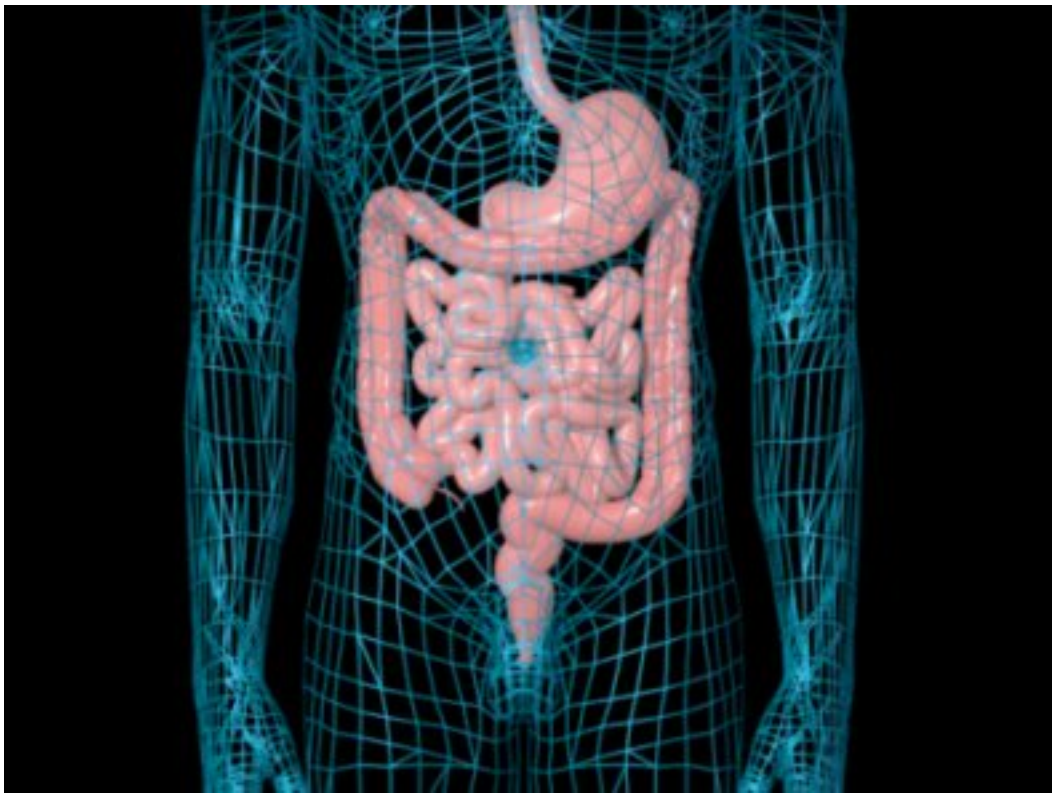
GASTROINTESTINAL PHYSIOLOGY

PHYL 301



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TOPIC 1 INTRODUCTION TO PHYSIOLOGY: OBJECTIVES

1. Understand the four basic GI processes: motility, secretion, digestion and absorption.
2. Motility: Differentiate between mixing and propulsive movements in the GI tract lumen.
3. Secretions: Understand how GI exocrine glands produce and secrete their products.
4. Digestion: Outline the enzymes involved in, and the products of, the digestion of proteins, fats and carbohydrates.
5. Absorption: Describe the sites of nutrient absorption in the GI tract
6. Gross Anatomy: Identify the GI tract organs and the accessory organs that comprise the GI system.
7. Anatomy: Describe the 4 layers of the wall of the GI tract and state the function of each.
8. Describe how intrinsic muscle excitability, the enteric nervous system, the autonomic nervous system and hormonal influences regulate GI tract function.

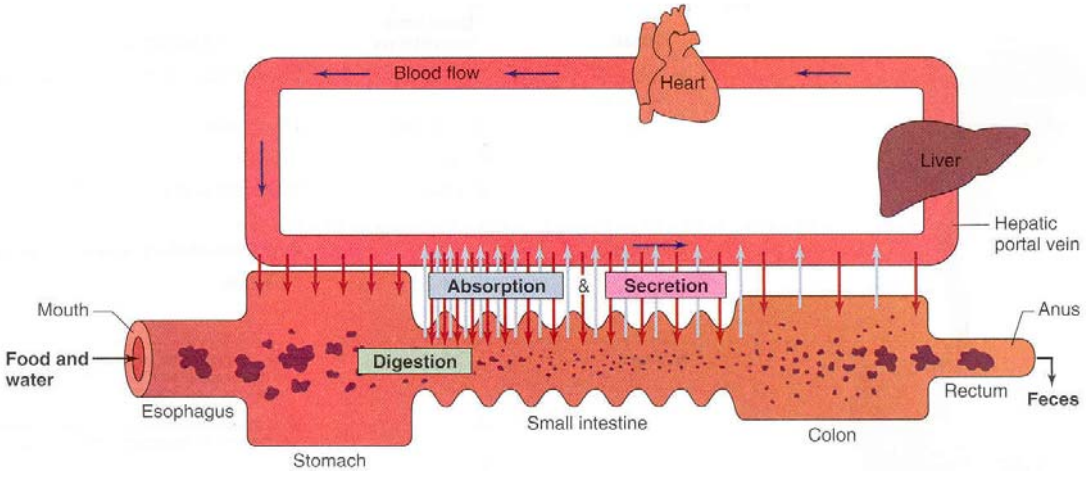
INTRODUCTION TO G.I PHYSIOLOGY

- The primary role of the gastrointestinal (GI) system is to process and transfer nutrients, fluid and electrolytes from ingested foods into the internal environment.
- These processes are under neuronal (local and central nervous systems) and hormonal control.
  - The local nervous system is termed the enteric nervous system. nerve cell bodies are in GI tract (local) and extrinsic (autonomic)
  - The **autonomic nervous system** mediates the central nervous system influences.
  - Enterogastrones are hormones that influence the movement of the contents in the GI tract and secretions that enter its lumen.

THERE ARE 4 BASIC G.I. PROCESSES

Motility: muscular contractions that mix and move forward the contents of the GI tract.

Secretion: glands located along the GI tract secrete their contents into the tract, assisting in motility, digestion and absorption.



Digestion: the biochemical breakdown of large particles and molecules into smaller, absorbable particles.

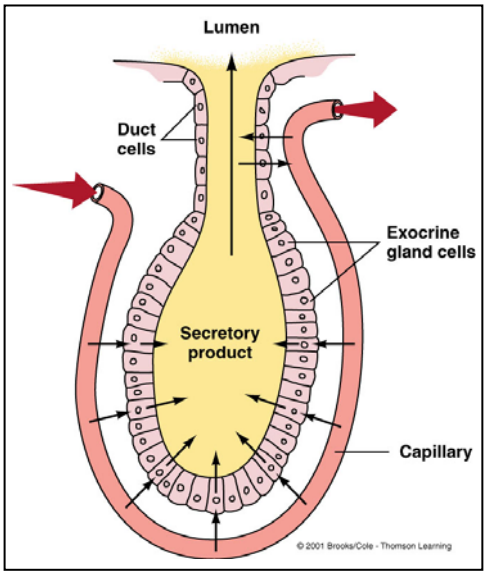
Absorption: small particles are absorbed from the GI tract into the blood or lymph.

MOTILITY

- Smooth muscle cells in the wall of the GI tract confer the ability to move GI tract contents.
- Smooth muscle cells maintain a constant level of contraction (tone) at their approximate length mid-point, allowing either further contraction or relaxation from this point.
  - –tone maintains a steady-state pressure on GI tract contents and allows the wall of the tract to recover following distension.
- There are two broad categories of movement (motility) superimposed on this background muscle tone:
  - i. Mixing movements redistribute luminal contents locally, enhancing the exposure of these contents to digestive secretions and exposing luminal contents to GI tract absorbing surfaces.
  - ii. Propulsive movements push luminal contents forward along the tract. The rate of propulsion depends on the specific function of that GI region (e.g. esophagus = rapid, small intestine = slow).

SECRETION

A stereotypical GI secretory (exocrine) gland

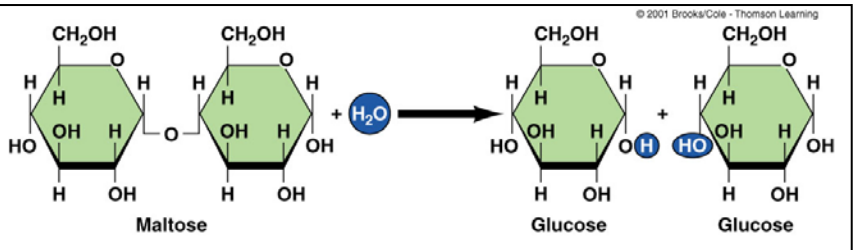


- Digestive juices are secreted into the lumen by **exocrine glands**.
- These digestive juices typically consist of water, electrolytes, and specific organic substances that perform specific functions, including mucus, enzymes and bile salts.
- The production of these secretions **requires energy** for active uptake of raw materials and assembly of components in the endoplasmic reticulum.
- Neuronal or hormonal stimulation results in the release of gland secretory products into the GI tract.
- Most exocrine secretions are **reabsorbed** following the completion of their physiological duties.

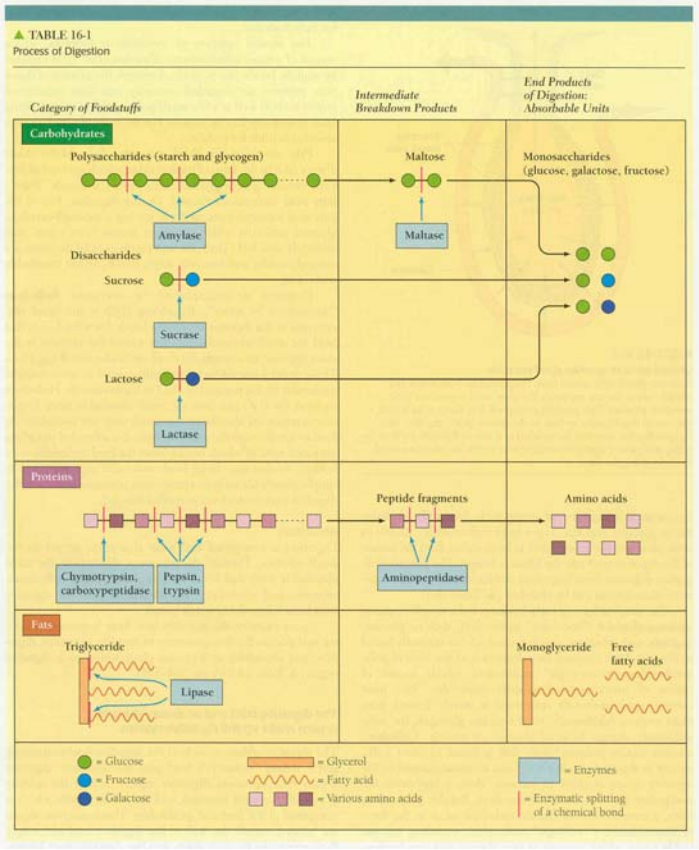
DIGESTION

- Digestion refers to the biochemical breakdown of foodstuffs into their molecular components.
- There are three primary categories of energy-rich nutrients ingested by humans:
  1. **Carbohydrates** comprised of either single sugar molecules (in a 6-carbon ring formation) called **monosaccharides** or linked sugar molecules called **disaccharides** or **polysaccharides**.
  2. **Proteins** comprised of chains of **amino acids** linked together by peptide bonds.
  3. **Fats** most often comprised **triglycerides** (three long chain carbon molecules called fatty acids linked to a three-carbon glycerol backbone).

Nutrient-specific enzymes mediate the addition of an H_2O molecule to bonds linking component molecules together causing the molecules to split, a process termed hydrolysis.



A SUMMARY OF THE DIGESTION OF THE THREE PRIMARY NUTRIENT CATEGORIES:



The enzymes involved include:

- Carbohydrates

  Amylase, sucrase, lactase, maltase.

- Proteins

  Pepsin, trypsin chymotrypsin, carboxypeptidase, and aminopeptidase.

- Fats

  Lipase.

ABSORPTION

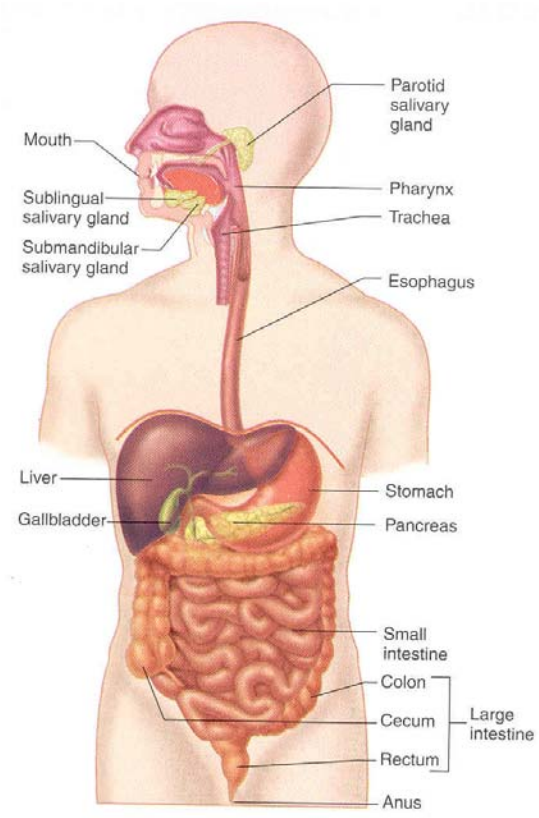
- The absorption of digested nutrients, water and electrolytes predominantly occurs across the membrane of epithelial cells, in the small intestine.
- These nutrients travel through the epithelial cells into the blood (carbohydrate and protein breakdown products) or the lymphatic system (fat breakdown products).
- Water absorption also takes place in the large intestine.

GI SYSTEM: GROSS ANATOMY

The gastrointestinal system includes:

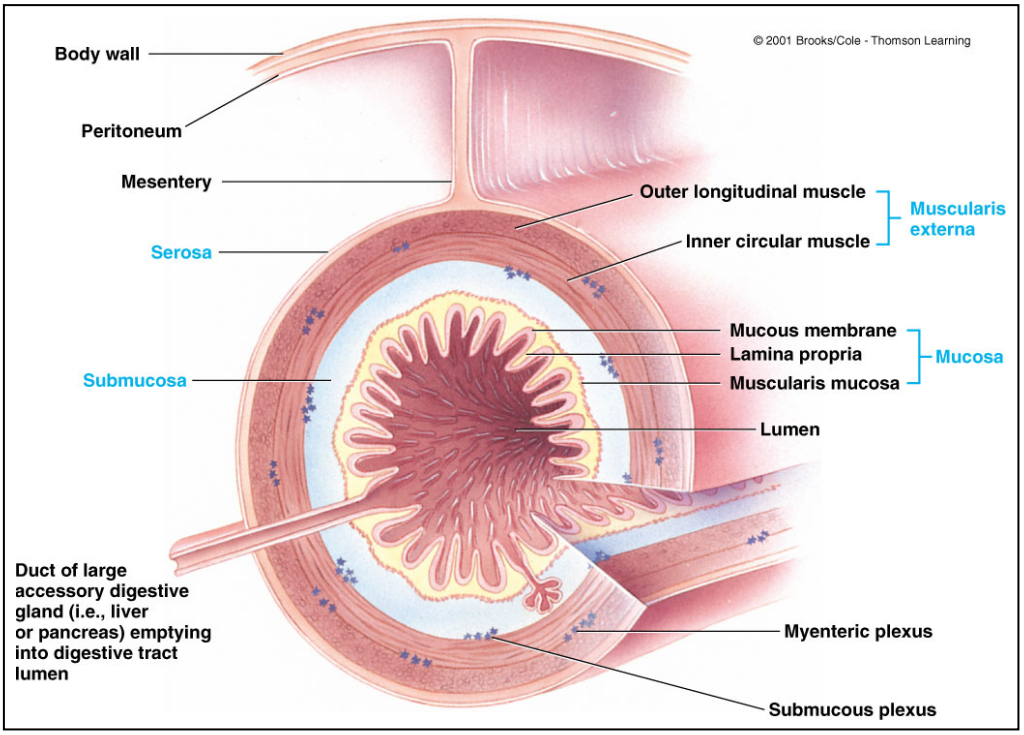
- **gastrointestinal tract** (mouth, pharynx, esophagus, stomach, small intestine and large intestine).

- **accessory organs** (salivary glands, liver, gallbladder and pancreas)
  - not part of the tract but secrete substances into it.



LAYERS OF THE G.I TRACT WALL:

The wall of the GI tract has the same general structure throughout and is anatomically and functionally subdivided into 4 primary layers.



1. The **Mucosa** lines the luminal surface of the GI tract and is subdivided into 3 components,

i. Mucus Membrane: a layer of epithelial cell linked together by tight junctions. Cells in this layer may include exocrine cells (e.g. secreting mucus or digestive enzymes), endocrine cells that secrete GI hormones and epithelial cells specialised for nutrient absorption.

ii. Lamina Propria: a thin layer of loose connective tissue upon which the epithelium rests. It also contains immune cells, capillaries and lymph ducts

← scaffold- cells turn over quickly

iii. Muscularis Mucosa: a thin layer of smooth muscle cells that can influence local luminal mixing by folding mucosa.

