MEDICINE 438's

GIT PHYSIOLOGY

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IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

Lecture I: General Principles of GIT Physiology

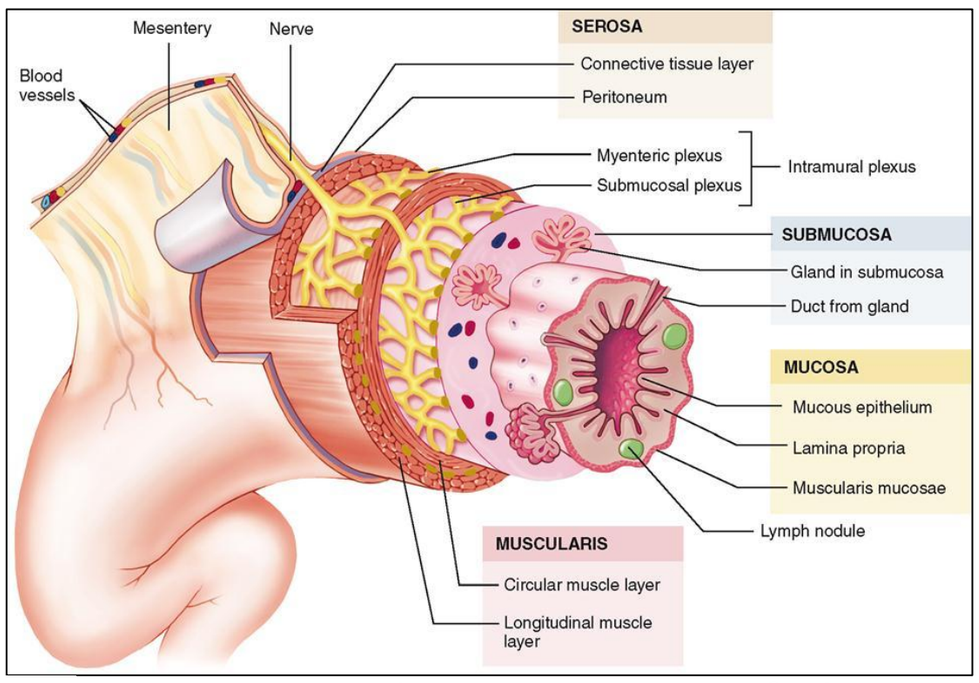


Figure 1-1 Functional anatomy of the wall of GIT

The General Characteristics of Smooth Muscle

2 Main muscle layers

1. Longitudinal Smooth Muscles

★ **Contraction:**
- Expands the lumen.
- Shortens the segment.

2. Circular Smooth Muscles

★ **Contraction:**
- Reduces the diameter of the lumen
- Increases the length.

2 Muscle classification

1. Unitary (single-unit)

★ **Contracts**
- in the absence of neural or hormonal influence.
- in response to stretch.

★ **Examples:**
- Stomach & intestine.

★ Cells are electrically coupled via **gap junctions.**

2. Multi-unit

★ **Does not Contract**
- in the absence of neural or hormonal influence.
- in response to stretch.

2 Types of contraction

1. Phasic (rhythmical)

Smooth muscle cells contract **rhythmically** or intermittently.

➢ **Periodic** contractions followed by relaxation

★ **Example:**

Walls of the GI tract.
- Gastric antrum
- Small intestine
- Esophagus.

2. Tonic

Smooth muscle cells continuously active maintaining a **"tone"**

➢ **Continuous** partial contraction.

★ **Examples:**
- sphincters:
  - Lower esophageal .
  - Ileocecal .
  - Internal anal.

Molecular Basis of Smooth Muscle Contraction

1. ↑ Intracellular ca^{+2} concentration by:
   - Entry to cell
   - Ca^{+2} release from sarcoplasmic reticulum
2. Ca^{+2} binds to calmodulin (CaM)
3. Ca^{+2} -calmodulin activates Myosin Light Chain Kinase (MLCK)
4. MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity
5. Active myosin crossbridges slide along actin and create muscle tension.

How Does Smooth Muscle Contraction Stop?

- Dephosphorylation by Myosin Phosphatase → Deactivation of phosphorylated myosin heads
- Drop in Ca^{+2} → Deactivation of MLCK

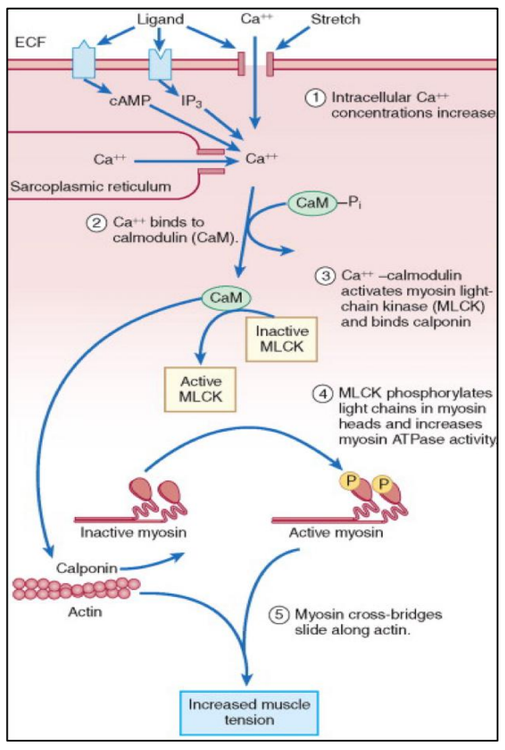


Figure 1-2

GI Smooth Muscle: Each muscle layer functions as a syncytium.

Electrical Activity of GI Smooth Muscle

Slow Waves

Definition: Rhythmic oscillating depolarization and repolarization in the resting membrane potential.

Origin: Interstitial cells of Cajal (ICC)

- It's the GI pacemaker.
- Abundant in myenteric plexuses (between smooth muscle layers)
- form a network with each other
- synaptic-like contacts to smooth muscle cells.

Function: Determine the rhythm of GI contraction

Features:

- No Ca entry (only Na)
- Not action potentials (because it's below threshold)
- No muscle contraction

Intensity: 5-15 **mV**

Frequency: Ranges in different parts of GI tract

- Stomach: **3**/min
- Duodenum: **12**/min
- Ileum: **8-9**/min

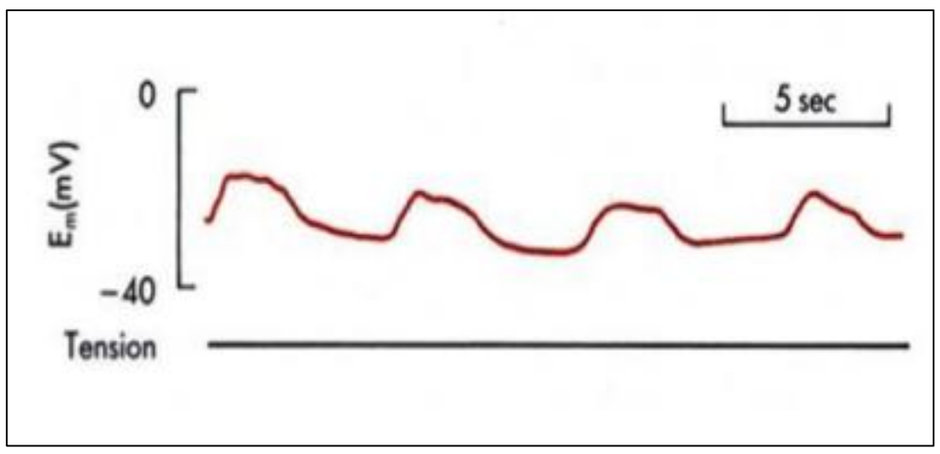


Figure 1-3

Spike Potentials

★ True Action potentials

Generation:

- Automatically when the resting membrane potential becomes more positive <-40 mV (Resting membrane potential : **-50 - -60 mV**)
- At the peaks of slow waves.

Frequency: 1-10 spikes/min

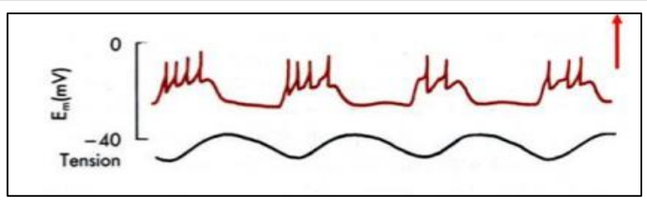
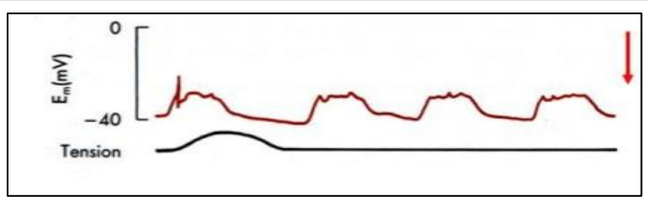
Duration:

Each spike lasts as long as 10-20 **ms**

10-40 times as long as the action potentials in large nerve fibers

Direct Relation with slow waves:

↑ slow wave potential (above threshold) → ↑ frequency of the spike potentials

Factors **depolarize** the membrane	Factors **hyperpolarize** the membrane
1- Muscle stretch. 2- Acetylcholine 3- Specific GI hormones.	Sympathetic stimulation ▪ Epinephrine (mainly). ▪ Norepinephrine.
	
With parasympathetic input, the membrane at the plateau of the slow wave depolarizers all the way to threshold; action potentials occur "on top of" the slow wave, and these set off contractions. The contraction / tension follows slightly after the electrical response.	If resting potential is shifted to more negative values (from sympathetic input) spikes and contractions will not occur.

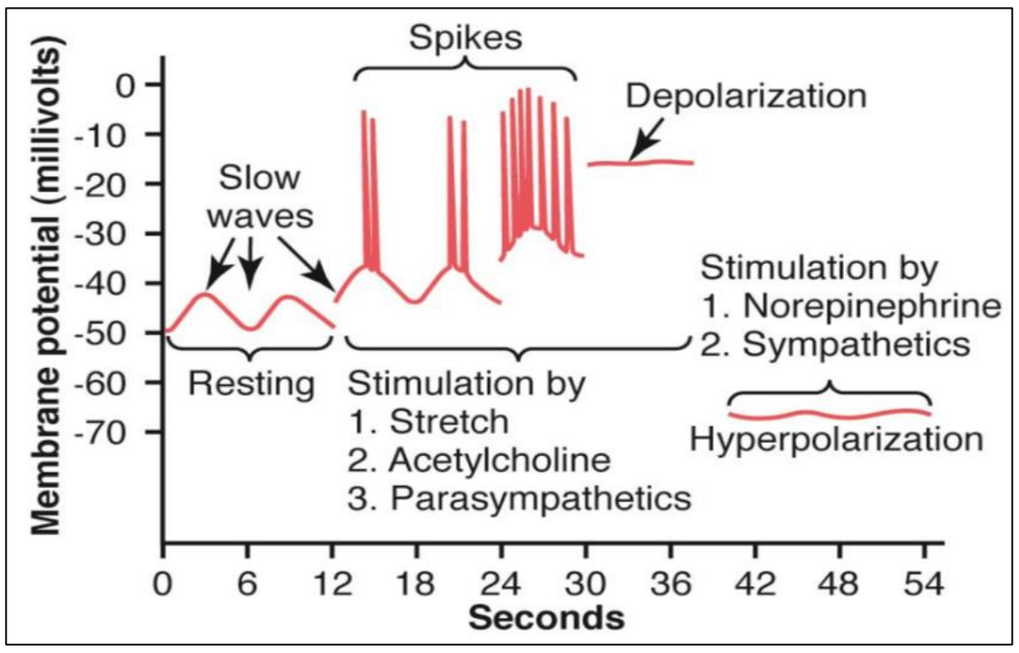


Figure 1-4

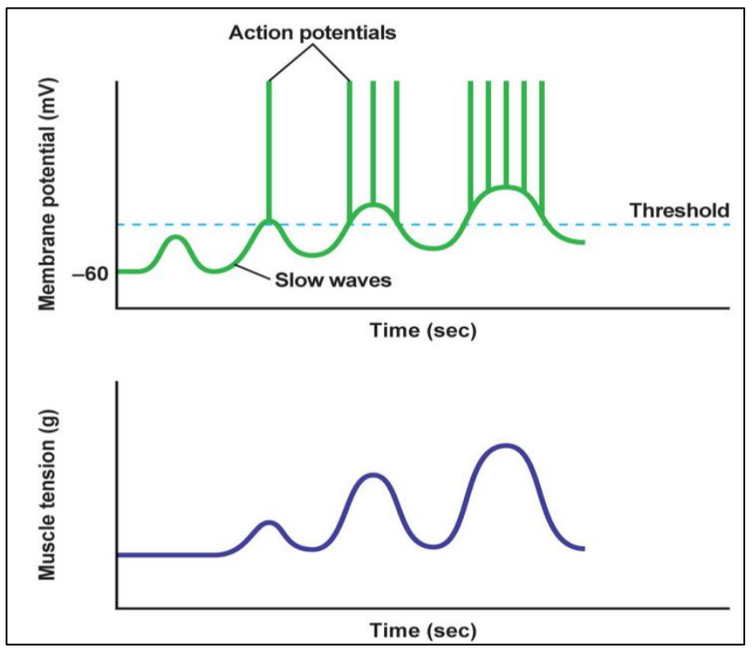


Figure 1-5

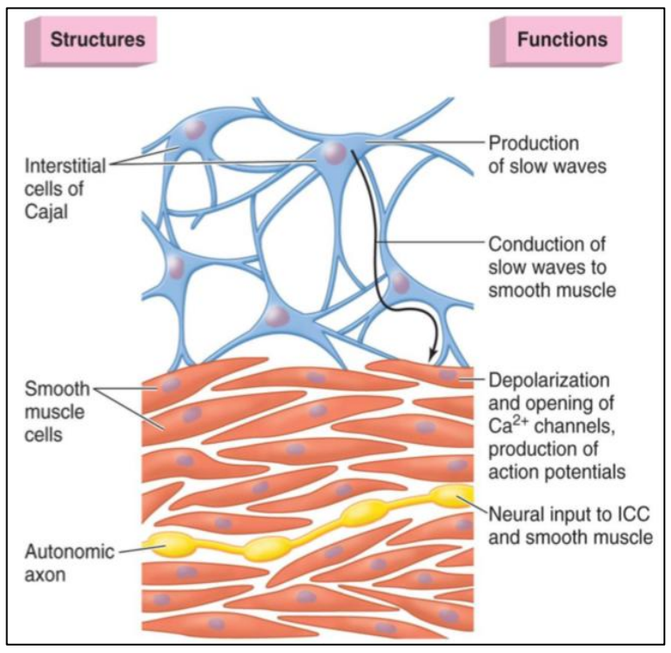


Figure 1-6

Control of GI Function

Neural | Hormonal | GI contents

1. Enteric Nervous system:

- The nervous system of GI tract.
- Its function is largely independent of the extrinsic NS.

2 main plexuses	
Myenteric "Auerbach's"	**Submucosal "Meissner's"**
between longitudinal & circular muscle layers.	In submucosa
Found throughout the GIT - Consists mostly of a linear chain of many interconnecting neurons. - Has excitatory & inhibitory motor neurons.	Only in small & large intestine
Controls GI **movement** "Motility"	Controls **secretions** & local **blood flow**.

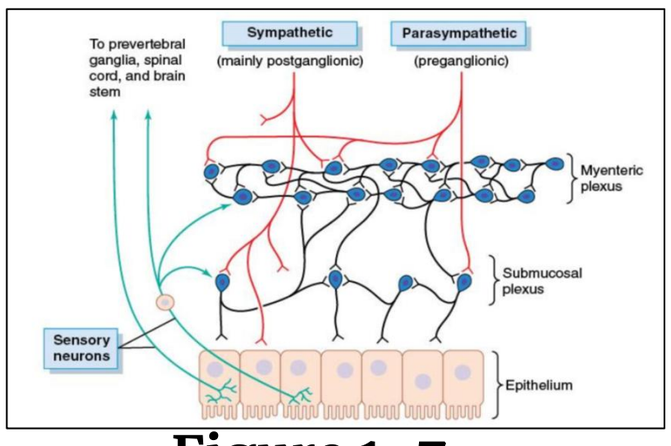


Figure 1-7

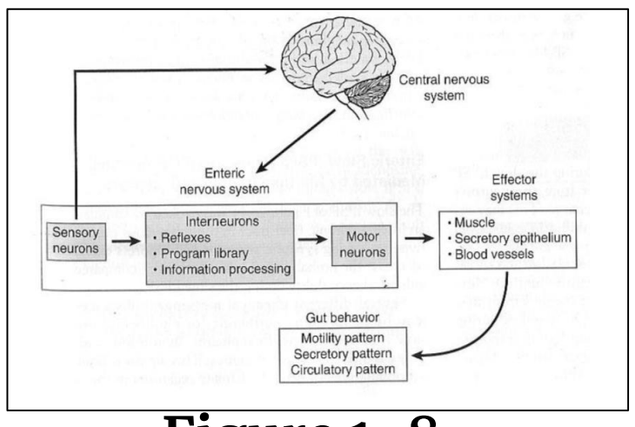


Figure 1-8

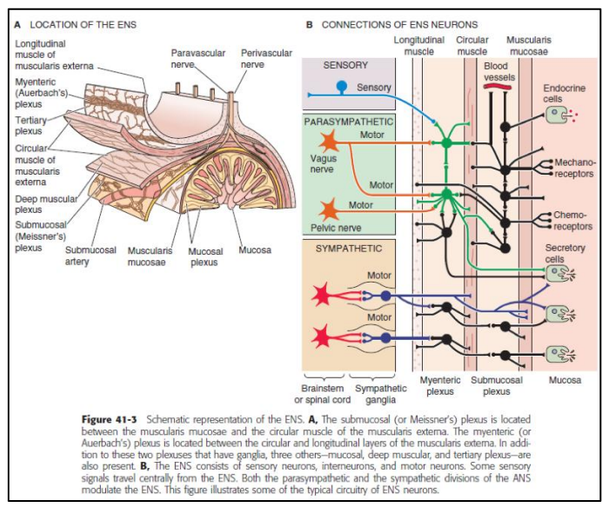


Figure 41-3 Schematic representation of the ENS. **A,** The submucosal (or Meissner's) plexus is located between the muscularis mucosae and the circular muscle of the muscularis externa. The myenteric (or Auerbach's) plexus is located between the circular and longitudinal layers of the muscularis externa. In addition to these two plexuses that have ganglia, three others—mucosal, deep muscular, and tertiary plexus—are also present. **B,** The ENS consists of sensory neurons, interneurons, and motor neurons. Some sensory signals travel centrally from the ENS. Both the parasympathetic and the sympathetic divisions of the ANS modulate the ENS. This figure illustrates some of the typical circuitry of ENS neurons.

Figure 1-9

2. Sympathetic nervous system:

- Origin: T5-L2
- Stimulation inhibits activity of the GI.

3. Parasympathetic nervous system:

- Vagus nerves (cranial division) & Pelvic nerves (sacral division).
- Stimulation causes general increase in activity of the enteric nervous system.

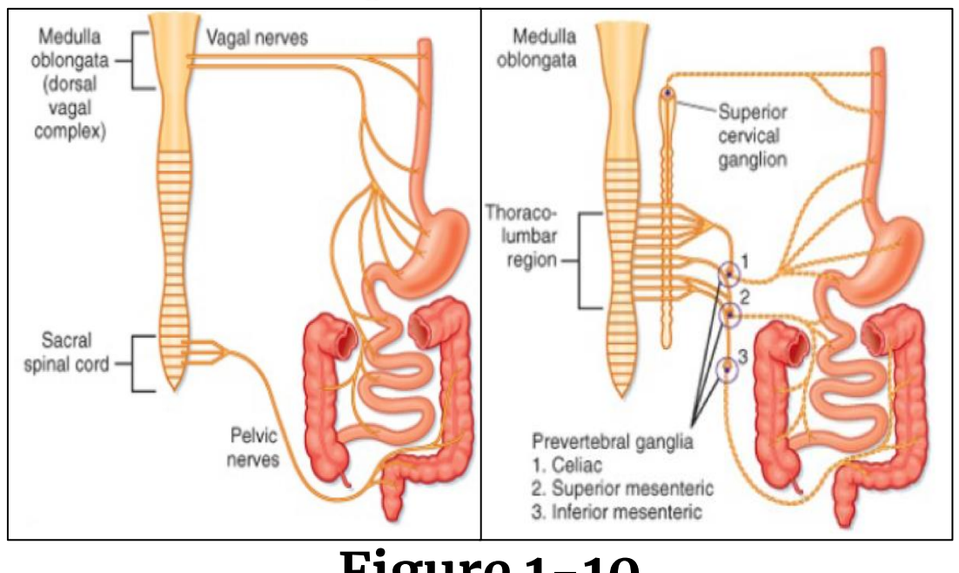


Figure 1-10

GI reflexes

Integrated within ENS
Local effects

- GI secretions
- Peristalsis
- Mixing movement

Integrated at Sympathetic ganglia
Signals Travel Long distance in GIT

- Gastrocolic
- Enterogastric
- Colonoileal

Integrated at spinal cord/brain stem

- Pain reflexes
- Defecation reflexes

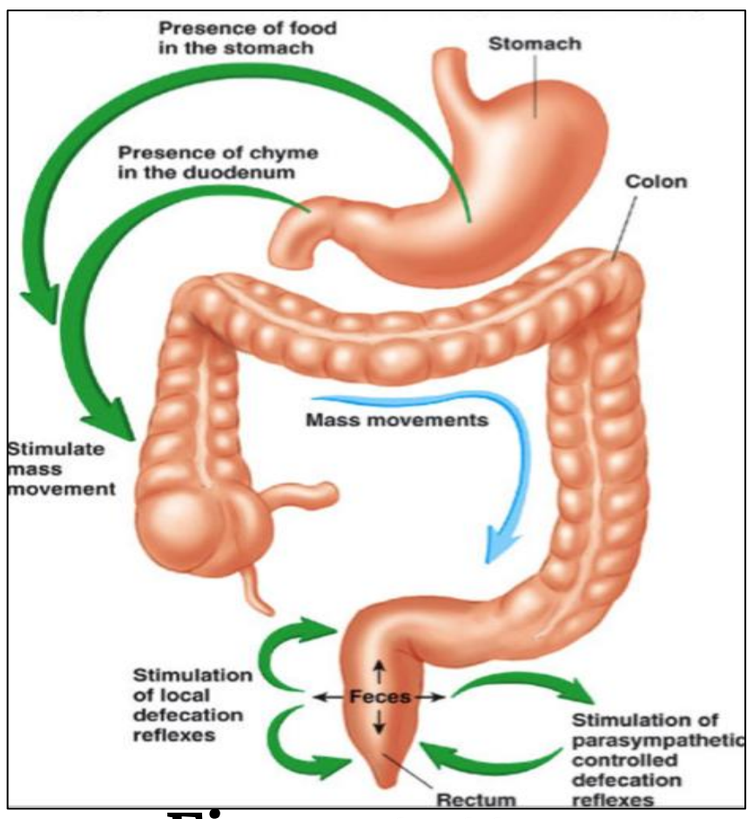


Figure 1-11

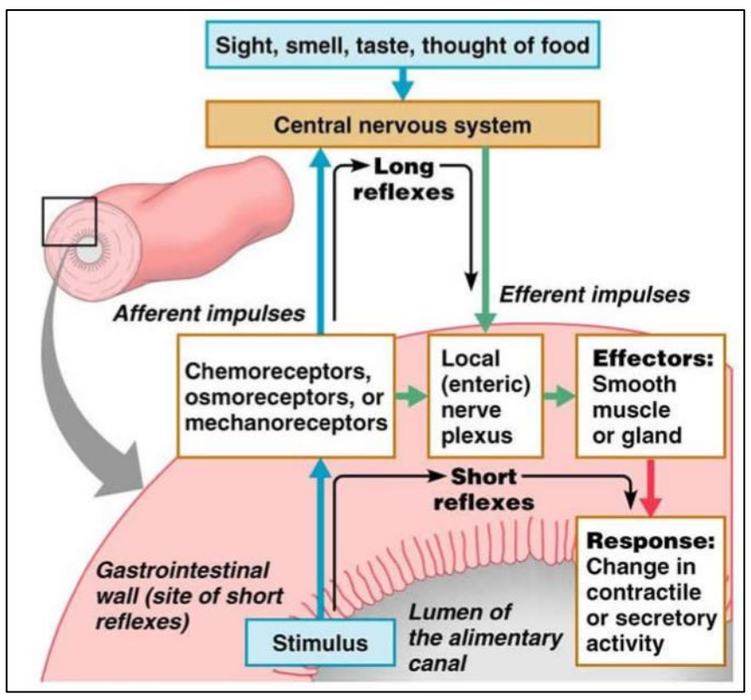


Figure 1-12

Functional Types of Movement in the GIT

Propulsive (Peristalsis)	Mixing (segmentation)
Progressive wave of contraction & relaxation. To push food forward	Non-propulsive segmental contractions. To break food into smaller pieces
Organizes propulsion of material over variable distances within the GI lumen.	★ Blend different juices with the chime. ★ Bring products of digestion in contact with absorptive surfaces.
★ **Propulsive (upstream) segment** - Contraction (circular Muscle) - Relaxation (longitudinal Muscle) ★ **Receiving (downstream) segment** - Contraction (longitudinal Muscle) - Relaxation (circular Muscle)	★ **Propulsive segment.** - Contraction (circular Muscle) ★ **Receiving segment.** - Relaxation (circular Muscle)
★ Stimulus: distention. **Others:** - Chemical irritation. - Physical irritation.	

