the stomach.

➔ Secretion of intestinal digestive juice by the crypts of Lieberkühn:

The **crypts of Lieberkühn** are small pits that line the small intestines. They contain two types of cells:

1) **Goblet cells**➔ secrete mucus that lubricate and protect the intestinal mucosa
2) **Enterocytes** (small intestinal epithelial cells)➔ secrete water and electrolytes. It acts as a vehicle for the absorption of substances from food (dissolves food)

Important note: the base of the crypts contains stem cells, which are important in renewing the intestinal epithelium

➔ Regulation of small intestinal secretions:

1) **Neural regulation**
- Mediated by acetylcholine (ACh) and vasoactive intestinal peptide (VIP)–secreting neurons

2) **Hormonal regulation**
- **Secretin**: increases duodenal secretions (by stimulating Brunner's glands) and plays an essential role in neutralizing gastric acid delivered from the stomach.

[Secretions of the large intestines (colonic secretions)]

Like the small intestine, the large intestine contains **numerous crypts of Lieberkühn.** They secrete:

- Mainly mucus
- A small amount of serous secretion rich in potassium (K^+) and bicarbonate (HCO_3^-)

These secretions:

1) Protect the mucosa from physical and chemical irritation.
2) Provide adherent material that binds fecal matter.
3) Help prevent bacterial invasion

Mucus secretion is regulated by:

1) Stimulation from direct contact with the intestinal epithelium.
2) Local neural reflexes
3) Parasympathetic activation through pelvic nerves.

Clinical Glimpse:
Gastro-enteritis is a condition where the intestinal lining becomes inflamed due to strong irritation. This leads to increased secretion of water and electrolytes resulting in diarrhea as a protective mechanism to wash away irritants, but it may cause dehydration if severe or prolonged.

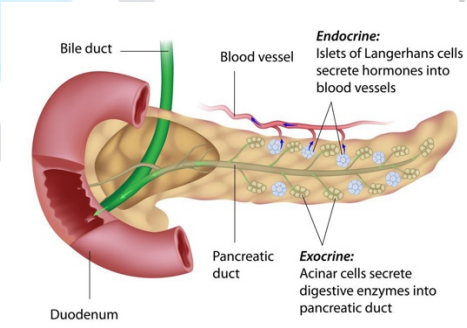
[Pancreatic secretions]

The pancreas is a large compound gland located parallel to and beneath the stomach. It is anatomically divided into:

- **Endocrine pancreas**: Made up of cell collections **(Islets of Langerhans)** which secrete hormones into the blood ➔ the most important ones: **insulin, glucagon, and somatostatin.** (you will study this in Endocrine system)

** **Note**: the word "endocrine" is used for hormones that are transmitted to their target via the blood.

- **Exocrine pancreas**: which secretes digestive enzymes and electrolytes from the acini into small ducts and eventually to the small intestines. They're secreted in response to the presence of food in the duodenum.



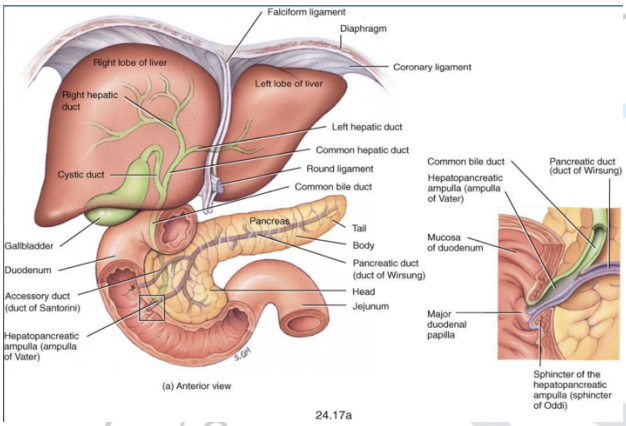
➔ Exocrine pancreas overview:

- The exocrine pancreas is made up of **acinar cells** (produce digestive enzymes) and **ductal cells** (secrete bicarbonate-rich fluid), which together drain into the pancreatic ducts and then the duodenum.

1- Acinar cells produce digestive enzymes (amylase, lipase, proteases).
2- Ductal cells secrete bicarbonate-rich fluid to neutralize stomach acid.

3- Secretions enter small ducts, which drain into larger ducts ➔ All merge into the main pancreatic duct
4- The pancreatic duct joins the common bile duct ➔ together they open into the duodenum via the Ampulla of Vater through sphincter of Oddi

The net pancreatic secretion is high in enzymes, hypotonic and alkaline.



➔ Pancreatic digestive enzymes:

The pancreas produces enzymes that digest all types of nutrients (carbs, fats, and proteins). These enzymes function optimally in alkaline environment.

Secreted by **Acinar cells**

1) **Carbohydrates digestion**
- Pancreatic **amylase** → breaks down most starches (except cellulose)

2) **Lipid digestion**
- Pancreatic **lipase** → An enzyme that breaks down triglycerides
- **Cholesterylesterase** → hydrolyzes cholesterol esters
- **Phospholipase** → splits phospholipids

3) **Protein digestion**
- Many enzymes are secreted that degrade proteins (Trypsin, chymotrypsin, Carboxypeptidase etc..)

Most of these enzymes (except amylase) are **secreted as inactive zymogens** (trypsinogen, chymotrypsinogen, procarboxypeptidase...) to prevent autodigestion of the pancreas. ➔ They get activated once they reach the small intestines by **Trypsin**.

BUT: IF trypsin activates all other enzymes, who activates trypsinogen? ➔ Activation of trypsinogen occurs by:
- **Enterokinase** (an enzyme secretes from the small intestinal mucosa)
- **Autoactivation**, where trypsin activates additional trypsinogen

In the pancreas, a molecule called **trypsin inhibitor** inhibits the activation of trypsin inside the pancreas, which prevents premature activation of all enzymes within the pancreas (we want these enzymes to be activated inside the intestine not the pancreas)

Clinical Glimpse:
When the pancreatic ducts get obstructed for whatever reason, the secretions accumulate and overwhelm the ability of the trypsin inhibitor to keep the enzymes inhibited. Trypsin activates pancreatic enzymes, and they start digesting the pancreas (autodigestion). This leads to a condition called acute pancreatitis, which may progress to **pancreatic insufficiency**.

Pancreatic insufficiency is characterized by decreased enzyme secretion and manifests clinically as malabsorption (since the pancreas doesn't secrete its enzymes, food digestion will be impaired, so they won't be absorbed)

➔ Secretion of bicarbonate ions:

The other major components of pancreatic secretions are water and bicarbonate ions

Secreted by **Ductal cells**

The process of formation and secretion involves the following steps:

1) CO_2 diffuses into the cell from the bloodstream and combines with water through the action of carbonic anhydrase to form H_2CO_3 ➔ H_2CO_3 dissociates into HCO_3^- and H^+

$$H_2O + CO_2 \rightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

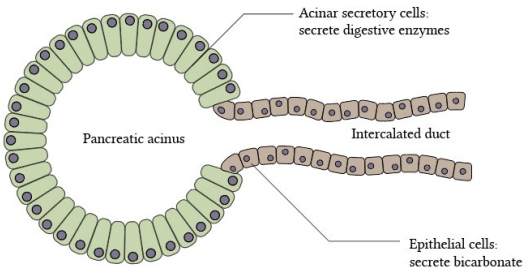
2) HCO_3^- is secreted into the pancreatic duct along with Na^+ and in exchange for Cl^-.
3) The sodium enters the cell actively in exchange for the previously formed H^+.

4) When the electrolytes accumulate, water moves into the lumen of the ducts by osmosis. The water drives the enzymes to the duodenum.

The final composition is altered by the secretion rate:

Effect of secretion rate on composition:

- **High flow rate → ↑ HCO_3^-, ↓ Cl^-**
- **Low flow rate → ↓ HCO_3^-, ↑ Cl^-**



➔ Regulation of pancreatic secretions:

1) **Neural control:**

- **Parasympathetic**: sends excitatory signals through the vagus nerve
- **Sympathetic:** indirect inhibition via vasoconstriction of the blood vessels that supply the pancreas.

2) **Hormonal regulation**

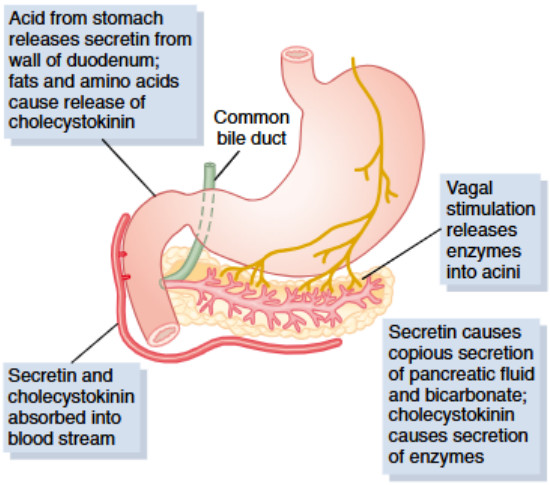
Cholecystokinin (CCK)

- **Source:** Released from duodenum & jejunum in response to dietary **lipids & proteins**
- **Function:** 3 main functions
  1) Stimulate pancreas to release digestive enzymes
  2) Stimulate gallbladder contraction to release bile
  3) Decreases gastric motility (to slow down food entry to the small intestine)

Secretin

- **Source:** Released from duodenum & jejunum in response to low PH (of the chyme that enters from the stomach)

- **Function:**
  1) Stimulate pancreas to release Bicarbonate (HCO3-) which is a base rich fluid ➔ to neutralize the acidic content of the stomach so that pancreatic enzymes can work (since they can't work in an acidic environment)
  2) Decreases gastric motility (to slow down food entry to the small intestine)



➔ Phases of pancreatic secretion:

1) Cephalic and Gastric Phases

- **Stimuli:**
  Cephalic: Sight, smell, taste, or thought of food.
  Gastric: Distension (stretching) of the stomach.
- **Mechanism:** Both phases are mediated by the Vagus nerve. Vagal endings release Acetylcholine (ACh).
- **Result:** ACh stimulates the acinar cells to produce large amounts of digestive enzymes.

Only a small amount of the total enzymes reaches the duodenum because there is very little water or bicarbonate secreted along with the enzymes yet, the enzymes sit in the pancreatic ducts and do not reach the duodenum in significant quantities, until the intestinal phase starts

2) Intestinal phase

This is the most important phase. It begins when food enters the duodenum and it is regulated by **two primary hormones and a reflex:**

- **Secretin:** Triggered by acidic chyme (HCl). It acts on pancreatic ductal cells to secrete large amounts of water and bicarbonate (HCO_3^-). This washes the previously made enzymes out of the pancreatic ducts and into the intestine.

- **Cholecystokinin (CCK):** Triggered by fats (fatty acids) and proteins (amino acids). It is the most potent stimulator of enzyme secretion from acinar cells.

- **Vagovagal (Enteropancreatic) Reflex:** Distension of the duodenum further stimulates the pancreas via the vagus nerve.