2. The **Submucosa** is a thick connective tissue layer that gives the GI tract elasticity. This region contains larger blood vessels, lymphatic vessels (whose branches travel into the mucosa and outward to the muscular layers of the wall), and exocrine glands.

Submucosal plexus: the submucosa of the small and large intestine also contains a network of interconnected neurons called the submucosal plexus which functions in controlling GI motility and secretion.

neural cell bodies grouped and fibers go to GI tract

3. The **Muscularis Externa** is the major smooth muscle layer of the GI tract. Coordinated contractions of this layer result in both local mixing and propulsive movements of luminal contents. There are two distinctive bands of muscle in this layer:

i. An inner circular layer with muscle fibres running circularly around the lumen. Contraction of this circular layer constricts the lumen (decreases its diameter).

ii. An outer longitudinal layer comprised of muscle fibres running along the length of the tract. Contraction of this layer results in a shortening of the GI tract.

ganglion

iii. Between the two muscle layers of the muscularis externa lies the **Myenteric Plexus**, a second dense network of interconnected neurons (the first being the submucosal plexus) that coordinate smooth muscle contractions.

4. The **Serosa** is a connective tissue outer covering that anchors the GI tract within the abdominal cavity. This layer also secretes a lubricating fluid to reduce friction between the GI tract and surrounding structures.

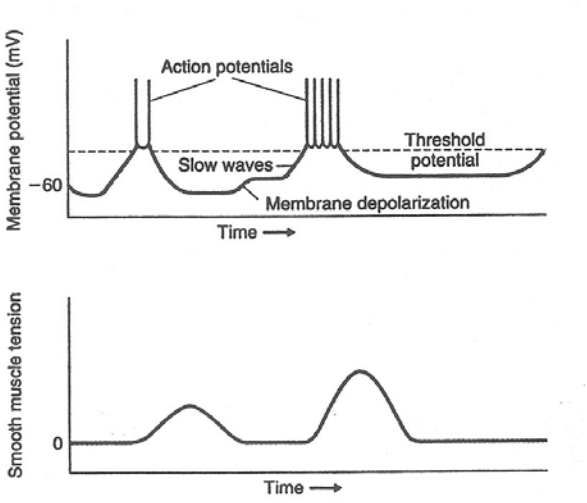
REGULATION OF THE G.I. TRACT:

Motility and secretion within the GI tract are tightly regulated processes involving the coordinated efforts of 4 separate factors:

1. The **intrinsic electrical properties** of smooth muscle cells.

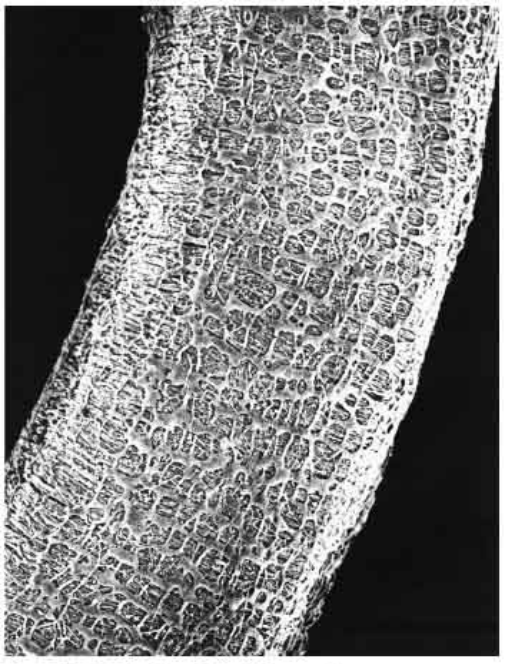
Some smooth muscles cells in the GI tract undergo spontaneous, transient membrane depolarisations. These specialised (non-contractile) pacemaker cells are called interstitial cells of Cajal and the depolarising potentials are termed slow waves. Slow waves propagate from pacemaker cells into adjacent smooth muscle cells through gap junctions connecting their cytoplasm, allowing the flow of electric current between them. In this manner, slow waves from pacemaker cells spread across interconnected smooth muscles.

If slow wave depolarisations reach action potential threshold, a burst of action potentials results, with the number of action potentials proportional to the duration the slow wave remains above threshold. Smooth muscle cells contract in response to a rise in intracellular Ca^{2+} levels associated with action potentials. As a generalisation, the greater the number of action potentials, the greater the elevation of intracellular Ca^{2+} and the greater the strength of contraction.



2. The **enteric nervous system** (ENS).

The two nerve plexuses within the GI tract (submucosal and myenteric) wall comprise the enteric nervous system (ENS). There are in the order of 10^8 neurons within the ENS, roughly equivalent to the number of neurons in the spinal cord. This makes the GI tract unique in that these organs have their own "minibrain". The ENS can operate entirely within the GI wall, without external input (e.g. the brain), and is thus considered reflexive. As with other neuronal tissue, the ENS functions via electrical communication between neurons and the release of neurotransmitters.



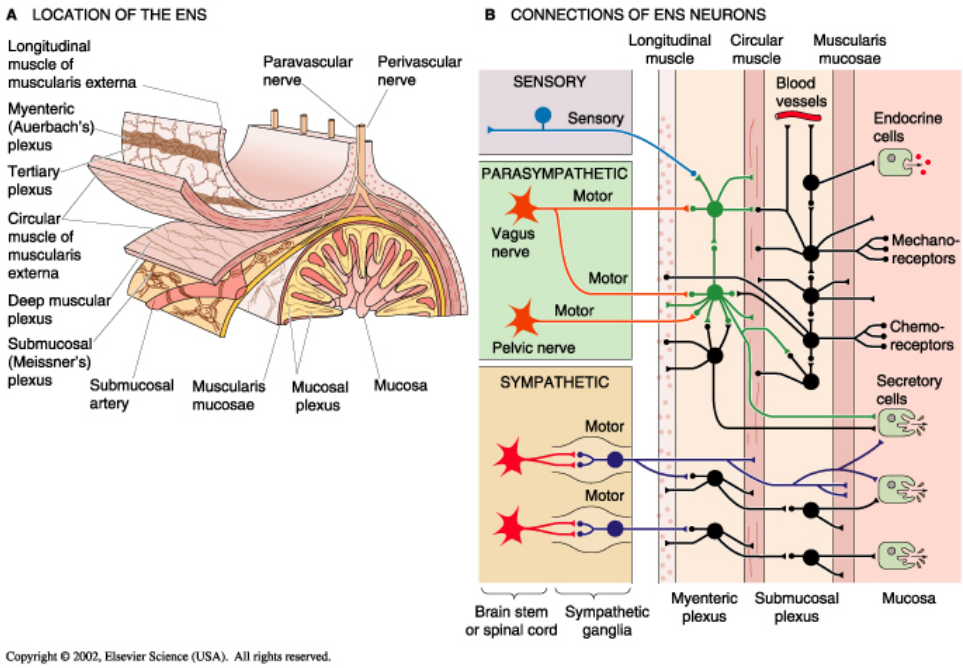
Components of the ENS include:

- **i. Sensory (afferent) neurons** including mechanoreceptors, chemoreceptors and osmoreceptors.
- **ii. Interneurons** (excitatory and inhibitory).
- **iii. Secretomotor cells** which influence smooth muscle, epithelial cells that secrete or absorb fluid and electrolytes and enteric endocrine cells.

hirschsprung's disease - swollen colon
- nerve cells in latter part of the colon are missing (both myenteric and submucosal plexi)
- muscles in that region dont relax. Contractions of muscles that normally push food through that part of the colon do not occur.
- region of intestine above "aganglionic" region swells resulting in constipation, swollen belly, etc
- 1/5400-7200 newborns

in the absence of the enteric nervous system, how do the muscles of the colon end up contracted?
- muscles themselves are naturally more contracted (not due to input - when you remove nerves, they just want to contract) - enteric system provides resting input)
- parasympathetic nervous system provides some basal input to contract muscles
- could be due to absence of NT
    eg) vasoactive intestinal peptide (VIP) - peptide NT found in neurons of the colon
        - when applied to colonic smooth muscle, causes relaxation

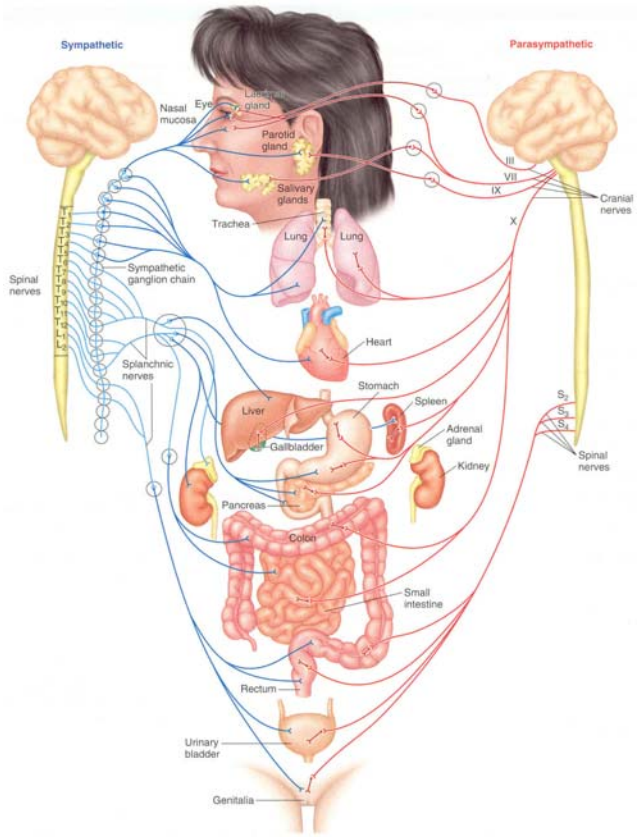
current therapy
- corrected by surgery - but there can be issues, does not work well- bypasses contracted part of bowel
- laxatives, high fiber diet to correct constipation



3. The **<u>autonomic nervous system</u>**.

Nerve fibres from both branches of the autonomic nervous system innervate the GI tract. These fibres can influence motility and secretion by:

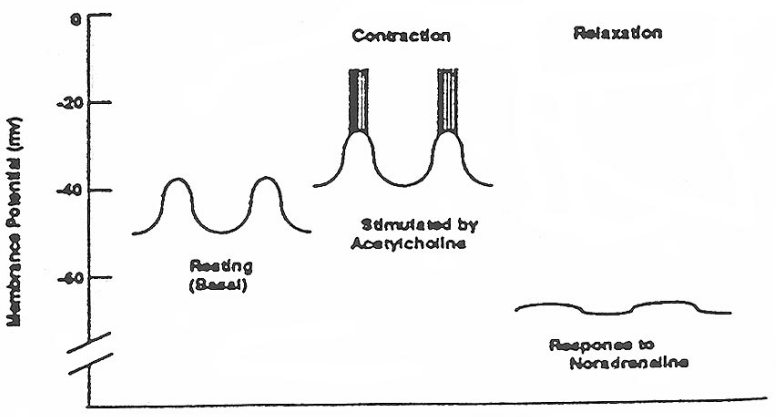
i. influencing ongoing ENS activity.
ii. directly affecting smooth muscle and glands.
iii. altering GI hormone levels.



Preganglionic **<u>Sympathetic</u>** fibres from the central nervous system synapse in prevertebral ganglia. Postsynaptic fibres enter the GI wall and synapse in the ENS or onto GI effector cells using norepinephrine (NE) as a neurotransmitter.

Preganglionic **<u>Parasympathetic</u>** fibres from the CNS enter into the GI wall, synapse with a postganglionic fibre within the ENS. The postganglionic fibre releases acetylcholine (Ach) onto their effector cells.

- As a generalisation, parasympathetic input results in an increase in motility and GI secretions. This occurs in periods during and immediately following the ingestion of a meal.
- In contrast, sympathetic drive results in decreased motility and a decreased volume of secretions. This occurs during a stress response.



4. **<u>GI hormones</u>**.

- Endocrine cells dispersed among epithelial cells in the mucosa release GI hormones in response to appropriate stimuli (more on these later).
- These hormones are carried via the bloodstream to other areas of the GI system where they influence that regions function.
- GI hormone effects on smooth muscle or glands can be excitatory or inhibitory.

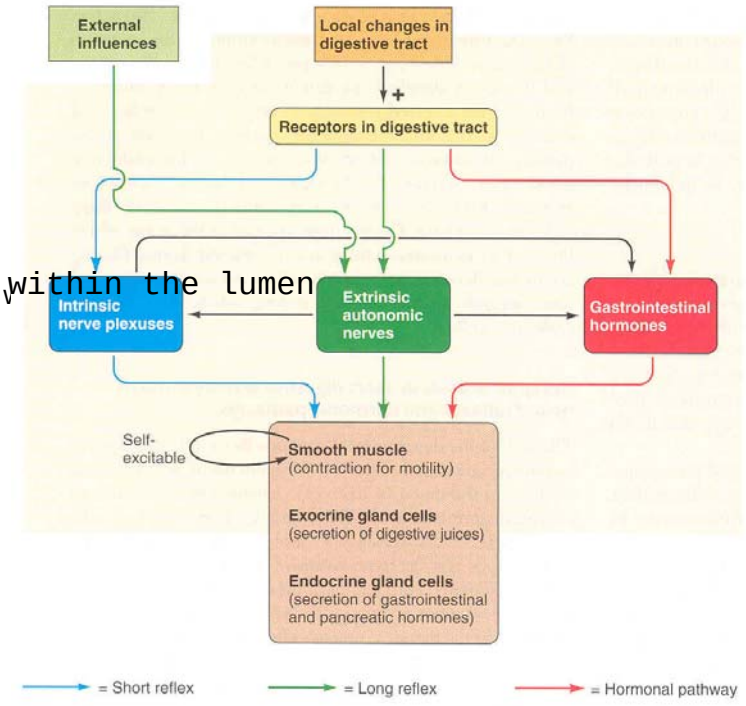
- Some GI Hormones include:
  - **Gastrin** from the stomach.
  - **Secretin** from the duodenum.
  - **Cholecystokinin** (CCK) from the duodenum.
  - **Gastric Inhibitory Peptide** (GIP) from the duodenum/jejunum.

SUMMARY OF GI REGULATION PATHWAYS

The GI tract alters its activity through both neuronal reflexes or hormonal pathways.
The wall of the digestive tract contains three main types of sensory receptors:

i. **Chemoreceptors** sensitive to chemical substances within the lumen
ii. **Mechanoreceptors** sensitive to stretch or tension within the GI tract wall
iii. **Osmoreceptors** sensitive to the osmolarity (concentration) of the luminal contents.

Stimulation of these receptors initiates neuronal reflexes (long or short) or hormonal release that initiate compensatory responses.

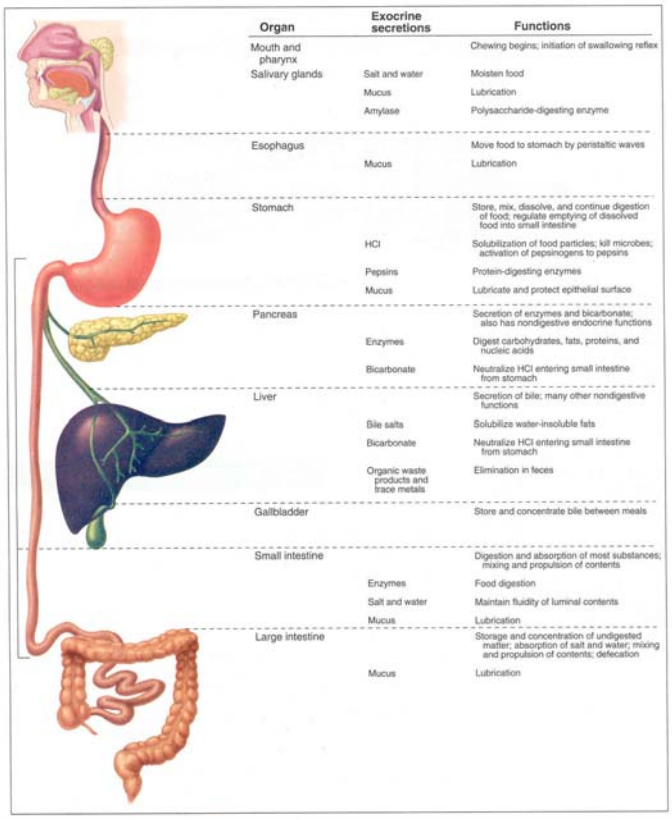


TOPIC 2: MOUTH, PHARYNX AND ESOPHAGUS

OBJECTIVES

1. Describe the anatomical components of the oral cavity and state their function in the process of chewing.
2. Secretion: Describe the components of salivary secretions and state their function and the factors controlling their release.
3. Motility: Describe the sequence of events contributing to, and factors that control, swallowing.
4. Digestion: Identify the nutrients/substances that are digested in the mouth and how they are digested.
5. Esophagus: Describe the role of the esophagus in swallowing. What is peristalsis and how is this coordinated?