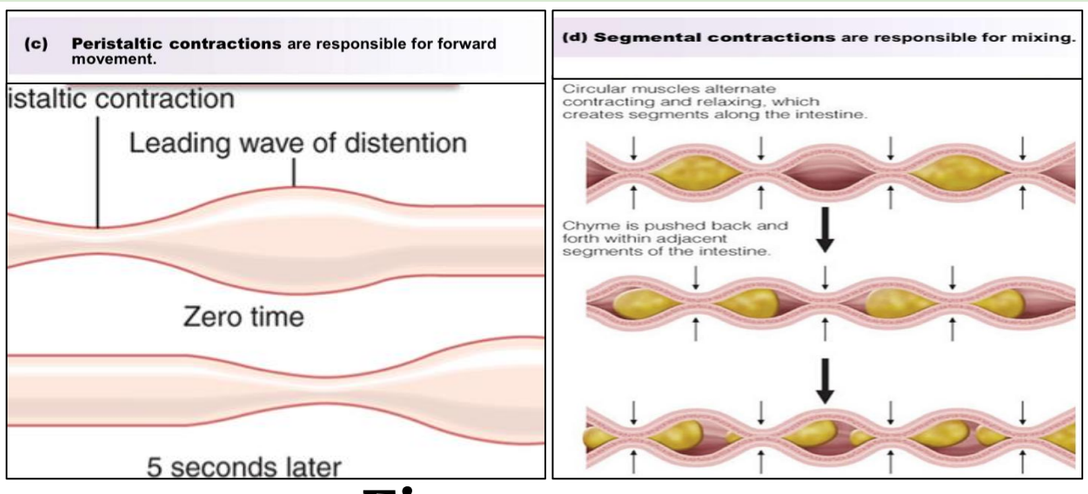


Figure 1-13

Lecture II: Esophageal Motility and Pathophysiology of Reflux Disease

Mastication (Chewing)

Functions:

1. To lubricate the bolus with salivary secretion.
2. To breakdown the bolus to small particles.
3. To begin digestion of carbohydrate (by amylase).

Table 27-1. Functions of Saliva and Chewing
Disruption of food to produce smaller particles
Formation of a bolus for swallowing
Initiation of starch and lipid digestion
Facilitation of taste
Production of intraluminal stimuli in the stomach
Regulation of food intake and ingestive behavior
Cleansing of the mouth and selective antibacterial action
Neutralization of refluxed gastric contents
Mucosal growth and protection in the rest of the GI tract
Aid in speech

Figure 2-1

Chewing (Stretch) Reflex

Food in mouth → Reflex inhibition to muscles of mastication → Jaw drops> The drop initiates a stretch reflex in jaw muscles → Rebound contraction → Jaw raises (closure of the teeth) → Bolus is compressed again against the linings of the mouth → Jaw muscles are once again inhibited > jaw drops → Rebound contraction (This process is repeated again and again)

Swallowing (Deglutition)

- Propels food from mouth to stomach.
- Complicated process since pharynx is a shared space between respiration & swallowing.
- Swallowing is initiated voluntarily in the mouth, but thereafter is under involuntary or reflex control. The reflex portion is controlled by the swallowing center in the medulla.
- Food should move without compromising respiration.

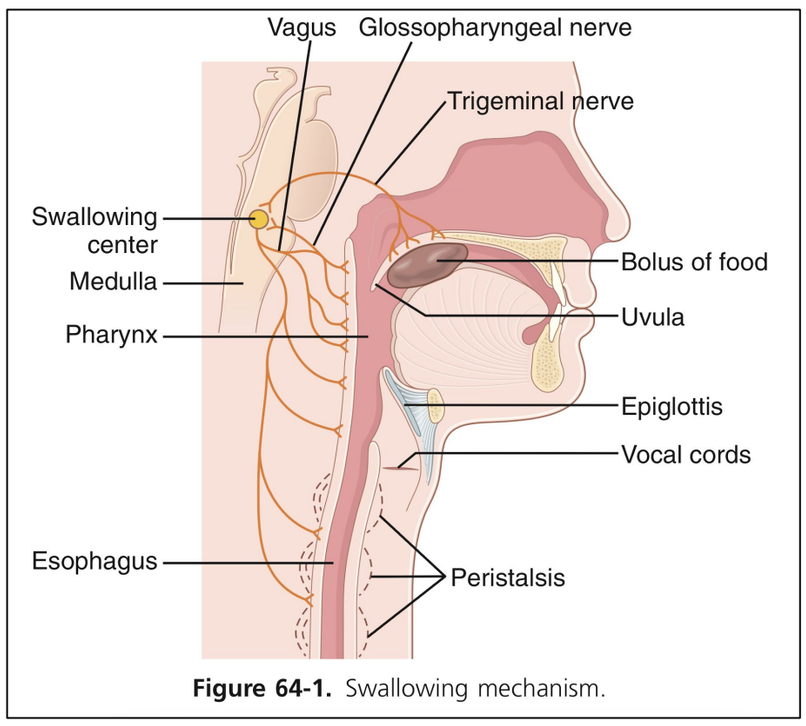


Figure 64-1. Swallowing mechanism.

Figure 2-2

Stages of Swallowing:

1 Voluntary Stage of Swallowing

Moves bolus of food from mouth → pharynx
Changes: food is squeezed posteriorly into the pharynx by the tongue.

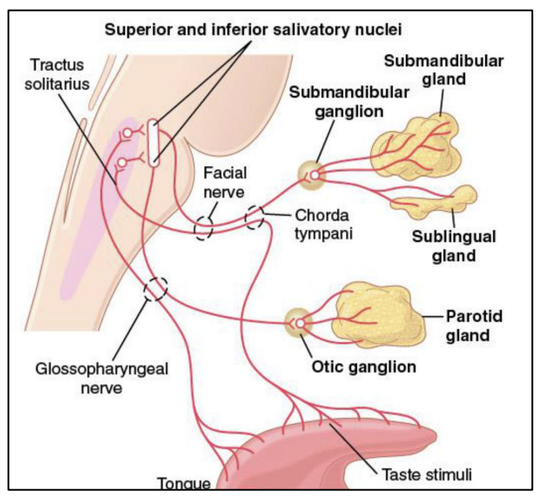


Figure 2-3

2 Pharyngeal Stage of Swallowing (Involuntary)

- Moves bolus of food from pharynx → esophagus.
- Food stimulates touch receptors in pharynx → impulses (Afferent fibers via CN V & IX) → to swallowing center in the brain stem → Motor efferent via CN V, IX, X, & XII → initiate a series of autonomic pharyngeal muscle contractions as follows: (continued on the next page)

2 Pharyngeal stage of Swallowing (Involuntary)

1

Soft palate & uvula → pulled upward to close off the nasopharynx

2

Palatopharyngeal folds (on each side of the pharynx) → pulled medially to approximate each other.
→ form a sagittal slit
→ food pass through it to the posterior pharynx.

3

- **larynx** → pulled upward and anteriorly (by the neck muscles).
- **Vocal cords** → close
- **Epiglottis** → bent over the airway as larynx is lifted.

- All these effects prevent food from going into the nose and trachea.
- Destruction of the vocal cords or the muscle that approximate them can cause strangulation.

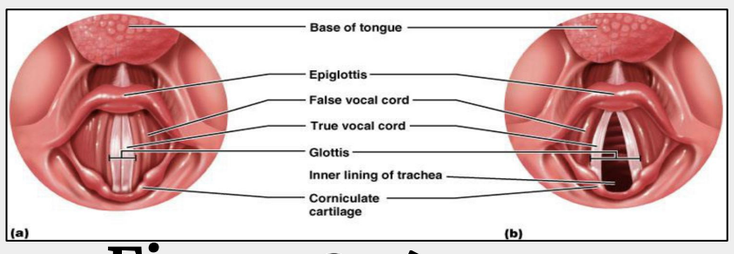


Figure 2-4

4

- **Esophagus** → opens due to the upward movement of the larynx.
- **Upper esophageal sphincter** → relaxes
- **Respiration** → inhibited (the swallowing center inhibits the respiratory center in the medulla during the swallowing cycle)

5

The entire muscular wall of the pharynx → contracts (superior, middle, then inferior parts) propelling the food by a wave of **peristalsis**.

3 Esophageal Stage

- Move food rapidly from pharynx → stomach.
- It's controlled partly by the swallowing reflex and partly by the enteric nervous system (ENS).
- When bolus of food passes through the upper esophageal sphincter, the swallowing reflex closes the sphincter so food cannot reflux into the pharynx.

Primary Peristalsis

Continuation of the peristaltic wave that started in the pharynx (to push bolus down).

Receptive Relaxation

A wave of relaxation (of LES & stomach) that travels along the myenteric plexus ahead of peristaltic wave.
→ Allows LES & stomach to prepare to receive the food bolus.

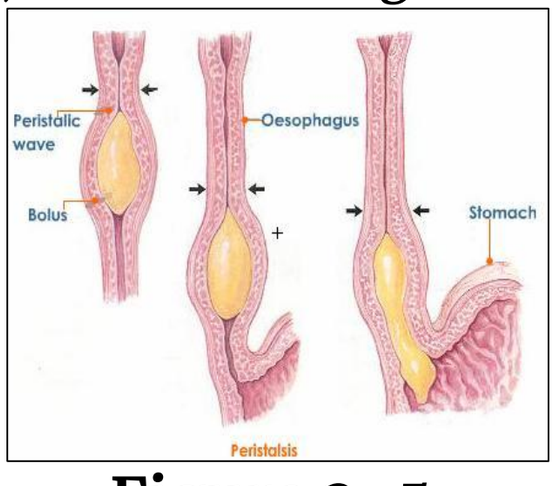


Figure 2-5

Secondary Peristalsis

- It occurs if the primary peristaltic wave fails to move the food to the stomach
- Starts at the point of esophageal distention by retained food → will continue until all the food is emptied into the stomach.

Esophageal Stage of Swallowing

The Upper Esophageal Sphincter (UES)

- **Formed of** skeletal muscle but is not under voluntary control.
- Located at the lower end of pharynx.
- Guards the entrance into the esophagus.

• **It prevents**:

- esophageal air insufflation during negative intrathoracic pressure events (eg: inspiration.)
- esophagopharyngeal/laryngeal reflux during esophageal peristalsis.

• **It relaxes during swallowing for about 1 sec → allowing the bolus to be forced through the relaxed UES.**

The Lower Esophageal (Gastroesophageal) Sphincter

- Formed by circular muscles.
- Extends *3cm* above its junction with stomach.
- Normally remains tonically constricted → Helps to prevent reflux of gastric juice.
- Relaxes ahead of esophageal peristaltic wave "receptive relaxation" → emptying of the propelled food into the stomach.

Lecture III: Gastric Motility and Secretion

Functional Anatomy of the Stomach

- stomach
  - physiologically
    - Orad (Reservoir): fundus and upper two thirds of the body
    - Caudad (Antral Pump): lower third of the body plus antrum
  - anatomical
    - fundus
    - body
    - antrum

Types of Gastric Glands

	Mucus secreting glands	Oxyntic (parietal) glands	Pyloric glands
secrete	Mucus HCO_3	Mucus HCl Pepsinogen IF	Mucus Gastrin
Found in	Cardia	Body & fundus (above the notch) Proximal 80% of stomach	Antrum (below the notch) *Distal 20% of stomach*

Types of Cells Present in Gastric Glands:

Cell type	Secretion	location
Oxyntic (parietal) cell	HCl & IF (intrinsic factor)	Body most distinctive cells in stomach
Peptic (chief)cell	Pepsinogen	Body
Mucus (neck) cells	Mucus, HCO_3^-	antrum
Enterochromaffin -like cells	Histamine	-
G cells	Gastrin (increases HCl secretion from Parietal cells)	antrum

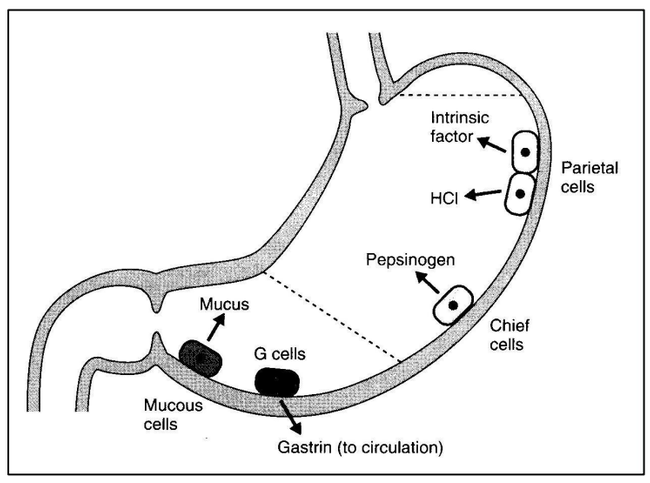


Figure 3-1

Gastric juice is composed of:

- HCL.
- Pepsinogen.
- Electrolytes.
- Intrinsic factor.
- Mucus (mucus gel layer).

Mechanism of HCl Secretion by Parietal Cells:

1. Cl^- is actively transported from the cytoplasm of the parietal cell into the lumen of the canaliculus.
2. Na^+ are actively transported out of the canaliculus into the cytoplasm of the parietal cell.
3. Water becomes (because it is a weak acid) dissociated into H^+ and OH^- *in the cell cytoplasm.* The H^+ are then actively secreted into the canaliculus in exchange for K^+.
4. CO_2, either formed during metabolism in the cell or entering the cell from the blood, combines under the influence of carbonic anhydrase with the OH^- to form HCO_3^-.
5. HCO_3^- then diffuse out of the cell cytoplasm into the extracellular fluid in exchange for Cl^- that enter the cell.

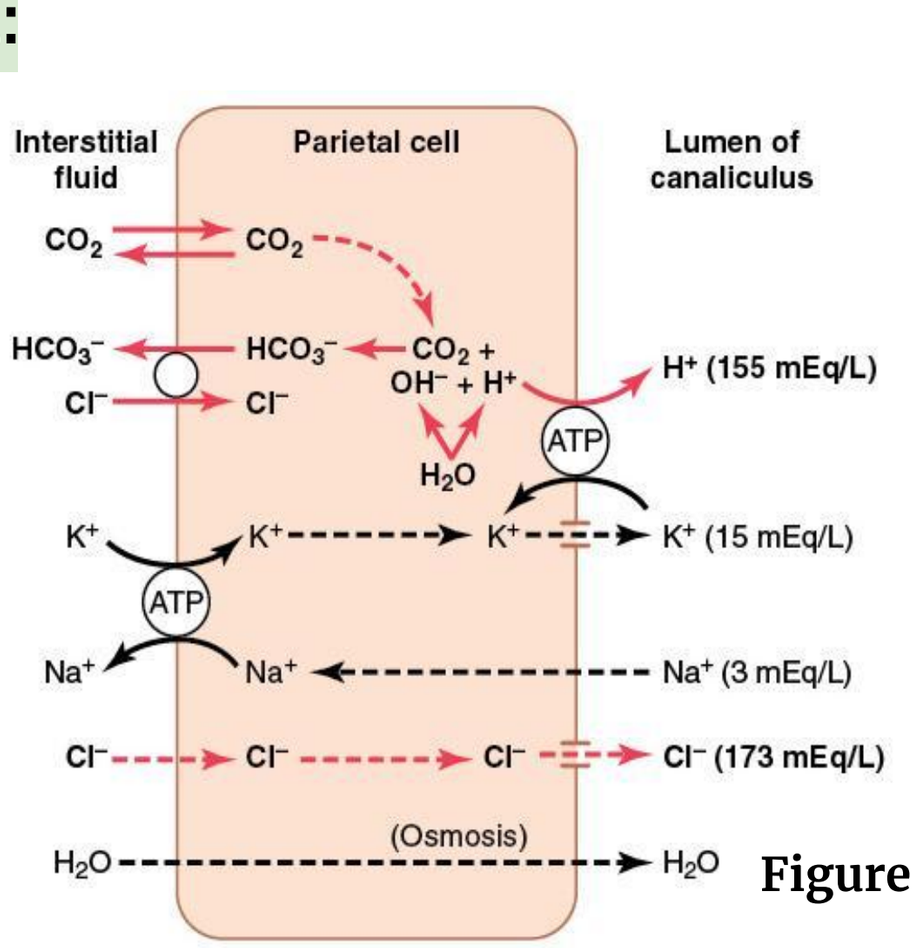


Figure 3-2

Control of HCL secretion

HCL secretion control

- **Neural**
  - **direct** → Ach act on parietal cells → increases HCL secretion
  - **indirect** → Act on G cells by releasing Gastrin releasing peptide(GRP) → secrete gastrin which act on CCK_B receptor of parietal cells → increases HCL secretion
- **Hormonal** → **Gastrin** (Endocrine secretion) → Act on enterochromaffin like cells (ECL) which secrete histamine → act on H2 receptor of parietal cell → increases HCL secretion.
- **Paracrine** → **histamine** → Histamine activate H2 receptor on parietal cells thus increase HCL secretion.
  H2 blockers are used for the treatment of peptic ulcer disease or gastroesophageal reflux disease. (e.g, Cimetidine)

Other Gastric Secretions-Pepsin:

- Several types of pepsinogen secreted from chief cells. They are activated by HCl into pepsin and once activated, they can activate more pepsinogen. These amino acids or peptides activate G cells to secrete Gastrin thus increasing HCL secretion.
- The optimum pH is (1.5-3.5) (1.8-3.5) , pH > 5 inactivates pepsin.
- it breaks down proteins into peptones & polypeptides.

Other Gastric Secretions-Mucus:

- Bicarbonate rich mucus layer protects the stomach mucosa. (Mucus is a protein, so it needs to be produced continuously because it gets degraded by pepsin).

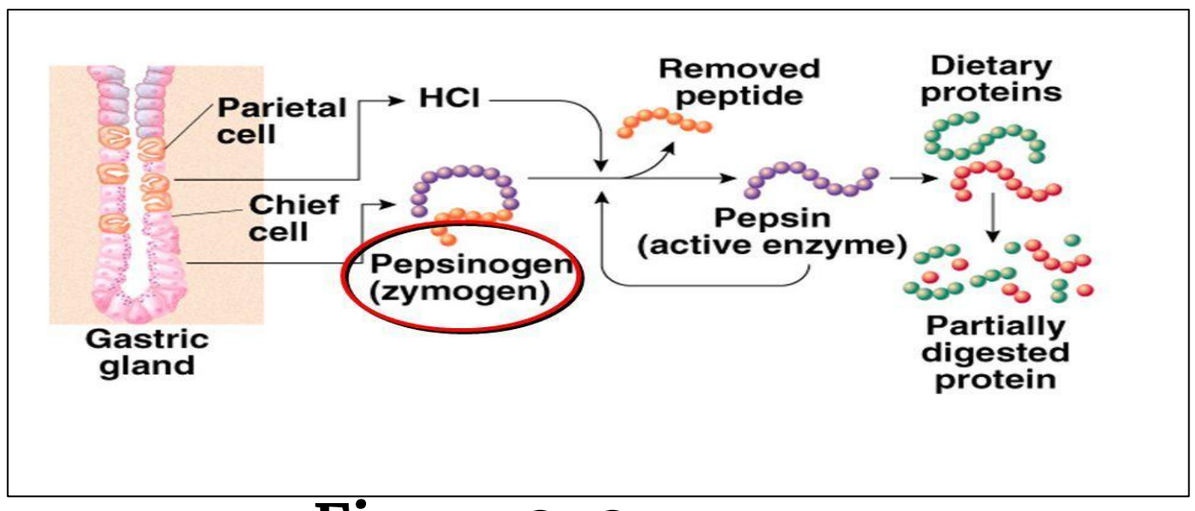


Figure 3-3

Function Of Stomach Movement:

1 Storage of food

- ★ stomach is stretched by food —(a vagovagal reflex is initiated)→ from the stomach to the brain stem and back to the muscular wall of it resulting in **reduction in muscular wall tone** which allows storage.

Stomach can store 0.8-1.5 L of food.

2 Mixing Of Food

- ★ Food presence causes weak peristaltic constrictor waves called **mixing/constrictor waves.**
- ★ It progress from the body → antrum and become intense, forcing the chyme to mix and move under high pressure from the antrum → the pylorus.
- ★ **Retropulsion** results when it move against a tight pylorus.

3 Regulate emptying of the chyme from the stomach into the small intestine(duodenum):

- ★ Rhythmical peristaltic contractions that can become **very strong** and **fuse** to form a continuing tetanic contraction lasting sometimes 2-3 minutes .
- ★ It's intense in young healthy people and increase by low blood glucose levels.
- ★ Hunger pain can begin after 12-24 hr of last food ingestion.

4 Hunger Contraction:

- ★ Rhythmical peristaltic contractions that can become very strong and fuse to form a continuing tetanic contraction lasting sometimes 2-3 minutes .
- ★ It's intense in young healthy people and increase by low blood glucose levels.
- ★ Hunger pain can begin after 12-24 hr of last food ingestion.

5 The main functions of the upper part of the stomach (Reservoir part):

- ★ To maintain a continuous compression.
- ★ To accommodate the received food without significant gastric wall distention or pressure (Storage of food).