[Secretion of bile by the liver & functions of the biliary tree]

The **Liver** is a major accessory organ in the gastrointestinal system, and performs MANY essential functions, including:

1) **Metabolic processes** (processes all nutrients after their absorption)
2) **Detoxification** of drugs, hormones, and waste products.
3) **Synthesis** of plasma proteins, including clotting factors (their synthesis requires vitamin K), and hormone transport proteins.
4) **Storage** of glycogen, iron (ferritin), copper, and vitamins.
5) **Removal of bacteria** and foreign materials by reticuloendothelial cells (Macrophages).
6) **Synthesis and secretion of bile**

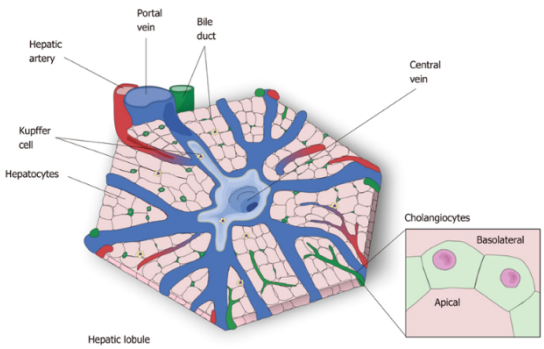
➔ Physiological anatomy of the biliary tree:

[Functional structure of the liver]

Hepatic lobule = The functional unit of the liver ➔ its organized in the following way:

- Hepatocytes (liver cells) are arranged in a hexagonal pattern around a **central vein** (the central vein drains into the hepatic veins).
- At the outer edges of the hexagonal structure of the lobule there are three vessels which are collectively called the **Portal Triad**, composed of:

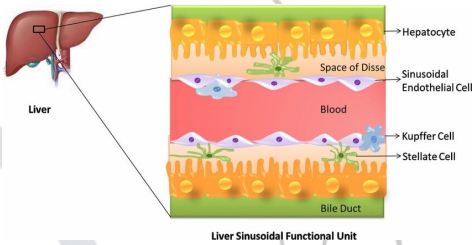
1) **A branch of the hepatic artery**
2) **A branch of the portal vein**
3) **A bile duct**



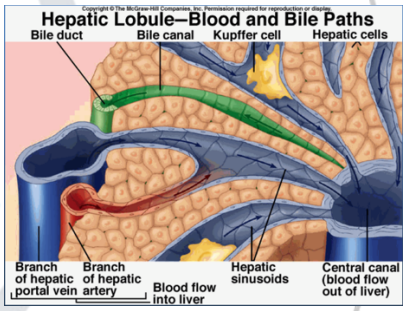
How blood flows through the liver?

- Blood from the hepatic artery and portal vein enters the liver at the periphery of the lobule
- It flows through **sinusoids** (special capillaries) toward the central vein
- As it flows, it passes between rows of hepatocytes
- **Each hepatocyte has two important sides:**
  One side faces the sinusoid → interacts with blood (exchange of nutrients, toxins)

  The other side faces the bile canaliculus → secretes bile



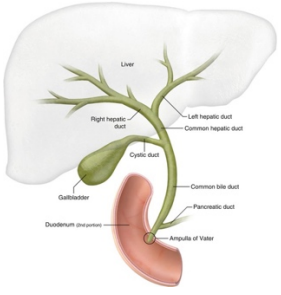
Liver Sinusoidal Functional Unit



- The space between hepatocytes and sinusoids is the **space of Disse** ➔ This is where lymph is formed

[Bile formation and flow]

In the hepatic lobule, **bile is secreted by hepatocytes into bile canaliculi**, which drain into progressively larger bile ducts, forming the hepatic ducts and finally the common bile duct, which empties into the duodenum.



[Bile synthesis]

Bile = fluid secreted by the liver into the biliary tree and stored in the gallbladder, it is composed of:

- **water and electrolytes**
- **bile salts**
- **bilirubin** (breakdown product of heme degradation)
- **cholesterol**
- **phospholipids**

Bile salts = amphipathic molecules (have both water-soluble and fat-soluble sides) derived from cholesterol that help digest fats.

- The liver synthesizes two primary bile acids from cholesterol:
  1) Cholic acid
  2) Chenodeoxycholic acid

- Bile acids are usually secreted as bile salts rather than as bile acids (these bile acids are conjugated with either glycine or taurine to form bile salts)
- In the intestines, bile salts are modified to secondary bile acids by the intestinal bacteria through a process of dehydroxylation.

  Cholic acid ➔ deoxycholic acid
  Chenodeoxycholic acid ➔ lithocholic acid

Primary Bile is isotonic and contains Na^+, K^+, and Cl^- ➔ The bile secretion enters the duct system where the cells lining the duct modify it by exchanging HCO_3^- for Cl^-.

[Storage and concentration of bile]

- **Between meals** ➔ bile is stored in the gallbladder until it's needed in the duodenum (after eating). In the gallbladder, it gets concentrated because water and large amounts of electrolytes (except calcium) get reabsorbed into the mucosa, this concentrates bile 5–20 times, leaving bile salts, bilirubin, and cholesterol behind.

- During meals ➔ The gallbladder contracts **AND** The sphincter of Oddi relaxes ➔ **So,** bile is released into the duodenum.

- Why does the gallbladder contract during meals?

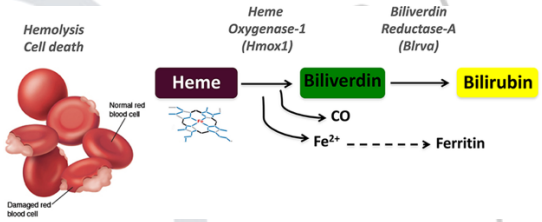
- Cholecystokinin (CCK) is released by the small intestine in response to fats and proteins, and CCK causes gallbladder contraction
- Local and vagal neural reflexes

****Note**: the prefix **"cholecyst"** means gallbladder.

[Excretion of bilirubin in bile]

- **Bilirubin** is a molecule that results from the breakdown of hemoglobin into heme and globin (amino acids) ➔ Bilirubin is YELLOW in color

- **Heme breakdown: Heme** is broken down to iron and **biliverdin**. ➔ Biliverdin is then transformed into **bilirubin**.



- **Bilirubin excretion into bile:**

1) Bilirubin enters the liver from the blood ➔ In the liver, bilirubin is conjugated (mainly with **glucuronic acid**) ➔ **Why do we do this step?** To increase bilirubin solubility and make it more water soluble ➔ so that we can excrete it into the bile (bile is a water rich fluid)
2) **Conjugated bilirubin (bilirubin + glucuronic acid)** is secreted by the liver cells into the bile
3) In the intestines, conjugated bilirubin is transformed by bacterial action into **urobilinogen**
4) **Urobilinogen** has 2 possible end points:

   - Some is reabsorbed and excreted in the urine as **urobilin** (urobilin is yellow and is what gives urine its color)
   - Remainder is excreted in feces as **stercobilin** (stercobilin is brown and is what gives stool its color)

**Important note:

Unconjugated bilirubin

- Not yet processed by the liver
- Insoluble in water → travels in blood bound to albumin

Conjugated bilirubin

- Processed in the liver (conjugated with glucuronic acid)
- Water-soluble → excreted in bile → enters the intestine

**Key point:
The bilirubin found in bile is the conjugated form.

Clinical Glimpse:
Bilirubin is yellow in color, so elevated bilirubin levels cause yellow discoloration of the skin and sclera, a condition known as **jaundice** ➔
It happens for 3 main reasons:

1) Too much bilirubin is produced (When red blood cells break down faster than normal)
2) The liver can't process it properly (The liver is responsible for handling bilirubin, so if it's not working well, levels rise)
3) Bile can't drain properly (A blockage prevents bilirubin from leaving the body)

➔ Function of bile salts in fat digestion and absorption:

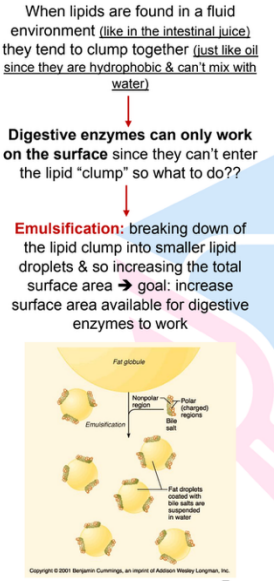
➔ Bile has two main functions:

1) It serves as a means for the excretion of several waste products.

2) Aids in fat digestion and absorption ➔ through bile salts, **HOW?**

- Emulsify large fat particles into smaller ones.

- Facilitate the absorption of digested fat (fatty acids, monoglycerides, cholesterol, and fat-soluble vitamins) through the intestinal mucosa in the form of complexes called **Micelles**.



➔ Enterohepatic circulation

The majority of bile salts are reabsorbed into the blood from the small intestines ➔ Then they get transported back to the liver via the portal circulation and **resecreted into bile** ➔ this is called the **"Enterohepatic circulation"**

- Only Around 20% of bile salts are lost in feces daily, and these are replaced by de novo synthesis in the liver (synthesis of new bile acids)
- During a normal meal, the bile salt pool circulates approximately twice.
- The daily rate of liver bile salt secretion is actively controlled by the availability of bile salts in the enterohepatic circulation.

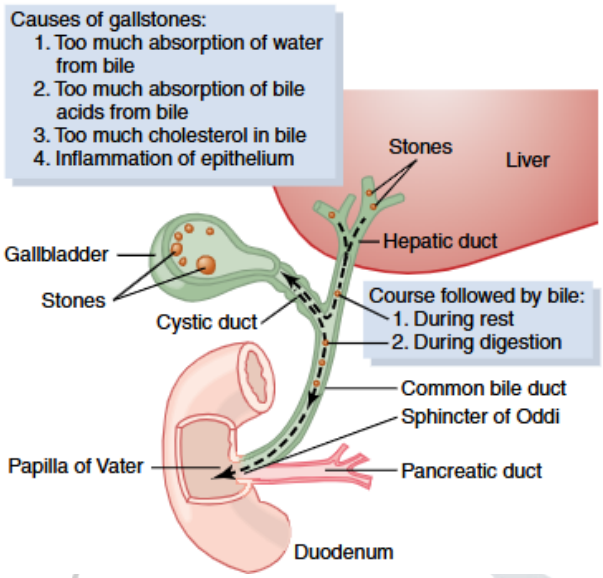
➔ Role of secretin in controlling bile secretion:

Secretin leads to increased secretion of sodium bicarbonate-rich watery solution by the bile ducts, which eventually reaches the small intestines and joins the bicarbonate from the pancreas, and helps in neutralizing HCl.