GENERAL FUNCTIONS OF GI COMPONENTS



Organ	Exocrine secretions	Functions
Mouth and pharynx		Chewing begins; initiation of swallowing reflex
Salivary glands	Salt and water	Moisten food
	Mucus	Lubrication
	Amylase	Polysaccharide-digesting enzyme
Esophagus		Move food to stomach by peristaltic waves
	Mucus	Lubrication
Stomach		Store, mix, dissolve, and continue digestion of food; regulate emptying of dissolved food into small intestine
	HCl	Solubilization of food particles; kill microbes; activation of pepsinogens to pepsins
	Pepsins	Protein-digesting enzymes
	Mucus	Lubricate and protect epithelial surface
Pancreas		Secretion of enzymes and bicarbonate; also has nondigestive endocrine functions
	Enzymes	Digest carbohydrates, fats, proteins, and nucleic acids
	Bicarbonate	Neutralize HCl entering small intestine from stomach
Liver		Secretion of bile; many other nondigestive functions
	Bile salts	Solubilize water-insoluble fats
	Bicarbonate	Neutralize HCl entering small intestine from stomach
	Organic waste products and trace metals	Elimination in feces
Gallbladder		Store and concentrate bile between meals
Small intestine		Digestion and absorption of most substances; mixing and propulsion of contents
	Enzymes	Food digestion
	Salt and water	Maintain fluidity of luminal contents
	Mucus	Lubrication
Large intestine		Storage and concentration of undigested matter; absorption of salt and water; mixing and propulsion of contents; defecation
	Mucus	Lubrication

Our previous discussion has outlined generalisations about the organisation and function of the GI system. What follows is a more specific description of the physiological function of each major component, from the mouth to the anus. Each component will be discussed in the context of:

- Motility
- Secretion
- Digestion
- Absorption

But first, an overview…

MOUTH

The mouth is the entry point into the GI system. Within the mouth the lips, tongue, palate, teeth and salivary glands contribute to GI processes.

Lips: help guide and retain food within the oral cavity.

Tongue: composed of skeletal muscle and is under voluntary control. The tongue in important for guiding food during chewing (keeps food bolus under teeth) and during swallowing (more later…).

Palate: forms the roof of the oral cavity, separating the mouth from the nasal passages and allowing breathing and chewing to occur simultaneously. Hanging from rear of the palate appears the uvula. This structure closes off nasal passages during swallowing.

Teeth: responsible for tearing, grinding and mixing of food. Upper and lower teeth normally fit together (occlusion) when the jaw is closed. This occlusion is responsible for grinding food during chewing.

Why Chew? Chewing serves to break food into smaller pieces for swallowing, mix food bolus with saliva and to stimulate the taste buds.

Chewing and reflexes. Chewing is initiated voluntarily but has reflexive skeletal muscle contractions of jaws, lips cheeks and tongue mediated by sensory afferents within the oral cavity. In addition, taste bud stimulation initiates long loop reflexive increases in salivary, gastric, pancreatic and bile secretions in anticipation of ingested nutrients.

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long loop = goes to CNS and response comes back out
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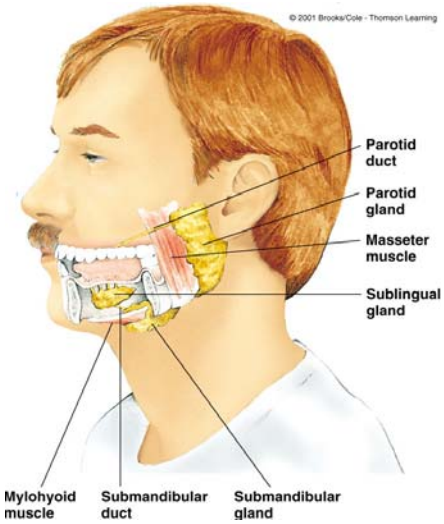
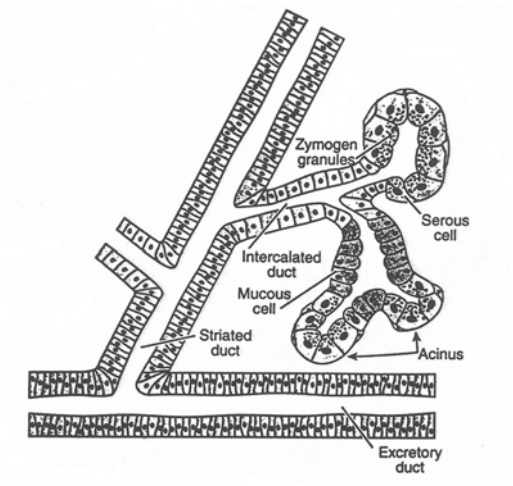
SECRETION: SALIVARY GLANDS

Saliva is the secretory product associated with the mouth. It is produced in three different pairs of salivary glands located outside the oral cavity. These include the parotid, submandibular and sublingual glands.



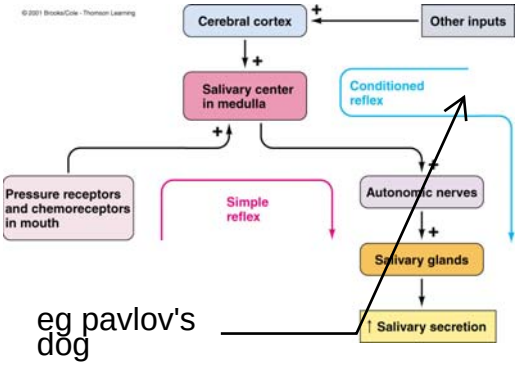


Saliva is composed of 99.5% water and 0.5% electrolytes and protein. The most important proteins are the enzymes amylase and lysozyme, and mucus. The functions of these substances include:

- **Fluid**: an important role in acting as a solvent for molecules that stimulate taste buds; Aids in speech by moistening lips and tongue; helps keep the mouth clean by flushing food residue away.
- **Mucus**: a thick and slippery substance that helps bind food together and lubricates the bolus as it travels toward the stomach. glycoprotein
- **Amylase**: an enzyme that breaks down polysaccharides into maltose (a 2-glucose molecule) thus beginning the digestion of carbohydrates.
- **Lysozyme**: an enzyme that lyses the cell wall of some bacteria thus conferring some protection against infection. ← helps amylase to function
- Saliva also **contains** **bicarbonate buffer** which neutralises acids from foods or bacteria in the oral cavity. An acidic environment is associated with dental caries.

CONTROL OF SALIVARY SECRETION

Saliva is continuously produced however the rate of production is under autonomic control. Approximately 1 to 2 litres of saliva are produced daily, ranging from a basal rate of ~0.5 ml/min to ~5 ml/min when maximally stimulated. A tonic background activity of parasympathetic input ensures enough saliva is produced to keep the mouth and throat moist at all times. Reflexive pathways can initiate saliva production, mediated by a salivary centre in the medulla of the brainstem. In a simple reflex, afferent fibers sense the presence of food in the mouth, send this information to the salivary centre which acts by autonomic nerves to increase saliva production. A conditioned reflex may activate the salivary centre upon the sight or smell of food resulting in saliva production.

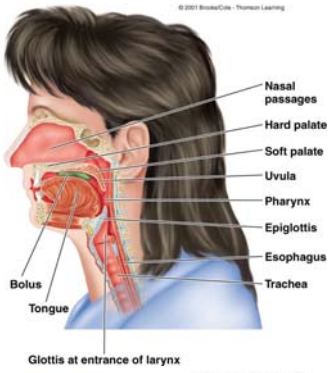


The actions of the two branches of the autonomic nervous system on salivary glands are not antagonistic.

- Parasympathetic stimulation results in increased production (mediated by Ach) of all secretions
- Sympathetic stimulation results in a decrease in fluid volume but an increase in mucus production = dry, sticky mouth.

MOTILITY: SWALLOWING

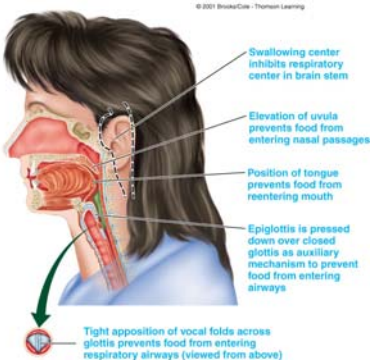
The motility associated with the mouth and pharynx is swallowing. Swallowing refers to the process of moving food from the mouth to the stomach. The initiation of swallowing is under voluntary control, however, once initiated the swallowing centre in the medulla oblongata takes over precise coordination of GI musculature during the swallowing reflex. Swallowing can be divided into three phases; **oral**, **pharyngeal** and **esophageal**.



i. **Oral Phase**: following the chewing of food, the oral phase of swallowing involves pushing a food bolus toward the back of oral cavity and up against the palate using the tongue.

ii. **Pharyngeal Phase**: the pharynx is located at the posterior of the oral cavity, at its junction with the nasal passages. Touch and pressure receptors in the pharyngeal palate are activated by the bolus and send info to the swallowing centre in the medulla via the trigeminal nerve (cranial nerve V). This initiates the reflexive component of swallowing.

- Contraction of the pharyngeal wall behind the bolus pushes food toward the esophagus.
- Tongue position during this phase prevents bolus from travelling back into mouth.
- The uvula elevates to seal the oral passages. ← supposed to be nasal
- The vocal cords contract and the epiglottis closes over the trachea, preventing bolus from entering the trachea and bronchi.

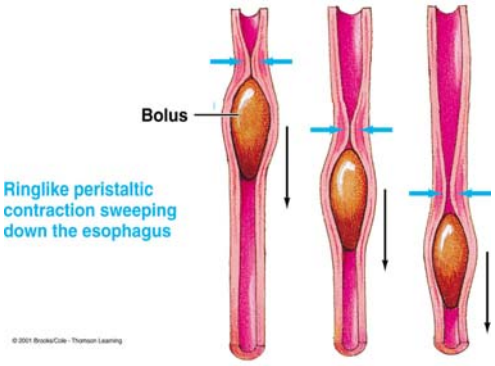


Esophagus and Swallowing

- The esophagus is a straight tube connecting the pharynx with the stomach.
- It has a large ring of circular muscle, a sphincter, at each end that controls the entry and exit GI luminal contents. The pharyngoesophageal sphincter remains closed except during swallowing. If it were open at other times, air would enter the esophagus and stomach during breathing.
- **Esophageal Phase of Swallowing**:
  - The swallowing centre relaxes pharyngoesophageal sphincter allowing food bolus to enter the upper esophagus.
  - The swallowing center then initiates primary peristaltic waves by interacting with the ENS.

ESOPHAGUS MOTILITY: PERISTALSIS

Smooth muscle in the inner circular layer of the muscularis externa contract pinching a ring of the esophagus. The outer longitudinal smooth muscle layer contracts in front of the pinched ring, reducing the length of the tube. This sequence propagates along the length of the esophagus, pushing luminal contents toward the stomach. This primary peristaltic wave takes 5-9 seconds to travel from the beginning to end of the esophagus.



Secondary peristalsis is reflexive and does not involve the swallowing centre. If luminal contents become lodged, the distension of the GI wall activates stretch receptors which, acting via the ENS, initiates a strong peristaltic wave to dislodge the luminal contents.

The second esophageal sphincter, the Gastroesophageal sphincter remains contracted until a peristaltic wave pushes a food bolus against this region. Reflexive relaxation, mediated in part by the vagus nerve (parasympathetic), occurs allowing luminal contents into the stomach. This sphincter then contracts again to prevent reflux of gastric contents (highly acidic) into the esophagus. The irritation of the esophagus (esophagitis) by gastric reflux is commonly known as "heartburn".

DIGESTION/ABSORPTION

- There is only minimal digestion that occurs in the mouth, pharynx and esophagus. As mentioned salivary amylase secreted into the oral cavity can hydrolyse carbohydrates. This process occurs until the luminal contents reaches the stomach. stops because of gastric acid
- There is no absorption of nutrients along this portion of the GI tract.

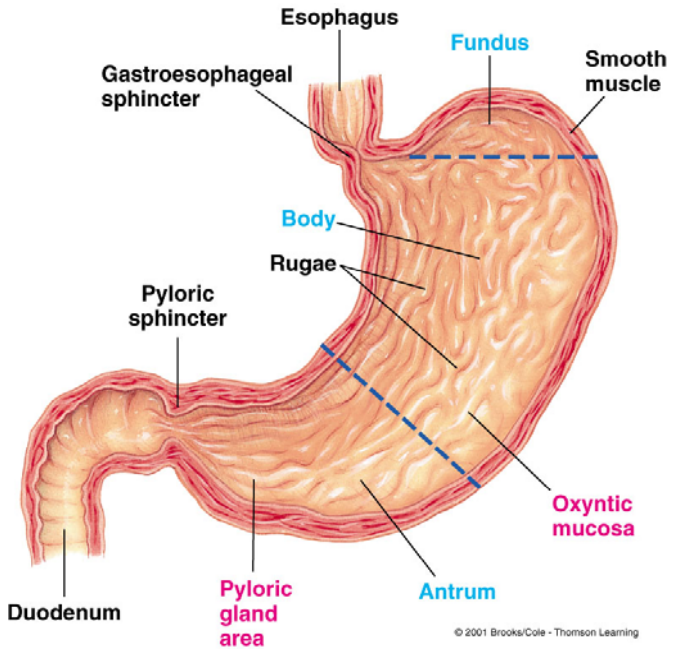
sublingual - can be absorbed under tongue - doesn't drain into liver/ portal blood flow

TOPIC 3: STOMACH

Objectives

1. Describe the anatomical components of the stomach and state a function for each.
2. Motility: Differentiate between gastric filling, storage and mixing processes in the stomach and state the and control mechanism(s) for each.
3. Motility: Describe the process of gastric emptying, why this is a tightly regulated process and the factors that control gastric emptying.
4. Secretions: Differentiate between gastric gland and gastric pits and list the products secreted by each in different regions of the stomach.
5. Secretions: Describe the gastric exocrine secretions, their function and the factors controlling their production and release.
6. Secretions: Describe the gastric paracrine and endocrine secretions, their function and the factors controlling their production and release.
7. Digestion: Explain how carbohydrate and protein digestion occur in the stomach.
8. Absorption: Does the stomach absorb nutrients? If so, identify each one.

The stomach is a highly involuted sac-like pouch located between the esophagus and the duodenum. It can be anatomically and functionally divided into three main sections; the **fundus** is that portion lying above the gastroesophageal sphincter, the **body** is the middle portion while the **antrum** is the most distal region, characterised by a thickening of the muscularis externa. There are differences in motility and secretions between these regions.



MAIN FUNCTIONS OF THE STOMACH

The stomach performs 3 primary roles in the GI system:

- Mixing and mechanical breakdown of stomach contents.
- Storage of ingested food and the regulated delivery of processed stomach contents to the duodenum.
- Secretion of hydrochloric acid (HCl) and enzymes involved in protein digestion.

These primary roles will be discussed in relation to motility, secretion, digestion and absorption.

GASTRIC MOTILITY

Motility associated with the stomach can be further categorised into filling, storage, mixing and emptying processes.

i. Filling

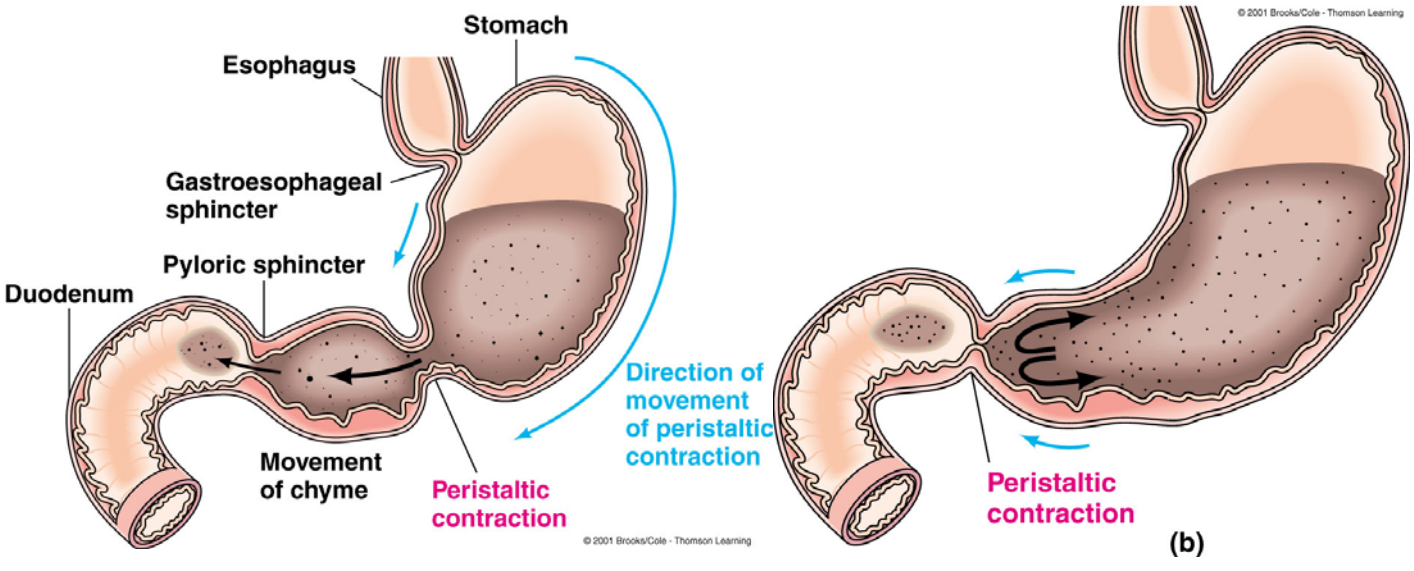
As a food bolus passes through the gastroesophageal sphincter, the stomach is reflexively relaxed in order to receive these contents, a process termed receptive relaxation. This relaxation is mediated via the ENS acting to inhibit the muscularis externa. In its relaxed state, the stomach can expand from a volume of ~50 ml (when empty) to ~1000 ml with little change in the tension in the gastric wall.

ii. Storage

Food is primarily stored in the stomach body. There are, however, periodic (3/minute) weak peristaltic contractions that occur in this region, propagating from the fundus toward the antrum. These contractions result from fundal pacemaker cells that generate slow wave depolarisations that reach action potential threshold in gastric smooth muscle cells. Because the muscularis externa in the body is thin, these peristaltic waves do little to move the stomach body contents.

iii. Mixing

The rhythmic slow wave propagation and associated muscularis externa contractions generate powerful **antral** peristaltic waves that force antral contents toward the pyloric sphincter, at the stomach's junction with the duodenum. These powerful contractions are responsible for gastric mixing and arise due to the thick muscularis externa present in the antrum. The pyloric sphincter is only open enough to let small amounts of liquid through with each peristaltic contraction. When this wave of contraction reaches the sphincter, it too closes so that solid luminal contents are diverted backward toward the stomach body resulting in vigorous mixing.



iv. Gastric **Emptying**

As suggested above, strong peristaltic contractions in the antrum are responsible for the emptying of liquefied gastric contents (chyme) into the duodenum through the pyloric sphincter. The volume of chyme that enters the duodenum is dependent upon the strength of contraction of the sphincter and the number of peristaltic waves per unit time.