6 Absorption of water and a few highly-lipid soluble substances (alcohol and Aspirin)

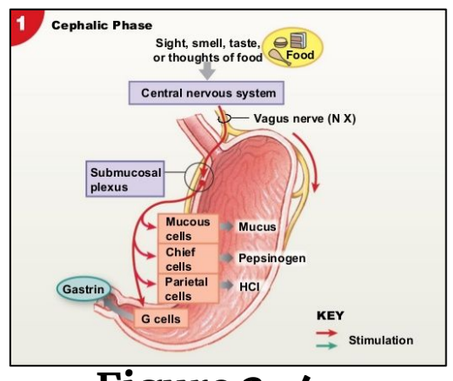
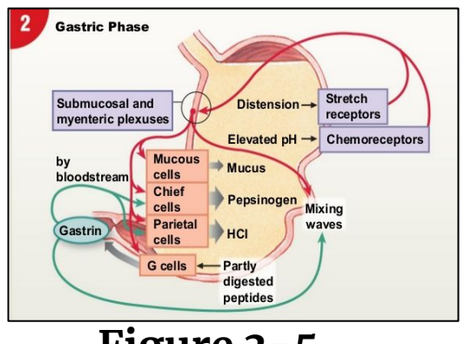
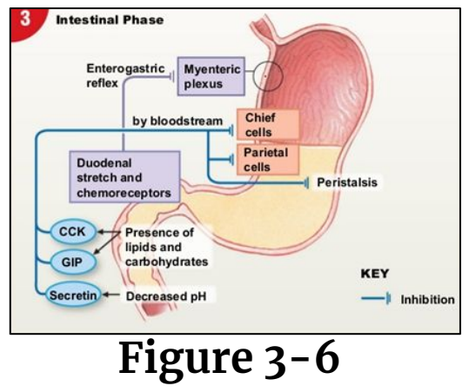
Retropulsion Phenomena

As the trailing contraction approaches the closed pylorus, the gastric contents are forced into an antral compartment of **ever-decreasing volume** and **progressively increasing pressure.**

Results in

Jet-like retropulsion through the orifice formed by the trailing contraction **reduces particle size to the 1-mm to 7-mm range that is necessary before a particle can be emptied into the duodenum.**

Gastric Secretion Phases

phase	Amount of HCL secreted	stimulus	mechanism	
Cephalic phase	30%	• Before food arrives at stomach. • Stimulated by (Smelling, taste , Chewing and swallowing).	**CNS send impulses** via vagus nerves (The nerve endings release ACh) which directly stimulates acid secretion from parietal cells. **CNS** send impulses via vagus nerves ,nerves also release gastrin-releasing peptide (GRP) which stimulates G cells to release **gastrin**, indirectly stimulating parietal cell acid secretion.	 Figure 3-4
Gastric phase	60%	• when food enters the stomach . • Stimulated by (distention , amino acid , small peptides).	**Distention of the stomach** stimulates mechanoreceptors, which stimulate the parietal cells directly through short local (enteric) reflexes and by long vago-vagal reflexes. **Digested proteins** in the stomach are also potent stimulators of **gastric acid secretion**, an effect mediated through gastrin release.	 Figure 3-5
intestinal phase	10%	• when chyme enters duodenum. • Stimulated by (protein digestion products in the duodenum).	**Inhibitory hormones (Enterogastrones):** **Somatostatin** (D-cells) in antrum. **Secretin** (S-cells) in duodenum. **Glucose-dependent insulinotropic peptide** (GIP) (K-cells) in duodenum.	 Figure 3-6

Stomach emptying:

- Stomach emptying is the result of intense peristaltic antral contractions against resistance to passage of chyme at the pylorus.
- The pyloric sphincter is characterized by strong circular muscle (as compared to the antrum) and remains tonically contracted most of the time. However, during pyloric constriction, watery chyme can still pass through the pylorus into the duodenum, but not food particles.
- Pyloric constriction is determined by:
  - Nervous reflex signals
  - Humoral reflex signals (from the duodenum and stomach).
- The rate of stomach emptying is controlled by signals from the stomach and duodenum, with the latter being far stronger and controls emptying of the chyme at a rate that allows the proper digestion and absorption in the small intestines.

Factors that regulate gastric emptying:

Gastric Factors that Promote Stomach Emptying

Powerful Duodenal Factors That Inhibit Stomach Emptying.

1 Effect of Gastric Food Volume on Rate of Stomach Emptying.

- **Increased gastric food volume → increased stretch in the stomach wall (which elicits local myenteric reflexes) → increased pyloric pump activity & the tonic contraction of the pyloric sphincter gets inhibited, leading to increased stomach emptying.**

2 Effect of the Hormone Gastrin on Stomach Emptying.

- **Gastrin is released from the antral mucosa in response to the presence of digestive products of meat.**
- **It promotes the secretion of acidic gastric juices (e.g. HCl) by the stomach gastric glands (or oxyntic glands) located on the inside surface of the body and fundus of the stomach; (i.e. proximal 80% of the stomach).**
- **It also enhances the activity of the pyloric pump and motor stomach function (moderate effect) and probably promotes stomach emptying.**

Factors that regulate gastric emptying:

Gastric Factors that Promote Stomach Emptying

Powerful Duodenal Factors That Inhibit Stomach Emptying.

1 Inhibitory Effect of **Enterogastric Nervous Reflexes** from the Duodenum.

- When food enters the duodenum, multiple nervous reflexes are initiated from the duodenal wall and pass back to the stomach to regulate stomach emptying depending on the volume of chyme in the duodenum.

These duodenal reflexes are mediated by three routes:

★ Directly from the duodenum to stomach through the **ENS** (enteric nervous system) in the gut wall.

★ Through extrinsic nerves that go to the prevertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach.

★ Through the vagus nerves reflex (to a slight extent) → the brain stem → inhibit the normal excitatory signals that are transmitted to the stomach through the vagus nerves.

These reflexes inhibit the pyloric pump and increase the tone of the pyloric sphincter thus decreasing stomach emptying.

The duodenal factors that can initiate the enterogastric inhibitory reflexes include:

- Duodenal **distention.**
- Duodenal **irritation.**
- Duodenal **acidity.**
- **Osmolality of the chyme** in the duodenum.
- **Protein** (and may be fat) content of the chyme in the duodenum.

2 Hormonal Feedback from the Duodenum Inhibits Gastric Emptying , Role of Fats and the Hormone Cholecystokinin

- **Fat entering the duodenum or acidity of chyme or excess quantities of chyme causes** (probably a receptor mediated mechanism) **the release of:**

★ cholecystokinin (CCK) , acts as an inhibitor to block increased stomach motility caused by gastrin.

★ other inhibitory hormones such as (secretin and gastric inhibitory peptide (Glucose-dependent insulinotropic peptide GIP) from the epithelium of the duodenum and jejunum.)

Release of CCK, secretin, and GIP: they circulate and inhibit the pyloric pump and increase the tone of the pyloric sphincter thus decreasing stomach emptying.

Hormones Summary

Hormone	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	G cells of the: ➔ Antrum ➔ Duodenum ➔ jejunum	★ Protein ★ Distention of the stomach ★ Vagal stimulation ★ Gastrin releasing peptide (GRP) (Acid inhibits release)	Stimulates: - Gastric H^+ secretion - Growth of gastric mucosa
Cholecystokinin (CCK)	I cells of the: ➔ Duodenum ➔ Jejunum ➔ ileum	★ Protein ★ Fatty acids ★ Acids	Stimulates: - Pancreatic enzyme secretion - Pancreatic HCO_3^- secretion - Gallbladder contraction - Growth of the exocrine pancreas - Relaxation of the sphincter of Oddi Inhibits: Gastric emptying
Secretin	S cells of the: ➔ Duodenum ➔ jejunum ➔ ileum	★ Acids ★ Fat (in the duodenum)	Stimulates: - Pepsin secretion - Pancreatic HCO_3^- secretion - Biliary HCO_3^- secretion - Growth of the exocrine pancreas Inhibits: Gastric H^+ secretion
Glucose-Dependent Insulinotropic Peptide (GIP)	K cells of the: ➔ Duodenum ➔ jejunum	★ Protein ★ Fatty acids ★ Oral glucose	Stimulates: Insulin secretion from pancreatic β cells Inhibits: Gastric H^+ secretion
Motilin	M cells of the: ➔ duodenum ➔ jejunum	★ Fat ★ Acid ★ Nerve	Stimulates: Gastric motility Intestinal motility

LECTURE IV: Physiology of the Pancreas

Pancreas

Lying parallel to and beneath the stomach, it is a large compound gland with most of its internal structure similar to that of the salivary glands. It is composed of:

Endocrine portion 1-2%

(Made of Islets of Langerhans)

Secrete hormones into the blood.

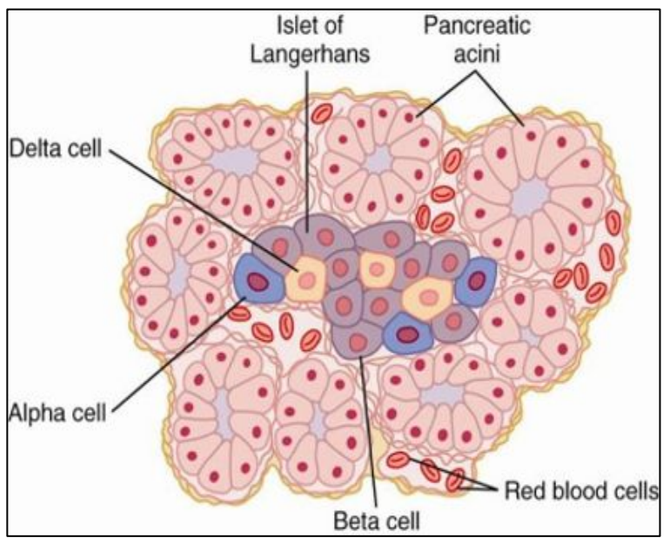


Figure 4-1

Exocrine portion 95%

(Acinar gland tissues)

Made of acinar & ductal cells.

secretes digestive enzymes, HCO_3^- and water into the duodenum .

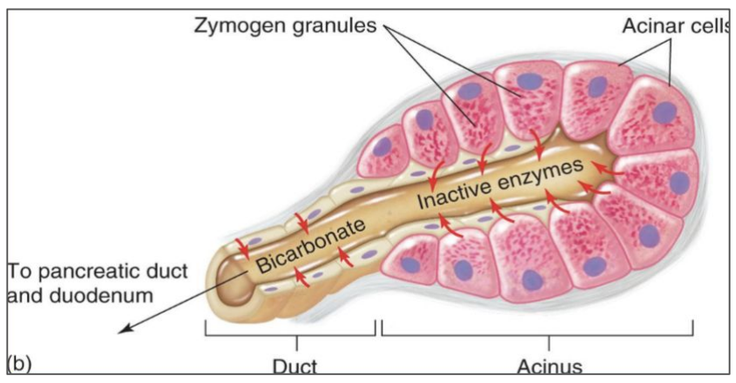


Figure 4-2

- The pancreatic digestive enzymes are secreted by **pancreatic acini**.
- Large volumes of sodium bicarbonate solution are secreted by the **small ductules** and **larger ducts** leading from the acini.
- Pancreatic juice is secreted in response to the presence of chyme in the upper portions of the small intestine.
- Insulin and Glucagon are crucial for normal regulation of glucose, lipid, and protein metabolism.

Pancreatic Secretion

- **Amount ≈ 1.5 L/day in an adult human.**
- **The major functions of pancreatic secretion:**

1. To neutralize the acids in the duodenal chyme to optimum range (pH=7.0-8.0) for activity of pancreatic enzymes.
2. To prevent damage to duodenal mucosa by acid & pepsin.
3. To produce enzymes involved in the digestion of dietary carbohydrate, fat, and protein.

Pancreatic Juice: Refers to the final combined product secreted by the exocrine pancreas.

- **Digestive enzymes**
  - **Proteolytic:**
    - ★ **For protein:** Trypsin, Chymotrypsin, Carboxypolypeptidase
  - **Amylolytic:**
    - ★ **For lipids:** Pancreatic lipase, Cholesterol Esterase, Phospholipase A2
    - ★ **For carbohydrates: Pancreatic** Amylase
  - **Nucleolytic:**
    - ★ **For DNA & RNA.**
- **An electrolyte solution rich in HCO3-**

Pancreatic Enzymes for Digesting Proteins Are:

Trypsin (active form of Trypsinogen)	Chymotrypsin (active form of Chymotrypsinogen)	Carboxypolypeptidase (active form of Procarboxypolypeptidase)

These enzymes become activated only after they are secreted into the Intestinal Tract.

Trypsinogen is activated by:

- Enteropeptidase (**enterokinase**), an enzyme secreted by the intestinal mucosa when chyme comes in contact with the mucosa.
- Trypsinogen can be autocatalytically activated by trypsin formed from previously secreted trypsinogen.

Chymotrypsinogen and Procarboxypolypeptidase:

They are activated by trypsin to form chymotrypsin and carboxypolypeptidase.

Trypsin Inhibitor

- Secretion of trypsin inhibitor prevents digestion of the pancreas itself.
- Proteolytic enzymes of the pancreatic juice do not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself.
- The same cells that secrete proteolytic enzymes into the acini of the pancreas secrete another substance called **trypsin inhibitor**.
- Trypsin inhibitor is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas.
- Because trypsin activates the other pancreatic proteolytic enzymes, therefore trypsin inhibitor prevents activation of the other enzymes as well.

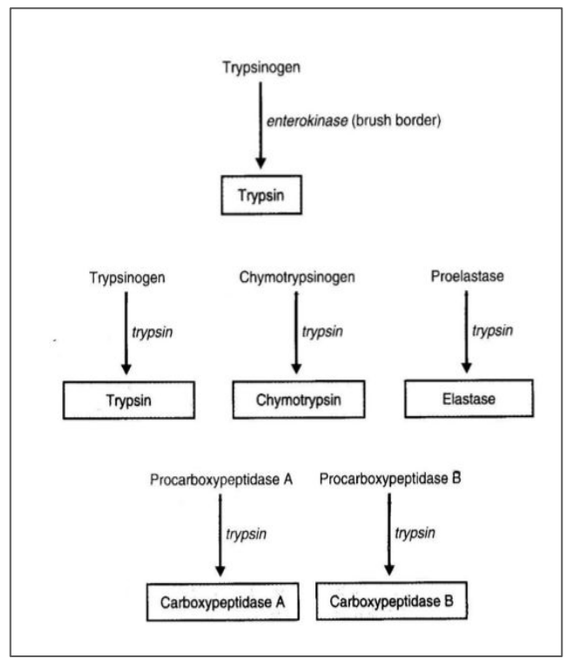


Figure 4-3
Activation of digestive enzymes in small intestine

Enzymes For Digesting Carbohydrate:

- **Pancreatic amylase**: it hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few tri-saccharides.

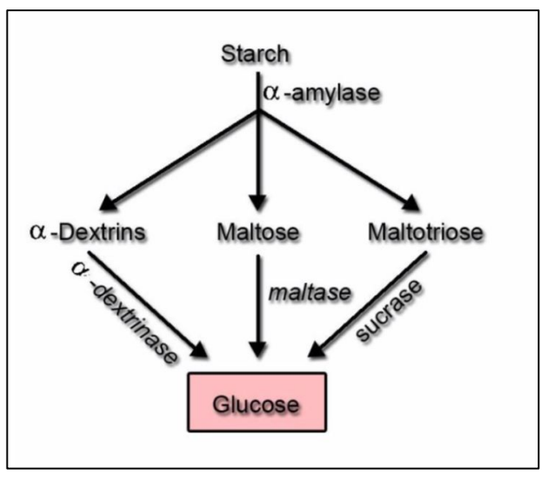


Figure 4-4

Enzymes For Digesting Fat:

(1) Pancreatic lipase (2) Cholesterol esterase (3) Phospholipase

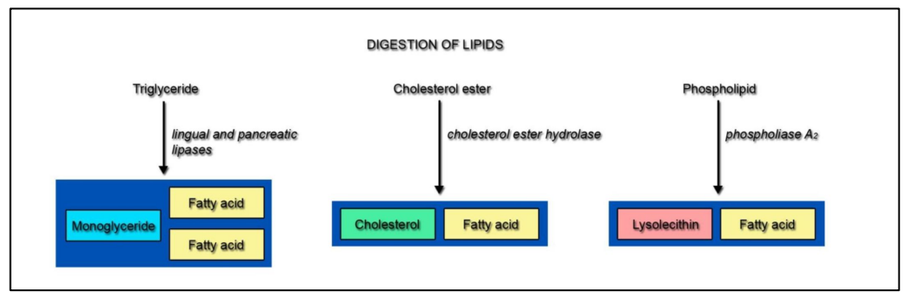


Figure 4-5

Pancreatic Secretions

- The pancreas secrets about **1 L/day** of HCO_3^- rich fluid from the epithelial cells of the ductules and ducts.
- HCO_3^- is exchanged for Cl^-. Secretin increases the rate of this exchanger.

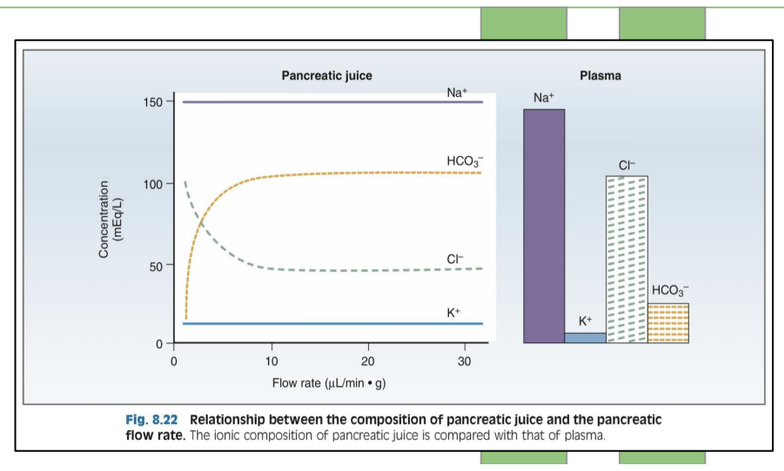


Fig. 8.22 **Relationship between the composition of pancreatic juice and the pancreatic flow rate.** The ionic composition of pancreatic juice is compared with that of plasma.

Figure 4-6, Flow Rate & Pancreatic Secretion

Mechanism of HCO_3^- Secretion

01 Basolateral membrane contains Na^+-K^+ ATPase and a Na^+-H^+ exchanger. By this step, H^+ goes to the blood and combines with HCO_3^- which results in CO_2 & H_2O formation.

02 CO_2 and H_2O combine in ductal cells to form H_2CO_3.

03 H_2CO_3 dissociates into H^+ and HCO_3^-.

04 H^+ is transported into blood by Na^+-H^+ exchanger at basolateral membrane of ductal cells.

05 HCO_3^- is secreted into pancreatic juice by Cl^--HCO_3 exchanger at apical membrane of ductal cells, followed by osmotic flow of water.

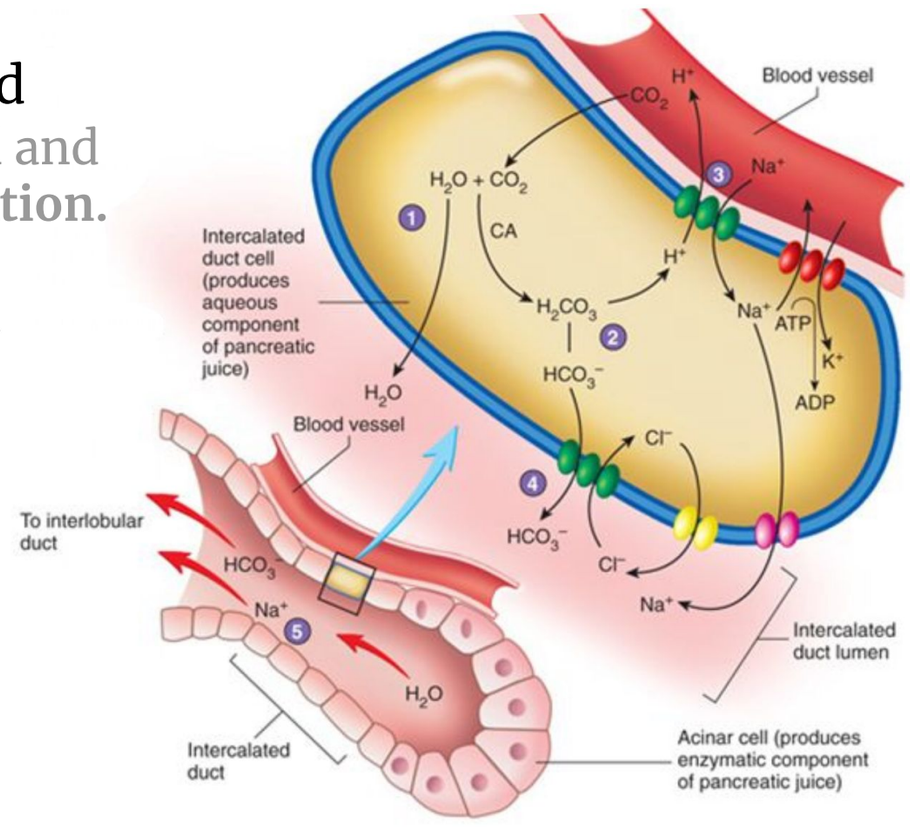


Figure 4-7

- Absorption of H^+ causes **acidification** of pancreatic venous blood.

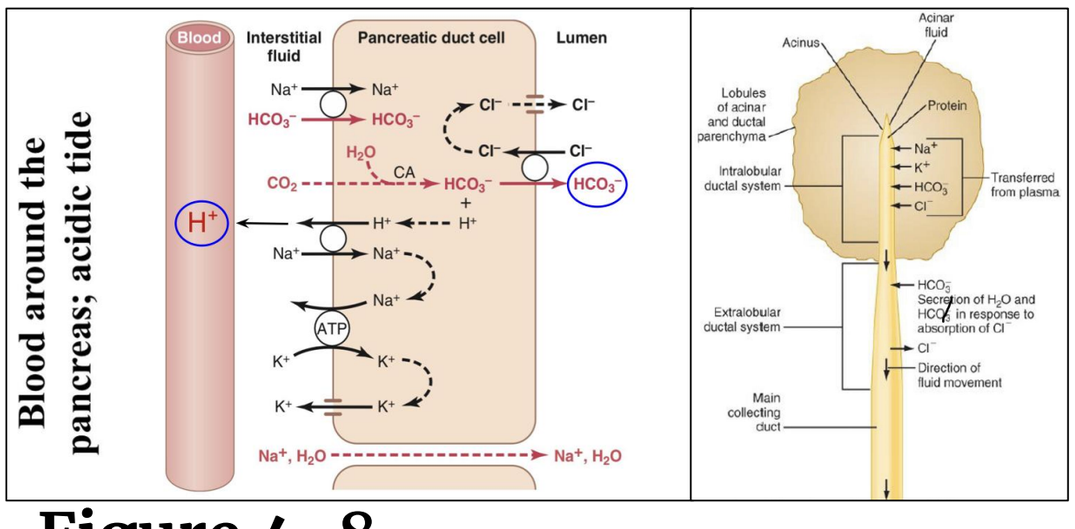


Figure 4-8

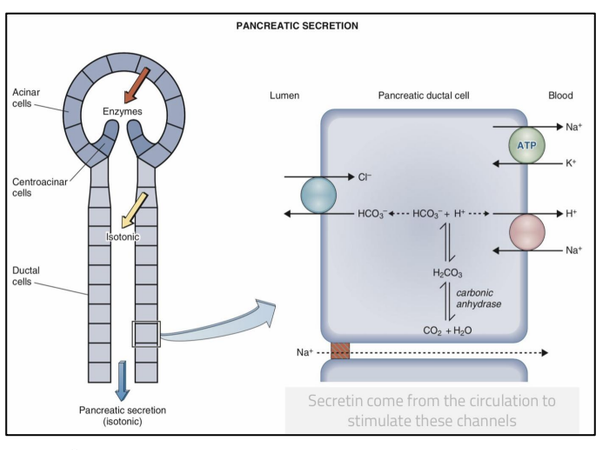


Figure 4-9, Secretion of Isosmotic Sodium Bicarbonate Solution

Phases of Pancreatic Secretion

★ Pancreatic secretion is under neural and hormonal control.
★ It normally results from the combined effects of the multiple basic stimuli which potentiate each other.

Phase	Cephalic (20%)	Gastric (5-10%)	Intestinal (70-75%)
Stimulus	Smell, taste, chewing and swallowing	Protein, gastric distention	Amino acid and fatty acids in chyme
Mediator	Through Vagus nerve	Through Vagus nerve	Through hormonal stimulation (Secretin, CCK) and enteropancreatic reflexes.

Pancreatic Secretion Is Under Neural and Hormonal Control:

01

Parasympathetic

Stimulation through Ach on ***acinar cells***, results in increase in enzyme secretion and HCO_3^-.

Acetylcholine:

- **Released**:

  from the **para-sympathetic vagus** nerve endings & other **cholinergic nerves** in the enteric nervous system.

02

Secretin

Tends to stimulate a HCO_3^- rich secretion by activating ***ductal cells***.

- **Release:**

  From "**S**" cells in the mucosa of the **duodenum & jejunum** (present as in an inactive form: prosecretin).

- **Stimulus:**

  Mainly **acid chyme** with pH less than 4.5-5.0 in the duodenum.

03

Cholecystokinin

Stimulates a marked increase in enzyme secretion by stimulating the ***acinar cells***.

- **Release:**

  From enteroendocrine "**I**" cells in the mucosa of the **duodenum & upper jejunum**.

- **Stimulus:**

  By **proteoses**, **peptones** (products of partial protein digestion) & **long-chain fatty acids** in the chyme.

★ **Acetylcholine and cholecystokinin** stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes.

★ **Secretin** stimulates secretion of large quantities of H_2O & $NaHCO_3$ *solution* by the pancreatic ductal epithelium.