➔ Liver secretion of cholesterol and gallstones formation

- Cholesterol is not water-soluble, so it cannot travel alone in bile
- To stay dissolved, it is packaged into tiny structures called **micelles** by bile salts and lecithin (a type of phospholipid)
- **Normal situation:**
  Bile salts + lecithin keep cholesterol dissolved → no problem

- **When things go wrong:** If bile becomes too concentrated or there aren't enough bile salts/lecithin ➔ Cholesterol can no longer stay dissolved ➔ **Result:** Cholesterol precipitates (comes out of solution) ➔ Over time, it forms **gallstones in the gallbladder**



The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Physiology

Energetics, metabolic rate, dietary balance, and regulation of food intake

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[Overview]

➔ **Outline of this lecture:**

1) **Introduction to work and energy**
2) **Metabolic rate**
   a. Basal metabolic rate
   b. Measurement of the metabolic rate
   c. Factors affecting the metabolic rate
3) **Dietary balance**
4) **Regulation of food intake**
   a. Hypothalamic regulation of food intake
   b. Theories of food intake regulation
5) **Obesity**
6) **Inanition**

[Introduction to work and energy]

The primary purpose of the chemical transformation of food particles into smaller, absorbable molecules is for them to be utilized by body cells for cellular function. ➔ Foodstuff undergoes many processes in the cells of the human body to produce the energy needed to complete their activities.

[Energetic compounds in the human body]

#1: Adenosine triphosphate - ATP

- Carbohydrates, fats, and proteins are used by the cells to produce large quantities of **adenosine triphosphate (ATP)**, a compound that stores energy within its phosphate bonds.

- ATP is considered the main energy source for almost all cellular functions, "**Energy currency**" of the cell.

- The cellular functions that need energy can also be referred to as "**body work**", which could be external (related to interactions with the external environment) or internal (within the body itself), and includes:

1) **Chemical work**: chemical reactions such as building cellular components, protein synthesis, secretion of hormones and enzymes, etc.
2) **Mechanical work**: muscle contraction, heart pumping, etc.
3) **Electrical work**: nerve conduction.
   - The Na^+/K^+ ATP pump uses the energy produced from the breakdown of ATP to move sodium out of the cell, and potassium inside, thus maintaining a concentration gradient across the membrane.

➔ **ATP Formation by Chemical Reactions:**

Energy production in the body occurs through:

- Aerobic metabolism (oxygen-dependent)
- Anaerobic metabolism (oxygen-independent)

1) Anaerobic reactions

- Anaerobic reactions, such as glycolysis, can produce **some** ATP molecules when there is a lack of oxygen, such as:

1) States of hypoxia
2) High activity and inadequate oxygen supply ➔ increased oxygen demand and inability to keep up (e.g. skeletal muscles during exercise.)

- This leads to the accumulation of **lactic acid.**

2) Aerobic reactions

- **Most of the energy** is produced through these reactions.
- It is mediated by highly controlled enzymatic reactions.
  These reactions use chemical burning of foodstuff by using O_2 to produce energy.
- These reactions result in **the production of water (H_2O) and carbon dioxide (CO_2)**.
  For example, the breakdown of glucose gives the following reaction:
  $\mathbf{C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2}$

- From aerobic reactions, we can calculate something called the "**Respiratory Quotient**" (RQ), which represents the ratio of CO_2 produced to O_2 consumed.

- The RQ is different for each molecule.

1) For glucose, the RQ is 1 ➔ which means the amount of CO_2 produced = the amount of O_2 consumed.
2) For fat. RQ is 0.7 ➔ means $CO_2 < O_2$
3) For protein, RQ is 0.8 ➔ means $CO_2 < O_2$
4) For mixed food (containing carbs, fats and proteins), RQ is 0.82.

- The **Respiratory Exchange Ratio (RER)** is one parameter that can be used to determine the RQ. It represents the volume of oxygen absorbed by the lungs over a period of time, compared to the volume of

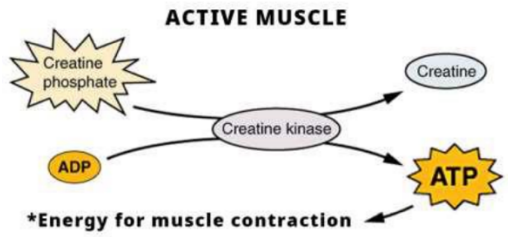
carbon dioxide produced. ➔ **Under steady-state conditions: RER ≈ RQ**

- Determining the RQ can help us **deduce the main type of foodstuff used for metabolism** in the body.

#2: Phosphocreatine

- **Creatine** is a compound formed from amino acids and stored abundantly in the muscles.
- **Phosphocreatine** (creatine + 1 phosphate group) can be **used to recycle ATP molecules** through the following reaction:

Phosphocreatine + ADP ↔ ATP + Creatine.



- The abundance of creatine leads to more storage of energy, which can be later used to convert ADP to ATP when there's a decrease in ATP concentration.

[Metabolic rate]

Metabolism refers to all the chemical reactions in the body. And the **metabolic rate** is normally expressed in terms of the rate of heat liberation during chemical reactions.

Heat is the end product of almost all the energy released in the body when energy transforms from one form to another. ➔ Because heat is the final form of energy released during metabolism, measuring heat production provides an estimate of total metabolic activity.

The unit for measuring heat is called a **calorie**. **Calorie**, spelt with a capital C, refers to 1 Kilocalorie (1000 calories).

➔ Basal metabolic rate:

Basal metabolic rate (BMR): refers to the minimal amount of energy the body consumes to exist. It is measured under basal conditions.

We measure the BMR in a person who is awake, under specific, basal conditions:

1) Fasting from food for at least 12 hours.
2) After a night of restful sleep.
3) No exercise or physical activity for at least one hour before and during the test.
4) Elimination of psychological and physical factors that might cause excitement.
5) Comfortable temperature (not too hot or cold).

➔ Measurements of the metabolic rate:

We can measure the metabolic rate by measuring the heat produced by the body directly and indirectly.

#1: Direct methods

The direct calorimetry

- Direct calorimetry measures the actual heat produced by the body.
- **Device:**

A **calorimeter**, which is: A thermally insulated chamber + Surrounded by circulating water

- **Principle:**

Heat produced by the body is absorbed by the surrounding water. ➔ The temperature change of water is measured and used to calculate heat production.

This video simplifies the concept of direct calorimetry.

#2: Indirect methods

Indirect calorimetry

- It is a noninvasive method that measures a person's metabolic rate by measuring oxygen consumption and carbon dioxide production.

1) **The closed-circuit method**
   - **Device:** spirometer (a device a person breaths in) equipped with pure oxygen and a substance that absorbs CO_2.

- **Principle:** During chemical reactions, 95% of energy is produced by oxygen consumption. Which means, we can, indirectly, measure the amount of heat produced in the body by measuring the amount of oxygen consumed.

- **Mechanism:** the patient is attached to the spirometer, and they inhale pure oxygen.
  ➔ By measuring oxygen consumption and carbon dioxide production, we can get an estimate of energy/heat production.

This video simplifies the concept of indirect calorimetry.

- The heat produced is calculated as the amount of heat/m^2 surface body/hour. Our body produces about **4.825** Calories per 1L of oxygen (*this is a fixed number*)

****Example:**

To measure the heat/m^2/hour, we will need:

- **O_2 consumption** in liters from the spirometer
- **Body surface area**, from a predesignated table, by knowing the person's height and weight.

If oxygen consumption over 5 minutes was 1000ml of pure oxygen. ➔ Over an hour, this would be:

➔ 1000ml x 12 = 12 L/hour *(an hour has 12 5-minute intervals)*.

➔12 L/hour x 4.825 Cal./L = 57 Cal./hour.
In a person with a surface area of 1.7m^2,

➔ 57 $Cal.hour^{-1}$ / 1.7m^2 = 34 Cal. $hour^{-1}/m^2$.

2) The open-circuit method

- **Device:** a bag that collects expired air during physical activity.

- **Principle:** By knowing the concentration of O_2 in the collected air and the atmosphere, we can measure the difference between them and know how much air was consumed. Then, we calculate the metabolic rate using the same equations mentioned previously.

➔ Factors affecting the metabolic rate:

- Factors associated with an increase in the Metabolic Rate

1) **Younger age:** the metabolic rate calculated for the surface area of the body decreases with age. It is higher in children and less in old people.
2) **Some hormones:**
   a. Thyroid hormone: increases the metabolic rate
   b. Male sex hormones: increase the MR by 10-15%
   c. Growth hormone: increases the BMR by 15-20%
3) **Sympathetic stimulation:** increases the MR.
4) **Exercise:** increases metabolic rate. This increase is well related with the strength of exercise.
5) **Fever:** during infection there is an increase in metabolic rate.

Also, the metabolic rate depends on the daily activities. For a lay in bed all day the metabolic rate is about 1600 Cal/day. Eating process increases the rate by 200 Cal, exercise increases the metabolic rate etc…

- Factors associated with a decrease in the MR

1) **Sleep:** decreases the MR
2) **Malnutrition:** decreases the MR
3) **Tropical climate المناخ الاستوائي:** people living in tropical regions have lower metabolic rates.

[Dietary balance]

Food is the main source of energy for our bodies, and we must consume it in amounts that satisfy our metabolic needs. Food contains different proportions of carbohydrates, proteins, fats, vitamins, and minerals.

The energetic value of food depends on its constituents:

1) **Carbohydrates: provide 4Cal/g.**
2) **Fats: provide 9Cal/g.**
3) **Proteins: provide 4Cal/g.**

- **Notice:** fats provide more than double the energy per gram compared to carbohydrates and proteins.

Vitamins and minerals do not provide energy but are essential for metabolic processes.

A decrease in the consumption of one or more elements leads to malnutrition and disease. ➔ For example, the body requires intake of around 30-55g/day of protein to maintain its normal stores. A **chronic deficiency in dietary protein** leads to a condition known as **Kwashiorkor** – a type of malnutrition that is characterized by:

1) Growth failure
2) Lethargy
3) Mental depression
4) Hypoproteinemic edema (swelling of the legs and abdomen) (due to decreased plasma oncotic pressure from low albumin)

According to the laws of thermodynamics, ***energy is neither created nor destroyed, but it transforms from one form to another***. ➔ So, we need to maintain a balance between energy input (food) and output/ energy expenditure (internal and external work).

Balance can be either neutral, positive, or negative.

1) **Neutral** balance ➔ the food (input) **equals** the expenditure (output)

2) **Positive** energy balance ➔ the food (input) is **greater than** the expenditure (output) ➔ The extra amounts are stored in our bodies as excess weight.

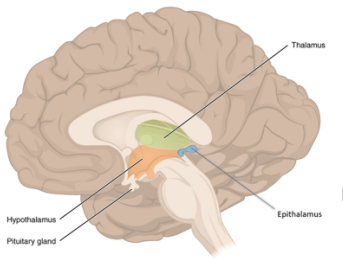
3) **Negative** energy balance ➔ the food (input) is **less than** the expenditure (output) ➔ This results in a decrease in body weight

Healthy adults usually maintain a constant body weight by maintaining a long-term balance between the input and output. Which is controlled by systems that regulate the magnitude of input according to the expenditure.