There are two apparent problems that the body must overcome in relation to the emptying of gastric contents into the duodenum. First, the stomach receives a variable input in terms of frequency, quantity and consistency of food whereas the duodenum requires a stable environment with a controlled delivery and consistency of contents. Second, gastric contents are highly acidic while the duodenum requires a basic environment.

To solve these problems, gastric emptying is under complex regulation, influenced by both **gastric** and **duodenal factors**. The focus of this regulation is controlling the strength of contraction of the pyloric sphincter and the strength and rate of gastric peristaltic contractions. If the pylorus is relaxed, or if peristaltic contraction force and rate is increased, a greater volume of chyme will leave the stomach. If the pylorus is contracted or peristalsis is reduced, gastric emptying is reduced.

The strength and rate of peristaltic contractions is influenced by the modulation of slow wave amplitude in smooth muscle cells of the muscularis externa. Factors that result in depolarising the slow waves will increase the frequency and number action potentials in smooth muscle cells and, consequently, the rate and strength of peristalsis. Conversely, slightly hyperpolarising slow waves results in reduced peristaltic activity.

Factors that regulate gastric emptying:

Gastric Factors (minor)

- The **amount** of chyme in the stomach. All else being equal, the greater the volume of gastric contents, the greater the rate of gastric emptying.

- The **degree of fluidity** of gastric contents. Gastric contents only leave the stomach when they are in of a thick, liquid consistency. The sooner the appropriate degree of fluidity, the sooner gastric contents are emptied.

Duodenal Factors (major)

Once in the duodenum, the processing of chyme takes time and requires a specific environment (more on this later) thus, the duodenum can delay gastric emptying until it is prepared to receive more chyme. This control over gastric emptying is mediated by **neural** and/or **hormonal** factors. Each of these will be discussed.

- **Neuronal Response**: is mediated by either short-loop reflexes within the enteric nervous system or long-loop reflexes mediated by the autonomic nervous system. Together, these reflexes are known as **enterogastric reflexes**.

- **Hormonal Response**: involves the release of several hormones from mucosal cells in the duodenum into the general circulation. These hormones are collectively termed **enterogastrones** and include cholecystokinin (CCK), gastrin and secretin.

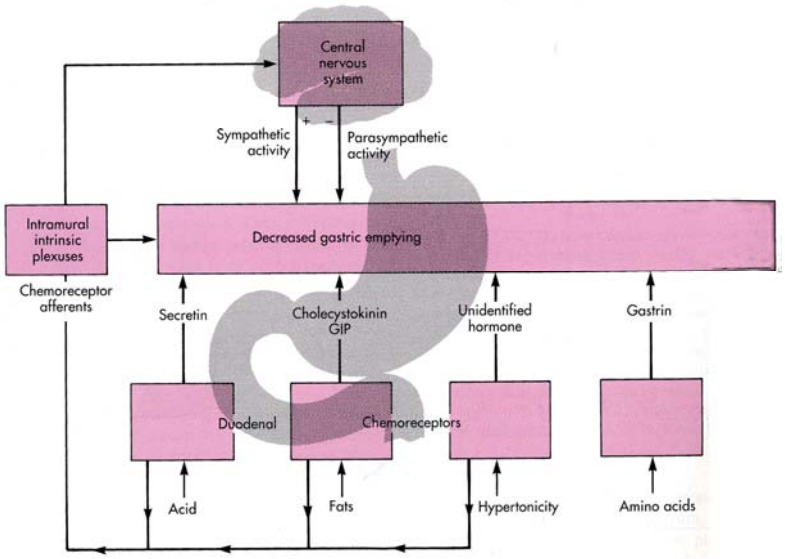
DUODENAL REGULATION OF GASTRIC EMPTYING

The duodenal mucosa contains receptors sensitive to the presence of **acid**, certain **fats and fat digestion products**, **osmotic pressure**, and **peptides and amino acids**. The stimulation of each of these sensors generates a neuronal or hormonal response to slow further emptying.

Acid: duodenal luminal contents with a pH below 3.5 activate a neuronal reflex and the release of secretin from the duodenal mucosa, both of which inhibit antral contractions and stimulate the contraction of the pyloric sphincter.

Fats: the presence of monoglycerides or fatty acids stimulates the release of CCK from the duodenum and activates a neuronal reflex, both of which reduce gastric emptying.

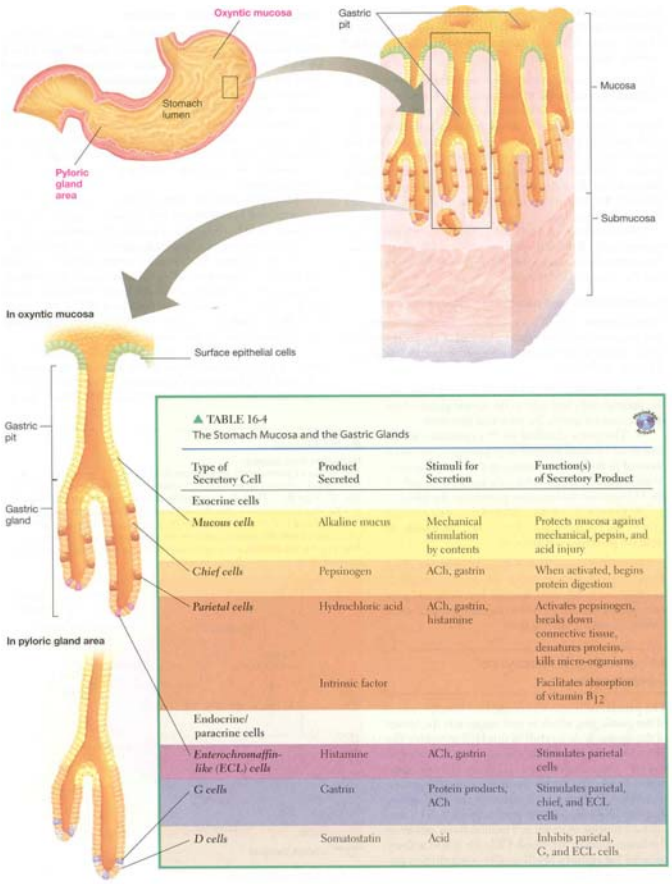
Osmotic Pressure: hypertonic (concentrated) chyme in the duodenum resulting from the digestion of carbohydrates and proteins into smaller molecules triggers chemoreceptors that mediate the release of an unidentified hormone and a neuronal response to decrease in gastric emptying.



Peptides and amino acids: the presence of peptides and amino acids stimulates the release of the hormone gastrin. The net effect of gastrin is to constrict the pylorus and reduce emptying.

GASTIRIC SECRETIONS

The cells that produce gastric secretions are found in numerous specialised infoldings of the stomach mucosa, which is functionally divided into the **oxyntic mucosa**, lining the fundus and body, and the **pyloric gland area** (PGA) lining the antrum. The first portion of one of these infoldings is called the **gastric pit** while the base is the **gastric gland**. A variety of cell types line these gastric involutions, some cells produce exocrine secretions while others produce paracrine or endocrine products. Gastric pits from all regions of the stomach produce mucus, but gastric gland secretions vary between the oxyntic mucosa and the PGA.



▲ TABLE 16-4
The Stomach Mucosa and the Gastric Glands

Type of Secretory Cell	Product Secreted	Stimuli for Secretion	Function(s) of Secretory Product
Exocrine cells			
Mucous cells	Alkaline mucus	Mechanical stimulation by contents	Protects mucosa against mechanical, pepsin, and acid injury
Chief cells	Pepsinogen	ACh, gastrin	When activated, begins protein digestion
Parietal cells	Hydrochloric acid	ACh, gastrin, histamine	Activates pepsinogen, breaks down connective tissue, denatures proteins, kills micro-organisms
	Intrinsic factor		Facilitates absorption of vitamin B_{12}
Endocrine/ paracrine cells			
Enterochromaffin-like (ECL) cells	Histamine	ACh, gastrin	Stimulates parietal cells
G cells	Gastrin	Protein products, ACh	Stimulates parietal, chief, and ECL cells
D cells	Somatostatin	Acid	Inhibits parietal, G, and ECL cells

Exocrine secretions involved in digestion/absorption of nutrients or the protection of gastric mucosa include:

- **Mucus** from mucous cells in gastric pits.
- **HCl** and **intrinsic factor** from parietal cells in gastric glands of the oxyntic mucosa.
- **Pepsinogen** from chief cells in gastric glands of the oxyntic mucosa.

Endocrine and **paracrine** secretions involved in the control/regulation of GI functions include:

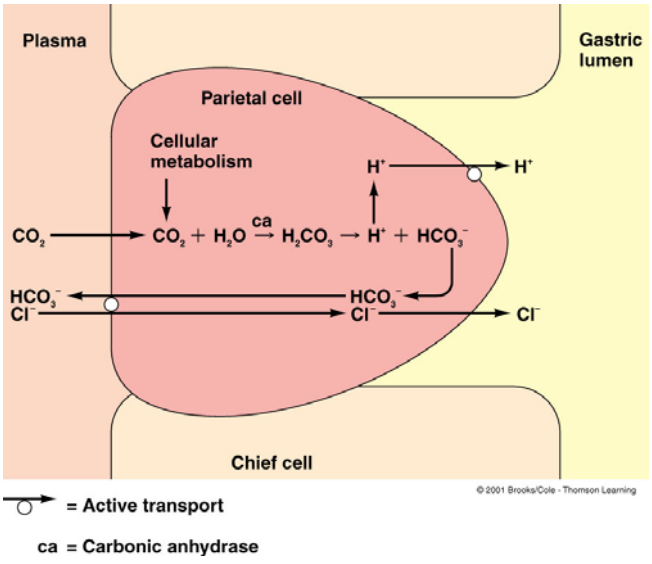
- **Histamine**, a paracrine substance, from enterochromaffin-like (ECL) cells in gastric glands of the oxyntic mucosa
- **Gastrin** from G cells in gastric glands of the PGA.
- **Somatostatin** from D cells in gastric glands of the PGA.

The Secretion of Hydrochloric acid

- Parietal cells actively secrete HCl into the lumen of gastric pits, which empty into the stomach. The pH of the stomach can reach be as low 2.

- Separate ionic pumps in the membrane of parietal cells are responsible for the movement of both H^+ and Cl^- ions against their concentration gradients.

- The H^+ ions pumped into the lumen of the stomach arise from the dissociation of H_2O molecules. When a H^+ ion leaves the parietal cell, it is replaced via the activity of carbonic anhydrase which dissociates H_2CO_3 into H^+ and HCO_3^- (bicarbonate). This bicarbonate molecule is actively pumped into the plasma via a Cl^-/HCO_3^- cotransporter, keep electrical neutrality of the plasma



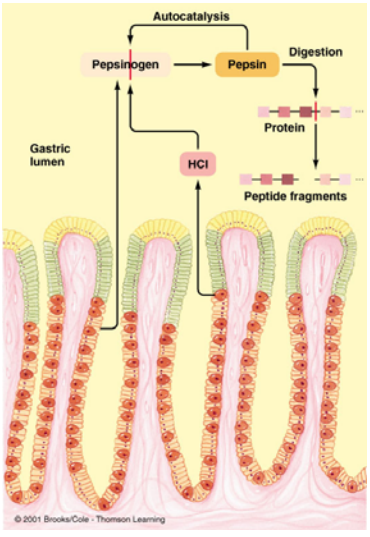
Function of HCL

While HCl is not directly involved in the digestion of nutrients it performs three functions that assist GI activity.

i. HCl converts the inactive protease pepsinogen into its active form, pepsin. In addition, the low pH environment of the stomach is optimal for pepsin activity.
ii. HCl aids in the breakdown of connective tissue and muscle fibres, reducing the size of ingested food particles.
iii. HCl acts to break the tertiary structure of proteins (i.e. disulphide bonds, not the peptide bonds), increasing the exposure of peptide bonds to enzymes in the duodenum.
iv. The concentrated HCl helps kill ingested microorganisms.

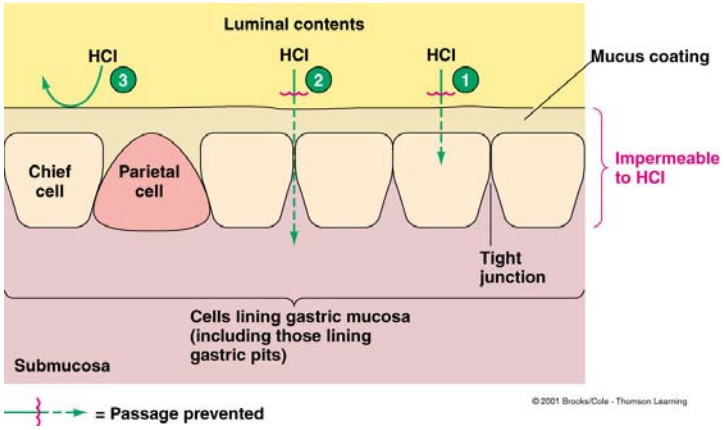
Pepsinogen

Pepsinogen is the inactive form of pepsin, an enzyme that cleaves certain peptide bonds between amino acids. Because the proteolytic actions of pepsin would digest proteins within chief cells and the wall of the stomach itself, this enzyme is produced and stored in its inactive form in zymogen granules within chief cells until needed.



Once secreted into the stomach lumen, HCl cleaves pepsinogen into active pepsin. When activated, pepsin can act to cleave other pepsinogen molecules, a process called autocatalysis, and can digest ingested proteins in the stomach.

Gastric Secretions - Mucus



Mucus is secreted by mucous cells both in gastric pits and on the epithelial surface of the stomach lining.

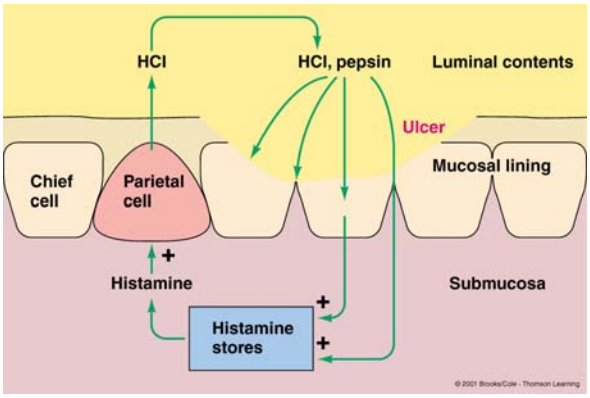
This mucus forms a protective barrier separating the gastric contents from the epithelial surface.

- Mucus lubricates the gastric mucosa, protecting against mechanical injury (e.g. friction)
- Mucus inhibits pepsin that comes into contact with the gastric mucosa, protecting the stomach wall against autodigestion.
- Mucus is alkaline and neutralises gastric acid at the epithelial surface (but not within the gastric lumen), protecting against acid injury. The pH in the mucus layer adjacent to epithelial cells is ~7.

Gastric Secretions – Gastric Ulcers

When the mucus barrier breaks down, pepsin and acid from the lumen can digest the epithelium and deeper gastric wall layers. This produces a peptic ulcer that is associated with pain and gastric bleeding (presents as blood in stool). If untreated, a peptic ulcer can erode and perforate the wall of the stomach, allowing caustic gastric juices into the abdominal cavity.