★

★ **Secretin** Causes the pancreas to secrete large quantities of fluid containing a high concentration of HCO_3^- (up to 145 mEq/L = ~5X normal) but a low concentration of Cl-.

$$HCl + NaHCO_3 \rightarrow NaCl + H2CO_3$$ ($H2CO_3$ dissociates into CO2 and H2O).

★ **Cholecystokinin** effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70-80% of the total secretion of the pancreatic digestive enzymes after a meal.

Regulation of Pancreatic Secretion

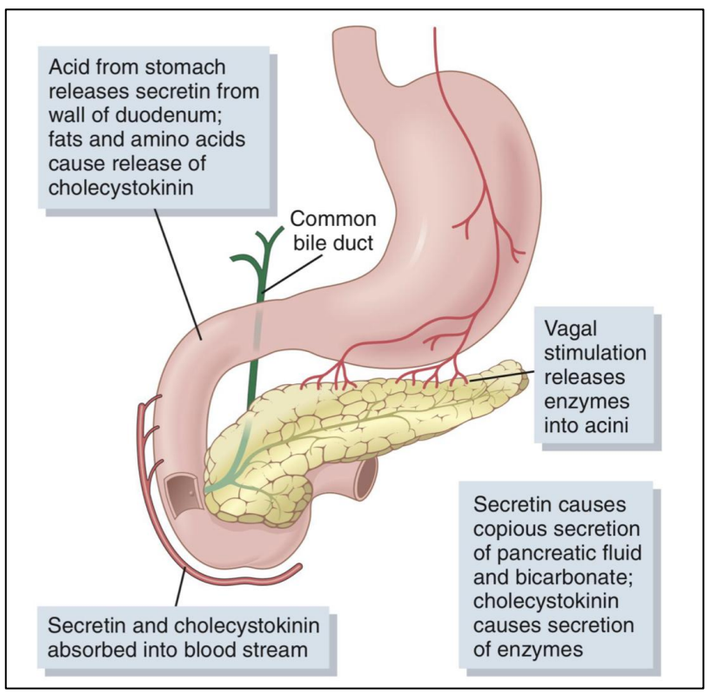


Figure 4-10

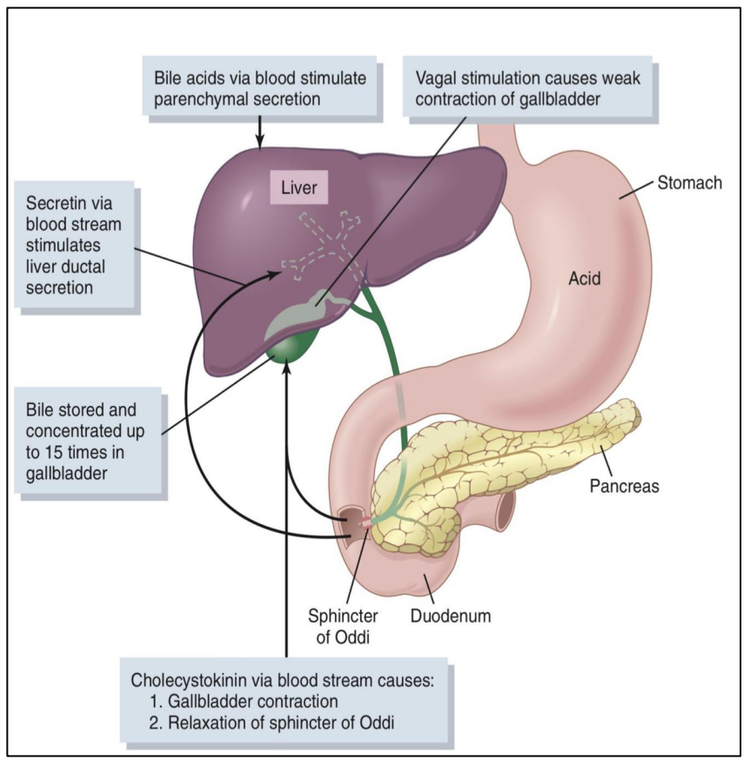


Figure 4-11

Lecture V: PHYSIOLOGY OF THE SMALL INTESTINE: MOTILITY AND SECRETION

Motility in the Small Intestine

The movements of the small intestine can be divided into five main types of movement:

Segmenting / Mixing contractions

- **Stimulus** → distention.
- activated by enteric nervous system (ENS).
- It's a localized contraction of circular smooth muscles that constricts (divide) the intestine into spaced segments, last for fraction of min.
- chain of **sausages appearance** (As one of segmentation contractions relaxes, a new often begins at points between the previous ones).
- blocked by the drug **atropine**.

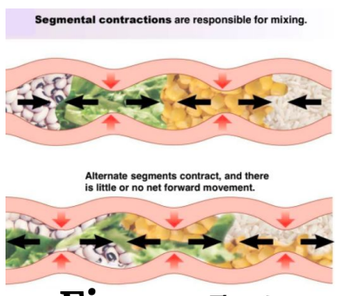


Figure 5-1

The significance of segmentation contraction:

- ★ Blend different juices with the chyme.
- ★ Bring products in contact with absorptive surfaces.

Mixing V.S Peristalsis

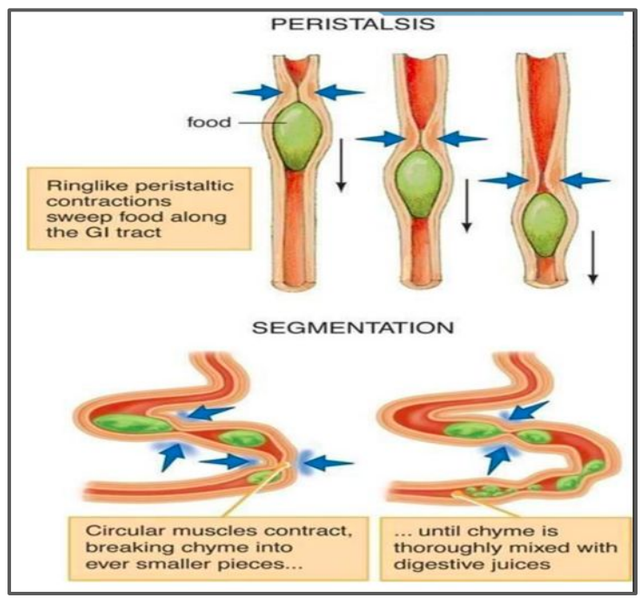


Figure 5-2

Propulsive / Peristalsis contractions

- **Stimulus** → distention.

A contraction ring appears, moves forward occur in any part of the small intestine, at velocity of 0.5 to 2.0 cm/sec, it's faster in proximal intestine slower in the terminal intestine.

- **3 - 5 hours** are required for passage of chyme from the pylorus to the ileocecal valve.
- Myenteric plexus is important for these movements
- **blocked by atropine**.
- **Its divide into:**
- ★ **Receiving segment** that contract longitudinal and relax circular muscles.
- ★ **Propulsive segment** that contract circular and relax longitudinal Muscles.

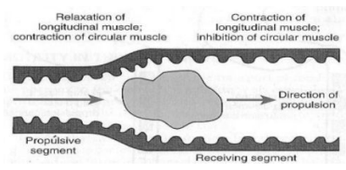


Figure 5-3

The significance of peristaltic contractions:

- ★ Organize propulsion of material over variable distances within the intestinal lumen.

Migrating motor complex (MMC)

They're bursts of depolarization accompanied by peristaltic contraction that begins in empty stomach during interdigestive period (after absorption occurs)

- ★ Travels along whole length of small intestine to reach ileocaecal valve after 1.5-2 h. Where it disappears then a new wave starts.
- ★ Its activity **terminates** as soon as food is ingested.
- ★ Its function is to propel/sweep any remnants in stomach & small intestine into colon during the interdigestive period(in between meals).
- ★ Regulated by autonomic nerves and by release of hormone **motilin**.

Antiperistalsis

A wave of contraction in the alimentary canal that passes in an **oral direction**(i.e. upward or backwards) and propel the chyme in the opposite direction.

Occurs between:-

- ★ Stomach and duodenum to allow more time for neutralization of chyme.
- ★ Ileum and caecum to allow more time for absorption.
- ★ Mostly physiological

Peristaltic rush

Powerful rapid peristalsis due to intense irritation of intestinal mucosa (eg: infectious diarrhea).

- ★ **Initiated** mainly by extrinsic nervous reflexes to brain stem and back to gut.
- ★ Sweeps the contents of intestine into the colon and thereby **relieving the small intestine** of irritative chyme or excessive distension.
- ★ Pathological

Movement of Villi

The villous movement consists of **fast shortening** and **slow lengthening** as well as **side to side movements**.

- ★ Villous contractions are initiated by local nervous reflexes in response to chyme in small intestine.
- ★ They are stimulated by **villikinin** hormone released by intestinal mucosa when it comes in contact with digestive products.
- ★ They facilitate absorption and lymph flow from central lacteals into lymphatic system.

Control of Intestinal Motility

NEURONAL

- **Vagal**(parasympathetic): excitation increases intestinal and villous movements.
- **Sympathetic**: excitation decreases intestinal and villous movements.

Gastroileal reflex:

Initiated by gastric distension mediated by vagus nerve.
Impulses are conducted through myenteric plexus to initiate a fast peristaltic wave passing to the ileum.
The ileocaecal valve relaxes allowing chyme to pass into cecum.

HORMONAL

- Gastrin, CCK, insulin and serotonin stimulate intestinal motility.
- Gastrin and CCK relax ileocaecal sphincter.
- Secretin and glucagon inhibits intestinal motility and contract ileocaecal sphincter.
- Motilin secreted from duodenum stimulates intestinal motility and regulate MMC.

*Remember that **Villikinin** stimulates movement of the villi.

Source of Small Intestinal Secretions

Brunner's Glands

★ **Located in** the wall of the first few centimeters of the duodenum.

★ Secrete large amounts of alkaline **mucus to protect** the mucosa, which contains a large amount of bicarbonate ions.

stimulated by:
- secretin, tactile (chyme contacts brushborder) and vagal stimulation.

inhibited by:
- sympathetic stimulation.

Crypts of Lieberkühn

★ **Located in** small pits which lie between intestinal villi
★ Secrete Intestinal juices.

★ The enterocytes of the mucosa contain the following digestive enzymes:
➔ Aminopeptidases, Oligopeptidases, Intracellular di / tri peptidases for splitting small peptides into amino acids.
➔ sucrase, maltase, lactase, a-dextrinase for splitting disaccharides into monosaccharides.

At a volume of **1800 ml/day** (Composition: **0.6 % organic** (enzymes & mucus), **1 % inorganic** (electrolytes) substance and a

stimulated by :
- Distension, tactile and irritating stimuli.
- Hormones as gastrin, secretin, CCK.
- **Inhibited by:** sympathetic stimulation.

Absorptive Surface

- The absorptive surface of the small intestinal mucosa shows many folds called **valvulae conniventes**, well developed in the duodenum and jejunum. They increase the surface area of the absorptive mucosa X **3-fold**.
- The presence of **villi** on the mucosal surface enhances X **10-fold.**
- The epithelial cell on each villus is characterized by a **brush border**, (Provides the surface area equivalent to a tennis court) consisting of as many as 1000 microvilli (X **20- fold**).

All these increase the intestinal surface 600x

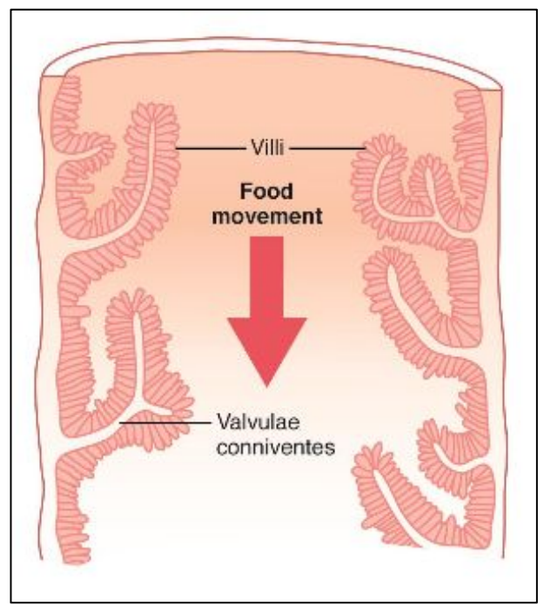


Figure 5-4

Digestion and absorption of :

Carbohydrates | Protein | Fats

→ Digestion of Carbohydrate

In the Small Intestine:

The enterocytes lining the villi contain 4 enzymes (lactase, sucrase, maltase, and a-dextrinase, which are capable of splitting the disaccharides lactose, sucrose, and maltose plus other small glucose polymers, into their constituent monosaccharides.

These enzymes are located in the enterocytes covering the intestinal microvilli brush border, so disaccharides are digested as they come in contact with these enterocytes.

→ Absorption of Carbohydrate

All the carbohydrates in the food are absorbed in the form of **monosaccharides** only a small fraction are absorbed as **disaccharides**.

- Glucose and galactose absorption occurs in a co-transport mode with active transport of Na+ (2ry active transport) (fastest).
- Fructose is independent on Na+ but it transports in luminal membrane via facilitated diffusion.

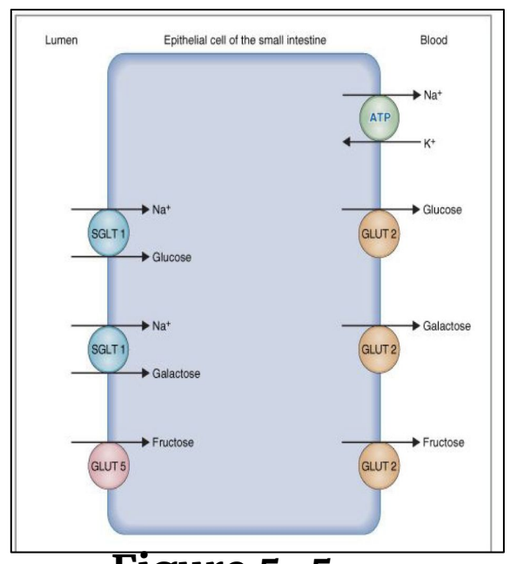


Figure 5-5

Digestion and absorption of :

Carbohydrates | Protein | Fats

→ Digestion of Proteins:

Digestion of protein in the intestines:

A small percentage of proteins are digested to amino acids(AA) by the pancreatic juices.

Most remain as dipeptides and tripeptides to be digested by Peptidases (di/tri peptidases) in the Enterocytes mainly in the duodenum and jejunum(intracellularly).

Most protein digestion occurs in the duodenum and jejunum by aminopeptidases, oligopeptidases and Di/tri peptidases.

→ Absorption of Proteins:

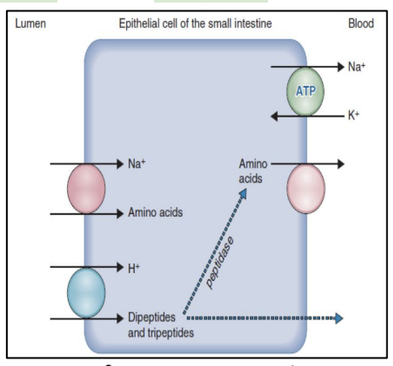


Figure 5-6

- Proteins are absorbed in the form of dipeptides, tripeptides, and a few free amino acids.
- D- AA are transported by **passive diffusion**.
- L- AA are transported by **2ry active transport**.
- Di and tripeptides cross the brush border by active transport protein carrier. Then they're hydrolyzed by brush border and cytoplasmic oligopeptidases.
- AA leaves the cell at the basolateral membrane by **facilitated transport.**

Digestion and absorption of :

Carbohydrates | protein | fats

Digestion of Fat:

- Bile salts and lecithin in the bile help fat digestion by <u>make the fat globules</u> readily fragmentable with the water in the small intestine (emulsification of fat)--> Bile salts break the fat globules into very small sizes, so that the water-soluble digestive enzymes can act on the globule surfaces.

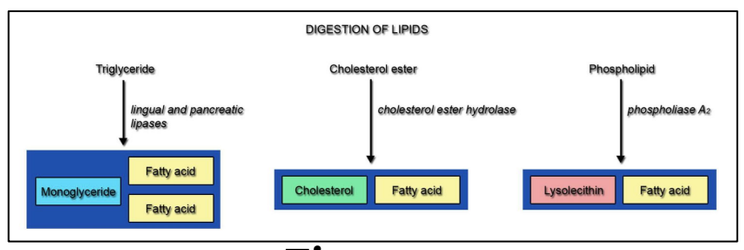


Figure 5-7

Absorption of Fat:

- Bile salts have the ability to form micelles.
- Bile salt & lecithin are amphipathic molecules, each composed of a sterol nucleus (fat-soluble) and a polar group(water-soluble).

The polar parts are (-ve) charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids.

Micelles are small spherical, cylindrical globules 3 to 6 nm in diameter composed of 20 to 40 molecules of bile salts, Which carry Fatty acids(FA) & monoglycerides(MG) to the luminal borders of the intestinal epithelial cells.

Long chain Fatty acids (FA) & monoglycerides (MG), cholesterol and fat soluble vitamins are incorporated into the interior of the micelle.

Water and Electrolytes Secretion & Absorption

The permeability of the tight junctions varies with the type of epithelium.

- Leaky epithelia are in the small intestine and gallbladder.
- A tight epithelium is in the colon.

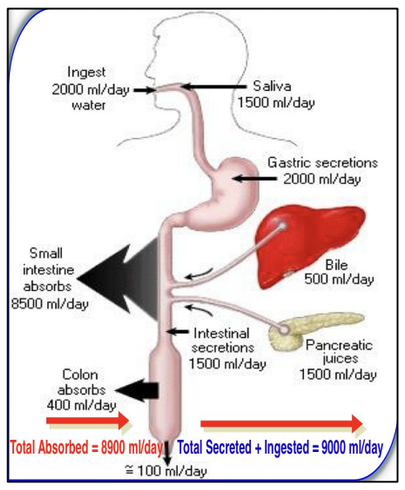


Figure 5-8

Water and Na+ absorption

Electrolytes and H2O cross intestinal epithelial cells by either transcellular or paracellular route.

Na+ moves into the intestinal cells by the following mechanisms:

- **Passive** diffusion.
- **Na+** - **glucose** <u>or</u> **Na+** - **amino acid** co-transport.
- **Na+** - **Cl-** exchange.
- **Na+** - **H+** exchange[1].

The next step is osmosis of water into the **paracellular** spaces..

Aldosterone Enhances Na+ Absorption.

This effect is important in the colon because it allows virtually no loss of NaCl and water.

Cl^- absorption

Cl^- absorption accompanies Na+ absorption by the following mechanisms:

- **Passive** diffusion
- **Na+** - Cl^- cotransport
- Cl^- - **HCO-** exchange

Ca++ absorption

Low plasma Ca++ → Elevated Parathyroid hormone activates Vitamin D:-

25-hydroxy-vitamin D3 → 1,25-dihydroxy-vitamin D3

Which stimulates synthesis of **Calcium binding protein** and **Calcium-ATPase** in enterocytes

absorption and secretion of K+

- K+ is absorbed in the small intestine by **passive diffusion**.
- K+ secretion in the colon is **stimulated by aldosterone.**
- Excessive loss of K+ in diarrheal fluids causes **hypokalemia**.

Secretion of HCO_3 in the ileum

The epithelial cells on the surfaces of the villi in the ileum and large intestine have a special capability of secreting bicarbonate ions **in exchange for absorption of Cl-**.

So it provides **alkaline bicarbonate ions** that **neutralize acid** products formed by bacteria in the large intestine.

Lecture VI: PHYSIOLOGY OF THE COLON

Parts Of The Colon

- It consists of the **ascending**, **transverse**, **descending** & **sigmoid colon**, **rectum** and **anal canal**.
- The transit of radiolabeled chyme through the large intestine occurs in 36-48 hrs.

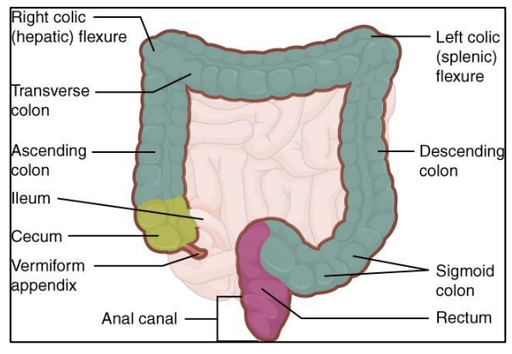


Figure 6-1

Mucous Membrane Of The Colon

- **Lacks** villi and has many **crypts of Lieberkühn**.
- The crypts consist of simple short glands lined by **mucous-secreting goblet cells** (provides an adherent medium for holding fecal matter together).
- The epithelial cells contain almost no digestive enzymes.

FUNCTIONS OF THE COLON

1. **Absorb** — Vitamins produced by bacteria (NOT dietary vitamins)
2. **Reabsorb** — Water and compact material into feces
3. **Store** — Fecal matter prior to defecation

Function
The physiology of different Colon regions

Ascending Colon
Specialized for processing chyme delivered from the terminal ileum.

Transverse Colon
The primary site for the removal of water and electrolytes and the storage of feces.

Rectosigmoid Region
It maintains fecal continence together with anal canal & pelvic floor musculature.

Descending Colon
A conduit between the transverse and sigmoid colon. Has the neural program for power propulsion (mass movement), involved in defecation reflex.

How the Rectosigmoid Region, Anal Canal & Pelvic Floor Musculature Maintains Fecal Continence?

- The sigmoid and rectum are reservoirs with a capacity of up to 500 mL.
- Fibers of puborectalis pass around the anorectum and join behind it to form a U-shaped sling (physiological valve).
- The **puborectalis muscle** and e**xternal anal sphincter** comprise a functional unit that maintain continence.

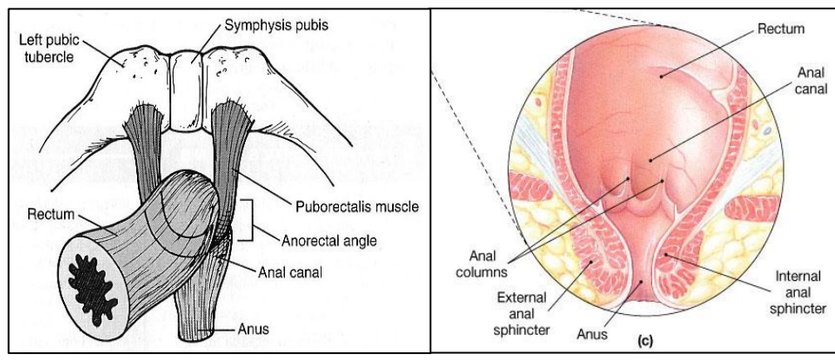


Figure 6-2

Effect Of Parasympathetic Stimulation On Secretion

- Stimulation of the **pelvic nerves** (nerves of defecation reflex) cause:
  - Increase in peristaltic motility of the colon.
  - Marked increase in mucus secretion.
- During **extreme parasympathetic stimulation**, so much mucus can be secreted into the large intestine that the person has a bowel movement of **ropy mucus** as often as every 30 minutes; this mucus often contains little or no fecal material.

Absorption In The Large Intestine

- Little absorption occurs in the large intestine.
- Most of absorption occurs in the proximal half of the colon (absorptive colon). Whereas the distal colon function for storage (storage colon).
- The large intestine can absorb a maximum of 5 - 8 liters of fluid and electrolytes each day.

Water	About 0.5- 1.5L/day is absorbed.
Sodium and Chloride	Cl^- is absorbed in exchange for HCO_3^- which is secreted.
vitamins	Vitamins as vit. K, biotin, B5 , folic acid and some amino acids and short chain fatty acids resulting from bacterial fermentation of CHO are absorbed.
others	Reabsorption of organic wastes (urobilinogens & Stercobilinogen) and toxins. Reabsorption of bile salts.