[Regulation of food intake]

➔ Hypothalamic control of food intake:

Hypothalamus = is a small part of the brain that acts like **a control center for your body ➔** It keeps things balanced by controlling things like hunger, temperature, sleep, and hormones



The hypothalamus contains the body's centers that control hunger, appetite, and satiety. They are known as ➔ **feeding and satiety centers**

The hunger center

- **Location**: lateral hypothalamus
- **Function**: stimulation leads to hunger and excess feeding (hyperphagia).

The satiety center

- **Location**: ventromedial nuclei of the hypothalamus.
- **Function**: stimulation leads to a feeling of satiety and decreased feeding.

The feeding centers receive signals from the body stores and cells regarding their energy needs. ➔ These signals govern the feeding behaviors of the body.

Destruction of these centers leads to the opposite of their actions ➔ e.g. if hunger center is destroyed, person will not feel hunger

➔ Other higher centers:

It is thought that other areas in the brain, such as the amygdala and the prefrontal cortex, contribute to the regulation of food intake, but the mechanism is not fully understood.

- Destruction of bilateral amygdales lead to "**psychic blindness**" in the choice of food, which results in poor control over the quantity and quality of eaten food.

➔ Theories of food intake regulation:

[Long-term regulation]

1) **Glucostatic theory** of hunger and feeding regulation

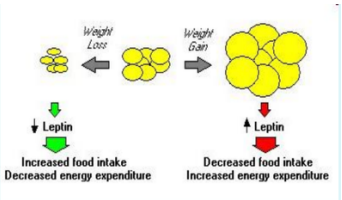
- The basis for this theory is that **low blood glucose causes hunger**. **An increase in blood glucose after a meal causes satiety**.

- Some proposed that the effect is mediated by **insulin**.
  ⬆ in blood glucose leads to ⬆ in insulin, which in turn ⬆ glucose utilization and ATP production by the cells, which sends neural signals to the hypothalamus to stop feeding.

2) **Lipostatic theory**

- The basis for this theory is that the **presence of fat products in the blood** (like ketoacids and fatty acids**) inhibits feeding**.

- Others suggested that the **presence of high fat storage** results in the secretion of the **leptin hormone**. ➔ **Leptin**, also known as the satiety hormone, is a hormone produced by adipose cells and **acts on the hypothalamus to reduce feeding**. It is **responsible for long-term regulation of body weight**.



3) **Aminostatic theory**

- This theory states that the concentration of amino acids in the blood affects feeding behaviors. **Higher levels induce satiety, and low levels trigger hunger**.

4) **Effect of body temperature**

- **Cold conditions** lead to **overeating**, while in **warm conditions,** there is a tendency to eat less because **cold increases the metabolic rate** (to maintain body temperature), which in turn increases the need for energy.
- The theory is that there are **interactions between the temperature regulatory centers and the feeding centers** in the hypothalamus that increase feeding in cold conditions to provide more stores and nutrients to match the increase in the metabolic rate.

5) **Psychosocial factors**

- **Eating habits are influenced by social norms**. We're accustomed to three meals per day, so missing one meal can lead to a feeling of hunger (**psychological**).
- **Food is also considered a pleasurable activity** that people enjoy together. The smell and taste of food increase appetite and food intake.

[Short-term regulation]

These have rapid effects on feeding

1) **Gastrointestinal filling**

- Eating causes distention of the stomach and duodenum, which sends **signals via the vagus nerves to suppress the feeding** centers and stop food intake.

2) **Hormonal factors**

- Presence of food in the digestive tract leads to the release of many hormones that affect eating behaviors, mainly by **suppressing feeding**, for example:
  a. **Cholecystokinin** ➔ release in response to fat in the duodenum.
  b. **Insulin** ➔ released in response to food in the duodenum and glucose in the blood.
  c. **Gastric inhibitory peptide (GIP) or glucose-dependent insulinotropic polypeptide** ➔ released in response to fats and carbs in food.

(This hormone acts also to increase insulin release from pancreatic islets.)

3) **Suppression by oral receptors**
- Oral processes like **salivation, chewing, tasting, and swallowing can interfere with feeding behaviors**.
- The main mechanism is by "metering" the amount of food eaten, so after a certain amount has passed through the oral cavity, feeding is inhibited.

➔ These long- and short-term factors regulate food intake by sending signals to the hypothalamus. Some neurotransmitters are released in the area and affect feeding behaviors, such as:
1) Neuropeptide Y
2) Serotonin
3) Dopamine

[Obesity]

Obesity results from a long-term, continuous imbalance between food intake and energy expenditure **(positive energy balance**), which results in deposition of fat in adipose tissue stores.

Obesity: it is an **increase in the amount of adipose tissue** by more than 20% of ideal body weight.

Overweight: it is an **increase in body weight** (which can be adipose tissue or muscle mass).

➔ **Causes of obesity:**

As mentioned before, we have long and short-term regulatory mechanisms that regulate food intake. The abnormalities in these regulatory mechanisms can lead to decreased response of the hypothalamic centers to signals that inhibit feeding, which results in an uncontrolled intake of food. These include:

1) **Neurogenic abnormalities**
- **Abnormal functional or structural organization of the hypothalamic nuclei** that results in a change in the response to the regulatory mechanisms and impaired satiety.
- For example, lesions in the satiety center leading to excessive eating. Or genetic absence in leptin receptors. Or abnormalities in the feeding center.

2) **Genetic factors**
- Obesity runs in families, and many genetic abnormalities have been implicated in obesity.
- For example**, congenital absence of the OB gene (leptin-producing gene in adipocytes)** or the presence of a mutated gene results in obesity.
- Other abnormalities were found in the leptin receptor-producing gene.

3) **Psychogenic factors**
- **Eating habits can influence the development of obesity**. The norm is to eat three filling meals per day.
- For some people, eating can be an **emotional response or related to stress**. In others, it's **related to mental illnesses** like depression.

4) **Childhood overnutrition**
- Overfeeding a child results in **the formation of more fat cells**, which increases the capacity of adipose cells to store more fat. This can result in lifetime obesity.
- In contrast, in adults, overnutrition results in **cell hypertrophy** of the existing fat cells rather than the formation of new fat cells. (increase in size, not number).

5) **Other causes:**
   a. Lack of exercise
   b. Disorders of the endocrine system, such as hypothyroidism.

➔ **Treatment of obesity:**
It is a multidimensional process that involves decreasing the input and increasing the expenditure.
1) **Decreasing input**: controlled diet or other procedures, such as using drugs that inhibit feeding centers.
2) **Increasing output**: exercise.
3) **Manage underlying conditions**

[Inanition]

Inanition = the opposite of obesity, which is caused by long-term decreased availability of food (input) or excessive expenditure (**negative energy balance**). It can also be related to some psychogenic or hypothalamic abnormalities.

Causes may include conditions like **anorexia nervosa**, where the patient loses all desire to eat food due to psychological problems, which can lead to severe inanition (cachexia هزال).
Or **destruction of hypothalamic hunger centers**.

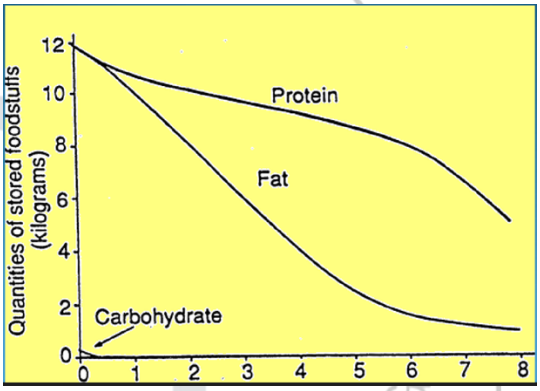
[Depletion of body stores during starvation]

1) **Carbohydrates**
   - The **main and preferred source of energy** in the human body is **carbohydrates**.
   - Their availability is limited, and some are stored as glycogen in the liver and muscles ➔ however, the body stores a small amount of glycogen only.
   - **Glycogenolysis** is the process of breaking down glycogen into glucose to replenish the metabolic pool. This supplies the body for a few hours ➔ Therefore, if there is starvation, after few hours the body will begin using other stores (fat and proteins) to provide energy supply for the body needs.

2) **Fats**
   - The energy stored in fat is **100 times greater** than the energy provided by carbohydrates.
   - The body begins using fat stores at a constant rate over the starvation period.
   - Fats are broken into ketone bodies and fatty acids, which **induces acidosis in the body**.
   - Ketone bodies can cross the blood-brain barrier and are used for energy by the brain.

3) **Proteins**
   - Proteins undergo three phases of depletion: rapid, slow, and then depletion until death:

1) First phase: **rapid depletion** of proteins that are easily mobilized from the protein stores. These are usually used for direct metabolism and the formation of glucose during gluconeogenesis.
2) Second phase: a **decrease in the rate of depletion and gluconeogenesis**.
3) Third phase: **occurs after the depletion of all fat stores** (5-6 weeks of starvation). This phase will be followed by death.



The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Physiology

Digestion and Absorption

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[Overview]

➔ What we will talk about in this lecture:

1) General considerations
    a. Basic mechanism of digestion
    b. Basic anatomy of absorption
2) Digestion and absorption of carbohydrates
    a. Digestion of carbohydrates
    b. Absorption of carbohydrates
3) Digestion and absorption of proteins
    a. Digestion of proteins
    b. Absorption of proteins
4) Digestion and absorption of lipids
    a. Digestion of lipids
    b. Absorption of lipids
5) Absorption of water and electrolytes
    a. Absorption of water
    b. Absorption of electrolytes
6) Absorption of vitamins

[General considerations]

- **Digestion الهضم:** The breakdown of complex food substances into smaller, soluble molecules that can be absorbed.

- **Absorption الامتصاص :** The process by which digested molecules pass across the intestinal epithelium into the blood or lymph for distribution to the body.

➔ Why do we need digestion?

- The body's primary food groups are **carbohydrates, proteins, and lipids**. However, they cannot be absorbed in their original form due to their large size, as it is difficult for them to cross the gastrointestinal mucosa. Therefore, they must undergo extensive digestion before absorption.

- These major compounds (macromolecules) are like Lego chains made from multiple small building blocks.
    1) **Carbohydrates**: are built from multiple *saccharides* (**polysaccharides**).
    2) **Proteins**: are built from multiple *amino acids* (**polypeptides**).
    3) **Lipids**: are built from multiple *fatty acids,* and glycerol forming **triglycerides**.

➔ Basic mechanism of digestion:

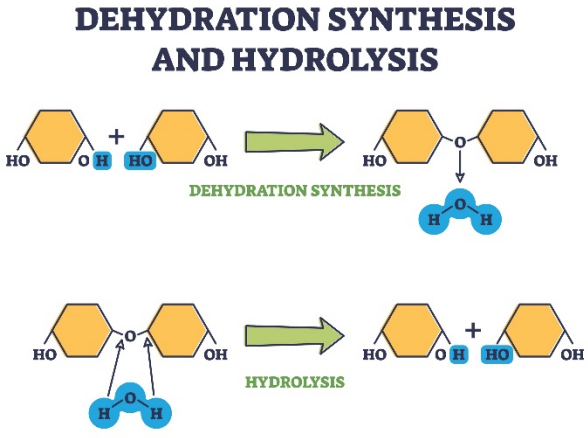
Digestion: the process of breaking down. It's mediated by various enzymes that breakdown carbohydrates, proteins, and lipids to smaller molecules that are more easily absorbed.

To understand how digestion works we need to know how these large molecules are produced!!! ➔ These large molecules are formed through a process called **Condensation**, in which a water molecule is removed from each adjacent building block, connecting them.

- A hydrogen atom (H) is removed from the first molecule.
- A hydroxyl group (OH) is removed from the second molecule.
- The removal of water forms bonds between the building blocks.

Digestion, or the breakdown of these compounds, occurs via the reverse process, **hydrolysis**, in which a water molecule is added to break the bond between the smaller building blocks.

- A hydrogen ion (H^+) is added to the first molecule.
- A hydroxide ion (OH^-) is added to the second molecule.



➔Hydrolysis of carbohydrates:

Carbohydrates are formed by the condensation of small molecules called monosaccharides into disaccharides and polysaccharides.

Digestion of these molecules is carried out by multiple enzymes secreted by the gastrointestinal tract.

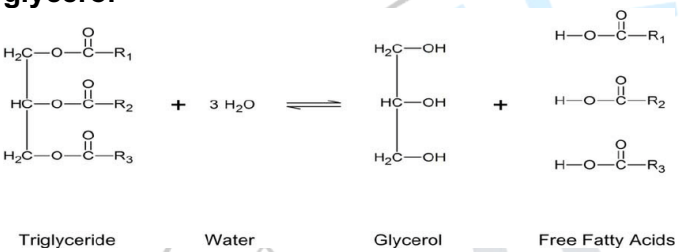
Polysaccharide/disaccharide + water ➔ Monosaccharide + monosaccharide + ... etc.

➔**Hydrolysis of lipids:**

Remember the main types of lipids in our diet:

- **Triglycerides:** Glycerol + 3 fatty acids (most dietary lipid is in this form)
- **Phospholipids:** Lipids with a phosphate group
- **Cholesterol-esters:** Cholesterol + 1 Fatty acid

Triglyceride hydrolysis requires 3 water molecules to break remove the 3 FAs from glycerol



➔ **Hydrolysis of proteins:**

Proteins are composed of amino acids linked by peptide bonds formed during condensation. ➔ The addition of H_2O reverses this process, breaking polypeptides down into amino acids.

➔ Basic Anatomy of Absorption:

Absorption is the process by which digested nutrients move across the gastrointestinal epithelium into the blood or lymph to be distributed to the body for use or storage.

- It usually occurs in specialized epithelial cells.

➔ **Absorption across the GI tract:**

- **Esophagus**: no absorption
- **Stomach**: minimal absorption
- **Small intestines**: most of the absorption occurs here
  - Most nutrients are absorbed before reaching the ileum (the last part of the small intestine)
- **Large intestines (colon)**: mainly absorption of water and electrolytes.

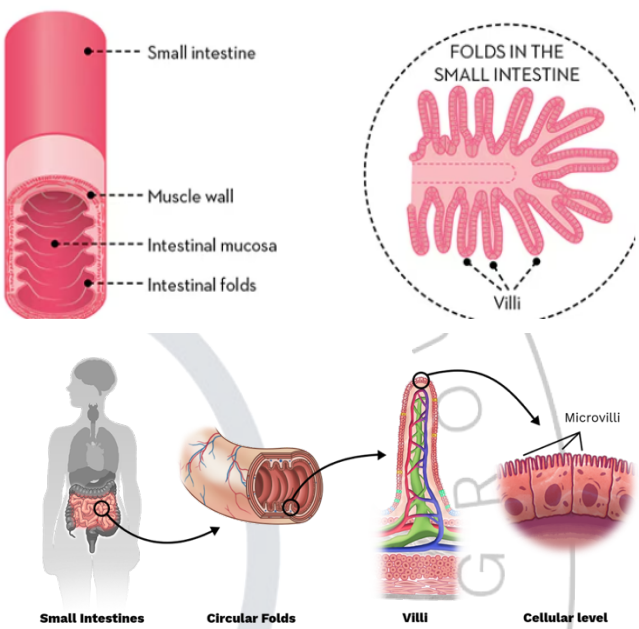
➔ **Why does the majority of absorption occur in the small intestine?**

The small intestines have specialized structures that massively increase their absorptive capacity by **increasing the surface area available for absorption**.

- **The small intestinal mucosa has:**

1) **Folds**➔ called **Folds of Kerckring** (circular folds) increase the surface area by 3-folds.
2) **Villi** ➔ which are small, finger-like projections that increase the surface area by 10-fold
3) **Microvilli**➔ microscopic projections on epithelial cells increasing surface area 20-fold.

This leads to a **Total increase in absorptive surface area 600-fold**.

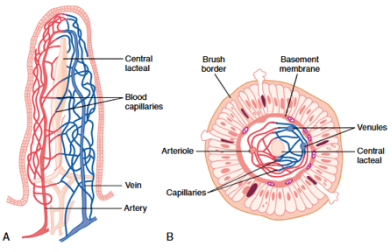


➔ **What are the intestinal villi?**

These are **finger-like projections** that form the intestinal mucosa. They have a specialized structure that contains:

1) A **capillary network**, which removes absorbed nutrients to the circulation rapidly. This maintains a concentration gradient between the lumen and the blood in the capillaries.
2) A **lymphatic network** of **lacteals** (small lymphatic vessels) that removes absorbed lipids and maintains a gradient for lipid absorption.

An illustration of an intestinal villus with a cross-section that shows the arrangement of blood capillaries and the lacteal within it.



Important note: digested carbs and proteins are absorbed into the blood directly, however digested lipids are absorbed first into the lymphatics (lacteals) which are then carried to the blood

➔Other structures that aid in digestion and absorption

1) **Brush border enzymes**:
   - Located on the luminal membrane of absorptive cells (microvilli) ➔ meaning: these enzymes are anchored to the surface of the intestinal epithelial cells and are facing towards the lumen of the intestine
   - Responsible for final digestion of carbohydrates and proteins.
2) **Enteric innervation**:
   - Mainly the submucosal plexus.
   - Regulates intestinal secretion of secretory cells and blood flow to the intestines.
3) **Smooth muscle cells of the muscularis mucosa**:
   - Allow villi to move and the luminal folds to shift.
   - Enhance mixing of chyme and maximize exposure to the absorptive surface.

[Digestion and absorption of carbohydrates]

Carbohydrates are complex molecules that exist in different forms from multiple dietary sources. These forms include:

1) **Starch**: The most abundant dietary carbohydrate. It is a branched polymer of glucose (polysaccharide) with units connected by **α-1,4 with α-1,6 bonds** at branch points.
2) **Sucrose** (sugar cane/table sugar): a disaccharide formed by glucose and fructose.
3) **Lactose**: a disaccharide formed by glucose and galactose. Primarily found in milk.
4) **Maltose:** a disaccharide formed by 2 glucose molecules
5) **Cellulose**: a polymer of glucose units connected through **β-1,4** linkages. Humans lack the enzymes required to digest the **β** bonds in cellulose; therefore, it is not a source of nutrition, and any ingested cellulose is excerted in feces

We ingest monosaccharides, disaccharides and polysaccharides

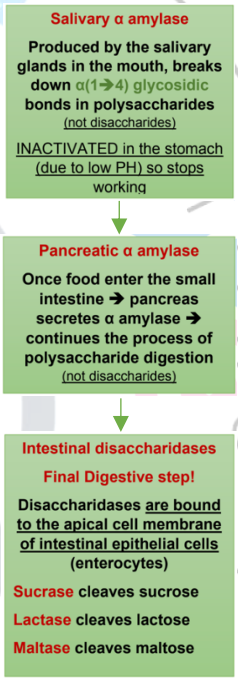
BUT

we **can only absorb monosaccharides** (in the small intestine)

SO?
We have to breakdown di- and polysaccharides into monosaccharides

➔ Digestion of carbohydrates:

➔ Overview of steps:



➔ Important points to remember:

- We start with polysaccharides ➔ converted to disaccharides ➔ converted to monosaccharides ➔ absorption of monosaccharides!

- Carbohydrate digestion begins in the oral cavity, continues in the stomach, and is completed in the small intestine. Multiple enzymes participate at different levels.

➔ **Carbohydrate digestion enzymes:**

#1: Salivary α-amylase (ptyalin)

1) **Source:** Salivary glands (mainly the parotid gland)
2) **Function:** Hydrolyzes starch into the disaccharide maltose and other small, branched polymers of glucose called α-limit dextrins.
3) **Site of action:** Oral cavity (inactivated in the stomach)
4) **Characteristics:**
   - Its optimal activity at neutral pH
   - It becomes inactive once the food mixes with stomach acid and pH falls below 4.
5) **Extent of digestion:**
   - Minimal digestion occurs in the mouth.
   - Digestion may continue in the center of the food bolus in the stomach where pH remains >4.
   - Digests approximately 20–40% of ingested starch.

#2: Pancreatic α-amylase

1) **Source:** Pancreatic acinar cells
2) **Function:** Further hydrolysis of starch into:
   - Maltose (two glucose molecules)
   - Maltotriose (three glucose molecules)
   - α-limit dextrins.
3) **Site of action:** small intestines (mainly the duodenum)
4) **Characteristics:**
   - More potent (higher activity) than salivary amylase
5) **Extent of digestion:**
   - Digests approximately 50–80% of starch

#3: Brush border enzymes

1) **Source:** Luminal membrane of intestinal epithelial cells that line the intestinal mucosa (they are anchored to the surface of the cells)
2) **Function:** Final hydrolysis of polysaccharides and disaccharides into monosaccharides.
3) **Site of action:** small intestines (the brush border of the duodenum)
4) 4 enzymes are found at this site:
   - **Lactase**: breaks lactose into glucose and galactose.
   - **Sucrase**: splits sucrose into fructose and glucose.
   - **Maltase**: splits maltose and other glucose polymers to glucose
   - **Dextrinase**: breaks the **α-1,6 linkage** in α-limit dextrins.

Final products of digestion that are absorbed: **glucose, fructose, and galactose**.

➔ Absorption of Monosaccharides:

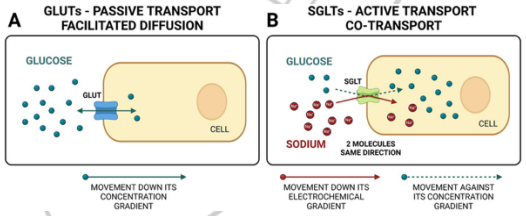
Carbohydrates are absorbed primarily as monosaccharides in the **small intestine**.

[Glucose absorption]

Glucose is the most abundant form of monosaccharides absorbed by the body ➔ Its absorption occurs in two main mechanisms:

1) Sodium-dependent co-transport (Secondary active transport)

- Na^+ is actively pumped out of the enterocyte at the **basolateral membrane** by the Na^+/K^+ ATPase. This lowers intracellular Na^+ concentration.
- The decrease in sodium levels inside the cell causes Na^+ to move from the intestinal lumen through the brush border into the cell. The channel that mediates this process is **Na^+-glucose co-transporter (SGLT-1)** which requires the binding of other substances, such as **glucose**, to function.
- This process depends on the pumping of sodium out of the cell, so it's considered **secondary active co-transport**.
- At the end, glucose exits the cell at the basolateral membrane by **facilitated diffusion** into capillary blood of the villus.



2) Solvent drag (Paracellular transport)

- When the concentration of glucose in chyme is high, it increases the osmotic pressure in the paracellular space.
- This increases the flow of water through the tight junctions between cells, which carries anything dissolved in fluids so, dissolved glucose may be carried along with this water flow.
- This mechanism becomes significant when luminal glucose concentration is very high.

[Galactose absorption]

Absorbed by the **same Na^+-dependent co-transport mechanism** as glucose. **Secondary active co-transport**.

[Fructose absorption]

Unlike glucose and galactose, fructose is absorbed by **facilitated diffusion** through a specific transporter via (**GLUT-5**). This process is independent of sodium. Fructose exits the cell at the basal membrane as it diffuses passively (via GLUT-2).

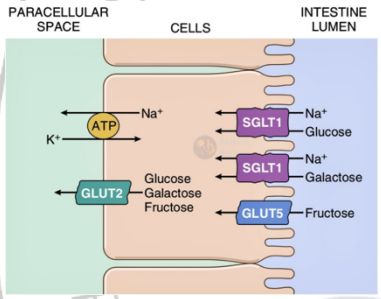
Summary

#1: Entry from lumen into enterocyte:

- Glucose & galactose ➔ via SGLT1 (Na+ dependent pathway)
- Fructose ➔ GLUT5 (Na+ independent pathway)

#2: Leaving enterocyte to the blood

- ALL 3 via GLUT2 (Na+ independent pathway)



Clinical glimpse:

Lactose intolerance inability to tolerate eating lactose (milk containing foods) due to **lactase enzyme deficiency** (can be genetic OR acquired) ➔ **What happens?**

Remember, we said we can only absorb Monosaccharides! ➔ So, if we have deficiency of lactase ➔ lactose left undigested and can NOT be absorbed!

Unabsorbed Lactose consequences? ➔ Lactose Remains inside the intestinal lumen ➔ draws in water into the lumen by the principle of osmosis (unabsorbed lactose acts as an osmotically active substance)

So, **diarrhea**!!

+

Normal Intestinal bacteria ferment lactose (degrade it to produce H2 gas/ CO2 / acids)

So,

(انفاخ و غازات!) **flatulence/bloating**

[Digestion and absorption of proteins]

Proteins are polymers of amino acids linked together by peptide bonds. Approximately 60 grams of protein are digested and absorbed by the gastrointestinal tract each day. This protein load is derived not only from dietary intake but also from endogenous sources, including mucus, digestive enzymes, and desquamated epithelial cells.

- Proteins can't be absorbed by the intestine (they are too large) So! Proteins must be digested first into: **dipeptides / tripeptides & single amino acids ➔ these can be absorbed**

➔ Digestion of proteins:

Digestion of proteins occurs in the stomach and the small intestine, with most of the digestion taking place in the small intestine (So it doesn't start in the mouth like carbohydrate digestion)

- Protein digestion is achieved by **enzymes produced by 3 different organs**:
  1) Stomach (digestion begins here)
  2) Pancreas
  3) Small intestine

#1: Digestion in the stomach ➔ the enzyme Pepsin

Pepsin is the main proteolytic enzyme of the stomach.

- **Source:** Gastric chief cells (from the oxyntic glands)
- **Site of action:** Stomach
- **Function:** Hydrolysis of proteins into smaller peptides and polypeptides
- **Optimal pH to function:** 2–3 (provided by hydrochloric acid in the stomach)
- **Inactivation:** Becomes inactive at pH >5 in the small intestine

In the stomach, food forms a **semisolid mass**, which limits enzyme access to the **surface only**, preventing digestion of the interior of the food bolus. As a result, protein digestion in the stomach is relatively limited. Pepsin is responsible for digesting approximately **20% of ingested proteins**, converting them into smaller polypeptides.

An important characteristic of pepsin is its ability to **digest collagen**, a major component of connective tissue in meat, facilitating further digestion in the intestine.

Important reminder:

Pepsinogen = zymogen (inactive proenzyme) ➔ activated into the active enzyme "Pepsin" by 1 of 2 ways: stomach HCL **OR** other pepsin molecules cleave & activate it called "autocatalytic activation"

#2: Pancreatic Proteolytic Enzymes

Most of the protein digestion occurs in the small intestine through the action of pancreatic enzymes.

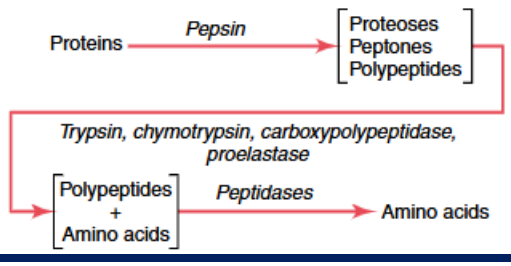
- **Source:** Exocrine pancreas (pancreatic acinar cells)
- **Site of action:** Small intestine
- **Function:** These enzymes continue protein digestion by hydrolyzing polypeptides into small peptides and free amino acids, accounting for the majority of protein breakdown.

The pancreas secretes many different enzymes:

- **Endopeptidases** (-endo means "inside" ➔ cleave peptide bonds that are within the polypeptide chain)
  - Trypsin
  - Chymotrypsin
- **Exopeptidases** (-exo means "outside" ➔ cleave peptide bonds that are at the end of the chain)
  - Carboxypeptidases
  - Aminopeptidases

➔ Why the pancreas secretes multiple different enzymes not just one?

Each enzyme has a different specificity for the amino acid R-groups adjacent to the peptide bond (e.g trypsin cleaves only when the -COOH group of the peptide bond is contributed by arginine or lysine)



#3: Brush border peptidases

- **Source:** Luminal (brush border) membrane of intestinal epithelial cells
- **Site of action:** Small intestine
- **Function:** Brush border enzymes convert small peptides into oligopeptides (di-, tri-, and tetrapeptides) and free amino acids.

#4: Cytosolic Peptidases

- **Source:** Cytosol of intestinal epithelial cells (enterocytes)
- **Site of action:** Inside enterocytes of the small intestine
- **Function:** Hydrolysis of di- and tripeptides into free amino acids
- **Important note:** These enzymes complete protein digestion after peptide absorption into the enterocyte ➔ tri- and di- peptides can enter the small intestinal cells but they CAN'T leave ➔ so they are degraded inside the cells into single amino acids ➔ So, what enters the blood is FREE amino acids ONLY (no di & tri peptides)

➔ Final Products of Protein Digestion

- **~99% amino acids**
- **Small amounts of di- and tripeptides**

➔ Absorption of proteins:

Protein absorption depends on:

- **Molecular size** (amino acids vs peptides)
- **Chemical nature** of amino acids (neutral, acidic, or basic)

Free amino acid absorption

↓

Transported by multiple types of carriers:

1) **Na^+- dependent carriers** ➔
   a. for neutral amino acids
   b. for proline and hydroxyproline
   c. for phenylalanine and methionine
2) **Na^+-independent carriers** ➔ for basic and neutral amino acids

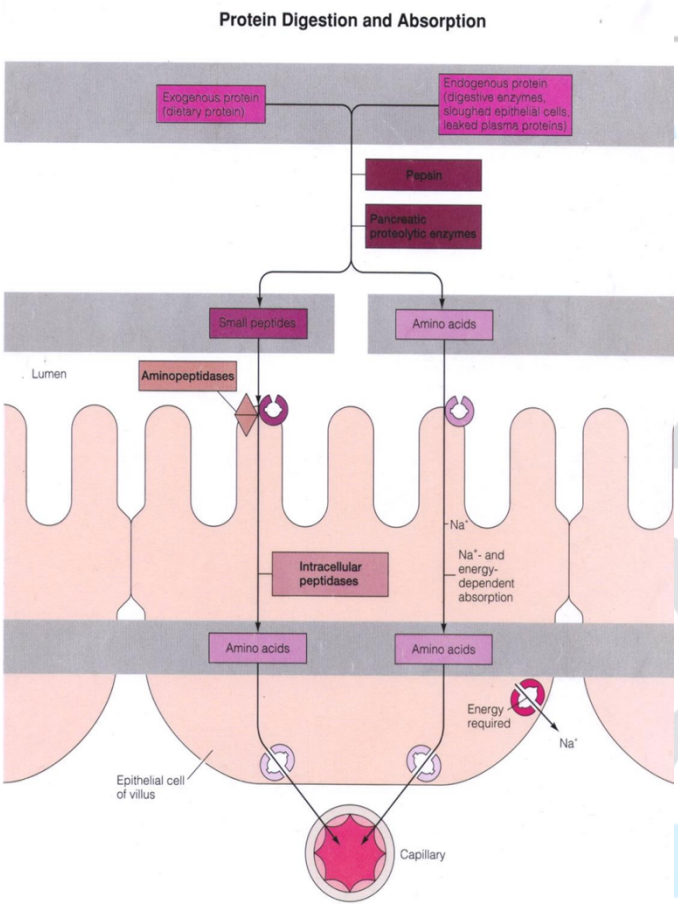
Di- and tripeptides

↓

Enter enterocytes via a **H+ linked peptide transporter** ➔ inside the cells they are broken down into free amino acids

Free amino acids are **released** from enterocytes into the **blood** by sodium-independent transporters on the basolateral membrane (Facilitated diffusion) So, **what enters the blood is FREE amino acids ONLY** (no di & tri peptides)

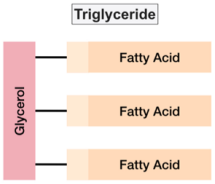
[Summary image of protein digestion/absorption]



[Digestion and absorption of lipids]

Remember the main types of lipids in our diet:

- **Triglycerides:** Glycerol + 3 fatty acids (most dietary lipid is in this form)



- **Phospholipids:** Lipids with a phosphate group
- **Cholesterol-esters:** Cholesterol + 1 Fatty acid

➔Role of Bile and Lecithin in Lipid Digestion and Absorption

Bile is a secretion of the liver that is essential for lipid digestion and absorption ➔ Although bile contains no digestive enzymes, it plays a crucial role by **solubilizing lipids.**

➔Properties of Bile Salts

Bile salts are **amphipathic molecules**, meaning they contain:

- Hydrophobic portion → the sterol nucleus
- Hydrophilic portion → hydroxyl groups, peptide linkage, and amino acid conjugates

➔ Digestion of lipids:

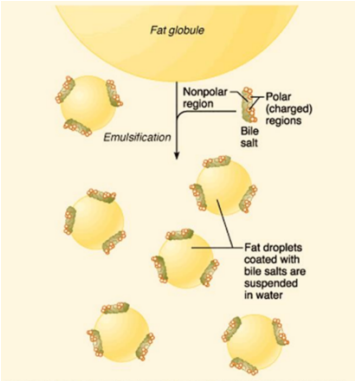
When lipids are found in a fluid environment (like in the intestinal juice) they tend to **clump together** (just like oil since they are hydrophobic & can't mix with water)

↓

Digestive enzymes can only work on the surface since they can't enter the lipid "clump" so what to do??

↓

Emulsification: breaking down of the lipid clump into smaller lipid droplets & so increasing the total surface area ➔ goal: increase surface area available for digestive enzymes to work



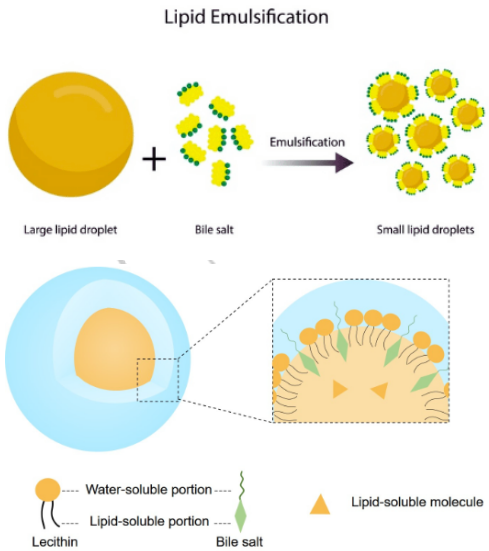
Emulsification occurs in two ways:

1) In the **stomach** ➔ mechanical mixing via peristalsis through brisk mixing (agitation) of fat with the gastric secretions
2) In the **duodenum** (major site), by the Action of **bile salts and lecithin** (a type of phospholipid). ➔ **amphipathic molecules** (have a hydrophilic part & a hydrophobic end)

   Hydrophilic part interacts with intestinal watery fluid

   Hydrophobic part interacts with the lipids

   This decreases the surface tension between fat and the surrounding environment, making it easier for water to break down the fat globules into smaller molecules.



Important reminder: Enterohepatic Circulation

- Bile salts are not absorbed with lipids
- They remain in the intestinal lumen and are actively reabsorbed in the terminal ileum
- Returned to the liver via the enterohepatic circulation

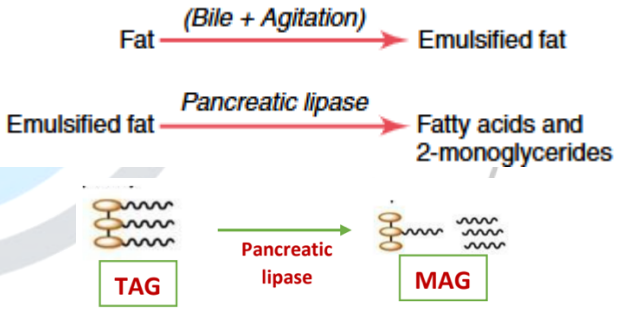
➔Lipid Digestion in the Stomach

- Minimal to no digestion or absorption of lipids occurs
- Bile salts are absent
- Lipids separate from the aqueous portion of the meal
- Fat empties into the duodenum more slowly than other nutrients

➔Lipid Digestion in the Small Intestine

Most lipid digestion occurs in the small intestine, particularly the duodenum.

- Lipids are emulsified into small droplets (0.5–1 μm) by bile salts.
- Different enzymes breakdown the different lipids:
  1) Phospholipids ➔ Phospholipase
  2) Cholesterol-ester ➔ Cholesterol esterase
  3) Triglycerides ➔Hydrolysis occurs through the action of **pancreatic lipases and co-lipase**. It acts on the water-oil interface and breaks the first and third ester linkages between glycerol and fatty acids.
  ➔ The result is: **Two free fatty acids and One 2-monoglyceride**.



- These products, along with cholesterol, phospholipids, and bile salts, remain incorporated within **micelles** (≈5 nm diameter).

➔ Absorption of lipids:

#1: Micelle Formation

- In aqueous environments, lipids and bile salts are arranged in a spherical shape, forming **micelles**. In these micelles, the hydrophobic portion is oriented towards the center, and the hydrophilic portion towards the periphery.

- This arrangement allows:

1- Lipids and other water-insoluble molecules to dissolve in the **core (center) of the micelle**

2- Transport of lipid digestion products through the aqueous intestinal environment

#2: Micelle transport towards the intestinal cells

- The micelles approach the brush border membrane of enterocytes (intestinal epithelial cells)!!
- The surface of these enterocytes is covered by a water rich fluid layer ➔ due to the hydrophilic surface of the micelles they can penetrate this layer to reach the enterocyte surface
- Absorption of lipid digestion products occurs via both passive diffusion

****Important note:** In contrast to carbohydrates and proteins:

- There are no brush border enzymes for lipid digestion
- There is no carrier-mediated transport system for lipid absorption at the luminal membrane

#3: Intracellular Processing of Lipids

Inside the intestinal epithelial cells ➔ reformation of complex lipids happens (the lipids that were broken-down in the intestine are reformed) ➔The following components are re-assembled:

- Triglycerides
- Cholesterol-esters
- Phospholipids

#4: Secretion and transport of the lipids to the lymphatic system

- The synthesized TAG/ cholesterol esters etc. are hydrophobic ➔ they must be packaged into particles that have a hydrophilic surface (so that it can be transported in the plasma) ➔ the hydrophilic surface is provided by phospholipids & Apolipoprotein B48

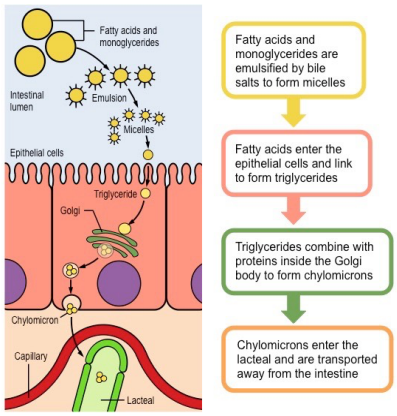
↓

- So, formation of: **Chylomicrons**
  A Lipoprotein = lipid + protein (apolipoprotein b48 in the case of chylomicrons)
- The chylomicron particles are released from epithelial cells by exocytosis into the **lacteals** (lymphatic vessels) ➔ from there they are transported to the blood

****Exceptions:**

- A small amount of short-chain fatty acids and free glycerol
- These molecules are water-soluble
- They diffuse directly into blood capillaries instead of lymphatics

The following illustration summarizes the entire process:



[Absorption of water and electrolytes]

➔ Absorption of water by osmosis:

Water is absorbed almost entirely by **osmosis**.

➔ Mechanism of Water Absorption:

- **Water absorption is driven by Na+ absorption** ➔ When Na^+ is actively transported out of the enterocyte at the basolateral membrane by the Na^+/K^+ pump ➔ This creates an osmotic gradient that causes water to move towards the capillaries (absorption):
  - Through epithelial cells (transcellular route)
  - Through tight junctions between cells (paracellular route)
- Water is then rapidly removed from the interstitial space by capillaries, which maintains the osmotic gradient and allows continuous absorption.

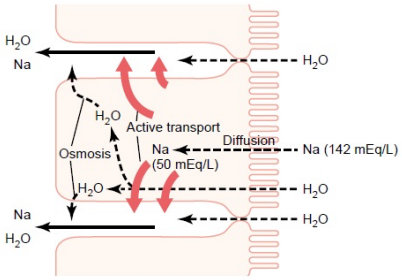


Figure 65–8

Absorption of sodium through the intestinal epithelium. Note also osmotic absorption of water—that is, water "follows" sodium through the epithelial membrane.

➔ **Water Secretion:**

- Water may move from the circulation into the intestinal lumen when hyperosmolar chyme enters the intestine from the stomach (hyperosmolarity of food pulls water towards the intestinal lumen)

➔ Absorption of electrolytes:

[Absorption of Sodium (Na^+)]

Sodium is absorbed actively from both the small intestine and the colon.

- At the luminal membrane, sodium enters the cell mainly by passive diffusion.
- At the basolateral membrane, sodium is actively pumped out by the Na^+/K^+ ATPase.
- Rapid removal of Na^+ from the cell is essential to maintain the electrochemical gradient.

Mechanisms of Sodium Absorption

- Co-transport with monosaccharides and amino acids (Na+ entry into intestinal cells is accompanied by sugar/amino acid entry)
- Passive diffusion, driven by electrochemical gradients

Regional Absorption

- Sodium absorption is greatest in the duodenum
- It gradually decreases distally (caudad) along the intestine

➔ **Effect of Aldosterone on sodium absorption:**

- Aldosterone is a hormone secreted by the adrenal glands in states of:
    1) Dehydration
    2) Low blood pressure
- Effects:
  Increases Na^+ absorption by enhancing:
    - Sodium Transporters
    - Enzyme activity
- Acts mainly in the colon
- Promotes conservation of sodium and water, preventing excessive loss in feces

[Absorption of chloride (Cl^-)]

- Chloride is absorbed mainly in the upper small intestine (duodenum and jejunum). ➔ A smaller amount of Cl^- is absorbed in the ileum and large intestine.

- Absorption occurs by passive diffusion.

- Chloride absorption is driven by sodium absorption:
    - As Na^+ is absorbed, an electrical gradient is created
    - Cl^- follows Na^+ to maintain electrical neutrality (*Na^+ has a positive charge, Cl^- has a negative charge*).

[Absorption of potassium (K^+)]

- Potassium is absorbed passively in the small intestine.
- In the colon, potassium is usually secreted in exchange for sodium.

[Absorption of calcium (Ca^{2+})]

- Calcium is absorbed actively throughout the small intestine.

- Mechanism:

1) Calcium binds to a carrier protein at the brush border membrane, which transports it into the cell
2) Once in the cell, it binds to a compound called **calbindin**, a cytosolic calcium-binding protein, which transports it across the cell.
3) It is then actively pumped out of the cell at the basolateral membrane.

- Regulation:

Calcium absorption is increased by:

- Vitamin D
- Parathyroid hormone

[Absorption of iron (Fe^{2+})]

- Iron can exist in **two** forms:
  1) Ferrous iron (Fe^{2+}) ➔ better absorbed
  2) Ferric iron (Fe^{3+})

- Absorption mainly occurs in the **upper part of the small intestines** (duodenum and proximal jejunum)

- The absorption mechanism is unclear; multiple ones have been proposed:
  1) Active transport at the luminal membrane
  2) Protein-bound: a protein called apoferritin is secreted by the epithelial cells, and it binds to ferrous iron (Fe^{2+}), forming ferritin. This complex is transported into the cell by receptor-mediated endocytosis.

- **Fate of Absorbed Iron**
  - Ferritin remains stored in epithelial cells, and when needed, iron is transported into the blood bound to transferrin.
  - If it wasn't used, iron is lost when cells are desquamated (intestinal lining renewal). This prevents excess iron from entering the blood, as it can be toxic. This is called a **mucosal block.**

- Factors that **enhance** iron absorption:
  1) Vitamin C (patients are always advised to take oral supplements with orange juice, or think of eating spinach, which is rich in iron, with lemon)
     - Vitamin C reduces ferric iron to ferrous iron which is easier to absorb ($Fe^{3+} \rightarrow Fe^{2+}$)
  2) Acidic pH in the stomach

  (hence why excessive use of proton pump inhibitors, which are drugs that inhibit HCL secretion might cause iron deficiency).

- Factors that **inhibit** iron absorption
  1) Phosphates
  2) Oxalates
  3) Phytic acid (found in cereal)
  4) Pancreatic juice

[Absorption of vitamins]

Most vitamins are absorbed in the upper part of the small intestine, except for Vitamin B_{12}.

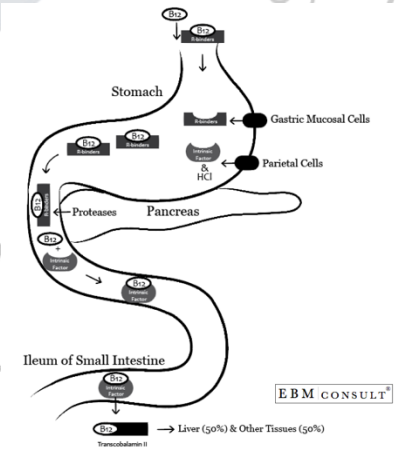
➔ **Absorption of Water-Soluble Vitamins:**
- Most are absorbed passively in the duodenum and jejunum
- Exceptions (absorbed actively):
  - Vitamin C
  - Vitamin B_1
  - Vitamin B_{12}

➔ **Absorption of Fat-Soluble Vitamins (A, D, E, K):**
- Follow the same pathway as lipids
- Solubilized in micelles
- Incorporated into chylomicrons
- Transported via the lymphatic system

➔ **Absorption of Vitamin B_{12}:**

- Requires **intrinsic factor**, secreted by oxyntic (parietal) cells of the stomach

- Absorption steps:
  1) Vitamin B_{12} binds to **R-binders** in the stomach
  2) The complex passes to the duodenum
  3) B_{12} is released from the R-binders and binds to **intrinsic factor**
  4) The intrinsic factor–B_{12} complex travels to the ileum
  5) Absorption occurs in the **ileum**



The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Physiology

Physiology Lab

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[Contraction of Smooth Muscle in the Small Intestine]

➔ **The experiment performed in this physiology lab demonstrates <u>the contraction of the smooth muscles in the small intestines</u>.**

The aim of the experiment:

1) To observe the spontaneous rhythmic contractions of the small intestine.
2) To investigate the effect of acetylcholine (ACh) and atropine on these contractions.

[Equipment]

- Small pieces (2–3 cm) of rat small intestine
- Glass hook
- Organ bath
- Tension transducer
- Computer software for recording and analyzing signals

- The **organ bath** contains a <u>warm</u> (37 °C) <u>oxygenated physiological buffer solution</u>. This is **essential to maintain the viability** of the small intestinal tissue.

- The **tension transducer** is used to **measure muscle contractions** and converts **mechanical force into electrical signals**.

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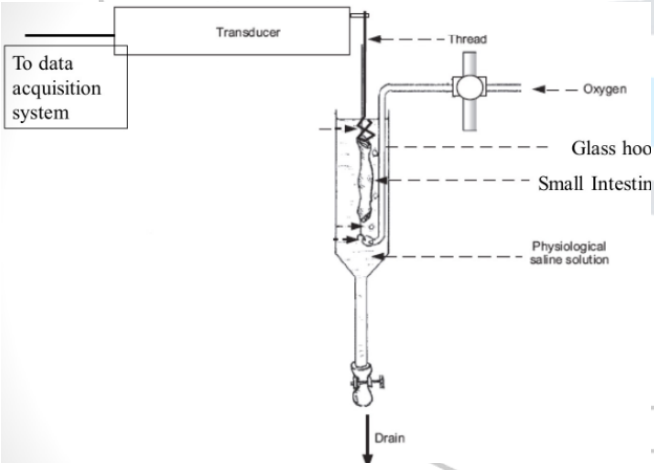
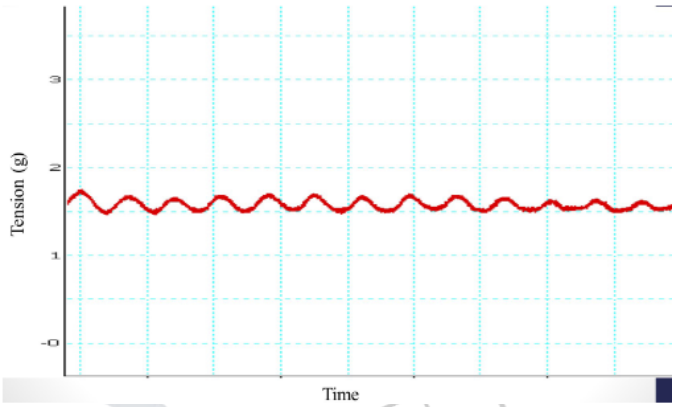


[Method]

<u>PART 1</u>

- The pieces of the small intestines (SI) are hung vertically by a thread to a glass hook in an organ bath.
- The SI is connected to a tension transducer by a thread.
- The tension transducer converts the mechanical contractions of the intestinal muscle into electrical signals.
- These signals are transmitted to a data acquisition system, and the software displays them as a graph showing tension versus time.



The graph produced by the recording system demonstrates **<u>that rhythmic contractions occur spontaneously in the smooth muscle</u>** of the small intestine, even in the absence of external neural or hormonal stimulation.

<u>PART 2</u>

Addition of ACh, followed by Atropine.

- After mounting the tissue, the preparation is allowed to rest for 15–20 minutes. This resting period allows the intestinal smooth muscle to recover its normal physiological activity after handling.
- Acetylcholine is added, followed by atropine, to determine their effect on muscle contraction. The signals are again displayed by the software as a graph of tension vs. time.
  1) Ach causes increased contractions
  2) Atropine (Ach receptor antagonist) causes decreased contractions

[Discussion]

- Phasic (rhythmic) contractions
Smooth muscle in many regions of the gastrointestinal tract undergoes phasic contractions, which are periodic cycles of contraction and relaxation.

These rhythmic contractions occur in several parts of the GI tract, including:
- Esophagus
- Antrum of the stomach
- Small intestine

Importantly, smooth muscle cells are capable of contracting rhythmically even in the absence of neuronal or hormonal stimulation, indicating that this activity is an intrinsic property of gastrointestinal smooth muscle.

- Slow waves
Slow Waves are rhythmic **fluctuations in the resting membrane potential** of smooth muscle cells.

Slow waves are:
- Periodic oscillations of the membrane potential
- Characterized by an upstroke, plateau phase, and repolarization
- Not true action potentials
- Present continuously, regardless of whether contractions occur

Slow waves are generated by specialized pacemaker cells known as the **Interstitial Cells of Cajal (ICC)** ➔ These cells function as the electrical pacemakers of the gastrointestinal tract.

Slow waves determine the **maximum frequency at which contractions can occur** at a particular location in the GI tract.

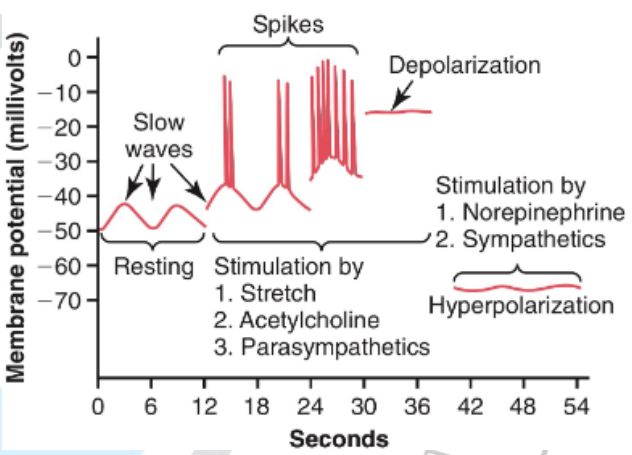
The frequency of slow waves varies along different regions of the gastrointestinal tract ➔ Typical frequencies in humans include:
1) 2–3/min in the stomach
2) ~12/min in the duodenum (highest)
3) 8–9/min in the ileum

On their own, they **do not** cause contraction. When the membrane potential exceeds -40mV, it triggers a "**spike potential**" that causes a contraction.

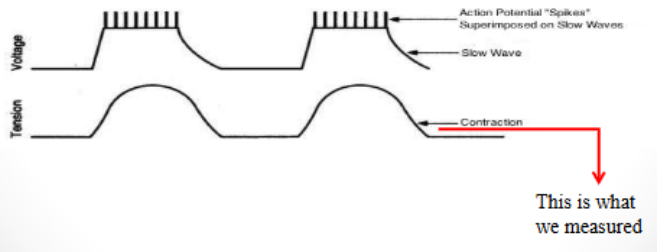
Spike potential is a transient membrane depolarization that occurs **on top** of the slow wave, leading to a contraction.

Spike potentials are:
- Transient membrane depolarizations
- Superimposed on the plateau phase of the slow wave
- Responsible for triggering actual muscle contraction

They are stimulated by:
1. Stretch of the intestinal wall
2. Acetylcholine
3. Certain gastrointestinal hormones



In this experiment, the equipment measures **mechanical contractions of the small intestine**, not the electrical slow waves themselves.



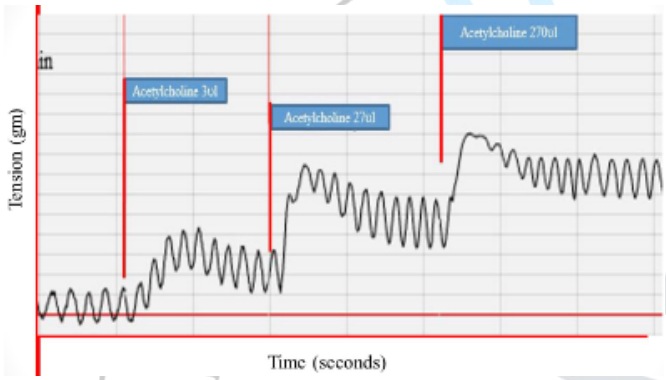
- Effect of acetylcholine

ACh is considered the major **excitatory** neurotransmitter in the small intestine.
It is released by:

1) Enteric neurons
2) Parasympathetic fibers (vagus nerve)

It increases the contractile force of the smooth muscle by

- **Increasing the number of spike potentials** (not slow wave frequency).
- **Acting on M3 muscarinic receptors**.



- Effects of atropine

Atropine is a **competitive antagonist of muscarinic receptors** ➔ It blocks the action of acetylcholine by competing for the same muscarinic receptor binding sites. ➔ As a result:

- The contractile effect of acetylcholine is inhibited
- Intestinal motility decreases

The use of atropine in this experiment confirms that the contractile response to acetylcholine is mediated through muscarinic receptors. (**ACh's effects are receptor-mediated**)