Ulcer formation is multifactorial:



- ~80% of peptic ulcers are associated with a gastric *H.pylori* infection, a bacterium that can burrow into the mucus lining for protection against gastric acid.
- *H. pylori* secretes a toxin resulting in a chronic inflammation of the gastric mucosa, weakening the mucosal barrier.
- Acid and pepsin can penetrate the weakened mucosal barrier and erode the stomach wall. Acid in the submucosa stimulates histamine release, enhancing gastric acid and pepsin production.
- Other contributing factors include chronic alcohol, NSAIDs and stress exposure.

Gastric Secretions – Intrinsic Factor

Parietal cells in gastric glands also secrete **intrinsic factor**, a compound required for the absorption of vitamin B_{12}, a substance necessary for red blood cell formation. Intrinsic factor binds to vitamin B_{12} in the stomach forming a complex that binds with specific receptors located in the terminal ileum. The binding of the receptor mediates receptor-triggered endocytosis of vitamin B_{12}. Failure to produce intrinsic factor results in reduced RBC count, a condition known as **pernicious anaemia**.

Gastric Secretions – Endocrine and Paracrine Secretions

The release and function of endocrine and paracrine secretions will be examined in the context of the control of gastric secretions discussion that follows.

CONTROL OF GASTRIC SECRETIONS

There are four chemical messengers that regulate the secretion of gastric juices. These are:

i. **Acetylcholine**. The neurotransmitter released from enteric nervous system nerve terminals in response to short reflexes and from parasympathetic (vagus) terminals in response to long reflexes.
   - Ach stimulates parietal (H^+), chief (pepsinogen), ECL (histamine) and G (gastrin) cell secretions.

ii. **Gastrin**. Secreted **into** the blood by G cells in PGA gastric glands in the presence of protein products in the stomach lumen.
   - Gastrin stimulates parietal, chief and ECL cell secretions. **Gastrin is the primary factor responsible for increasing gastric juice secretion during the ingestion of a meal**. Gastrin also promotes the growth (trophic) of the gastric and duodenal mucosa, maintaining their functionality.

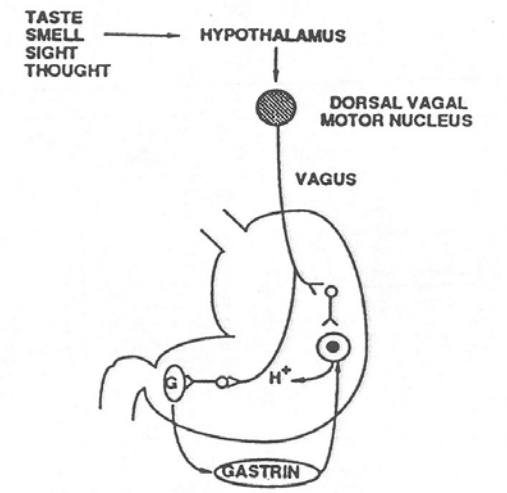
iii. **Histamine**. A **paracrine** substance released from ECL cells in oxyntic gastric glands in response to both gastrin and Ach. It acts locally to stimulate parietal cell H^+ production.

iv. **Somatostatin**. **Released** from D cells in PGA gastric glands. In contrast to the above substances, somatostatin is inhibitory and acts in a negative-feedback manner to turn off gastric H^+, pepsinogen and histamine production.

The secretion of gastric juices during the ingestion of a meal occurs in three phases; the **Cephalic**, **Gastric** and **Intestinal**.

Cephalic Phase

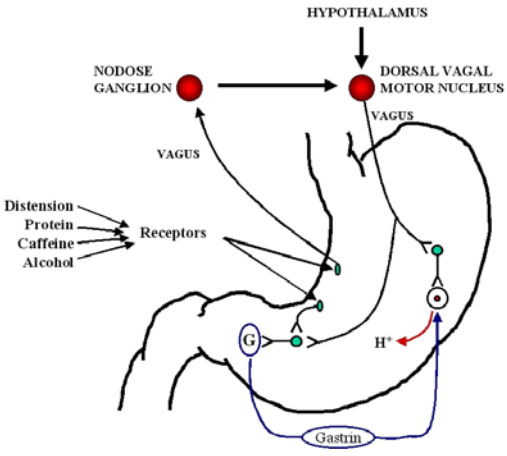
- An increased secretion of pepsinogen and H^+ in response to the sight, smell or thought of food and the process of swallowing.
- Initiated in the hypothalamus and mediated by activation of vagal efferents. Ach released from ENS nerve terminals in response to vagus input stimulates chief and parietal cells.
- Vagal input also stimulates G cell production of gastrin, further enhancing H^+ and pepsinogen release.



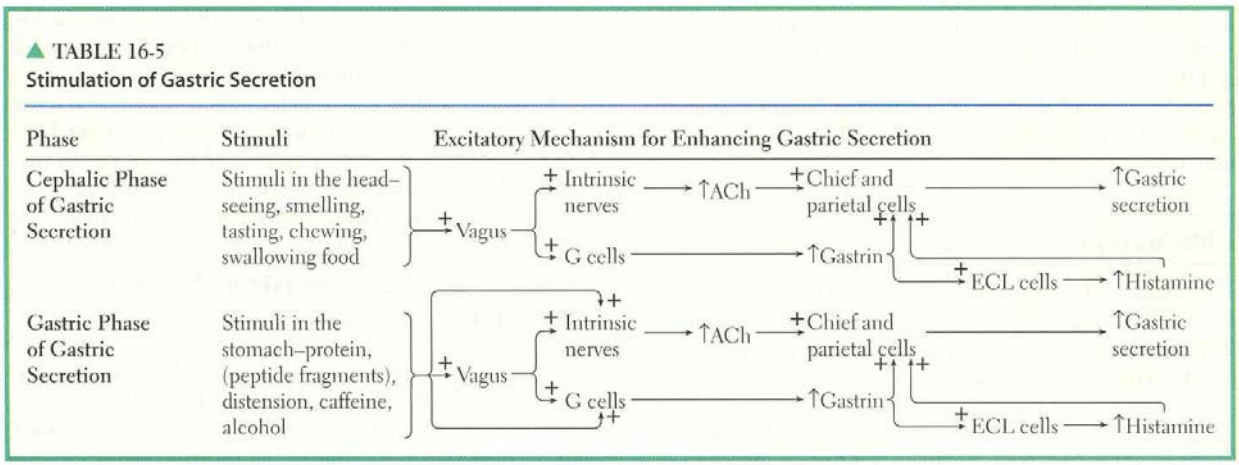
Gastric Phase

This phase begins when food actually enters the stomach. Stimuli within the ingested food activate gastric secretions through a variety of mechanisms.

- Proteins and peptides within the lumen are the most potent stimuli. Receptors in the ENS initiate short reflexes resulting in gastrin release from G cells. A long reflex loop also activates H^+, and gastrin secretion via vagal and ENS activity. Histamine release is also stimulated (not shown), augmenting H^+ secretion.
- Distension/ Caffeine/Alcohol can also stimulate gastric juice production, even in the absence of food. Caffeine and alcohol should thus be avoided in persons with peptic ulcers.



Summary of the Stimulation of Gastric Secretions



▲ TABLE 16-5
Stimulation of Gastric Secretion

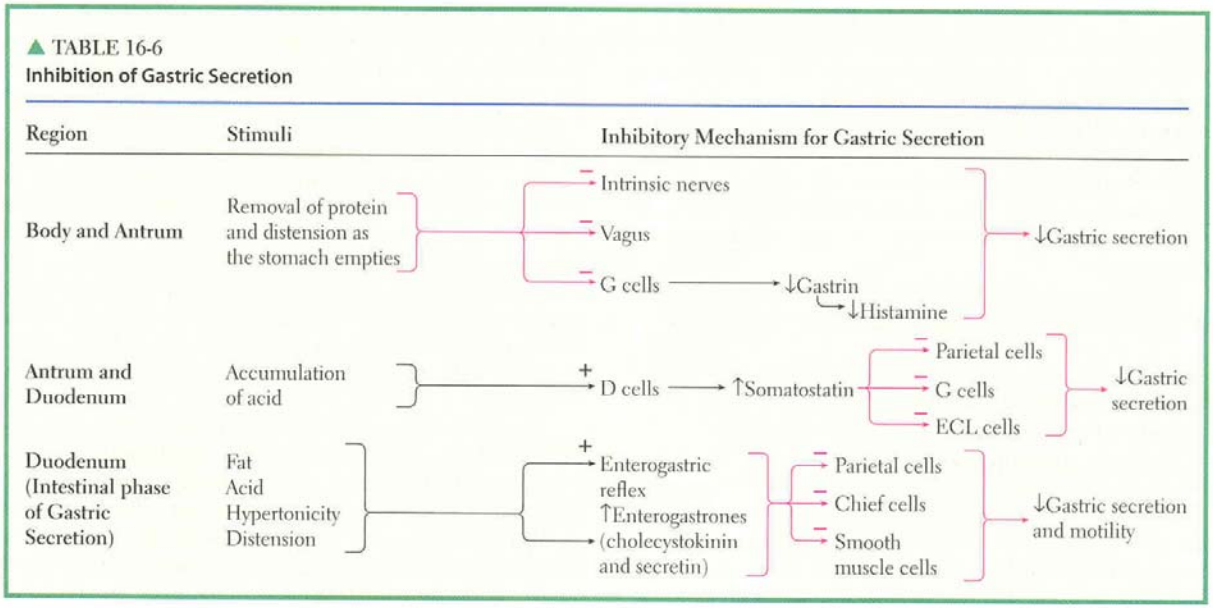
Phase	Stimuli	Excitatory Mechanism for Enhancing Gastric Secretion
Cephalic Phase of Gastric Secretion	Stimuli in the head–seeing, smelling, tasting, chewing, swallowing food	+ Vagus → + Intrinsic nerves → ↑ACh → + Chief and parietal cells → ↑Gastric secretion; + G cells → ↑Gastrin → + Chief and parietal cells; ↑Gastrin → + ECL cells → ↑Histamine → + Chief and parietal cells
Gastric Phase of Gastric Secretion	Stimuli in the stomach–protein, (peptide fragments), distension, caffeine, alcohol	+ Vagus → + Intrinsic nerves → ↑ACh → + Chief and parietal cells → ↑Gastric secretion; + G cells → ↑Gastrin → + Chief and parietal cells; ↑Gastrin → + ECL cells → ↑Histamine → + Chief and parietal cells

Intestinal Phase

This phase begins when gastric chyme begins to empty into the duodenum and, unlike the preceding phases of gastric secretion, it is inhibitory – shutting off gastric juice production as the ingested meal moves out of the stomach. There are several simultaneous components during the intestinal phase that reduce gastric secretions.

- As the meal leaves the stomach, the major stimulus for gastric juice production, **protein**, is removed.
- Somatostatin is released from D cells in PGA gastric glands in response to drop in pH as gastric contents leave the stomach. Somatostatin inhibits parietal, chief, and ECL cell activity.
- The presence of **fat**, **acid**, **hypertonic chyme** and **distension** in the duodenum has a negative feedback influence on gastric secretions via enterogastric reflexes and the enterogastrones CCK and secretin. Recall, these factors also decrease gastric emptying. This component is considered the intestinal phase of gastric secretion.

Summary of the Inhibition of Gastric Secretions



▲ TABLE 16-6
Inhibition of Gastric Secretion

Region	Stimuli	Inhibitory Mechanism for Gastric Secretion
Body and Antrum	Removal of protein and distension as the stomach empties	− Intrinsic nerves; − Vagus; − G cells → ↓Gastrin → ↓Histamine → ↓Gastric secretion
Antrum and Duodenum	Accumulation of acid	+ D cells → ↑Somatostatin → − Parietal cells; − G cells; − ECL cells → ↓Gastric secretion
Duodenum (Intestinal phase of Gastric Secretion)	Fat, Acid, Hypertonicity, Distension	+ Enterogastric reflex; + ↑Enterogastrones (cholecystokinin and secretin) → − Parietal cells; − Chief cells; − Smooth muscle cells → ↓Gastric secretion and motility

GASTRIC DIGESTION AND ABSORPTION

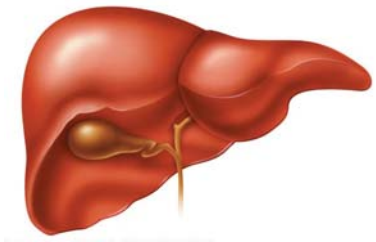
There are two digestive processes occurring in the stomach, **carbohydrate** and **protein**.

- **Carbohydrate** digestion, initiated in the mouth from salivary amylase, continues to occur in the food bolus as it is stored in the body of the stomach. This is a residual digestion, no further amylase is secreted in the stomach.
- **Protein digestion** resulting from pepsinogen and acid exposure occurs in the antrum of the stomach where the ingested food is thoroughly mixed with gastric juice.

The stomach only absorbs alcohol and aspirin.

- Nutrients **such** as carbohydrates, fats, proteins and water are passed onto the duodenum for absorption.
- Ethyl alcohol is partially lipid soluble and can diffuse across gastric epithelial cell membranes, entering the blood stream via submucosal capillaries. Interestingly, alcohol is absorbed more rapidly in the duodenum **because** of the larger mucosal surface area (more later), thus delaying gastric emptying with an accompanying meal (fat slows gastric emptying most effectively) can slow the effects of ingested alcohol on brain activity.
- Aspirin (**acetylsalicylic** acid) is a weak acid that remains un-ionised in the strongly acidic gastric juice. Un-ionised, acids are lipid soluble and cross the gastric epithelium, rapidly producing its effects.

TOPIC 4: PANCREAS AND BILIARY SYSTEM



Objectives

1. Describe the anatomical components of the pancreas and state a function for each.
2. Pancreatic Secretions: Identify each of the secretions of the pancreas and discuss their function and control mechanism(s).
3. Liver: Describe the anatomical and functional organisation of the liver.
4. Liver: Describe the hepatic-portal circulation. Why is this system unique?
5. Liver: Outline the enterohepatic circulation and explain the functional importance of this organisation.
6. Liver Secretions: Detail the components in bile and discuss the function of bile in fat digestion
7. Liver Secretions: Describe the factors that stimulate bile production and secretion and how bile production stops.

Following gastric processing, ingested food enters the duodenum for further digestion and absorption. However, the duodenum itself does not secrete digestive enzymes. Digestion here requires the secretions from two accessory digestive organs, the **pancreas** and **liver**. A person can survive without a stomach but the absence of these pancreatic and liver secretions, results in dramatic weight loss from malabsoption and is fatal if untreated. While both of these organs participate in many homeostatic processes, we will restrict are discussion to their influences upon the digestion and absorption of nutrients in the small intestine.

The **pancreas** supplies:

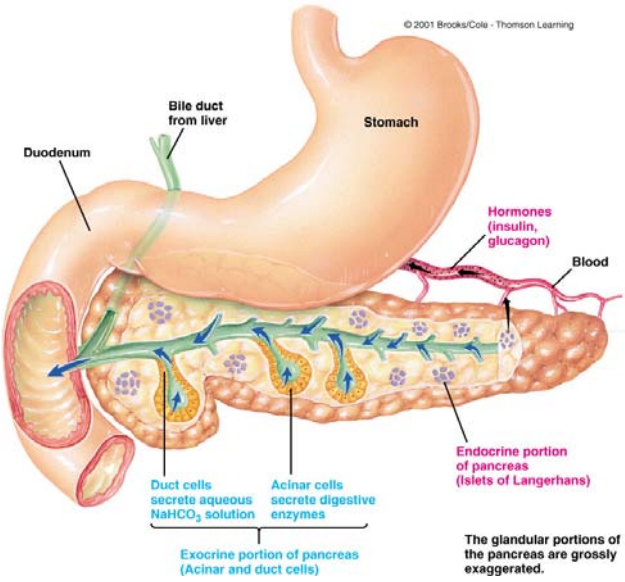
- enzymes that breakdown proteins, carbohydrates and fats.
- a copious supply of alkaline fluid to neutralise acidic gastric chyme.

The **liver** supplies:

- bile, a secretion that aids in fat digestion and absorption by breaking large fat globules into smaller droplets that can be more efficiently processed.

THE PANCREAS

- Located immediately below the stomach with a main **pancreatic duct** that drains into the **common bile duct**, from the liver, forming the ampulla (of Vater) bile duct. The ampulla drains into the proximal duodenum through the **sphincter of hepatopancreatic ampulla** (sphincter of Oddi).
- Pancreatic exocrine secretions are produced by cells that form small sacs called **acini**, each connected to a branch of the pancreatic duct.
- **Acinar cells** line the terminal end of an **acinus** and secrete the pancreatic digestive enzymes. **Duct cells** lining the neck of an acinus secrete the pancreatic aqueous alkaline fluid.



- The endocrine cells of the pancreas congregate, forming the Islets of Langerhans, whose secretions enter directly into the blood stream.