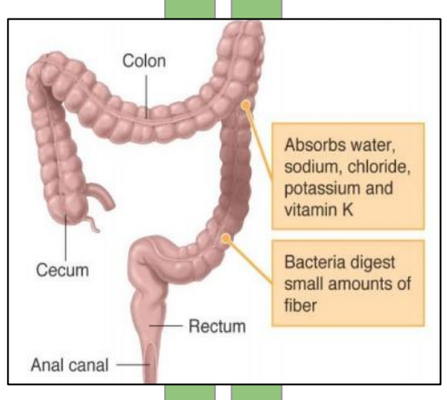


Figure 6-3

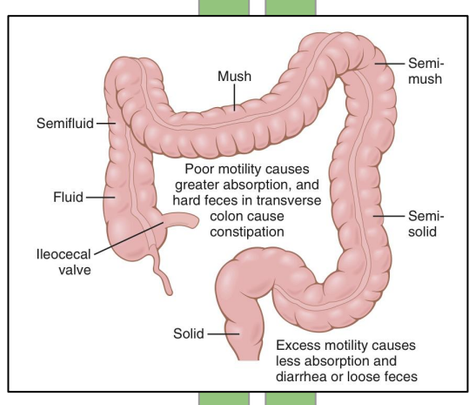


Figure 6-4

Gut Flora (Gastrointestinal Microbiota)

it's a complex community of microorganisms that live in GIT. It's established at 1-2 years after birth. They live in symbiosis with human & their effects are beneficial to the body.

24 PHYSIOLOGY OF THE COLON

Lecture Six

Function Of Bacterial Flora

1. Synthesis of **vitamin K** & some **B group vitamins**: **folic acid**, **biotin**, **thiamine, B12**.
   - The bacteria-formed vitamin K is important since the amount in our daily ingest food **isn't sufficient** to maintain adequate blood coagulation.
2. **Deconjugation** and **decarboxylation** of bile salts.
3. **Breakdown** of bile pigments to produce stercobilinogen.
4. **Decarboxylation** of amino acids to produce amine & histamine.
   The amines are excreted in feces and responsible for its smell.
5. **Breakdown** of urea by bacterial urease to ammonia.
   Most ammonia is absorbed and converted back into urea by the liver.
6. **Fermentation** of undigested oligosaccharides producing gases.

Motility In The Colon

Antiperistalsis

- Starts at the junction of ascending and transverse colon & traveling towards the cecum.
- Mixes contents
- Absorbs water

Mixing Movement (Haustrations)

- The motor events in **proximal colon** (**cecum** & **ascending colon**).
- Ring-like contractions (2.5 cm) of circular muscles divide the colon into pockets (haustra).
  (The longitudinal muscle also contracts at the same time)
- The contracted & relaxed segments remain in their respective state for longer periods.
- Uniform repetition of haustra occurs along the colon.
- Net forward propulsion happens when sequential migration of haustra occurs along the length of bowel.

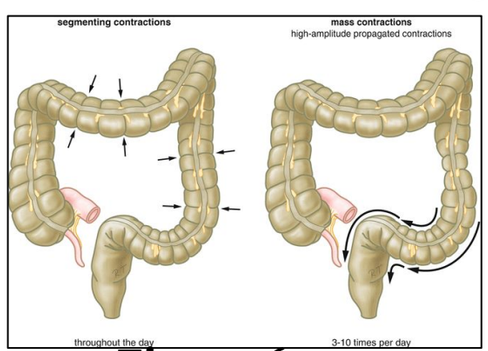


Figure 6-5

Propulsive (Mass) Movement

- The motor events in **distal colon** (**transverse** & **descending colon**).
- Starts in the middle of transverse colon, 15 mins after breakfast.
- Constrictive ring occurs at a distended point, then 20 cm of the colon distal to constriction, contracts as a unit forcing the fecal mass down the colon.
- Preceded by relaxation of circular muscle & downstream disappearance of haustral contractions.
- Completed in 30 sec. Another mass movement occurs 2-3 mins later.
- Mass movement persists for 10-30 mins. (They then cease but return perhaps a half day later).
- The desire of defecation is felt when a mass of feces is forced into rectum.

Initiation of Mass Movement

- Gastrocolic & duodenocolic reflexes after meals, They result from distension of the stomach & duodenum.
- Irritation of the colon. e.g. Castor oil.
- Threatening agents. e.g. Parasites & enterotoxins can initiate mass movement.

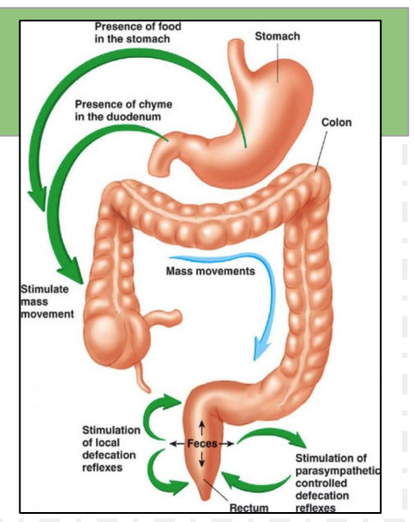


Figure 6-6

Control Of Colonic Motility

Stimulatory Enteric Motor Neurons Release:	Inhibitory Enteric Motor Neurons Release:
Acetylcholine	vasoactive intestinal peptide (VIP)
Substance P	Nitric oxide (NO)
The extrinsic autonomic nerves to the colon modulate the control of colonic motility by enteric nervous system	

The Rectum & Anal Canal

- The rectum is the last portion of GIT that terminates at the anal canal.
- Contains mechanoreceptors that detect distinction.
- Skin of anal canal is innervated by somatosensory nerves that transmit pain, temperature & touch signals to CNS.
- Contraction of anal sphincters (external & internal) and puborectalis muscle blocks the passage of feces and maintain continence with small volumes in the rectum.

when puborectalis is contracted, it pulls the junction of the rectum and the anal canal forwards, creating an angle in the bowel called the anorectal angle. This angle prevents the movement of stool stored in the rectum moving into the anal canal. Conversely, relaxation of the puborectalis reduces the pull on the junction of the rectum and the anal canal, causing the anorectal angle to straighten out. A squatting posture is also known to straighten the anorectal angle, meaning that less effort is required to defecate when in this position.

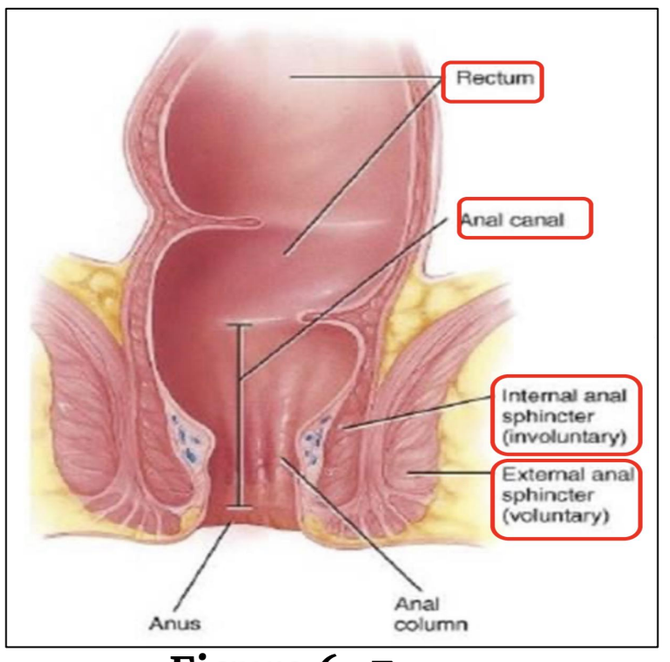


Figure 6-7

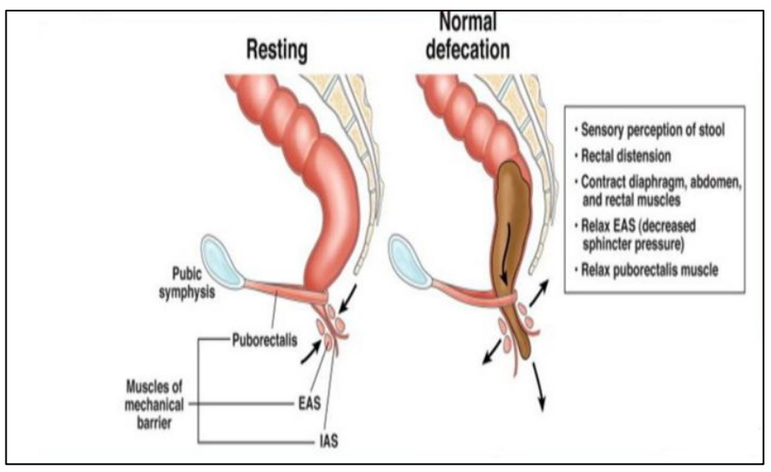


Figure 6-8

Fecal Incontinence

Fecal incontinence

Spinal reflex of defecation operates without interference from higher centers

CAUSES ARE:

- Altered rectal or anal sensation
- Diarrheal conditions
- Diminished rectal capacity
- Infants (physiological)
- Spinal cord lesion
- Weakness of anal sphincters (internal and external)
- Weakness of puborectalis

Defecation

- Most of the time the rectum is empty.
- Both internal & external anal sphincters are maintained in a state of tonic contraction.
- Defecation is a spinal reflex, influenced by higher centers.
- Gastrocolic & duodenocolic reflexes initiate a mass movement in the colon that pushes feces into the rectum.
- Rectal distension sends signals to cerebral cortex producing the desire to defecate.

- Defecation reflex:

1. Distention of rectum.
2. Stimulation of stretch receptors in rectum.
3.

a. Short (local) reflex:
   - Stimulation of myenteric plexus in sigmoid colon and rectum. (But the intrinsic myenteric defecation reflex functioning by itself normally is relatively weak. To be effective in causing defecation, it usually must be fortified by parasympathetic defecation reflex)

b. Long reflex:
   - Stimulation of parasympathetic motor neurons in sacral spinal cord (it will increase peristalsis throughout large intestine).

c. Stimulation of somatic motor neurons.

4. Results in:
   - Increases local peristalsis
   - Relaxation of internal anal sphincter
   - Contraction of external anal sphincter

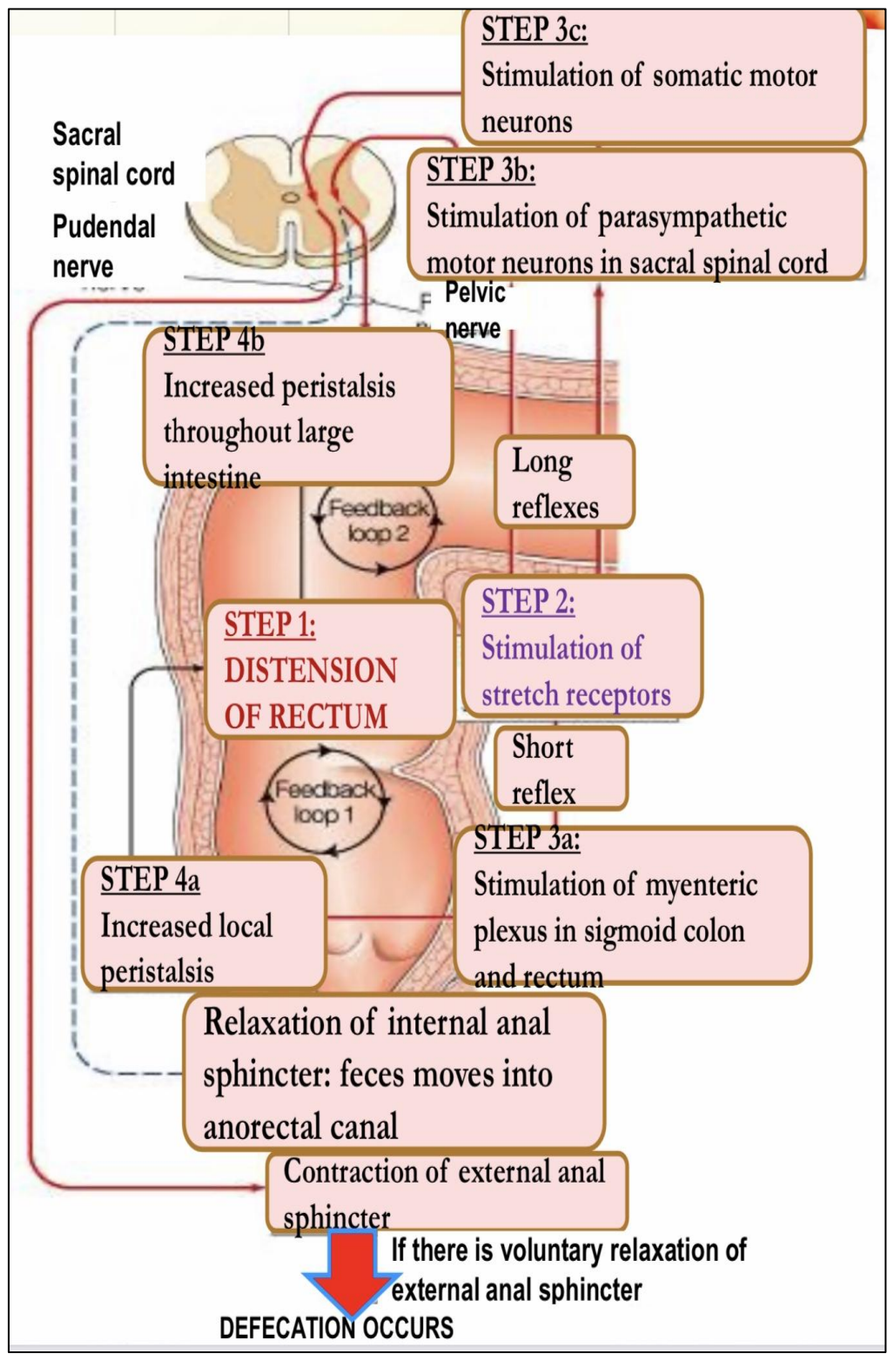


Figure 6-9

Different Situation For Defecation

Suitable Situation	Not Suitable Condition
Allowed defecation reflex. Stretch of rectal wall is sent to SC by **pelvic nerve.**	Inhibited defecation reflex from cerebral cortex
Efferent pelvic impulses cause reflex contraction of rectum & relaxation of internal anal sphincter.	Maintain voluntary tonic contraction of external anal sphincter.
Followed by reduction in tonic impulses to external anal sphincter, so it relaxes voluntary.	Return of tonic contraction of internal anal sphincter.
Feces leave rectum assisted by voluntary straining & contraction of pelvic floor muscles.	Accomodation of rectum to distinction. People who too often inhibit their natural reflexes are likely to become severely constipated.

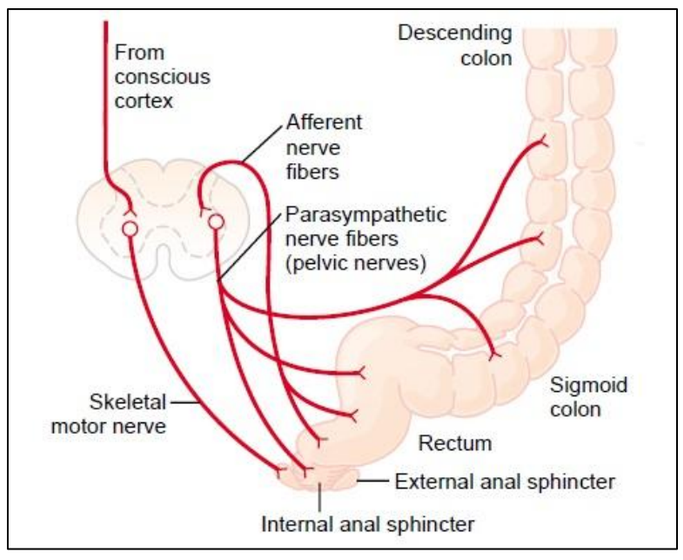


Figure 6-10

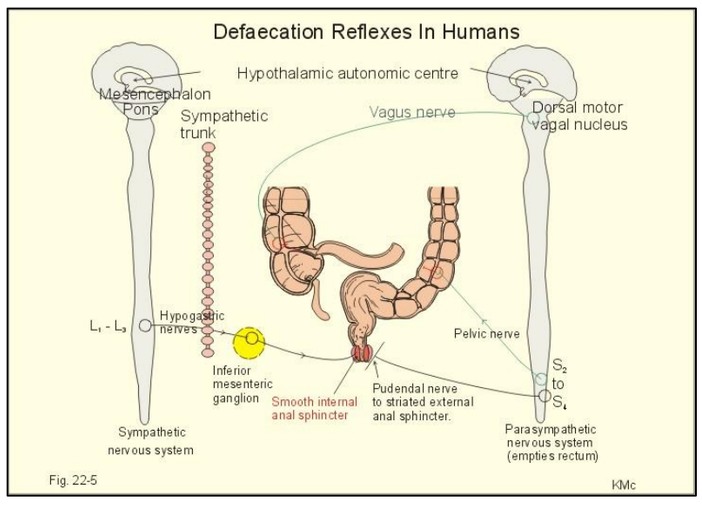


Figure 6-11

Summary Of Defecation Reflexes

Parasympathetic Defecation Reflex (Parasympathetic Pelvic Nerves)	
Stimulus	Feces enter the rectum - distention of rectal wall
Receptors	Stretch receptors in the rectal wall
Afferents	Sensory fibers terminating in S2-S4 cord level
Center	S2- S4 spinal cord segments
Efferents	Pelvic Parasympathetic Nerves
Effectors	Smooth muscle cells of Descending, Sigmoid colon & Rectum
Response	Peristaltic waves forcing feces towards rectum - Relaxation of internal anal sphincter

Intrinsic Defecation Reflex (Myenteric Plexus)	
Stimulus	Feces enter the rectum - distention of rectal wall
Receptors	Stretch receptors in the rectal wall
Afferents	Sensory fibers terminating in Myenteric Plexus
Center	Myenteric Plexus
Efferents	Motor signals to smooth muscles
Effectors	Smooth muscle cells of Descending, Sigmoid colon & Rectum
Response	Peristaltic waves forcing feces towards rectum - Relaxation of internal anal sphincter

Lecture VII: Coagulation Mechanisms

Hemostasis is defined as spontaneous arrest or stoppage of blood loss.

Coagulation: Formation of fibrin meshwork or threads to form a clot.

Blood clot: is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, plasma.

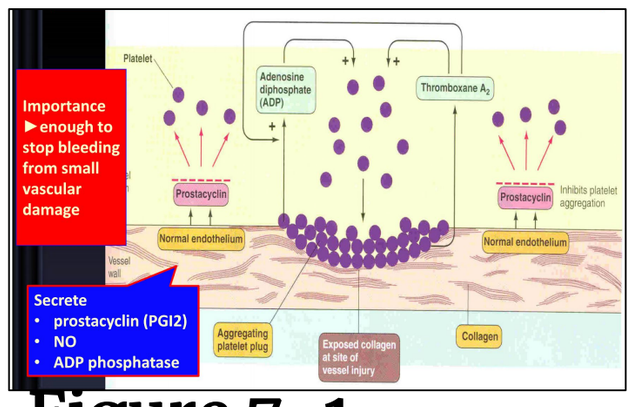


Figure 7-1

Clot formation: A series of biochemical reactions leading to the formation of a blood clot within few seconds after injury.

Mechanism of Hemostasis:

1. Vessel wall (vasoconstriction)
2. Platelets (production and activation of platelets followed by platelet plug formation)
3. Blood coagulation: clot formation and retraction (intrinsic & extrinsic pathways)
4. Fibrinolysis: Formed blood clot can either become **fibrous** or **dissolved.**
   - **Fibrinolysis (dissolving):** Breakdown of fibrin by naturally occurring enzyme ***plasmin*** therefore prevent intravascular blocking.

There is a balance between clotting and fibrinolysis

- Excess clotting → blocking of blood vessels.

Excess fibrinolysis → tendency for bleeding.

Prothrombin (II)	Thrombin	Fibrinogen (I)
Is a plasma protein, α2-globulin. Present in normal plasma in a concentration of **15 mg/dl.** It is unstable protein that can be split easily into **thrombin.** **Synthesized by the liver.**	Is a protein enzyme with weak proteolytic capabilities It acts on **fibrinogen** to form one molecule of **fibrin** monomer. **Fibrin monomers** polymerize with one another to form fibrin **fibers.** **Thrombin** is essential in platelet morphological changes to form a primary plug. **Thrombin** stimulates platelets to release **ADP** & **thromboxane A2**; both stimulate further platelets aggregation. It activates **Factor XIII** and **Factor V.**	is a high-molecular weight plasma protein Little or no **fibrinogen** leaks from blood vessels.[2]

Prothrombin (inactive thrombin) is activated by a long ***intrinsic*** or short ***extrinsic*** pathways.

- This reaction leads to the activation of **thrombin** enzyme from inactive form **prothrombin.**
- Thrombin will change **fibrinogen** (plasma protein) into **fibrin** (insoluble protein)

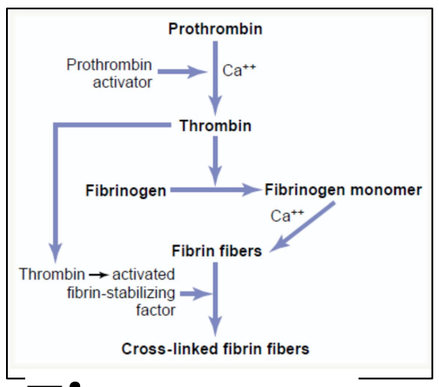


Figure 7-2

Intrinsic Pathway

The **trigger** is the activation of **factor XII** by contact with ***foreign surface, injured blood vessel, and glass.*** (all clotting factors present in the blood)

1. Activated **Factor XII** will activate **Factor XI**
2. Activated **Factor Xl** will activate **Factor IX**
3. Activated **Factor IX** + **Factor VIII** + **platelet phospholipid factor (PF3)** + **Ca^{++}** activate **Factor X**

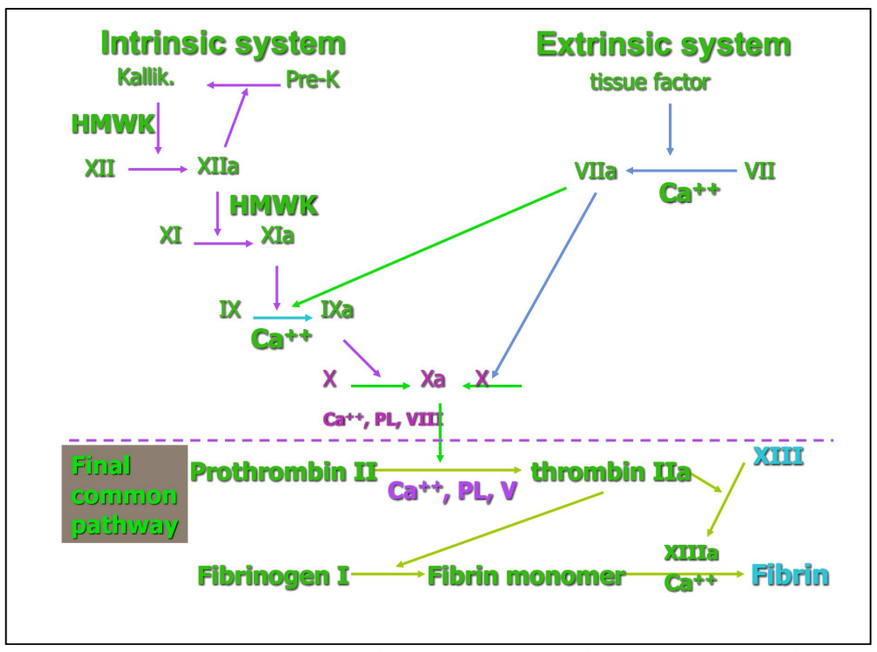


Figure 7-2 Classical model of coagulation.

Extrinsic Pathway

The **trigger** is ***release of tissue thromboplastin from damaged tissues and it is composed of phospholipids from the membranes of the tissue plus a lipoprotein complex that functions mainly as a proteolytic enzyme.***

1. **Tissue thromboplastin** activates **Factor VII**
2. **Tissue thromboplastin** + **Factor VII** + **Ca^{++}** activate **Factor X**

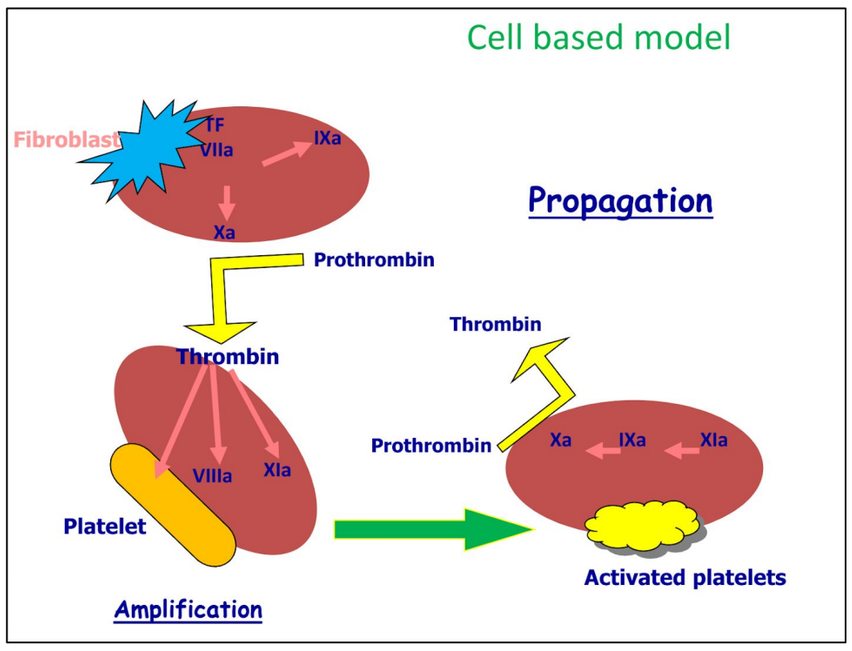


Figure 7-3 Cell-based model of coagulation

Common Pathway

Following the above steps, the pathway is common for both intrinsic and extrinsic pathways.

1. Activated **Factor X** + **Factor V** +**PF3** + **Ca^{++}** activate **prothrombin activator**; a proteolytic enzyme which activates **prothrombin**.
2. Activated **prothrombin** activates **thrombin.**
3. **Thrombin** acts on **fibrinogen** forming insoluble **fibrin** monomers.
4. **Factor XIII** + **Ca^{++}** causes additional strength of **fibrin** meshwork → strong **fibrin** (strong clot)

Plasmin is present in the blood in an inactive form "**plasminogen.**"

- It is activated by **tissue plasminogen activators** (t-PA) in blood.
  Uses: Tissue Plasminogen Activator (t-PA) used to activate plasminogen to dissolve coronary clots. (an example for this is streptokinase)
- Digests intravascular and extravascular deposit of **fibrin** → **fibrin degradation products (FDP)**
- Unwanted effect of plasmin is the digestion of clotting factors.

Plasmin is controlled by:

- **Tissue Plasminogen Activator Inhibitor (t-PAI)**
- **Antiplasmin** from the liver

I	Fibrinogen
II	Prothrombin
III	Tissue factor (Thromboplastin)
IV	Calcium
V	Labile factor
VI	No longer used (previously thought to be present, was mistaken for factor Va)
VII	Stable factor
VIII	Antihemophilic factor, antihemophilic factor A
IX	Antihemophilic factor B, christmas factor
X	Stuart-Prower factor, Stuart factor
XI	Plasma Thromboplastin Antecedent (PTA), antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin stabilizing factor
Pre-K	Fletcher factor, prekallikrein
HMWK	High molecular weight kallikrein, Fitzgerald factor

Conditions That Cause Excessive Bleeding

Vitamin K Deficiency

Required for synthesis of **prothrombin, factor VII factor IX,** and **factor X.**

- Deficiency is rare, but maybe seen in: Hepatitis, cirrhosis, acute yellow atrophy and gastrointestinal disease.

Thrombocytopenia

Very low number of platelets in blood (<50,000/µl)

- **Thrombocytopenia purpura:** hemorrhages throughout all the body tissues.
- **Idiopathic Thrombocytopenia:** unknown cause.

Pseudothrombocytopenia

1. Partial clotting of specimen
2. EDTA-platelet clumping
3. Platelet satellitism around WBCs
4. Cold agglutinins
5. Giant platelets

Hemophilia

- Bleeding tendency.
- X-linked recessive disease.
- Affects males.
- 85% due to **factor VIII** deficiency (hemophilia A).
- 15% due to **factor IX** deficiency (hemophilia B).

Prevention of Blood Clotting and Anticoagulants

Endothelial Surface Factors

- Smoothness of the endothelial cell surface (ECS)
- Glycocalyx layer
- Thrombomodulin protein

Fibrin Fibers

- Adsorbs 90% of **thrombin** to remove it from circulation.

Antithrombin III

- Combines the remaining **thrombin** and removes it from circulation.

Heparin

- Combines with **antithrombin III** and quickly removes **thrombin** from blood.
- **Sources:** Mast cells and basophils which are abundant in liver and lungs.

Lecture VIII: BILE SALTS & ENTEROHEPATIC CIRCULATION

Functions of The Liver

- The largest internal organ in the body, constituting about 2.5% of an adult's body weight.
- Receives 25% of the cardiac output via the hepatic portal vein and hepatic artery.
- Synthesizes many of the circulating plasma proteins.
- Performs important endocrine functions. (IGF-1, thrombopoietin and angiotensinogen secretion).
- Serves as an excretory organ for bile pigments, cholesterol, and drugs.
- The main digestive function of the liver is the **secretion** of bile (**normally 600-1000 ml/day**).

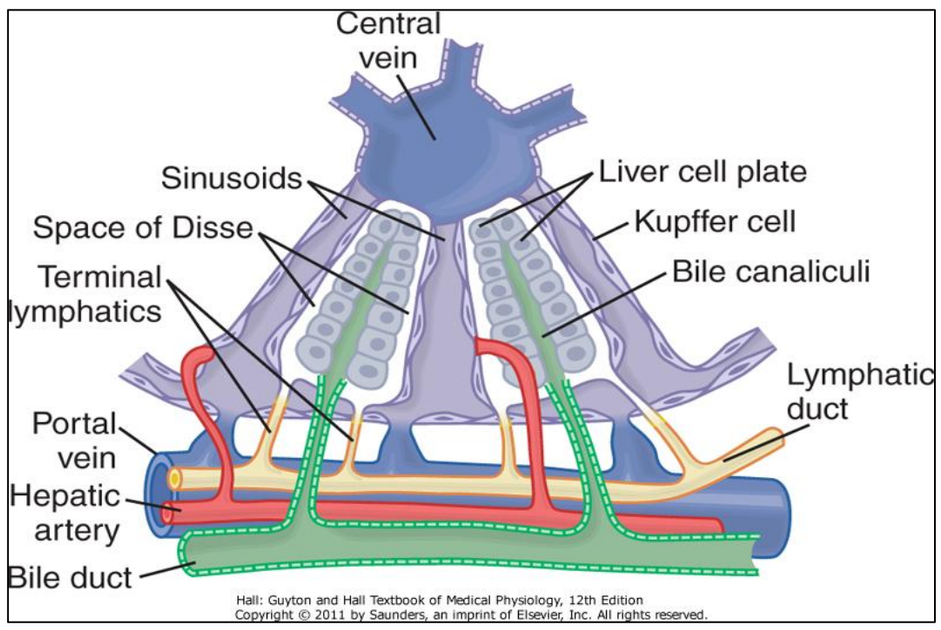


Figure 8-1 Bile Canaliculi & Ducts.

FUNCTIONS OF BILE

Fat Digestion And Absorption

- Emulsifying the large fat particles of the food into minute particles.
- They aid in absorption of the digested fat end products through the intestinal mucosal membrane, via micelles formation.

Excretion Of Waste Products From The Blood

These include especially bilirubin, an end product of hemoglobin destruction.

Stages of Bile Secretion

First Stage(Hepatic Bile):

- secreted by the hepatocytes into bile canaliculi that originate between the hepatic cells, and by this way bile can be emptied into the duodenum.
- **Hepatic bile:** Isotonic secretion, with high Na^+, Cl^- and HCO_3^- and low K^+ and Ca^{++}.
- There is an Active reabsorption of Glucose and A.A. to prevent bacterial growth.

Second Stage(Gallbladder Bile):

- Bile can be diverted for minutes up to several hours through the cystic duct into the gallbladder (second portion of liver secretion, added to the initial bile).
- **Gallbladder bile:** high bile acid anion and Ca^{++}; but low Na^+, Cl^-, HCO_3^- and H_2O.

COMPONENT OF BILE

Cholesterol
4%
(From Hepatocytes)

Bile acids (Bile salts)
65% of weight of bile
(From Hepatocytes)

Phospholipids (Lecithin), Phosphatidylcholine
20% as lecithin
(From Hepatocytes)

Bile pigments
0.3% as bilirubin
(From Hepatocytes)

Proteins
5%
(From Hepatocytes)

Ions and Water
(Aqueous alkaline solution)
Mainly HCO_3^- & H_2O
(From bile ducts epithelial cells), contribute to the volume of hepatic bile

Concentrating Bile in the Gallbladder

- Gallbladder concentrates the bile during every 12 hours of bile secretion (usually about 450 mL).
- Concentration is due to active transport of sodium, followed by secondary absorption of chloride ions, water, and most other diffusible constituents.
- Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

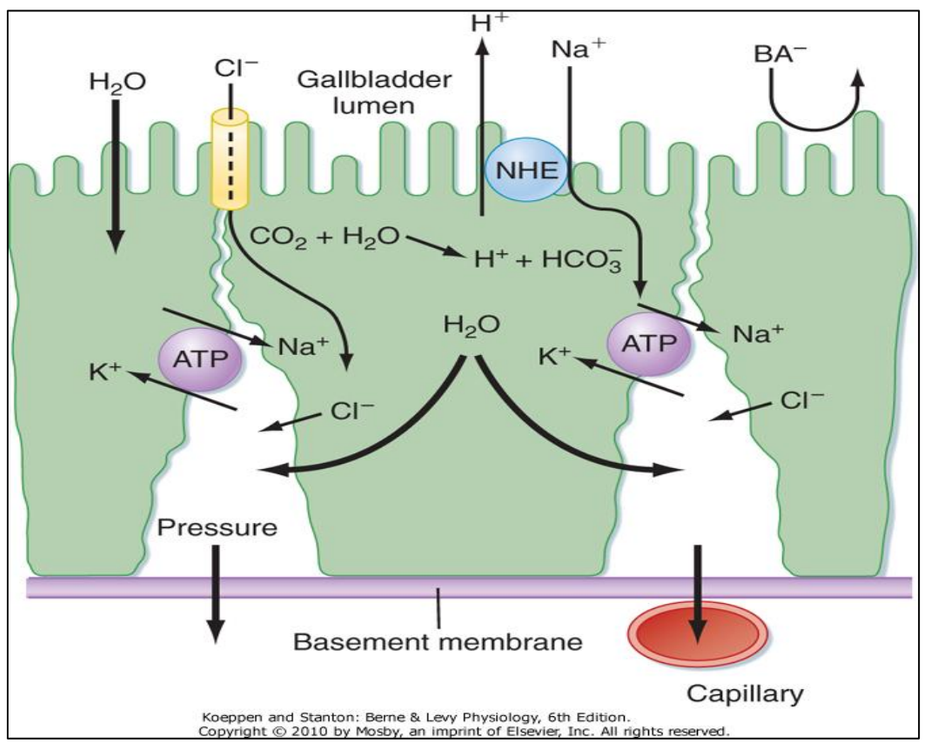


Figure 8-2 The Tight junction resist the passage of Bile Acid Anion .

Regulation of Bile Secretion

1. The major determinant of bile acid synthesis is its concentration in hepatic portal blood (**feedback** control).
2. Hormonal: CCK, Secretin & estrogen stimulate bile secretion.
3. Neural:
   - Parasympathetic (**vagal**) stimulation results in contraction of the gallbladder and relaxation of the sphincter of Oddi, as well as increased bile formation.
   - stimulation of the **sympathetic nervous system** results in reduced bile secretion and relaxation of the gallbladder.

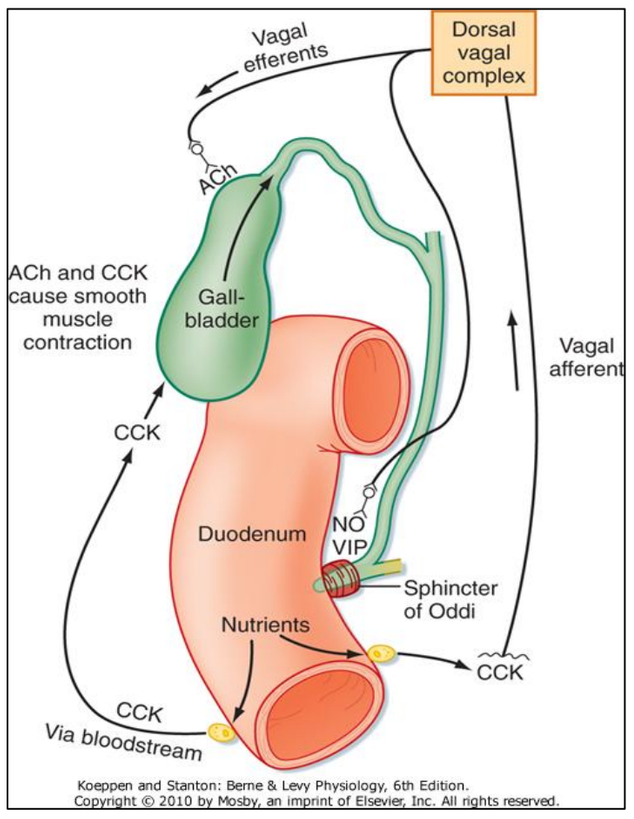


Figure 8-3, Neurohumoral control of gallbladder contraction and biliary secretion

Bile Acids & Bile Salts

- Bile acids are steroid acids, synthesized in the liver from cholesterol. During the conversion, hydroxyl groups (by 7α- hydroxylase) and a carboxyl group are added to the steroid nucleus.
- Bile acids are classified as **primary** or **secondary**.
- Primary: Cholic, Chenodeoxycholic acids.
- Secondary: Deoxycholic, Lithocholic acids.
- Bile acids are secreted as conjugates of **taurine** or **glycine** and it is converted into secondary bile acids by Dehydroxylation and Deconjugation processes done by intestinal bacteria.
- At a neutral pH, the bile acids are mostly ionized (zwitterion form)[1], more water soluble and are present almost entirely as salts of various cations (mostly Na+) e.g., sodium glycocholate and are called bile salts.

Function of Bile Acid

1. DIGESTION OF FATS
2. ABSORPTION OF FATS
3. ABSORPTION OF FAT-SOLUBLE VITAMINS (A, K, E, D)
4. STIMULATING BILE SECRETION AND FLOW A process known as “choleretic flow”
5. INCREASE SOLUBILITY OF CHOLESTEROL IN BILE

Role of Bile Salts To Accelerate Fat Digestion & Formation of Micelles

- Bile acids are amphipathic molecules that have the ability to form micelles(each bile salt molecule is composed of a sterol nucleus that is fat-soluble and a polar group that is water-soluble).
- The polar groups are (-) charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids and to remain in stable solution.
- The micelles act as a transport medium to carry the monoglycerides and free fatty acids to the brush borders of the intestinal epithelial cells.

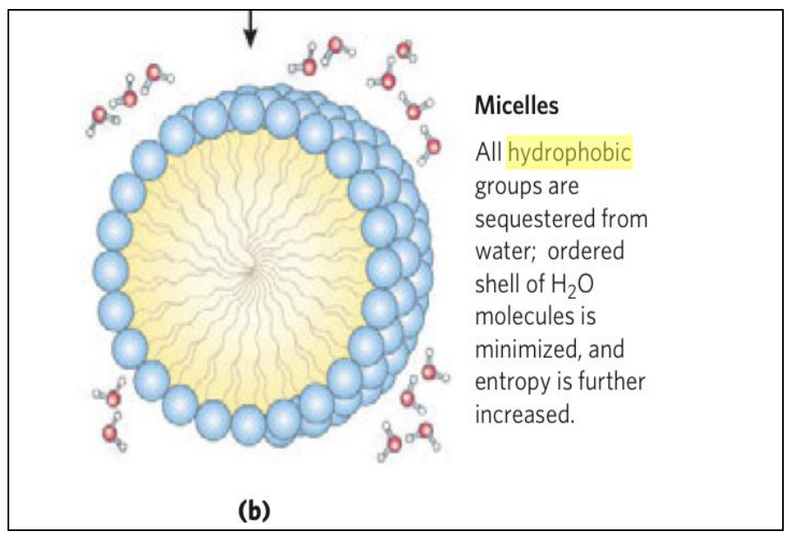


Figure 8-4

Enterohepatic Circulation (Portal Circulating) of Bile Salts

- The enterohepatic circulation of bile salts is the recycling of bile salts between the small intestine and the liver, (3-5) times a day; in a heavy eater, it may circulate (14-16) times a day.
- The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time is defined as the **total bile acid pool.** In healthy people, the bile acid pool ranges from 2-4 g.
- If e**nterohepatic circulation** is interrupted (e.g. due to obstruction or surgical removal or inflammation of the **terminal ileum**), bile flow is markedly reduced.

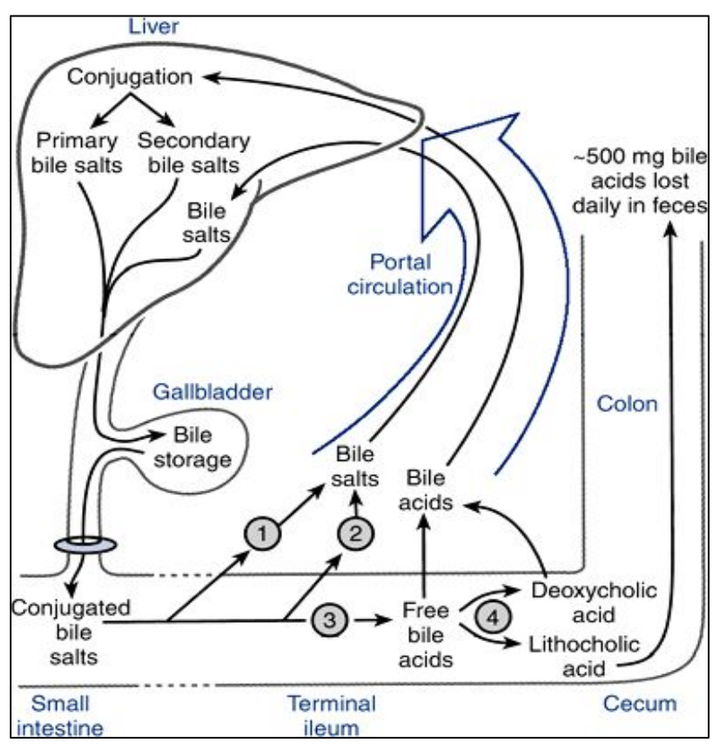


Figure 8-5

Absorption of Bile Acids in Intestinal Lumen

- **Bile salts or bile acids in the intestine lumen are absorbed via four pathways into portal circulation (enterohepatic circulation):**

1. An active carrier-mediated process (Apical Na+ dependent Bile salt transporter (ASBT) (Conjugated bile acids, 2ry active transported. Powered by Na gradient across the brush border membrane).
2. Simple diffusion (Unconjugated bile acids, less polar).
3. Deconjugation and/or transforming of bile salts to bile acids (by bacteria).
4. Transforming the primary bile acids to secondary bile acids (by bacteria).

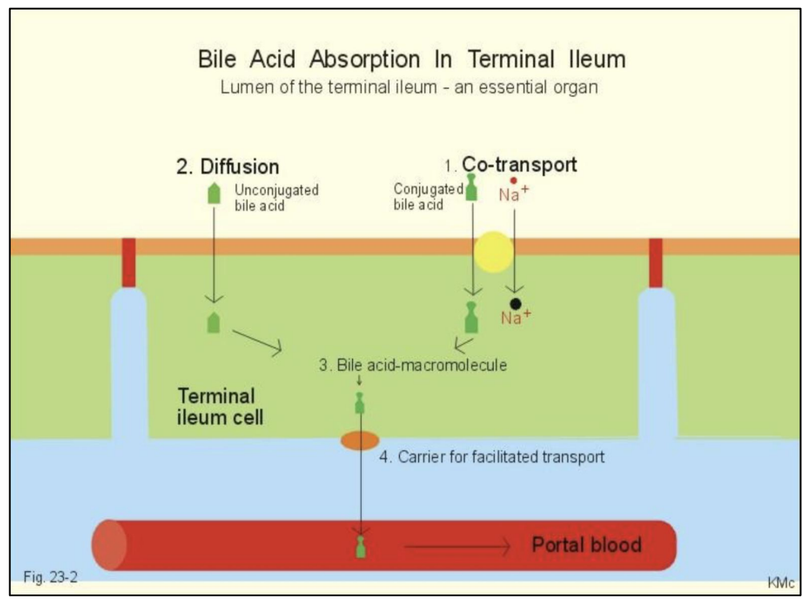


Figure 8-6

Absorption of Bile Acid or Bile Salt Back Into Hepatocytes

Bile salts or bile acids in the portal circulation are absorbed via four pathways into hepatocytes:

1. An active carrier-mediated process: Conjugated bile acids-Na co-transport (Bile salt-Na+ coupled (Ntcp).
2. Na-independent pathway (Bile acid-Na+independent (OATP).
3. Bile acid-HCO3 or Bile acid-OH exchange.
4. Passive diffusion (very little).

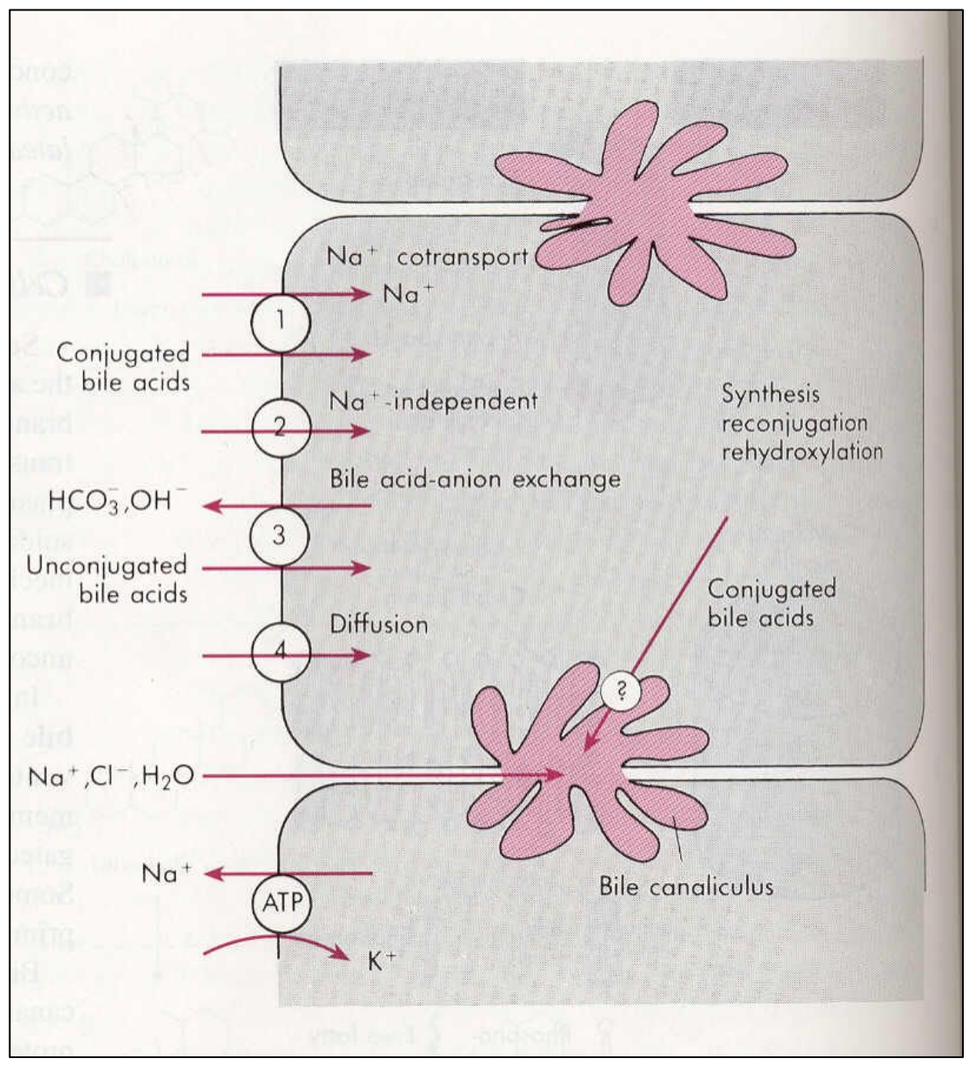


Figure 8-7

Lecture IX: Bilirubin Metabolism

Definition of Bilirubin

- Greenish yellow pigment excreted in bile, urine & feces, the major pigment present in bile is the orange compound bilirubin.
- It is water insoluble breakdown product of heme catabolism in senescent (aging) erythrocytes. Mononuclear phagocyte system (MPS)

Bilirubin is highly soluble in all cell membranes (hydrophobic) and very toxic, therefore, its excretion in the bile is one of the very important functions of liver.
Serum bilirubin level is an important clinical marker of hepatobiliary excretory function.