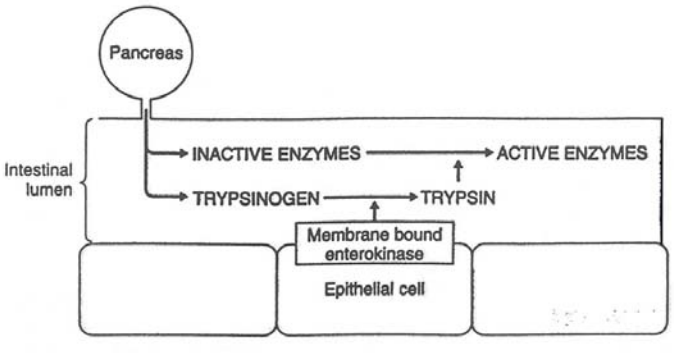
Pancreatic Proteolytic Enzymes

The pancreas secretes three different enzymes that digest proteins and peptides via the hydrolysis of peptide bonds between amino acids. These are:

- **Trypsinogen** (active form = trypsin)
- **Chymotrypsinogen** (active form = chymotrypsin)
- **Procarboxypeptidase** (active form = carboxypeptidase)

Pancreatic proteolytic enzymes have the potential to digest both the acinar cells and pancreatic ducts. As with gastric pepsinogen, these enzymes are manufactured in inactive forms and are stored **inactivated** in zymogen granules until stimulated for exocytotic release into the ducts leading to the duodenum. To ensure these enzymes remain inactive the pancreas also produces a substance, **trypsin inhibitor**, to block the actions of any inadvertently active trypsin within the pancreas.

Once the proteolytic enzymes enter the lumen of the duodenum, they are activated in a two-step process. First, inactive trypsinogen is cleaved to the active form, trypsin, by **enterokinase** bound to the membrane of epithelial cells in the brush border of the duodenal mucosa (more on the brush border later). Second, trypsin activates the other enzymes. All three activated enzymes act to digest ingested proteins in the lumen.



Pancreatic Amylase

This enzyme functions in a manner similar to salivary amylase. It breaks polysaccharides into disaccharides (maltose). Pancreatic amylase does not threaten pancreatic tissue and is secreted in an active form.

Pancreatic Lipase

Pancreatic lipase is the only enzyme that can digest fats. Without this important enzyme, ingested fats remain too large and cannot be absorbed. Clinically, this situation presents with ~60-70% of ingested fats being excreted in the feces. This symptom is called **steatorrhea** and is characterised by whitish, very loose, foul-smelling stool that, because of the high fat content, dramatically floats.

Pancreatic Aqueous Alkaline Secretion

Unlike gastric peptidase, pancreatic enzymes require a neutral pH environment. In addition, the duodenum is less well equipped than the stomach to deal with potential acid injury. As a result, duct cells in the exocrine pancreas secrete NaHCO3-rich aqueous solution to neutralise the acidic gastric chyme entering the duodenum. By volume, this is the largest component of pancreatic secretion (ranging from 1-2 litres/day).

CONTROL OF PANCREATIC SECRETIONS

The release of pancreatic secretions is under both autonomic and hormonal control.

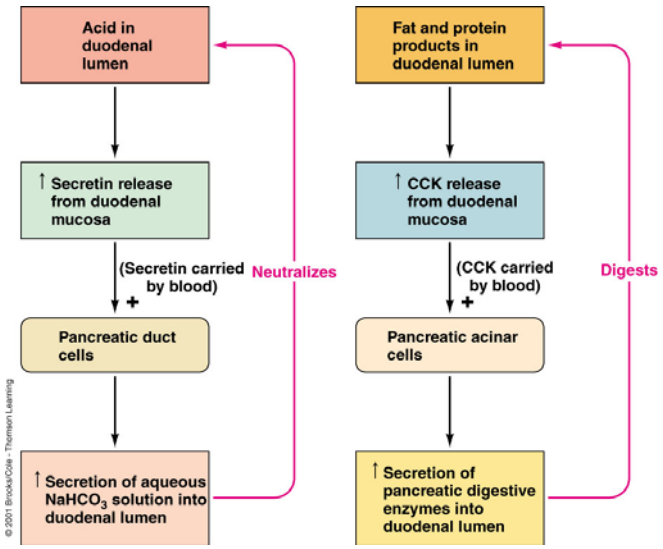
Autonomic influences are secondary to hormonal influences.

- **Parasympathetic** input increases all secretions.
- **Sympathetic** input decreases all secretions.

Hormonal influences dominate the control of pancreatic secretions. Two specific hormones are of importance in humans, Secretin and CCK.

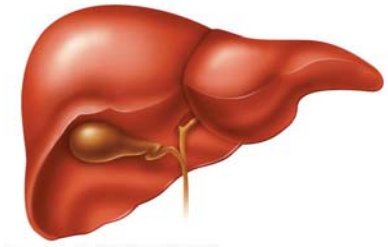
Secretin. The presence of acidic chyme in the duodenum is a strong stimulus for the release of the hormone secretin from duodenal mucosal cells. As may be expected, secretin acts upon duct cells in the pancreas to dramatically increase NaHCO3 production and secretion to neutralise this acid.

CCK. The presence of fat, and to a lesser extent protein, in the duodenum triggers the release of the hormone CCK from epithelial cells in the duodenal mucosa. Once in the pancreas, CCK stimulates the production and release of lipase and the proteolytic enzymes from acinar cells.



THE LIVER

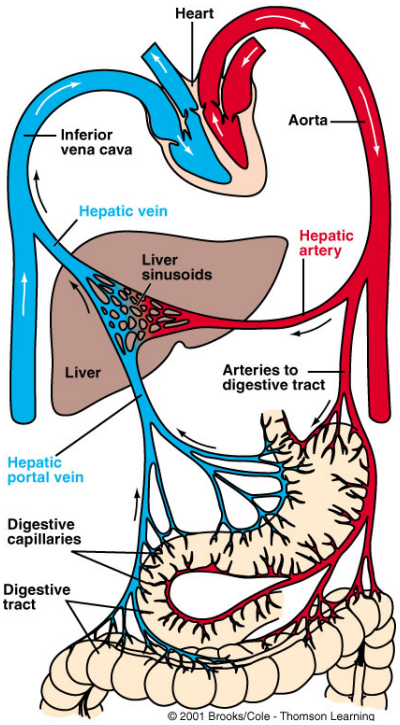
The liver is a large visceral organ that performs a variety of functions including: the metabolic processing of carbohydrates, proteins and fats; detoxification of metabolic by-products; the synthesis of plasma proteins; the storage of energy-rich glycogen and fats, vitamins, minerals; the removal of old red blood cells and the excretion of bilirubin from RBC destruction.



Of relevance to the GI system, the hepatocytes within the liver produce **bile salts** that are secreted into the duodenum via the common bile duct upon appropriate duodenal guidance.

A brief discussion of the unique **blood flow** to the liver and the functional organisation of the liver will help our understanding of the role of the liver in the GI system.

The liver is unique in that it receives two distinct blood sources: **venous** blood draining directly from the GI tract and **arterial** blood via the hepatic artery.

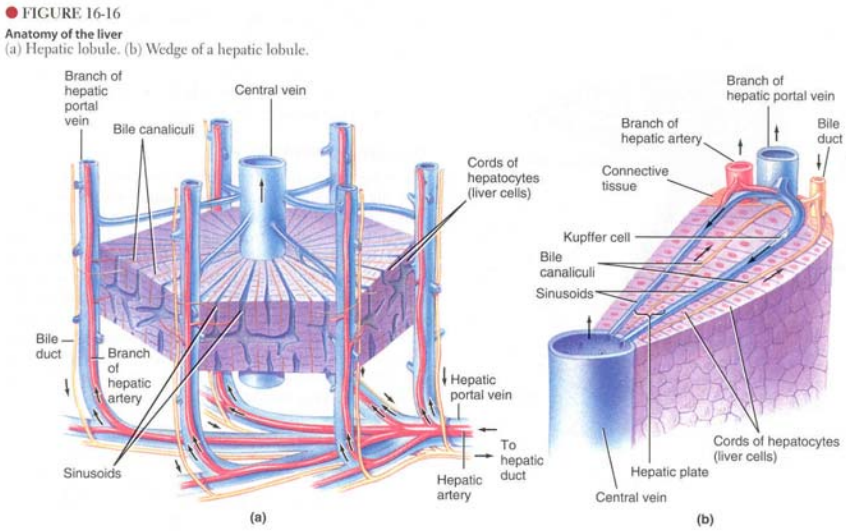


The **venous blood** enters the liver and breaks into a capillary network called **liver sinusoids** to allow the exchange between blood from the GI tract and hepatocytes before this venous blood enters the hepatic vein. This unique connection, called the **hepatic portal system**, allows the liver to process and detoxify substances absorbed from the GI tract prior to entering the general circulation. The liver is said to have **first-pass** at ingested nutrients.

The sinusoids are also perfused with **arterial blood** to provide hepatocytes with oxygen and metabolites from other body regions for processing.

FUNCTIONAL ANATOMYOF THE LIVER – THE HEPATIC LOBULE

The liver is organised into functional units called **lobules**. These are hexagonal arrangements of tissue surrounding a central vein. At each of the 6 'corners' there are found three vessels: a branch of the hepatic artery, a branch of the hepatic vein and a bile duct. Blood from both the artery and vein flow through the sinusoids toward the central vein that eventually drain into the hepatic vein. **Kupffer cells** line the sinusoid vessels, destroying old red blood cells and bacteria in the blood.



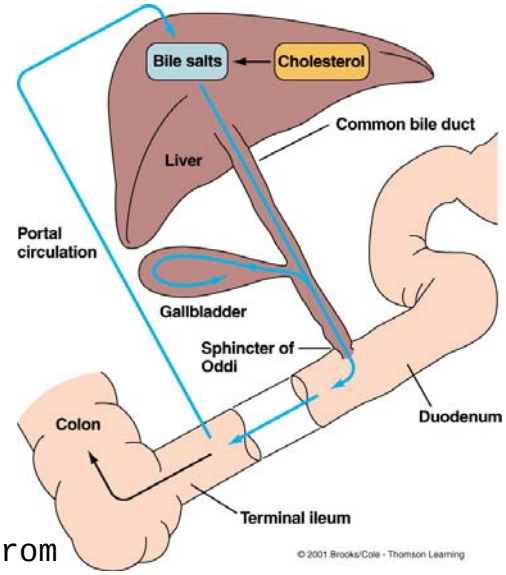
Hepatocytes are arranged between the sinusoids such that each hepatocytes borders a sinusoid. A thin bile passage, a **bile canaliculus**, also runs between each layer of hepatocytes, draining into the bile duct. Hepatocytes continuously secrete bile into the canaliculus. The bile ducts from different lobules converge and eventually form the common bile duct.

ENTEROHEPATIC CIRCULATION

The common bile duct delivers bile to the duodenum through the sphincter of Oddi. When no chyme is present in the duodenum and bile is not required, the sphincter is closed. The continuous flow of bile from hepatocytes in the liver is then diverted from the sphincter, back up the common bile duct and into the **gall bladder** for storage.

The gall bladder is a muscular sac that stores and concentrates the bile by absorbing water. When stimulated, the gall bladder contracts and expels its contents into the duodenum.

After performing their role in the digestion of fats, the majority of bile salts are reabsorbed in the terminal ileum. From here, they enter the portal circulation and travel back to the liver to be used again. This circuitous path is called the **enterohepatic circulation**. ~5% of bile salts are lost each day. This pathway helps keep the body cholesterol content in check.

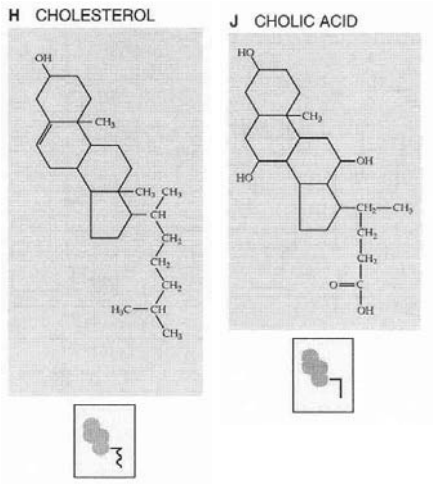


bile salts made from cholesterol

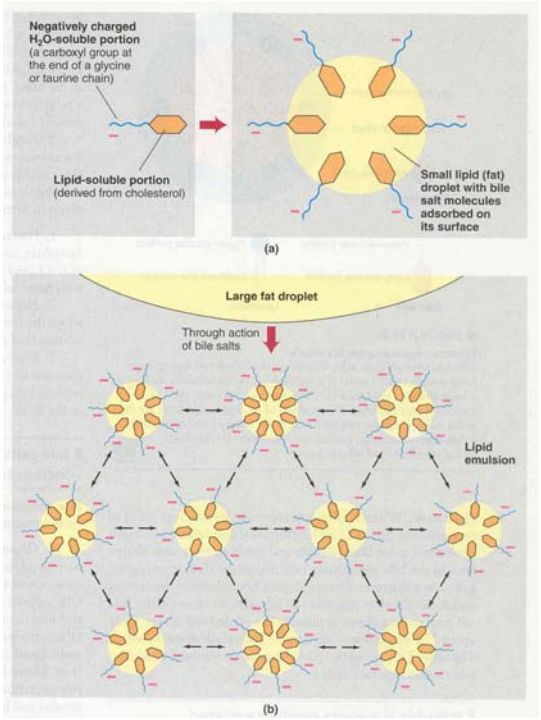
COMPONENTS OF BILE

Bile consists of an aqueous alkaline solution (similar to that from the pancreas), bile salts, cholesterol, lecithin and bilirubin.

- The **alkaline solution** is produced by duct cells, the rest originate from hepatocytes.
- **Bile salts** (deprotonated molecules; negatively charged) are derived from cholesterol. They consist of a hydrophobic cholesterol backbone and a negatively charged hydrophilic tail.
- **Lecithin** (phosphatidylcholine) is a component of cell membranes.
- **Bilirubin** is derived from iron-containing hemoglobin molecules and is the residual yellowish pigment resulting from RBC degradation. Bilirubin is a waste product and is excreted into the feces via bile. Bacterial action in the colon modifies the yellow pigment to the brown colour characteristic of feces. A blockage of bile release results in the build-up of bilirubin in the blood, a condition called jaundice.



THE ROLE OF BILE



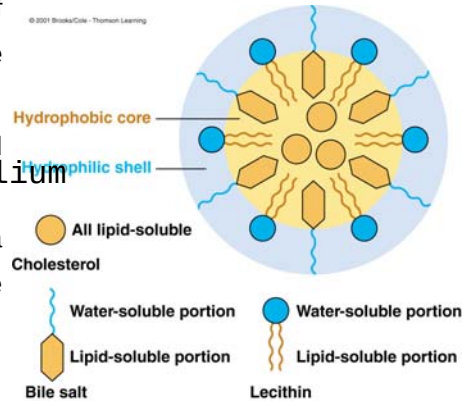
Fat is hydrophobic and, in the aqueous environment of the duodenum, ingested fats aggregate forming large macromolecules. Water-soluble lipase can only act on the surface of this fat aggregate. The larger the surface area (i.e. many small droplets) the greater the access lipase has to ingested fat.

Bile salts aid in fat digestion by acting as a **detergent** and **emulsify** large fat aggregates into smaller pieces.

To accomplish this, the cholesterol portion of bile salts dissolves in a fat droplet. The hydrophilic tail portion of the bile salt projects into the aqueous duodenal chyme creating a water soluble shell surrounding a fat core. In this formation, lipase has access to a greater surface area of fat. The negatively-charged tail portions of one 'droplet' repels other negatively-charged droplets preventing their coalescence into larger droplets.

The bile salt shell poses a problem for the access of lipase to the fat droplet, lipase must penetrate the bile salt layer. To overcome this problem, the pancreas also secretes a polypeptide, **colipase**, which anchors lipase to the bile salts at the surface of the fat droplet.

Bile and Micelles



In addition to their emulsifying role, the components of bile help from microdroplets of monoglycerides following lipase digestion. These microdroplets, **micelles**, aid in the absorption of digest fat products into duodenal epithelial cells.

A micelle is ~4-7 nm in diameter (1/106 of an emulsified fat droplet) and is composed of bile salts, cholesterol and lecithin molecules.

diffuse through epithelium

Bile salt, cholesterol and lecithin molecules form a hydrophobic core with a hydrophilic tail 'shell' allowing the micelle to dissolve in aqueous solution. Thus, the micelle acts to shuttle digested fat molecules to the epithelial surface.

CONTROL OF BILE SECRETION

Release

Hormonal and autonomic inputs regulate the release of bile from the gall bladder.

- **CCK** in the circulation in response to fats in the duodenum triggers the contraction of the gall bladder and the relaxation of the sphincter of Oddi.
- Vagal efferents, activated by the presence of chyme in the duodenum appears to augment this response.

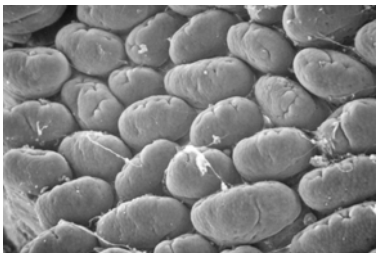
Production and secretion

- Neuronal – vagal input results in a slight increase in bile production.
- Hormonal – acid in the duodenum results in secretin release. Secretin stimulates the production and secretion of the $NaHCO_3$ component of bile.
- Bile **Salts** – The presence of bile salts in the blood from the reabsorption of bile salts via the enterohepatic circulation is the most potent stimulator of further bile salt production and release.