Unconjugated bilirubin

- Insoluble in water.
- Tightly complex to albumin.
- Toxic substance.

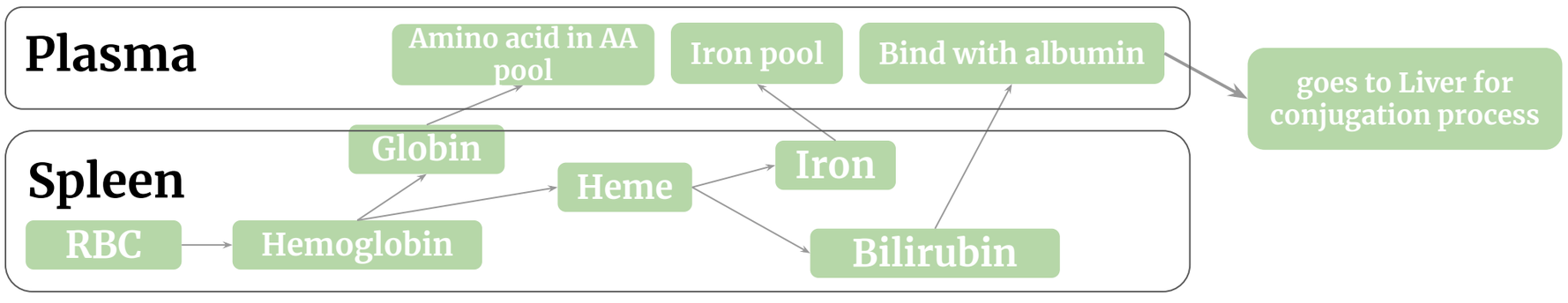
Conjugated bilirubin

- Water soluble
- Loosely bound to albumin
- Filtered through renal glomeruli and excreted in urine
- Non-toxic
- Present in low concentration in the blood

1 Formation of Bilirubin

Life span of RBCs is 60-120 days.

- Senescent RBCs are phagocytosed intravascularly or extravascularly by **reticuloendothelial system (RES) (Mononuclear Phagocytes System)** specially in the spleen,
- The **hemoglobin** is first split into **globin** & **heme** , and converts it into Biliverdin.
  - **Globin:** AA formed from breakdown of globin are stored in the body
  - **Heme:** heme ring is opened to give:
    - **Free ion :** Transported in blood by transferrin & stored in the body as a reservoir for erythropoiesis.
    - **Bile pigment (biliverdin):** reduced by **biliverdin reductase** to free bilirubin which is gradually released into the plasma.



2 Transport of Bilirubin in Plasma

★ Free bilirubin is **hydrophobic** it immediately combines with plasma proteins (mainly albumin) forming a water soluble compound (**hemobilirubin, unconjugated, indirect bilirubin**) which is rapidly transported to hepatocytes for further metabolism.

★ Even when bound to albumin it's called **free bilirubin**.

Albumin + bilirubin → **bilirubin-albumin complex (Unconjugated, indirect bilirubin hemobilirubin)**

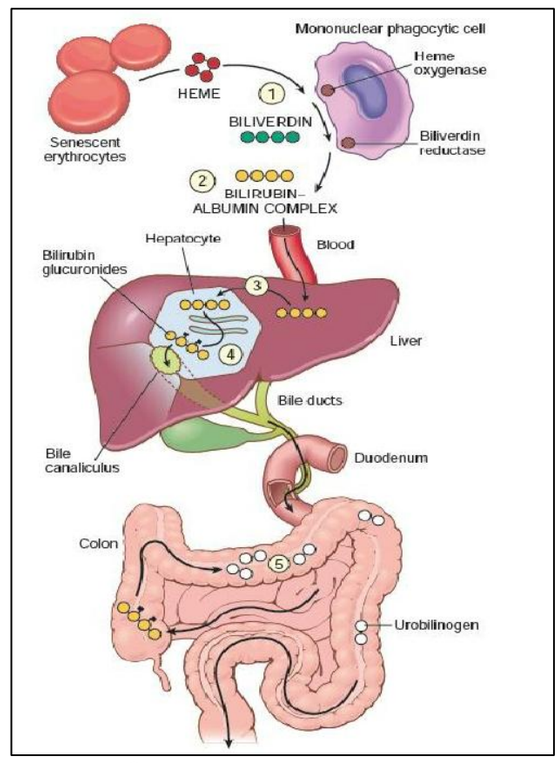


Figure 9-1

Significance of bilirubin binding to albumin:

- increase solubility of whole molecule.
- Prevent unconjugated bilirubin freely come into other tissue, cause damage.

3 Hepatic Phases

On coming in contact with the hepatocyte surface, unconjugated bilirubin is preferentially metabolized which involved 3 steps:

1. Hepatic uptake
2. Conjugation
3. Secretion in bile

1. Hepatic Uptake

- Bilirubin (lipid soluble) is absorbed through the hepatic cell membrane, mediated by a carrier protein

2. Bilirubin Conjugation

- In the smooth ER of hepatocytes, about **80%** of bilirubin conjugates with **uridine diphospho-glucuronic acid (UDPGA).**
- Each bilirubin molecule reacts **with 2 UDPGA** molecules catalyzed by the enzyme **glucuronyl transferase** to form bilirubin diglucuronide (**cholebilirubin**, **direct**, **conjugated bilirubin**) which is more water soluble than free bilirubin.
- **10** conjugate with **sulphate** or **other** substances.

3. Secretion in Bile

- **Cholebilirubin** is actively secreted into the bile canaliculi through an active carrier-mediated process
- its **energy-dependent**, **rate limiting step** is susceptible to impairment in liver disease.
- In normal adults this results in a daily load of **250-300 mg of bilirubin.**
- Unconjugated bilirubin is normally not excreted.

Fate of Conjugated Bilirubin

- **Majority** of conjugated bilirubin passes via the bile ducts to the intestine then colon where it is transformed by bacteria, which will deconjugate it back to bilirubin & convert it to the highly soluble colorless compound called Urobilinogen.
- **Small amount** 20% is deconjugated and converted to Urobilinogen in the small intestine & absorbed into the portal blood to the liver where it is extracted by the liver cells & conjugate again & excreted in the bile (enterohepatic circulation of bile pigments).
- **Small portion** of conjugated bilirubin returns to plasma either directly into the liver sinusoids or indirectly by absorption into the blood from the bile ducts or lymphatics. This represents 10% only this causes a small portion of the conjugated bilirubin in the ECF it bound less tightly to albumin & is excreted in the urine.

Fate of Urobilinogen

- **Most** of urobilinogen **(70%)** is converted into **stercobilinogen** in the large intestine, **oxidized** & excreted in the feces as **stercobilin** that **causes dark brown color of the feces.**
- **Some** of urobilinogen **(20%)** is reabsorbed through the intestinal mucosa into the portal vein & re-excreted by the hepatic cells in the bile (enterohepatic circulation).
- **Small** amount 5% of urobilinogen escapes to the general circulation & excreted by the kidneys in urine where it is **oxidized** to **urobilin** when the urine is exposed to air.

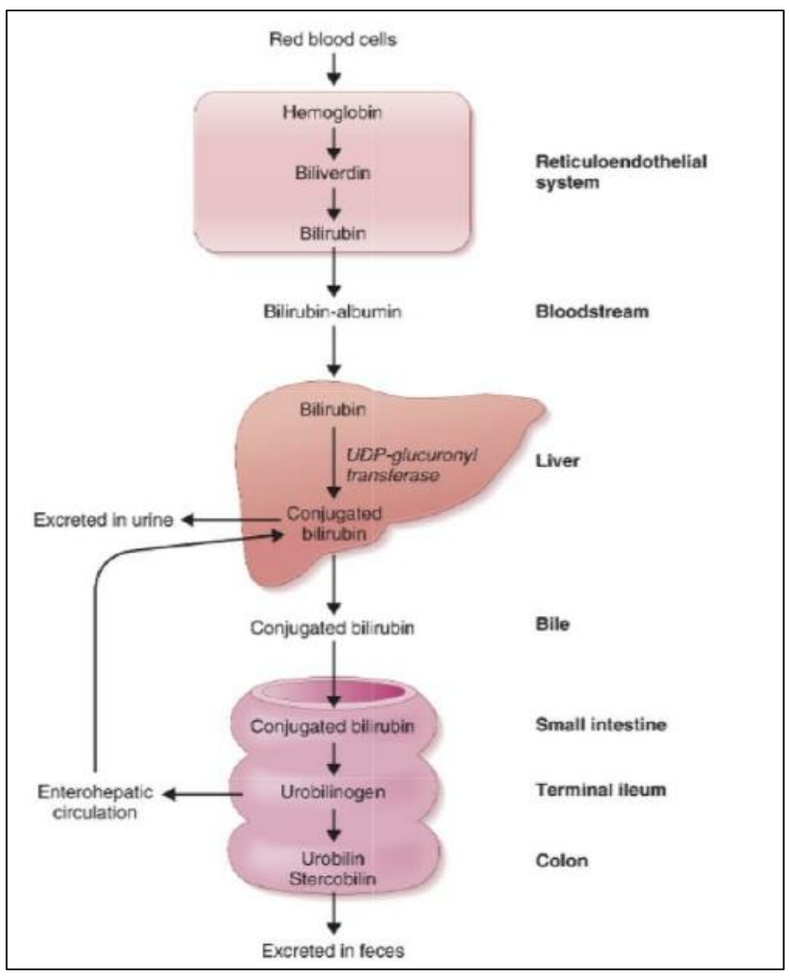


Figure 9-2

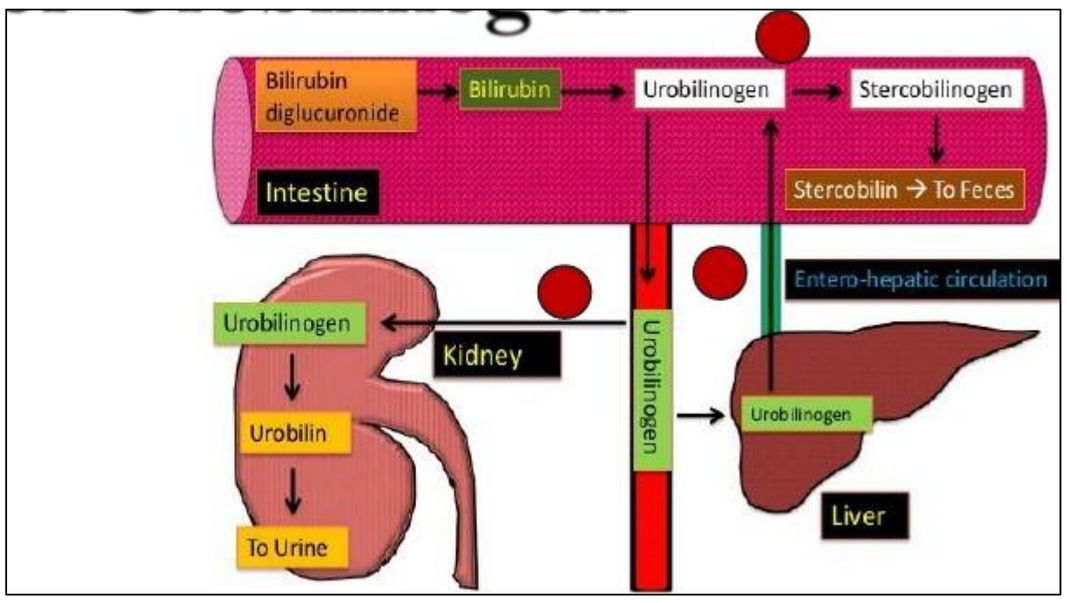


Figure 9-3 Urobilinogen fate

Types of Bilirubin in Serum

- **Direct bilirubin:** is conjugated (water soluble) bilirubin, it reacts rapidly with reagent (direct reacting).

- **Indirect bilirubin:** is unconjugated (water insoluble) bilirubin because it is less soluble, it reacts more slowly with reagent (reaction carried out in methanol).

- In this case both conjugated and unconjugated bilirubin are measured given **total bilirubin**.

Unconjugated is calculated by subtracting direct from total.

Total bilirubin = D + ID

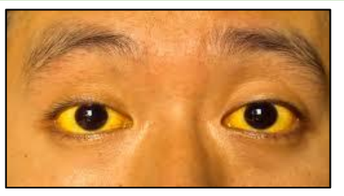
Total bilirubin (1-1.5 mg/dL) – conjugated = unconjugated.

Knowing the level of each type of bilirubin is of diagnostic importance.

Major Differences Between Unconjugated and Conjugated Bilirubin

Feature	Unconjugated bilirubin (Hemobilirubin)	Conjugated bilirubin (Cholebilirubin)
Normal serum level	The chief form of bilirubin in the blood	Present in low conc. in the blood
Water solubility	Absent	Present
Affinity to lipids	Present	Absent
Binding	Bind to albumin	Bind to glucuronic acid
Reaction to reagents	Indirect (Total minus direct)	Direct
Renal excretion	Absent	Present
Affinity to brain tissue	Present (kernicterus), toxic	Absent, less toxic

Jaundice(Hyperbilirubinemia, Icterus)



- It is the **yellow** coloration of the skin, sclera, mucous membranes and deep tissues.
- **The usual cause** is large quantities of bilirubin in the ECF, either free or conjugated bilirubin.
- The normal plasma concentration of total bilirubin is 0.3-1.2 mg/dl of blood .
- Subclinical jaundice occur when the Bilirubin level is from 1 to 2 mg/dl .
- The skin usually begins to appear jaundiced when the concentration of total bilirubin in the plasma is greater than 2 -2.5 mg/dl.

Classification Of Jaundice

1. Pre-hepatic (hemolytic) jaundice
2. Hepatic (hepatocellular) jaundice
3. Post-hepatic (obstructive) jaundice

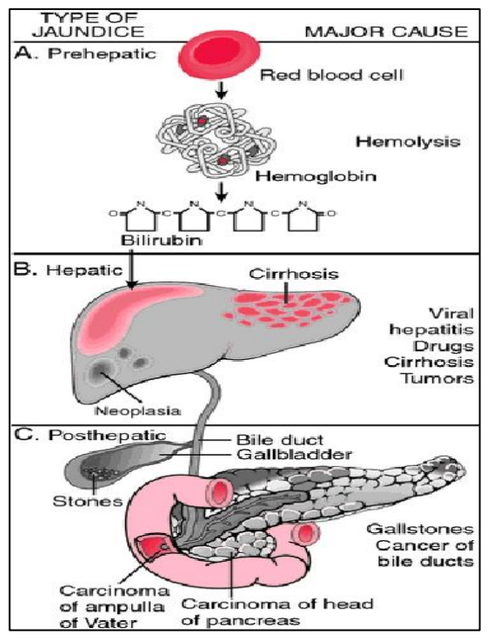


Figure 9-4

Prehepatic: Hemolytic Jaundice

- ★ The excretory function of the liver is not impaired.
- ★ It results from excess production of bilirubin (beyond the livers ability to conjugate it) following hemolysis
- ★ Excess RBC lysis is commonly the result of:
  - Autoimmune disease
  - Hemolytic disease of the newborn
  - Rh- or ABO- incompatibility
  - Structurally abnormal RBCs (Sickle cell disease)
  - Breakdown of extravasated blood

Therefore the plasma concentrations of free bilirubin (hemobilirubin) rises to levels much above normal but it is not filtered through the kidney, because they are unconjugated bilirubin.

- The urine is free from bilirubin
- The stools appear darker than the normal color due to excessive stercobilin formation

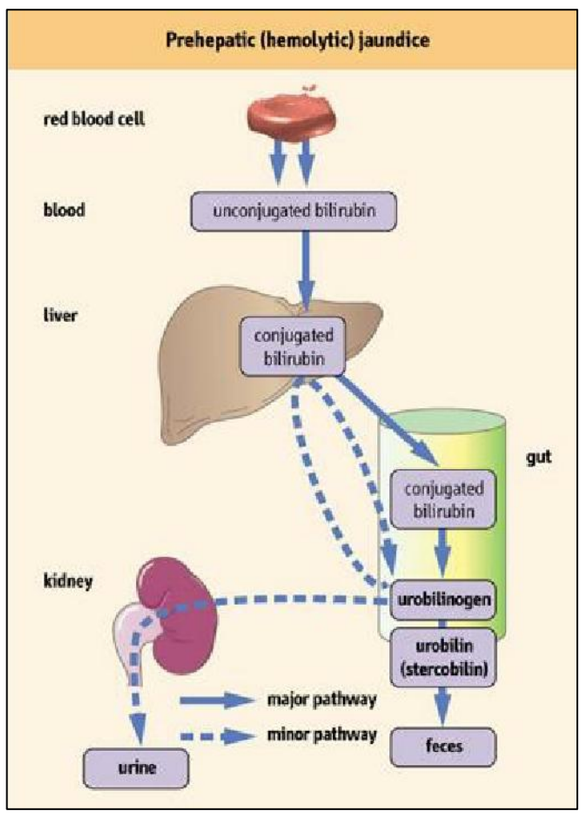


Figure 9-5

Hepatic: Hepatocellular Jaundice

Hyperbilirubinemia may be due to:

- ★ Impaired uptake of bilirubin into hepatic cells.
- ★ Disturbed intracellular protein binding or conjugation.
- ★ Disturbed active secretion of bilirubin into bile canaliculi. If there is a defect in the active transporter to the bile canaliculi, then the conjugated B. will leak outside (and here it will look like Obstructive jaundice)

Causes

- Damage of liver cells e.g., viral hepatitis, drugs, chemical, alcohol, or toxins.
- Autoimmune hepatitis. Hepatocytes will not be able to take up free bilirubin
- Genetic errors in bilirubin metabolism. (eg, enzyme)
- Genetic errors in specific proteins.

- The diseased liver cells are unable to take all the unconjugated hemobilirubin, increasing its concentration in the blood.
- There is intrahepatic biliary duct obstruction that leads to regurgitation of conjugated bilirubin to blood.
- Both types of bilirubin (conjugated & unconjugated) are present in blood in high concentration.

Clinical features

- Stools appear pale grayish in color due to deficiency of stercobilin.
- Urine appears dark brown due to filtration of excess conjugated bilirubin through the kidney.
- In this case, hyperbilirubinemia is usually accompanied by other abnormalities in biochemical markers of liver function {Alanine amine transferase (ALT) & Aspartate amine transferase (AST)

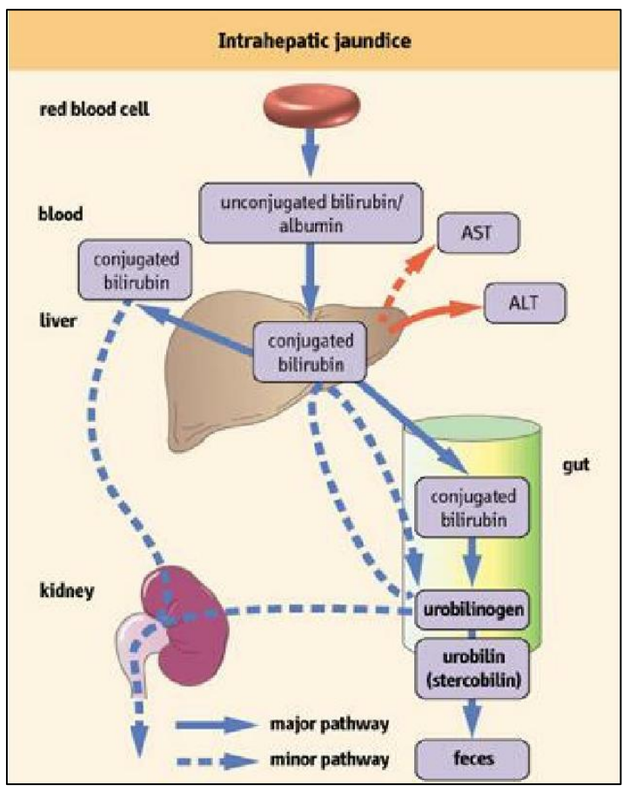


Figure 9-6

Posthepatic: Obstructive Jaundice

Causes

★ Intrahepatic bile duct obstruction such as in the liver canaliculi e.g
- Drugs
- Primary biliary cirrhosis
- Cholangitis.
- Hepatitis

★ Extrahepatic bile duct obstruction e.g
- Gallstones.
- Carcinoma of the head of the pancreas
- Cholangiocarcinoma

- The rate of bilirubin formation is normal, bilirubin enters the liver cells and become conjugated in the usual way.
- The conjugated bilirubin formed cannot pass into small intestine and it returns back into blood.
- In this type of jaundice, conjugated bilirubin is filtered through the kidney and appears in urine giving it dark brown color.
- Urine is free from urobilinogen.
- Stools are clay color due to absence of stercobilin.

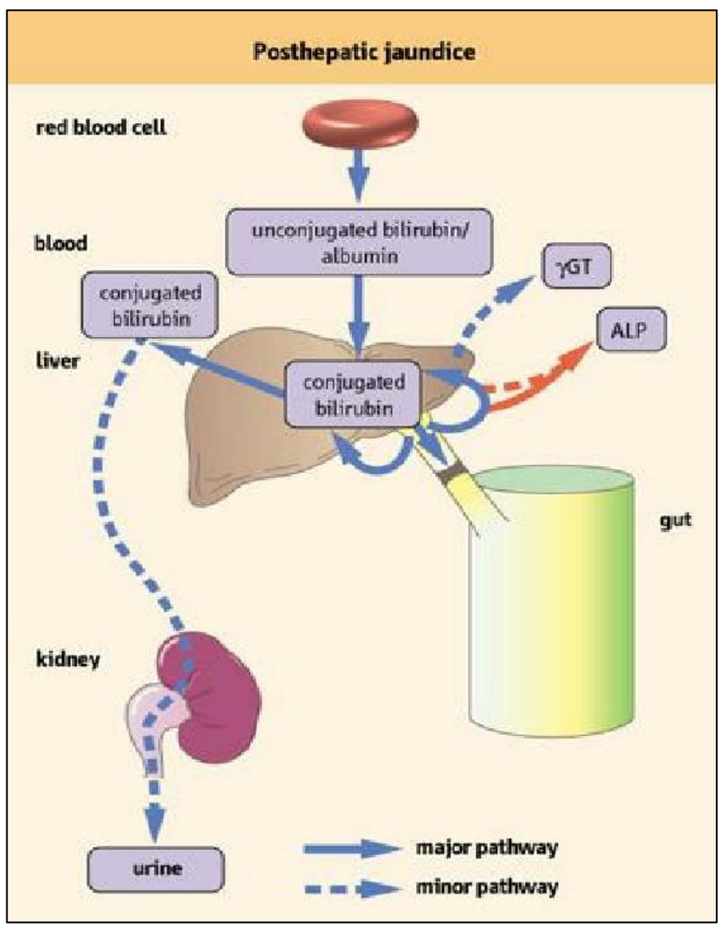


Figure 9-7

	Prehepatic hemolytic	Hepatic Hepatocellular	Posthepatic Obstructive
Unconjugated	Increased	Increased	Normal
Conjugated	Normal	Increased	Increased
Bilirubin	Indirect	Both	Direct
AST & ALT	Normal	Increased	Normal
ALP & yGT (y glutamyl transpeptidase)	Normal	Normal	Increased
Urine bilirubin	Absent	Present (dark brown)	Present (dark brown)
Urine urobilinogen	Present	Present	Absent
Stercobilin	Darker	Pale grayish	Absent (Clay colored)

Lecture X: Reticuloendothelial System and Spleen Functions

Innate Immunity (non specific)

Examples:

- ★ Complement
- ★ Barriers
- ★ Phagocytes (neutrophils, monocytes, natural killer cells)

Humoral Antibody mediated (B lymphocytes)

Acquired Immunity (specific, adaptive)

Cell mediated (T lymphocytes)

Note: Macrophages are key components of the innate immunity & activate adaptive immunity by transforming into Antigen Presenting Cells.