Inhibition

When fats have left the duodenum, CCK levels drop, the sphincter of Oddi closes and bile cannot enter the duodenum. Hepatocytes that are rapidly manufacturing bile continue to do so, depositing their bile in the gall bladder, until the circulating bile salt concentration in the enterohepatic circulation declines. This removes the strong activation on hepatocytes and bile production slows.

TOPIC 5 SMALL INTESTINE



Objectives

1. Describe the anatomical components of the small intestine and state a function for each.
2. Motility: Differentiate between segmentation and the migrating mobility complex and state the function and control mechanism(s) for each.
3. Secretions: Identify the secretions of the small intestine and discuss their function and control mechanism(s).
4. Digestion: Outline the steps involved in the digestion of protein, fats and carbohydrates in the small intestine.
5. Absorption: Describe the specific adaptations of the small intestine lumen to increase surface area. Explain why a large surface area is important.
6. Absorption: Describe the steps involved in the absorption of proteins, fats and carbohydrates in the small intestine. Explain the relevance of secondary active transport.
7. Absorption: Explain how water is absorbed and the importance of active Na+ uptake in this process.
8. Absorption: Describe how calcium and iron absorption differ from the three main nutrients.
9. Absorption: Describe how the GI tract maintains acid-base balance and the complications of diarrhea.

The small intestine, comprised of the duodenum, jejunum and the ileum, extends between the stomach and the large intestine and is the primary site of digestion and absorption in the GI tract. Once luminal material leaves the small intestine, no further digestion or absorption of nutrients (except water and Na^+) occurs.

Factors that reduce the effectiveness of small intestine physiology may effective the nutritive state of the body, the acid-base and electrolyte balance and will most certainly influence one's behaviour.

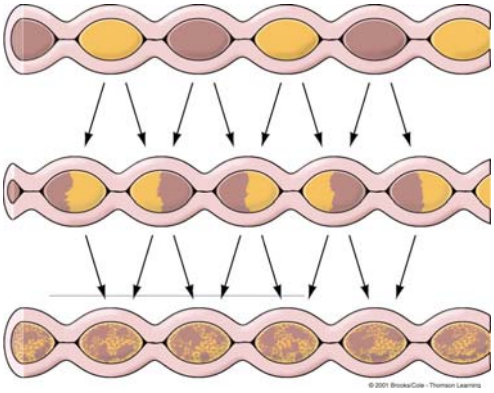
The processes of motility, secretion, digestion and particularly absorption will be discussed in greater detail.

MOTILITY IN THE SMALL INTESTINE

There are two predominant motility paradigms in the small intestine.

- **Segmentation** ensures that luminal contents are thoroughly mixed during the ingestion and processing of a meal.
- The **migrating mobility complex** acts to move luminal contents along the small intestine, toward the large intestine in the period between meals.

Segmentation



During a meal, motility in the small intestine is primarily **segmentation**.

Segmentation consists of alternating contractions and relaxations of adjacent sections of the small intestine such that a contraction pinches a ring of circular smooth muscle, constricting the lumen and forcing its contents in both lateral directions into relaxed regions. When a contracted region subsequently relaxes, the adjacent relaxed regions contract. This oscillating contraction pattern forces the luminal contents to mix back and forth.

Segmentation is initiated by:

- **Distension** of the lumen by the presence of chyme.
- The presence of the enterogastrone **gastrin**, released in the presence of gastric protein.
- **Parasympathetic** input (sympathetic input decreases segmentation).

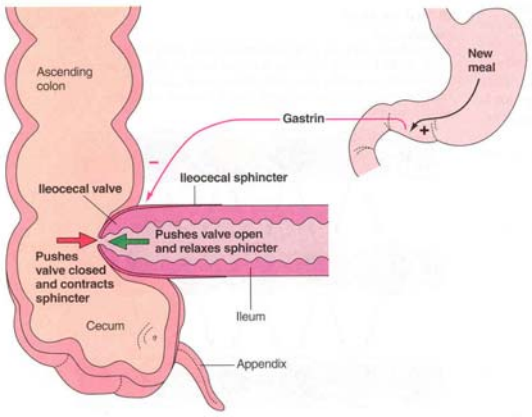
These factors increase the amplitude of the rhythmic slow wave depolarisations in circular smooth muscle in the muscularis externa, increasing the contraction of this circular muscle layer. The enteric nervous system coordinates the oscillating contract/relax pattern along the length of the small intestine.

Segmentation also helps movie chyme toward the large intestine. This slow movement results from less frequent segmental contractions in the ileum (9/min) than in the duodenum (12/min). This means that less chyme is pushed backward by the ileum than is pushed forward by the duodenum.

Migrating Motility Complex

Following the absorption of a meal, segmentation is replaced by the **migrating motility complex**. This motility pattern begins at the duodenal – gastric junction and consists of weak peristaltic contractions that travel for a short distance along the small intestine before fading. When this peristaltic wave dies out, a second wave begins slightly more distally than the initiation site of the first wave and travels slightly further toward the terminal ileum. In this manner, successive short peristaltic waves sweep luminal contents along the small intestine and into the large intestine, taking ~2 hrs to travel from stomach to large intestine. This cycle repeats itself until the ingestion of another meal initiates segmentation again. thought to ensure that any remaining food is removed

THE ILEOCECAL JUNCTION



Where the terminal ileum joins the initial portion of the large intestine, the **cecum**, there exists both a sphincter and a one-way valve controlling the movement of luminal contents.

The orientation of the **ileocecal** valve is such that the contents of the ileum can push through the valve but cecal contents pushing backward, effectively close the 'flaps' of the valve, preventing reverse flow.

The **ileocecal sphincter** is under neuronal and hormonal control. Distension on the ileal side causes the relaxation of the sphincter via the ENS. Gastrin also ~~inhibits~~ relaxes the sphincter. In contrast, pressure on the valve from the cecal side results in sphincter constriction.

These structures and processes prevent the bacteria rich contents of the large intestine from entering the nutrient rich small intestine where they would rapidly multiply.

SMALL INTESTINE SECRETION

As we have discussed, copious important digestive juices are secreted into the lumen of the small intestine during the ingestion of a meal. However, these juices originate from the pancreas and liver, not the mucosa of the small intestine itself.

Secretions of the Small Intestine

The mucosal epithelium of the small intestine itself does secrete ~1.5 litres of aqueous salt and mucus solution. This secretion, **succus entericus**, functions to lubricate the passage though the lumen and protect the mucosa against acid injury. Additionally, the water content of succus entericus provides the H_2O molecules required for the hydrolysis of chemical bonds during nutrient digestion. The stimulus for succus entericus production and release appears to the presence of luminal chyme.

Digestion in the Small Intestine

The majority of digestion occurs in the small intestine resulting from pancreatic enzyme secretion into the duodenum. However, proteins and carbohydrates require specific membrane-bound enzymes to complete their digestion.

- **Fats** are completely hydrolysed by pancreatic lipase to their absorbable components, monoglycerides and free fatty acids (FFAs), and packaged into micelles for absorption.
- **Proteins** are **reduced** to small peptide chains and some unitary amino acids by pancreatic proteolytic enzymes. Unlike fats, the peptide fragments require further hydrolysis by **aminopeptidases** in the **brush border** (more on this later) on the luminal surface of the epithelium prior to their absorption.
- **Carbohydrates**, **broken** into disaccharides and some monosaccharides by salivary and pancreatic amylase, are further hydrolysed by **disaccharidases** in the epithelial brush border prior to absorption.

Summary of the Digestion of the Three Primary Nutrients

▲ TABLE 16-7
Digestive Processes for the Three Major Categories of Nutrients

Nutrients	Enzymes for Digesting Nutrient	Source of Enzymes	Site of Action of Enzymes	Action of Enzymes	Absorbable Units of Nutrients
Carbohydrate	Amylase	Salivary glands	Mouth and body of stomach	Hydrolyzes polysaccharides to disaccharides	
		Exocrine pancreas	Small-intestine lumen		
	Disaccharidases (maltase, sucrase, lactase)	Small-intestine epithelial cells	Small-intestine brush border	Hydrolyze disaccharides to monosaccharides	Monosaccharides, especially glucose
Protein	Pepsin	Stomach chief cells	Stomach antrum	Hydrolyzes protein to peptide fragments	
	Trypsin, chymotrypsin carboxypeptidase	Exocrine pancreas	Small-intestine lumen	Attack different peptide fragments	
	Aminopeptidases	Small-intestine epithelial cells	Small-intestine brush border	Hydrolyze peptide fragments to amino acids	Amino acids and a few small peptides
Fat	Lipase	Exocrine pancreas	Small-intestine lumen	Hydrolyzes triglycerides to fatty acids and monoglycerides	Fatty acids and monoglycerides
	Bible salts (not an enzyme)	Liver	Small-intestine lumen	Emulsify large fat globules for attack by pancreatic lipase	

ABSORPTION IN THE SMALL INTESTINE

The small intestine absorbs all digested products of the three major nutrients, vitamins, electrolytes, and ingested and secreted water. There is normally no limitation to the absorption of these substances; if more food is ingested, more nutrients are absorbed. Interestingly, most absorption occurs in the duodenum and the jejunum. While the ileum normally only absorbs vitamin B_{12} and bile salts, it is capable of absorbing all nutrients.

Adaptations for absorption

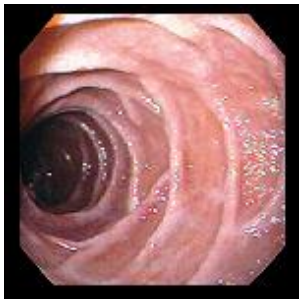
The luminal surface of the small intestine is organised to maximise the surface area of epithelial cell membrane in contact with luminal contents, increasing the efficiency of absorption. These include:

- The inner surface of the small intestine has large **circular folds**, or ridges, that are clearly visible on gross inspection and resulting in a threefold increase in surface area.
- Upon closer inspection, the folded luminal surface has a velvet-like appearance due to microscopic projections of the mucosal layer called **villi** (singular = villus) extending into the lumen like tiny fingers. Villi increase the surface area by a further 10 times.
- The surface of each villus is coated with epithelial and mucous cells. The luminal surface of the epithelium has between 3000 and 6000 hair-like microvilli projecting into the lumen. This **brush border,** visible only by electron microscopy, increases luminal surface area by a further 20 times.

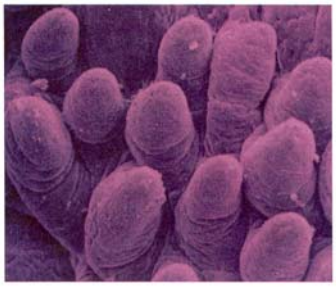
Tennis anyone?

Combined, these strategies increase the luminal surface area of the small intestine by ~600 times that of a smooth tube of equal length, to an area equal to a tennis court!

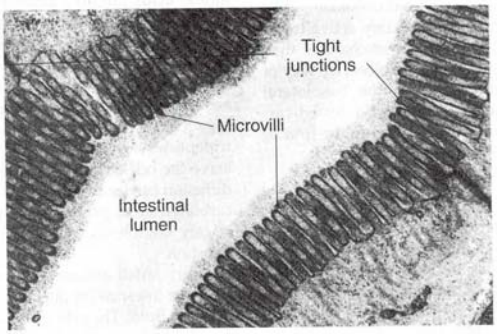
Small IntestineAbsorption – Anatomical Adaptations



Circular Folds



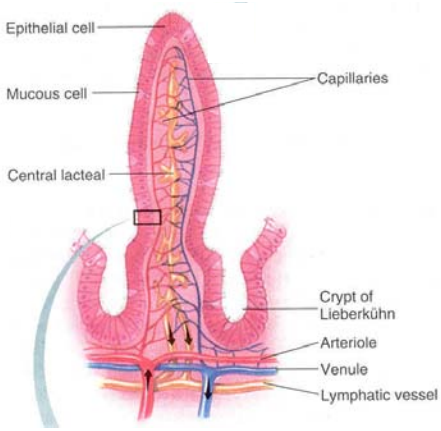
Intestinal Villi



Microvilli = Brush Border

It is helpful to understand the anatomical organisation of a villus. Each villus is comprised of:

Epithelial and mucous cells held together by tight junctions. The membrane of the epithelial brush border contains enzymes that hydrolyse peptides and disaccharides, enterokinase and transmembrane carrier proteins. A **connective tissue core** composed of the lamina propria, giving the villus its structure. A **network of capillaries** that receives arterial blood and drains into venous outflow. A **lymphatic vessel**, the central lacteal, which accepts fat digestion products and is involved in immune responses. To be absorbed, a substance must pass through an epithelial cell into the interstitial fluid in the connective tissue core and enter either a capillary or central lacteal.



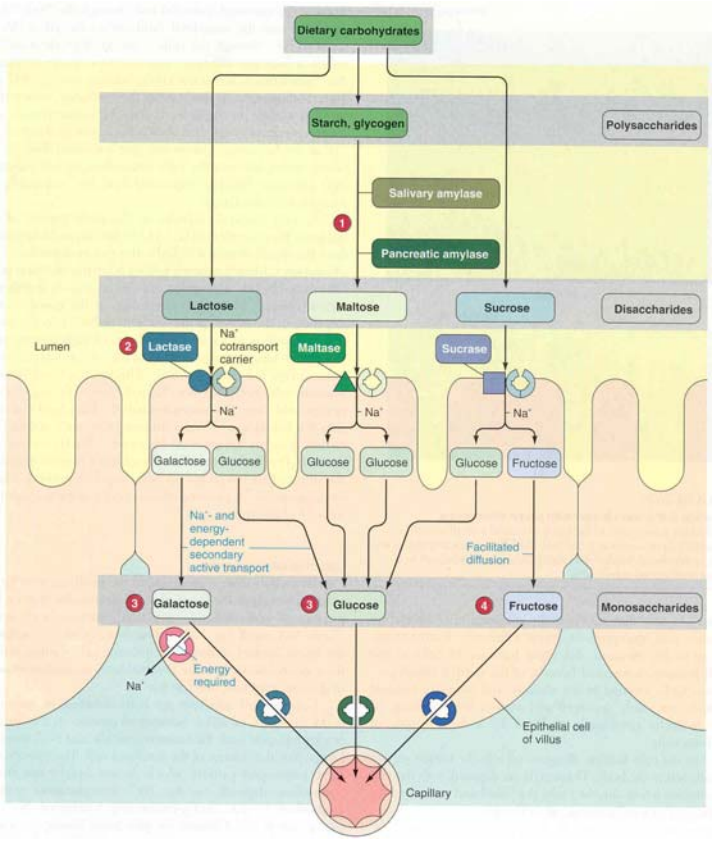
Between villi are small pits, the **crypts of Lieberkühn**, which have a dense population of **mucous cells** and are the primary locus for succus entericus secretion. In addition, these crypts have **stem cells** that constantly produce new epithelial cells, to replace the sloughing of surface epithelium (lost at a rate of ~100 million intestinal cells/minute!).

Carbohydrate Absorption

Recall that luminal amylase activity breaks down carbohydrates to maltose, sucrose and lactose. The disaccharidases in the brush border specifically hydrolyse these disaccharides into their constituent monosaccharides: glucose, galactose and fructose.

Glucose and **galactose** are absorbed via **secondary active transport**. The monosaccharide is **cotransported** into the cell with Na^+ ions travelling down their concentration gradient (the cytosolic Na^+ concentration is lower than in the lumen because of the active expulsion of Na^+ along the basolateral membrane). The monosaccharide now passively diffuses into the interstitial fluid through a membrane channel and enters a capillary. Of note, glucose may also pass through leaky tight junctions between adjacent epithelial cells.

Fructose passively diffuses through the epithelial cell by means of **facilitated diffusion**.



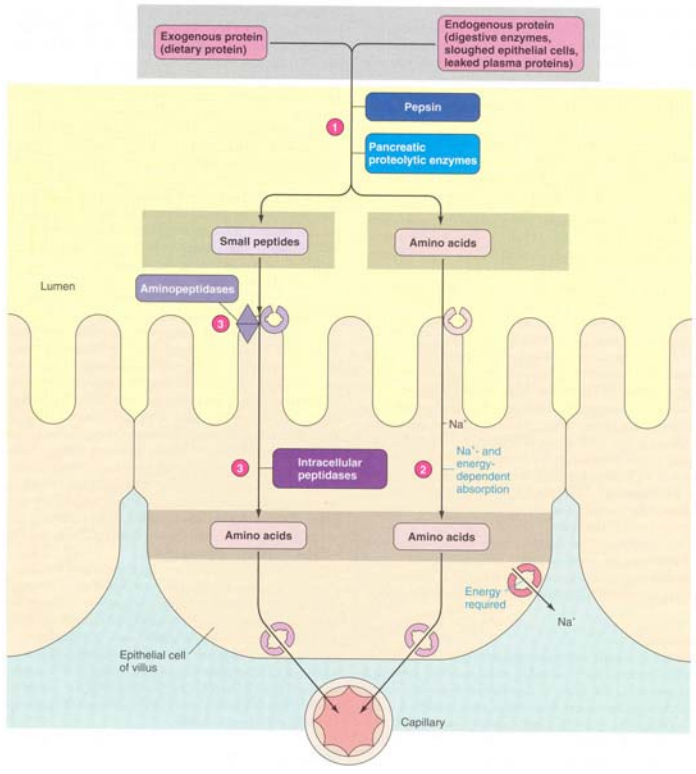
Protein Absorption

The digested protein products absorbed in the small intestine arise from **ingested** and **endogenous** proteins.

Endogenous proteins arise from three sources:

- digestive enzymes that have been digested themselves.
- proteins from sloughed epithelial cells along the GI tract.
- a small amount of plasma proteins that have leaked into the GI tract lumen.

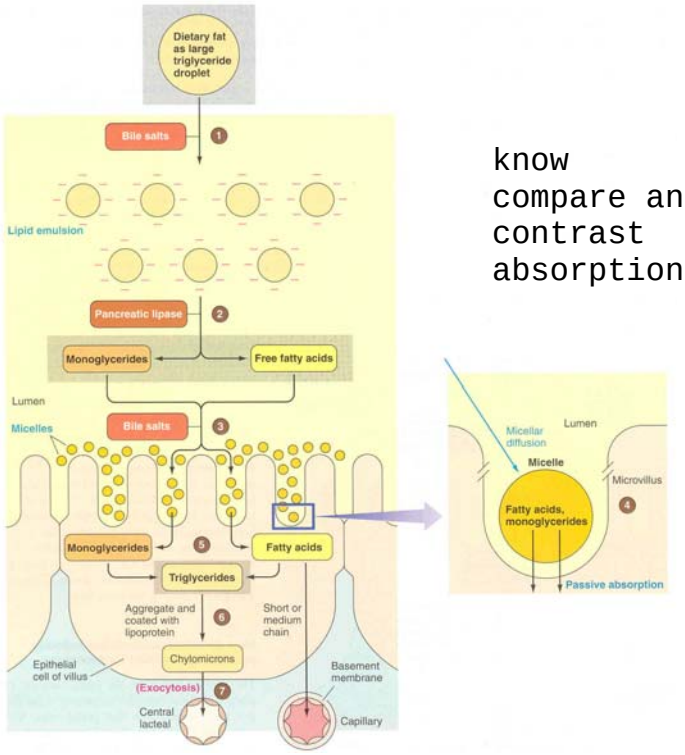
These endogenous proteins (~20 to 40 g) can account for half of each days protein absorption, an important recycling process.



Peptide fragments are hydrolysed to amino acids by **aminopeptidases** in the brush border and absorbed via secondary active transport along with Na+ ions, analogous to the cotransport of glucose/galactose. Amino acids also enter capillaries in the lamina propria of the villus.

Fat Absorption

Fat absorption is different than that of proteins and carbohydrates. Because fats are not water soluble, they must be specially packaged to dissolve in aqueous solution. However, they can easily diffuse across the lipid cell membrane and enter the cytosol. Additionally, fats are completely digested in the small intestine lumen and require no further processing by brush border enzymes.



know
compare and
contrast
absorption

In fat absorption:

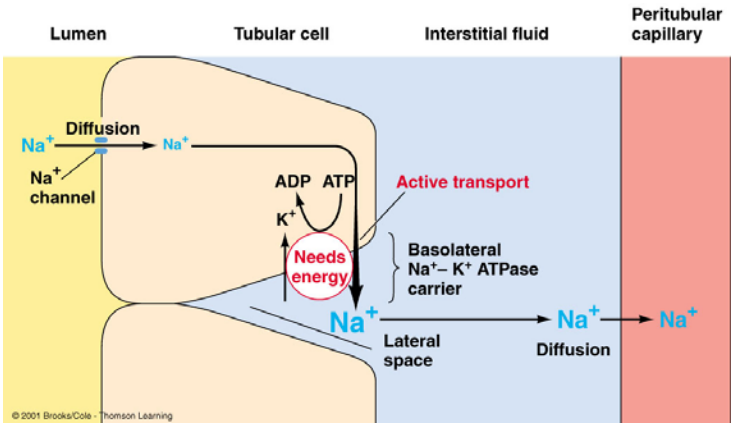
Micelles deliver monoglycerides and FFAs to the brush border membrane and the digested fat products diffuse into the cell. The bile salts, lecithin and cholesterol of the micelle are free again to aggregate with luminal fat digestion products.

In the epithelial cytosol, monoglycerides and FFAs are combined again to form **triglycerides** by cytosolic enzymes. Triglyceride molecules then aggregate with bipolar lipoproteins within the cytosol, forming **chylomicrons**, which are exocytosed into the interstial fluid.

Chylomicrons cannot cross the basement membrane of capillaries but can pass into the **central lacteal**. Thus fat is absorbed into the lymphatic system.

Na^+ and Water Absorption

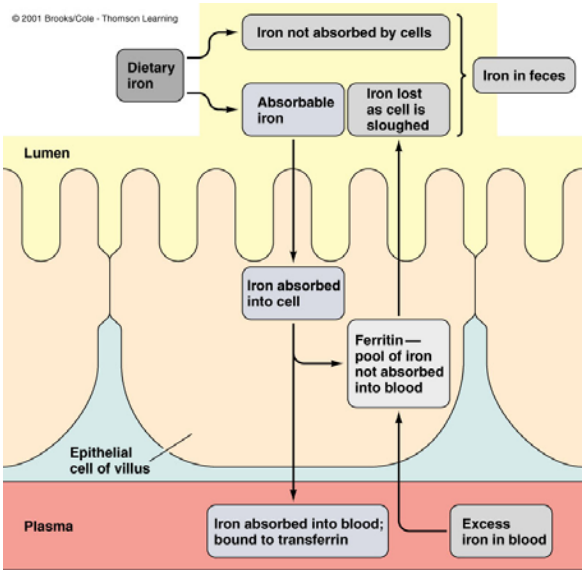
Water is another important nutrient absorbed primarily in the small intestine. Like glucose and amino acids, the active pumping of Na^+ ions into the interstitium via **Na^+/K^+ ATPase** activity along the basolateral membrane facilitates water absorption.



As Na^+ ions are pumped into the interstial fluid, the osmotic pressure of this hypertonic region will pull **water** in from the lumen. As water enters, hydrostatic pressure will move water into the capillary network.

The pumping of **Na^+ ions** out of the basolateral membrane also creates a concentration gradient favouring Na^+ entry into the epithelial cells across the brush border via Na^+ channels in the membrane. In addition, when the luminal Na^+ concentration is very high, Na^+ ions may passively diffuse into the villus interstitium by passing between epithelial cells via leaky tight junction connections.

Iron and Calcium Absorption



Unlike the three primary nutrients, iron and calcium represent two nutrients whose absorption occurs only when needed.

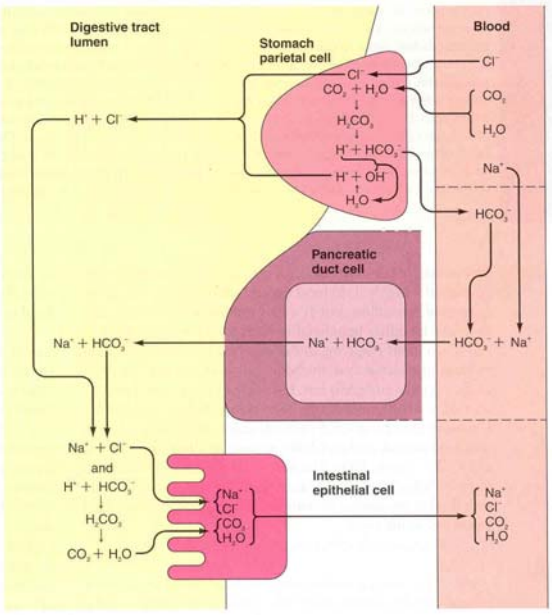
Iron is primarily needed for the hemoglobin molecule in RBC production. Typically daily intakes of iron range from 15 to 20 mg, however, the small intestines absorb only 0.5 to 1 mg (male) or 1.0 to 1.5 g (female) daily.

Only a fraction of ingested iron is in an absorbable form. Ferrous iron (Fe^{2+}) is absorbed more easily than ferric iron (Fe^{3+}); vitamin C can enhance iron absorption by increasing the Fe^{2+} pool; phosphate molecules can bind iron an prevent its absorption. Absorbable iron is actively transported into epithelial cells (a regulation site influenced by body iron need). Iron needed for RBC production immediately enters the blood while the rest is stored as **ferritin** in the epithelial cell until needed.

Calcium absorption is regulated at the site of active transport of Ca^{2+} into the epithelium. Brush border Ca^{2+} active transport is enhanced by **vitamin D** after it has been activated itself by the liver and kidney under the influence of parathyroid hormone. Normally, about 2/3 of ingested 1000 mg Ca^{2+} is absorbed each day.

BIOCHEMICAL HOMEOSTASIS

Despite the massive production of acid in the stomach and the equally massive alkaline secretion into the duodenum, the GI system maintains the acid-base balance of the body. The figure on the right summarises the acid-base balance that exists between the stomach, pancreas and small intestine. The secretion of H^+ and Cl^- in the stomach and Na+ and HCO_3^- from the pancreas are biochemically balanced. The absorption of all these electrolytes in the small intestine ensures that they are recycled and not lost in the feces.



The loss of any of these electrolytes in large quantities can produce an acid-base imbalance such as occurs in vomiting and diarrhea. Excessive vomiting results in the loss of stomach acid and can result in metabolic alkalosis. Diarrhea results in the loss of HCO_3^- in the feces and results in metabolic acidosis. Large systemic shifts in pH left uncorrected are detrimental to almost every biochemical reaction in the body.

Diarrhea

In addition to an acid-base imbalance, diarrhea can influence both nutrient and water absorption in the small intestine.

Diarrhea is a condition whereby the small intestine rapidly empties its contents, creating highly fluid fecal matter. Diarrhea can be helpful by expelling noxious stimuli from the intestinal tract. However, the rapid exit of chyme does not give the small intestine opportunity to absorb nutrients. This affects not only ingested food nutrients but the reabsorption of substances secreted along the GI tract. Prolonged diarrhea can therefore lead to malnutrition, dehydration and the aforementioned acid-base disturbance.

Diarrhea can be caused by:

- excessive intestinal motility from irritation of the GI tract wall, bacterial/viral infection or emotional stress.
- Hyper-osmotic chyme, resulting in luminal fluid accumulation and more fluid feces.
- Toxins from the bacteria *Vibrio cholera* and other micro-organisms can inhibit Na^+ absorption or stimulate Cl^- excretion resulting in osmotic fluid movement *into* instead of *from* the lumen. This is the leading cause of infant death in developing nations.

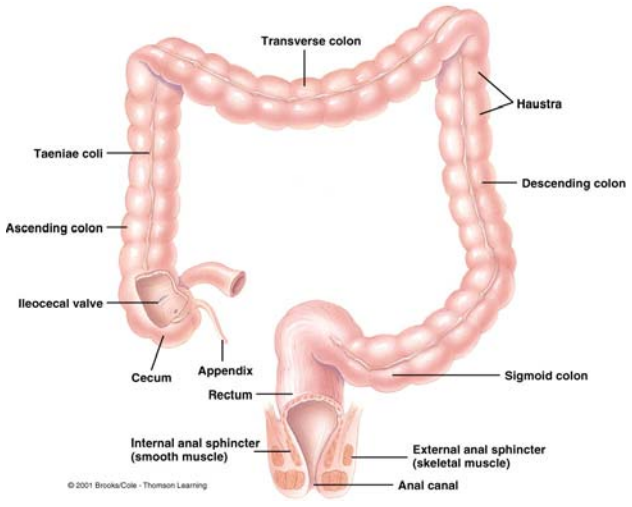
TOPIC 6: LARGE INTESTINE

Objectives

1. Describe the anatomical components of the large intestine and state a function for each.
2. Motility: Differentiate between haustral contractions and mass movements and state the function and control mechanism(s) for each.
3. Motility: Describe the defecation reflex and factors that control defecation.
4. Motility: Define constipation and discuss its potential causes and complications.
5. Secretions: Identify the secretions of the large intestine and discuss their function and control.
6. Digestion: Does digestion occur in the large intestine? If so, identify digestion products.
7. Digestion: Describe the benefits of colonic bacteria.
8. Absorption: Identify substances that are absorbed by the large intestine and factors that influence this absorption.

The large intestine consists of the **cecum**, **appendix**, **colon** and **rectum**. The cecum is a pouch situated at the junction with the small intestine. The appendix, a frequent site of infection, is a lymphoid tissue housing immune cells. The colon accounts for the majority of the large intestine is comprised of three, essentially linear, regions: the **ascending**, **transverse** and **descending** colon and the S-shaped **sigmoid colon**. The rectum stores fecal matter and empties through the anus.

The colon's primary role is to **absorb remaining water** in the feces and **store undigested material** before defecation.



LARGE INTESTINE MOTILITY

Motility is by far the most interesting aspect of large intestine physiology, characterised by haustral contractions, mass movements and the defecation reflex.

Haustral contractions are similar to small intestine segmentation but occur less frequently (1/ 30 min) and have less propulsive influence on luminal contents. When the a portion of circular muscle contracts in the large intestine, luminal contests are forced into sac-like haustra in relaxed regions. Haustration exposes colonic contents to the epithelial surface for water absorption.

Mass movements are familiar to all. Three to four times daily, usually following a meal, the ascending and transverse colon forcefully contract, pushing colonic contents into the descending colon and rectum. A mass movement can move fecal material ¾ of the length of the colon in a few seconds. Mass movements are triggered by the entry of food into the stomach via the **gastrocolic reflex**, mediated by gastrin and the autonomic nervous system.

The **defecation reflex** is initiated when a mass movement fills the rectum with fecal material. The distension of the rectum wall triggers the ENS to relax the internal anal sphincter (smooth muscle) and increase the contraction force in the sigmoid colon and rectum. Rectal distension also initiates a conscious urge to defecate. Defecation only occurs (normally) upon the voluntary relaxation of the external anal sphincter (skeletal muscle) at a convenient time. Remember that skeletal muscle is subject to fatigue when vigorously contracted for extended periods of time!

Motility and Constipation

If defecation is delayed for prolonged periods of time (normal variation in defecation frequency ranges from after every meal to once/week), feces can become too dry from water absorption, becoming hard and difficult to move. This can present as discomfort, headache, loss of appetite, nausea and mild depression thought to arise from irritation of the colon from distension.

Constipation may arise from:

- ignoring the urge to defecate.
- decreased intestinal motility associated with ageing, emotion or low fibre diet.
- obstruction associated with a tumour or muscle spasm.
- injury to nerves involved in defecation reflex.

Appendicitis

If fecal material becomes lodged in the appendix, its normal circulation may be impaired resulting in infection. If untreated an appendicitis may rupture, sending the infectious contents of the appendix into the sterile abdominal cavity. This is potentially lethal.

LARGE INTESTINE SECRETIONS

The secretions of the large intestine are designed to **protect** the mucosal epithelia from mechanical or acid injury. They consist of an **alkaline mucus solution**. The slippery mucus lubricates the colon wall while the alkaline component neutralises any acid produced by colonic bacteria. Mechanical and chemical stimulation initiate both long and short reflexes that increase the volume of secretions.

Large Intestine Digestion

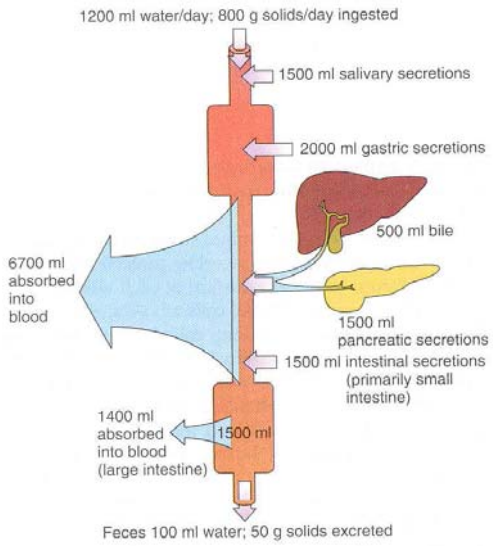
No digestion takes place in the large intestine. Interestingly, indigestible **cellulose**, a fibrous component of plant cell walls, is digested by colonic bacteria for their own purposes.

Large Intestine Bacteria

Bacteria colonise the large intestine, in part because of the slow transit time of colonic contents and lack of antibacterial enzymes or low pH environment. There are lots of bacteria here; as many as **500 species**, more individual bacteria than the body has cells. These bacteria are symbiotic: they provide vitamin K, promote the absorption of Ca^{2+}, magnesium and zinc by creating a slightly acidic environment, and they compete with potentially pathogenic microbes for food/space.

LARGE INTESTINE ABSORPTION

The colon does not have an extensive surface area for absorption like the small intestine, however, some absorption of **water**, **Na^+** and **Cl^-** occurs. Na^+ is actively absorbed, Cl^- follows passively (down the electrical gradient resulting from Na^+ movement) and water flows down the osmotic gradient created by Na^+ movement. **Vitamin K** is also absorbed in the colon.



Most water absorption occurs in the small intestine. Of the ~500 ml of remaining material entering the colon daily, 350 ml is reabsorbed as water. The remaining 150 g is excreted:

- 50 g as solid material including bilirubin (the main waste product), cellulose, bacteria and some salt.
- 100 g as water.