RETICULOENDOTHELIAL SYSTEM (RES)

- ➔ Reticuloendothelial system is an older term for the mononuclear phagocyte system. The term is not specific, Why? Because Most endothelial cells are not macrophages (not phagocytic).
- ➔ It is a network of connective tissue fibers inhabited (occupied) by phagocytic cells such as macrophages ready to attack and ingest microbes.
- ➔ Monocytes transform themselves into macrophages (in tissues) & this system of phagocytes is called as Monocyte- Macrophage Cell System.

Cellular Component Of RES

01 **Monocytes** In blood

02 **Macrophage**
Located in all tissues such as skin (histiocytes), liver (kupffer), spleen, bone marrow, lymph nodes, lung.

03 **Endothelial cells:**
specialized in bone marrow, spleen and lymph nodes.

General Functions of RES

Phagocytosis	Immune function	Breakdown of aging RBC	Storage and circulation of iron
Bacterial, dead cells, foreign particles (direct).	Processing antigen and antibodies production (indirect).		

Monocytes/Macrophages

- ➔ Life span: 10-20 hours in blood and months or years in tissues.
- ➔ Two types: mobile and fixed.
- ➔ Often remain fixed to their organs (tissue-resident). They filter and destroy objects which are foreign to the body, such as bacteria, viruses.
- ➔ Some macrophages are mobile, and they can group together to become one big multinucleated giant cells in order to ingest larger foreign particles. This is sometimes seen in chronic inflammatory diseases like TB.

Liver	Kupffer cells
Brain	Microglia
Lymph nodes, bone marrow, spleen	Reticular
Subcutaneous tissues, skin, mucosa	Tissue histiocytes (fixed macrophages)
Lungs	Alveolar cells

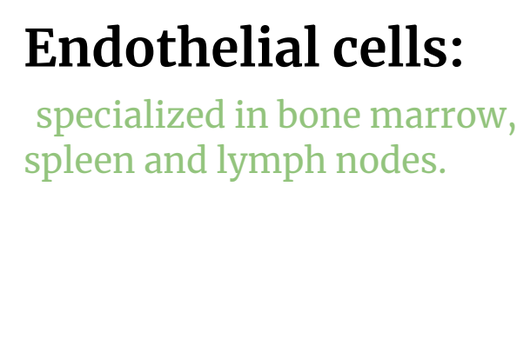


Figure 10-1

Phagocytosis

Phagocytosis	A part of the natural or innate immune process.
Macrophages	Powerful phagocytic cells:

- Ingest up to 100 bacteria.
- Ingest larger particles such as old RBC.
- Get rid of waste products.

Indirect Immune Function of RES

Ingest foreign body, process it and
present it to lymphocytes.

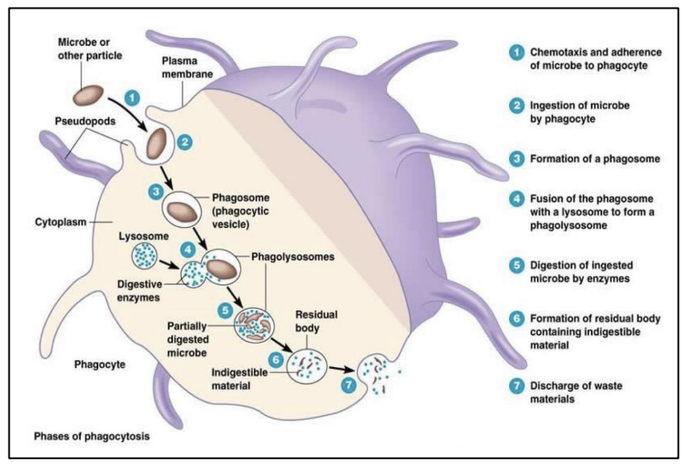


Figure 10-2

Lymphoid Organs

1 Thymus

high rate of growth and activity until puberty, then begins to shrink; site of T-cell maturation.

2 Lymph nodes

small, encapsulated, bean-shaped organs stationed along lymphatic channels and large blood vessels of the thoracic and abdominal cavities.

3 Spleen

structurally similar to lymph node, it filters circulating blood to remove worn out RBCs and pathogens.

Spleen

- Is soft **purple gray** in color located in the left upper quadrant of the abdomen.
- It is a **highly vascular** lymphoid organ.
- It plays an important roles in RBC integrity and has **immune function**.
- It holds a reserve of blood in case of **hemorrhagic shock.**
- It is one of the centers of activity of the RES and its absence leads to a predisposition toward certain infections.
- Despite its importance, there are no tests specific to splenic function.

Structural Function of Spleen

➔ White pulp (immunologic functions): Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.

➔ Red pulp (Hematological/filtering function): Surrounds white pulp, composed of Venous sinuses filled with whole blood and Splenic cords of reticular connective tissue rich in macrophages.

Functions of Spleen

01 Haematopoiesis (Hemopoiesis): fetal life.

02 Spleen is a main site for destruction of RBCs specially old and abnormal e.g. spherocytosis.

03 Blood is filtered through the spleen.

04 Reservoir of thrombocytes (platelets) and immature erythrocytes.

05 Recycles iron in red pulp.

Immune Functions of Spleen

Reservoir of lymphocytes in white pulp.

Site for Phagocytosis of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)

Site of B cell maturation into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response.

Destruction and processing of antigens.

Removes antibody-coated bacteria along with antibody-coated blood cells.

Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to blood-borne antigens.

It contains (in its blood reserve) half of the body monocytes within the red pulp, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages that promote tissue healing.

Splenectomy Indications

Hypersplenism: enlargement of the spleen (splenomegaly) with defects in the blood cells count.

Primary spleen cancers.

Haemolytic anaemias: Sickle cell anaemia, Thalassemia,hereditary spherocytosis (HS) and elliptocytosis.

Idiopathic thrombocytopenic purpura (ITP).

Trauma (very common)

Hodgkin's disease.

Autoimmune hemolytic disorders.

Risks & Complications of Splenectomy

Inflammation of the pancreas and collapse of the lungs.

Excessive post-operative bleeding (surgical).

Post-operative thrombocytosis and thus thrombosis.

Patient prone to malaria.

Overwhelming bacterial infection / post splenectomy sepsis.

Lecture XI: Platelets Structure and Function

- **Anuclear and discoid cell spherical when activated.**
- **Platelet count = 150 x103-300x103/ml.**
- **Size: 1.5–3.0 µm.**
- **Life span: 7–10 days.**

Platelet Ultrastructure

Showing presence of two types of Granules:

1- Alpha Granules, contains:
- von Willebrand Factor (vWF)
- Fibrinogen
- Chemokines (PF4,etc.)
- Thrombospondin
- P-selectin

2- Dense Granules (delta), contains:
- ADP/ATP
- Calcium
- Serotonin

3- Mitochondria
4- Open canalicular system
5- Microtubules

Platelet Receptors

- **Glycoprotein Ia and VI receptors for collagen.**
- **Glycoprotein Ib, IX and V receptors for Von willebrand factor.**
- **Glycoprotein IIb and IIIa receptors for Von willebrand factor and Fibrinogen.**
- **TPα receptor for Thromboxane A2.**
- **$P2Y_{12}$ receptor for ADP.**

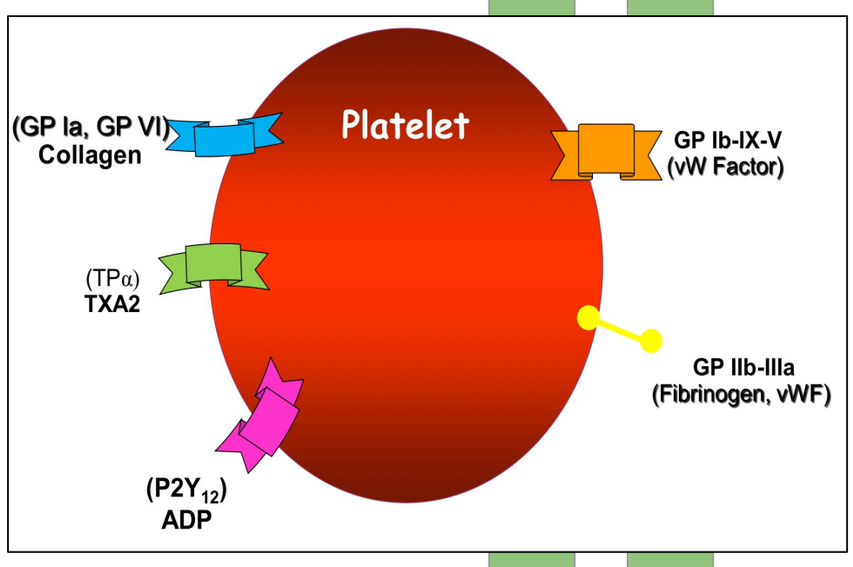


Figure 11-1

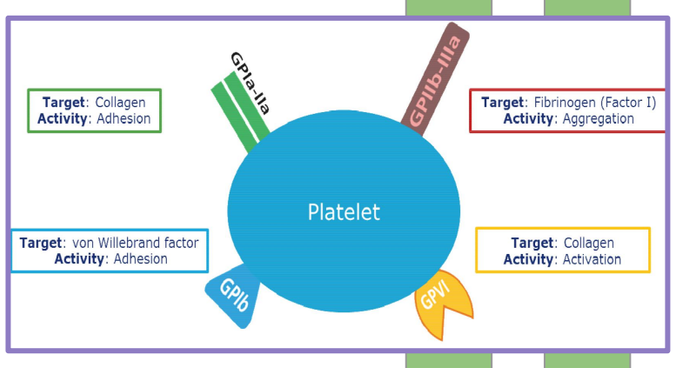


Figure 11-2 Showing the functions of different receptors

Platelet Plug Formation (Activation)

1. Adhesion
2. Shape change (Activation)
3. Aggregation
4. Release reaction
5. Clot retraction

Platelet Haemostatic Plug Formation

- Platelets activated by adhesion.
- Extend projections to make contact with each other.
- Release:
Thromboxane A2, serotonin & ADP >>> activating other platelets.
- Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel.
- ADP causes stickiness and enhances aggregation.

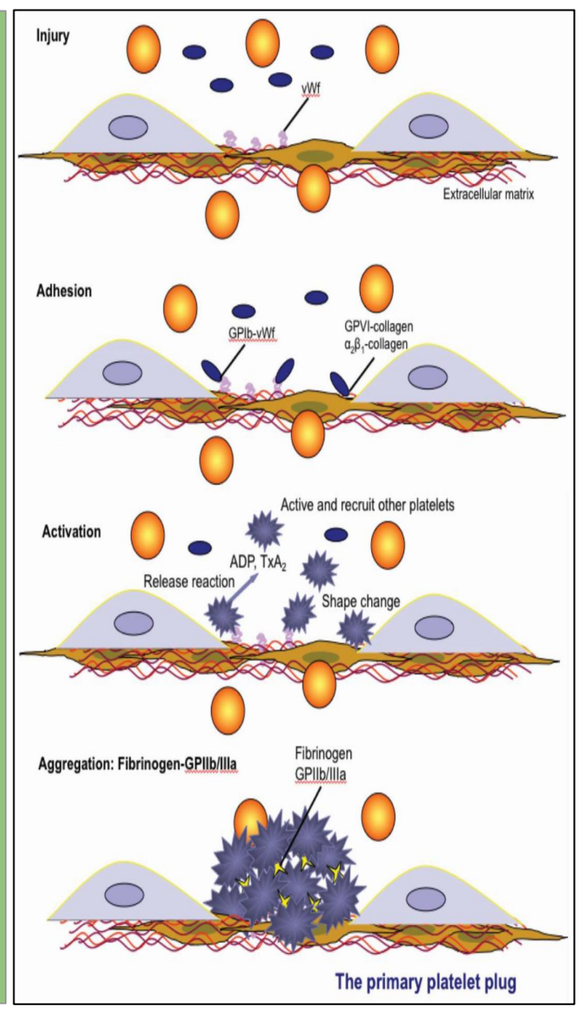


Figure 11-3

Platelet Aggregation

- Fibrinogen is needed to join platelets to each other via platelet fibrinogen receptors.

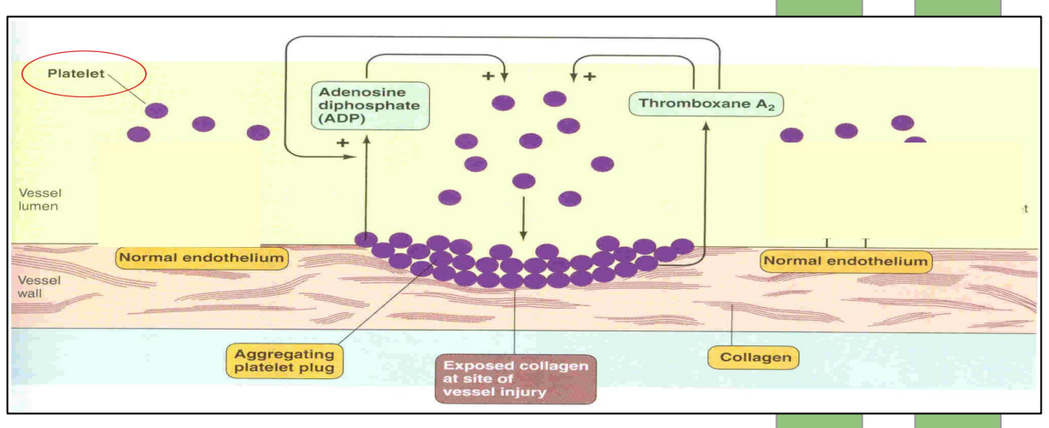


Figure 11-4

Normal endothelium secrete:
- Prostacyclin.
- ADP Phosphatase.
- NO.

TO PREVENT PLATELETS AGGREGATION

Release Reaction of the Platelets and Clot Retraction

- Activated Platelets Secrete:
1. ADP

2. 5HT (vasoconstriction)

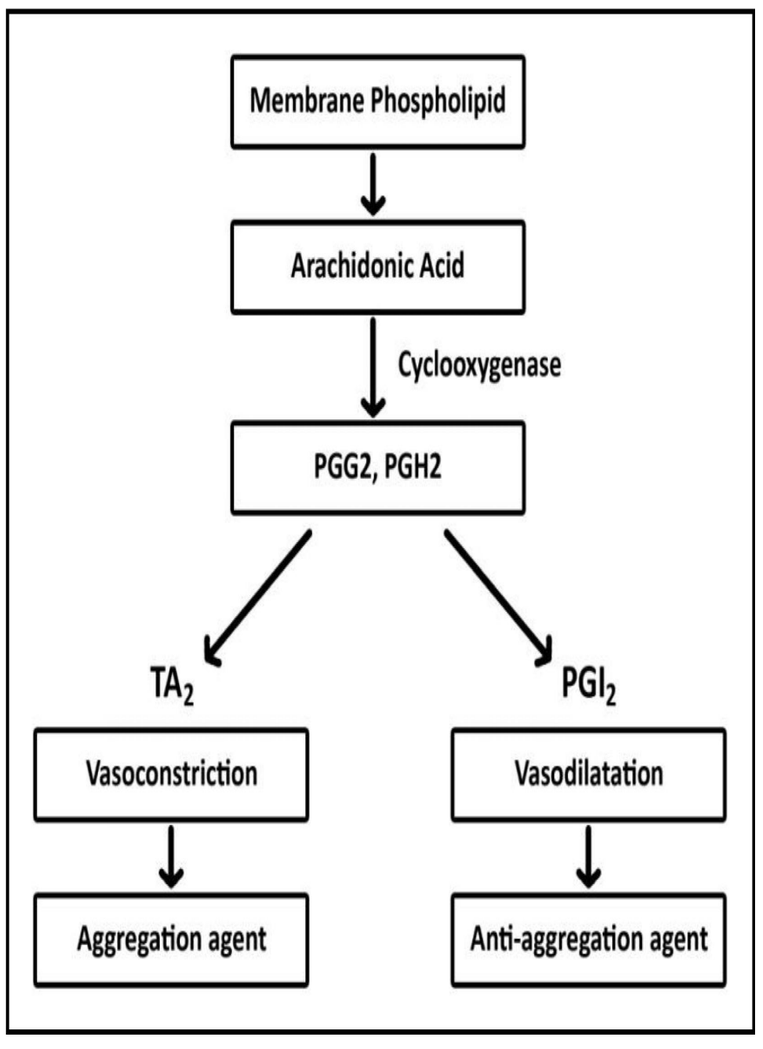
3. Platelet phospholipid (PF3) (clot formation)

4. Thromboxane A2 (TXA2)
is a prostaglandin formed from arachidonic acid, function:

- Vasoconstriction. - Platelet aggregation.

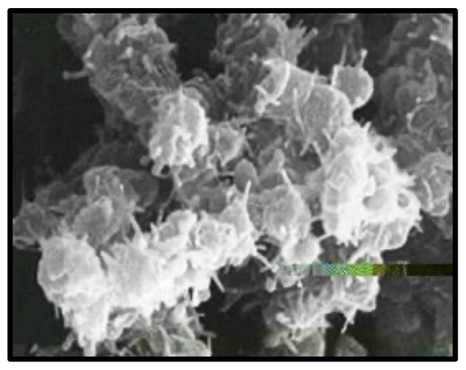
(TXA2 inhibited by aspirin)

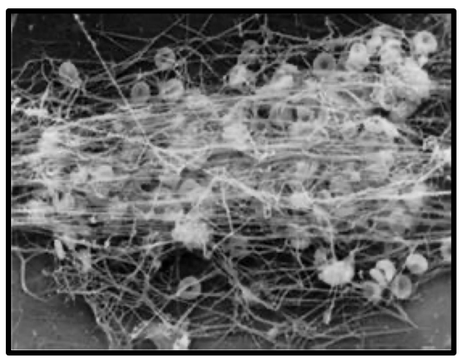
Clot Retraction: Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.



Platelet Function: Maintenance of Vascular Integrity

1- Initial arrest of bleeding by platelet plug formation





2- Stabilization of hemostatic plug by contributing to fibrin formation

An adequate number and function of platelets is essential to participate optimally in hemostasis.

Summary of Platelet Activation

- **Platelets are activated when brought into contact with collagen exposed when the endothelial blood vessel lining is damaged.**
- **Activated platelets release a number of different coagulation and platelet activating factors.**
- **Transport of negatively charged phospholipids to the platelet surface; provide a catalytic surface for coagulation cascade to occur.**
- **Platelets adhesion receptors (integrins): Platelets adhere to each other via adhesion receptors forming a hemostatic plug with fibrin.**
- **Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.**
- **GPIIb/IIIa: the most common platelet adhesion receptor for fibrinogen and von Willebrand factor (vWF).**

Platelet Disorders

1. Deficiency in number (thrombocytopenia)
2. Deficiency in function (thrombasthenia)

THROMBOCYTOPENIA

1. Decreased production (leukemia, various anemias, infections and medications)
2. Increased destruction (Autoimmune diseases, Idiopathic (immune) thrombocytopenic purpura, medications, pregnancy and infections)
3. Pseudothrombocytopenia (Partial clotting of specimen, EDTA-platelet clumping, giant platelets, satellitism around WBCs, cold agglutinins)
4. Abnormal distribution (splenomegaly with sequestration in the spleen)

CONGENITAL PLATELET DISORDERS

1- Disorders of Adhesion:

- Bernard-Soulier

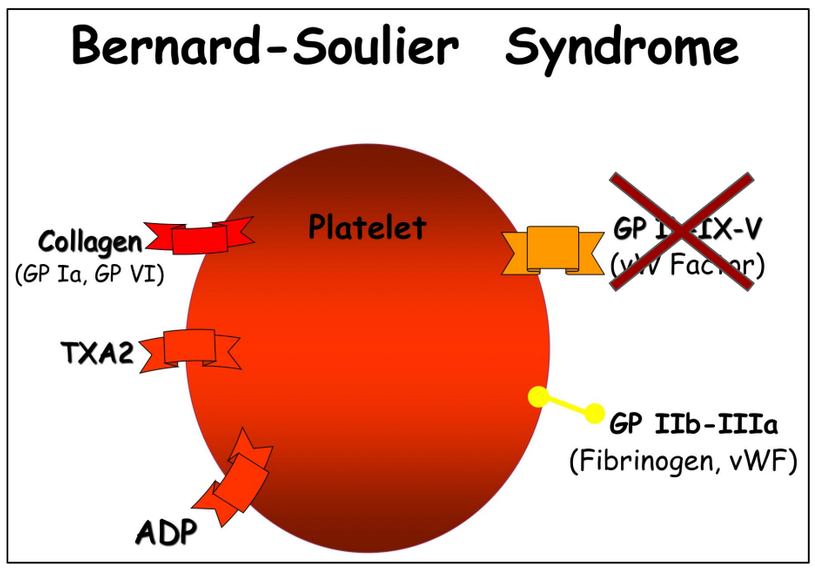


Figure 11-5
In Bernard-Soulier Syndrome, there is deficiency of vW factor receptors causing defects in **adhesion**.

2- Disorder of Aggregation:

- Glanzmann thrombasthenia

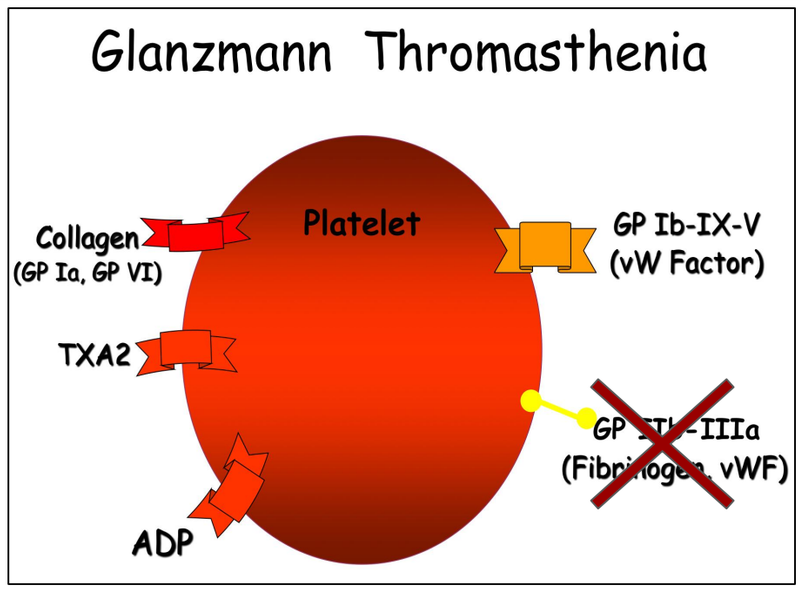


Figure 11-6
In Glanzmann Thrombasthenia, there is deficiency of fibrinogen receptors causing defects in **aggregation**.

3- Disorders of Granules:

- Grey Platelet Syndrome.
- Storage Pool deficiency.
- Hermansky-Pudlak syndrome .
- Chediak-Higashi syndrome.

4- Disorders of Production:

- Congenital amegakaryocytic thrombocytopenia.
- MYH9 related disorders.
- Thrombocytopenia with absent radii (TAR).
- Paris-Trousseau/Jacobsen.

Laboratory Testing for Platelet Functions

- Peripheral smear and platelet count (& shape)
- Electron-microscopy
- Bleeding time (Duke method)
- Platelet Aggregation (platelet aggregometry)
- Platelet Function Analyzer (PFA-100)
- Flow-cytometry
- Granule release products

Platelet Aggregation in Platelet Rich Plasma (PRP)

- It provides information on time course of platelets activation.
- Agonists:
  - ADP
  - Adrenaline
  - Collagen
  - Arachidonic acid
  - Ristocetin
  - Thrombin

  (Reference ranges need to be determined for each agonist)

Case Study

- **A 7 years old girl complaining of** severe bruising since birth and if she had injury she would bleed for days.
- She had epistaxis which lasted for days.
- Her mother said "she just bruise more easily than her older sister".

- **Investigation:**
  - **CBC:** RBC, WBC, Platelets. (All normal)
  - **Platelet morphology**: normal.
  - **Aggregometry**: Absent platelet aggregation in response to ADP, collagen, thrombin, and epinephrine.

Diagnosis Glanzmann's Thrombasthenia (Defects in aggregation)

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REFERENCES

- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology