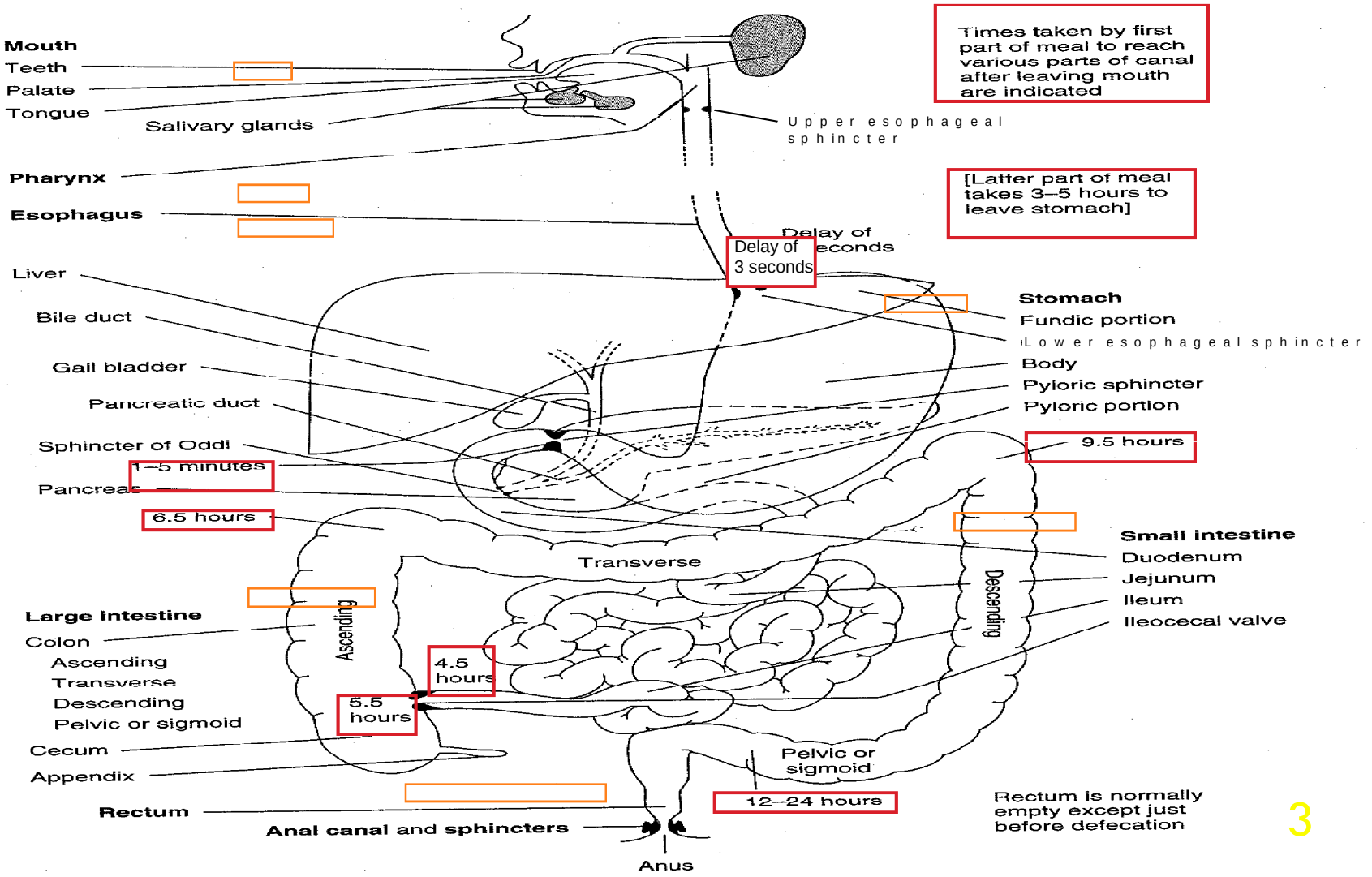
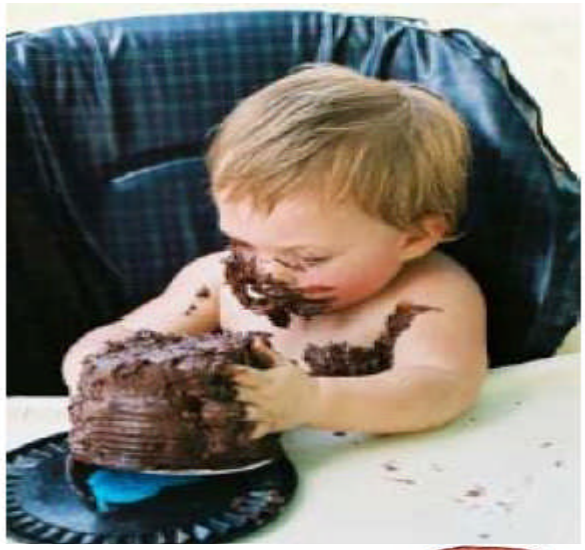
DIGESTIVE PHYSIOLOGY

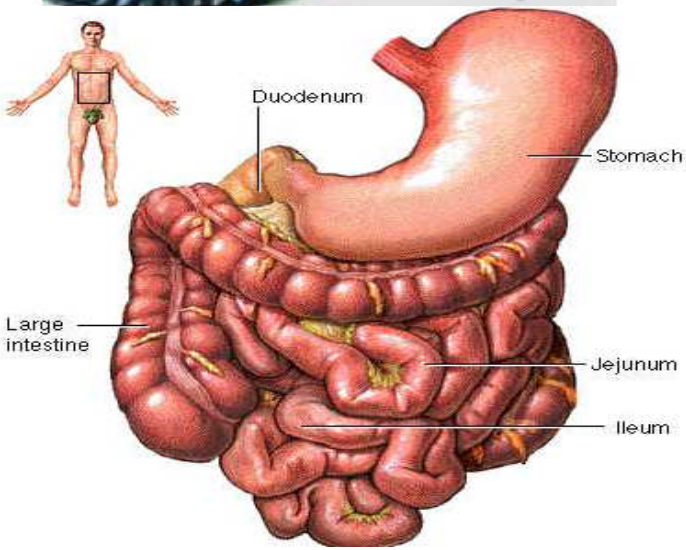
D.HAMMOUDI.MD

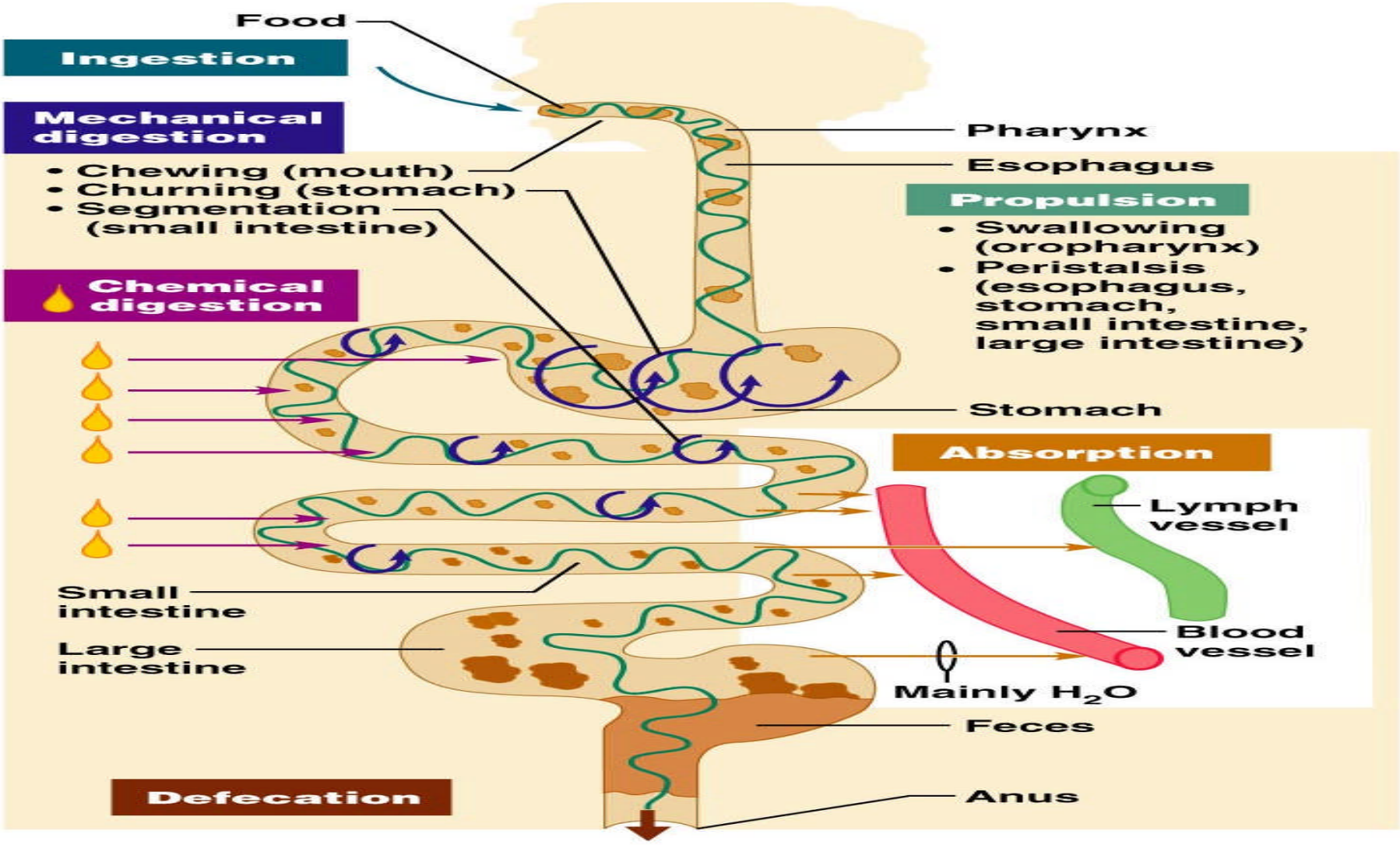

Mouth
Teeth
Palate
Tongue
Salivary glands
Pharynx
Esophagus
Upper esophageal sphincter
Times taken by first part of meal to reach various parts of canal after leaving mouth are indicated
[Latter part of meal takes 3–5 hours to leave stomach]
Delay of 3 seconds
Liver
Bile duct
Gall bladder
Pancreatic duct
Sphincter of Oddi
1–5 minutes
Pancreas
6.5 hours
Stomach
Fundic portion
Lower esophageal sphincter
Body
Pyloric sphincter
Pyloric portion
9.5 hours
Small intestine
Duodenum
Jejunum
Ileum
Ileocecal valve
Transverse
Ascending
Descending
Large intestine
Colon
Ascending
Transverse
Descending
Pelvic or sigmoid
Cecum
Appendix
4.5 hours
5.5 hours
Pelvic or sigmoid
12–24 hours
Rectum
Anal canal and sphincters
Anus
Rectum is normally empty except just before defecation

Digestive Process

- The GI tract is a "disassembly" line
  - Nutrients become more available to the body in each step
- **<u>There are six essential activities:</u>**
  - **Ingestion,**
  - **propulsion,**
  - **mechanical digestion**
  - **Chemical digestion,**
  - **absorption,**
  - **defecation**

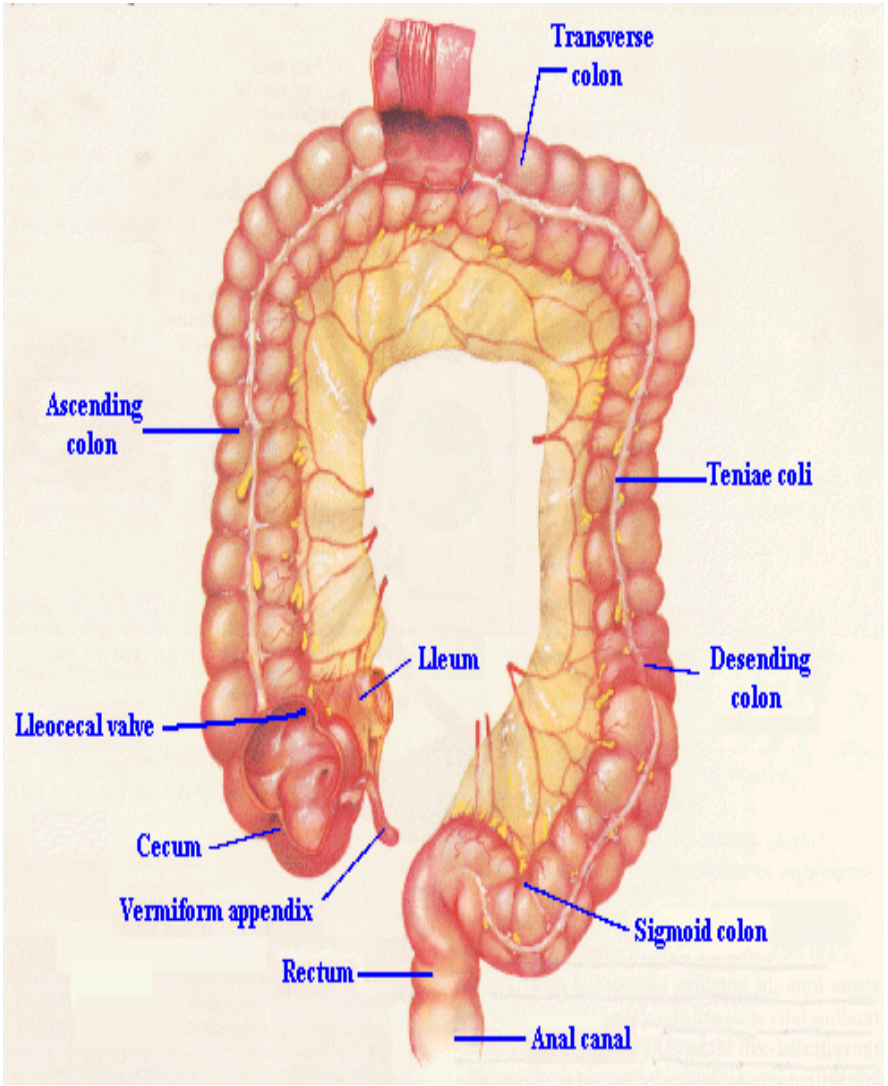





Food
Ingestion
Mechanical digestion
• Chewing (mouth)
• Churning (stomach)
• Segmentation (small intestine)
Chemical digestion
Pharynx
Esophagus
Propulsion
• Swallowing (oropharynx)
• Peristalsis (esophagus, stomach, small intestine, large intestine)
Stomach
Absorption
Lymph vessel
Blood vessel
Mainly H_2O
Small intestine
Large intestine
Feces
Defecation
Anus

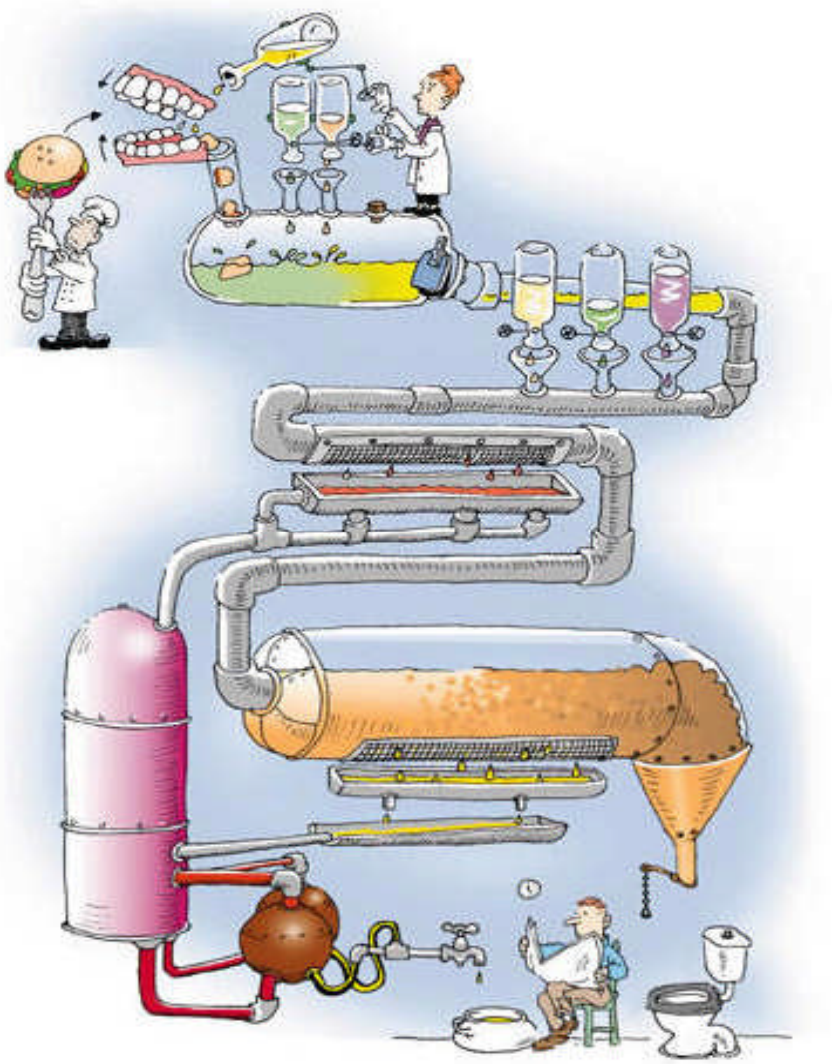
Digestion

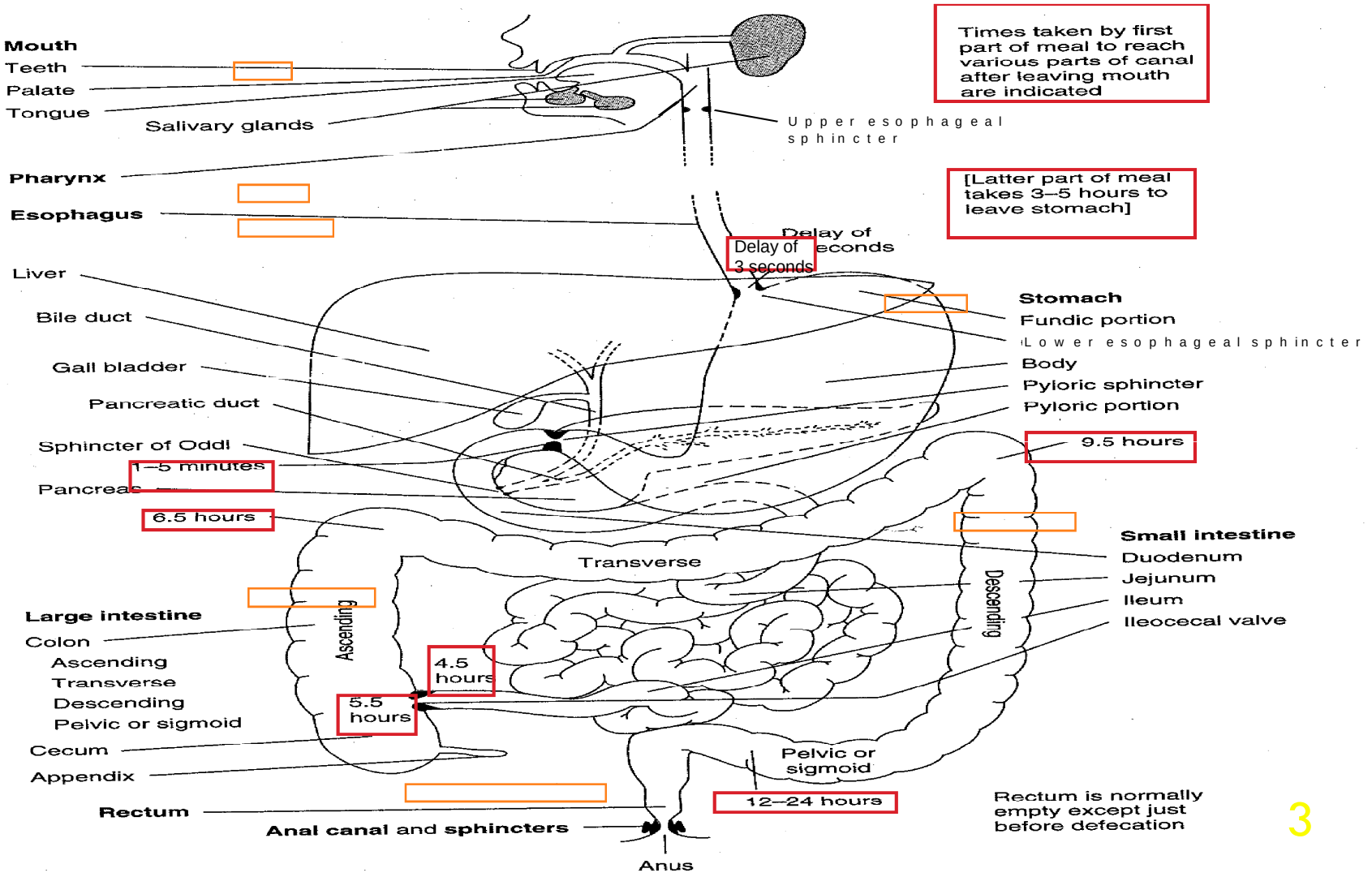
- Processing of food
- Types
  - Mechanical (physical)
    - Chew
    - Tear
    - Grind
    - Mash
    - Mix
  - Chemical
    - Catabolic reactions
    - Enzymatic hydrolysis
      - Carbohydrate
      - Protein
      - Lipid



Digestion, what is it?

- Mechanical breakdown of food
- Chemical breakdown of food
- Absorption of nutrients

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Functions of the digestive system

- Ingestion
- Mechanical processing
- Digestion
- Secretion
- Absorption
- Excretion

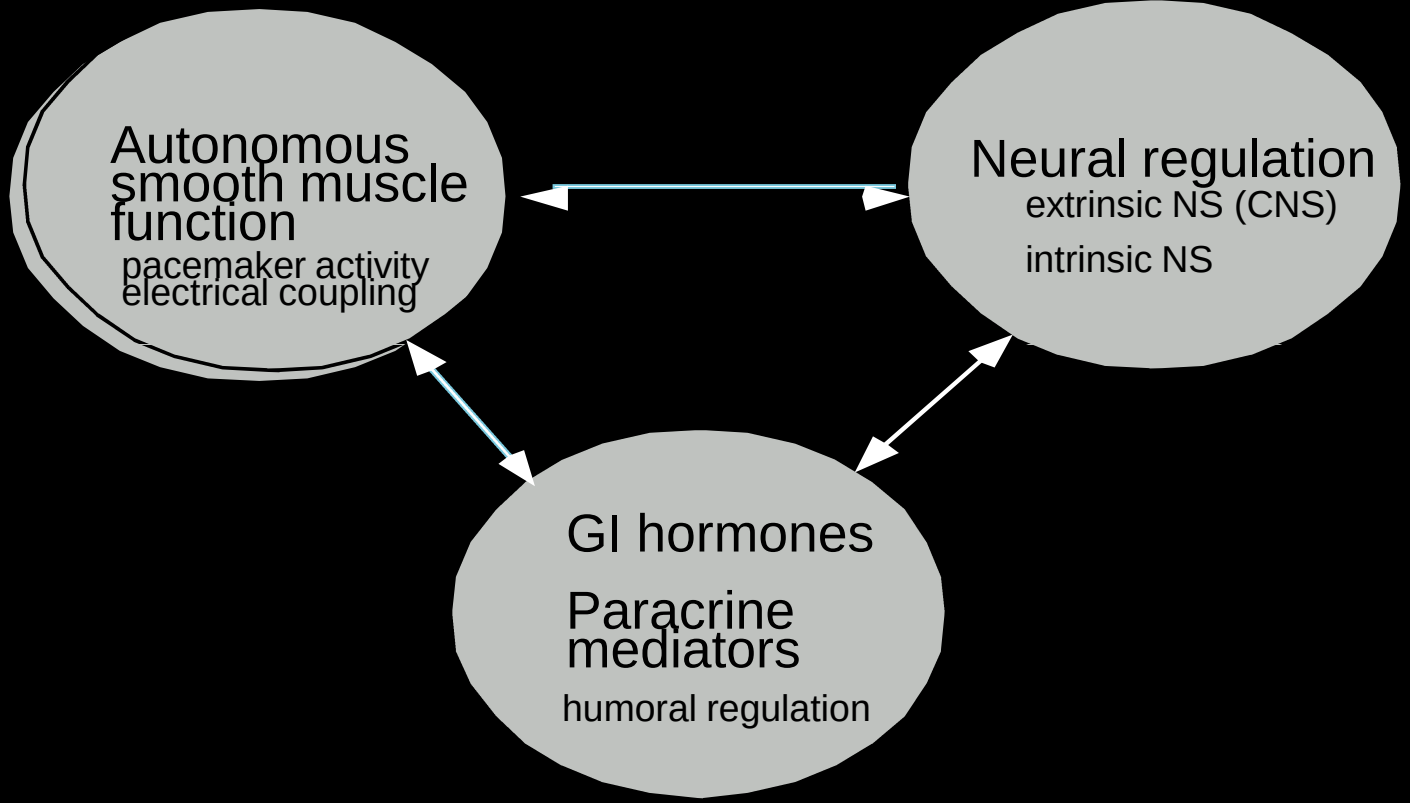
4 basic digestive processes

- MOTILITY
- SECRETION
- DIGESTION
- ABSORPTION

Functions

- 4 major activities of GI tract
  1. **Motility**
     - Propel ingested food from mouth toward rectum
  2. **Secretion**
     - Aid in digestion and absorption
  3. **Digestion**
     - Food broken down into absorbable molecules
  4. **Absorption**
     - Nutrients, electrolytes, and water are absorbed

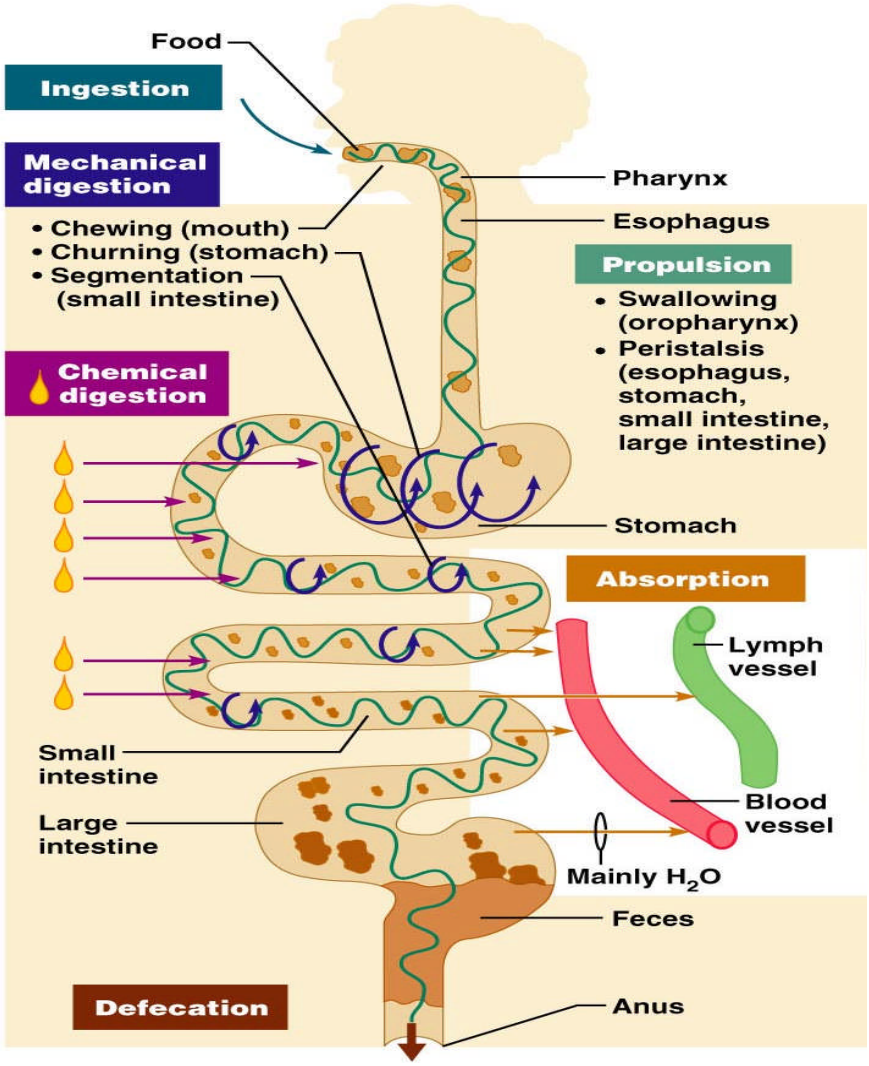
Regulation of GI function



Digestive Enzymes

- Are secreted by:
  - salivary glands
  - tongue
  - stomach
  - pancreas

- Break molecular bonds in large organic molecules:
  - carbohydrates, proteins, lipids, and nucleic acids
  - in a process called hydrolysis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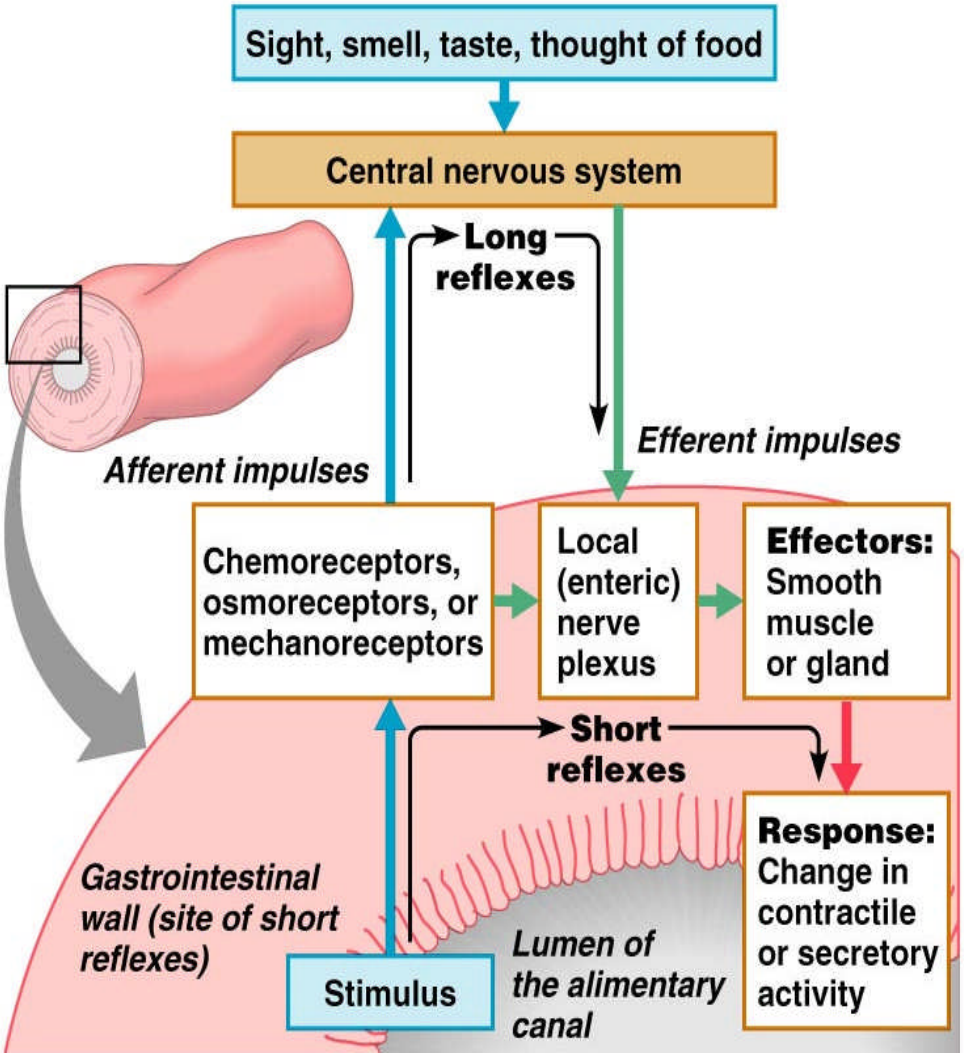
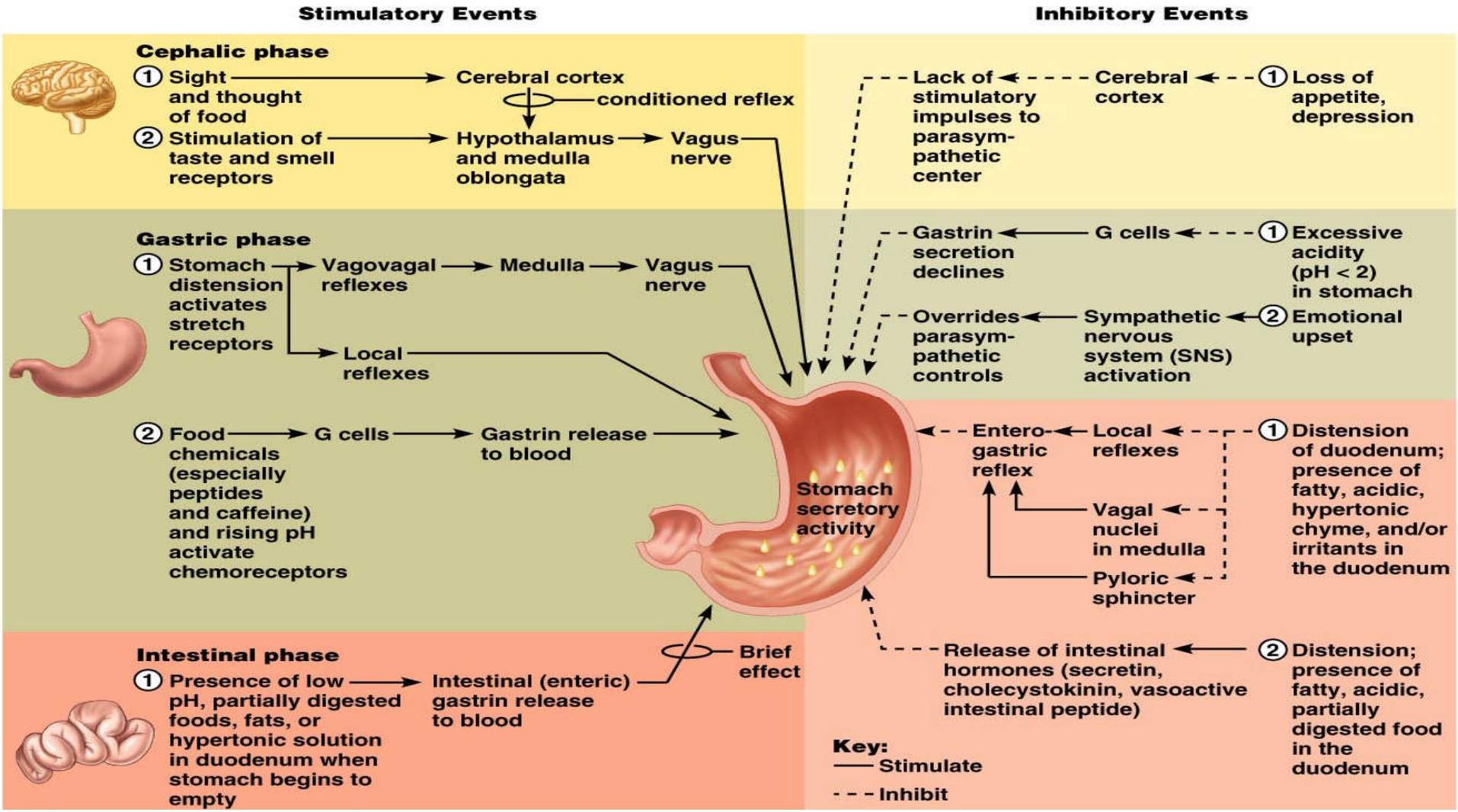
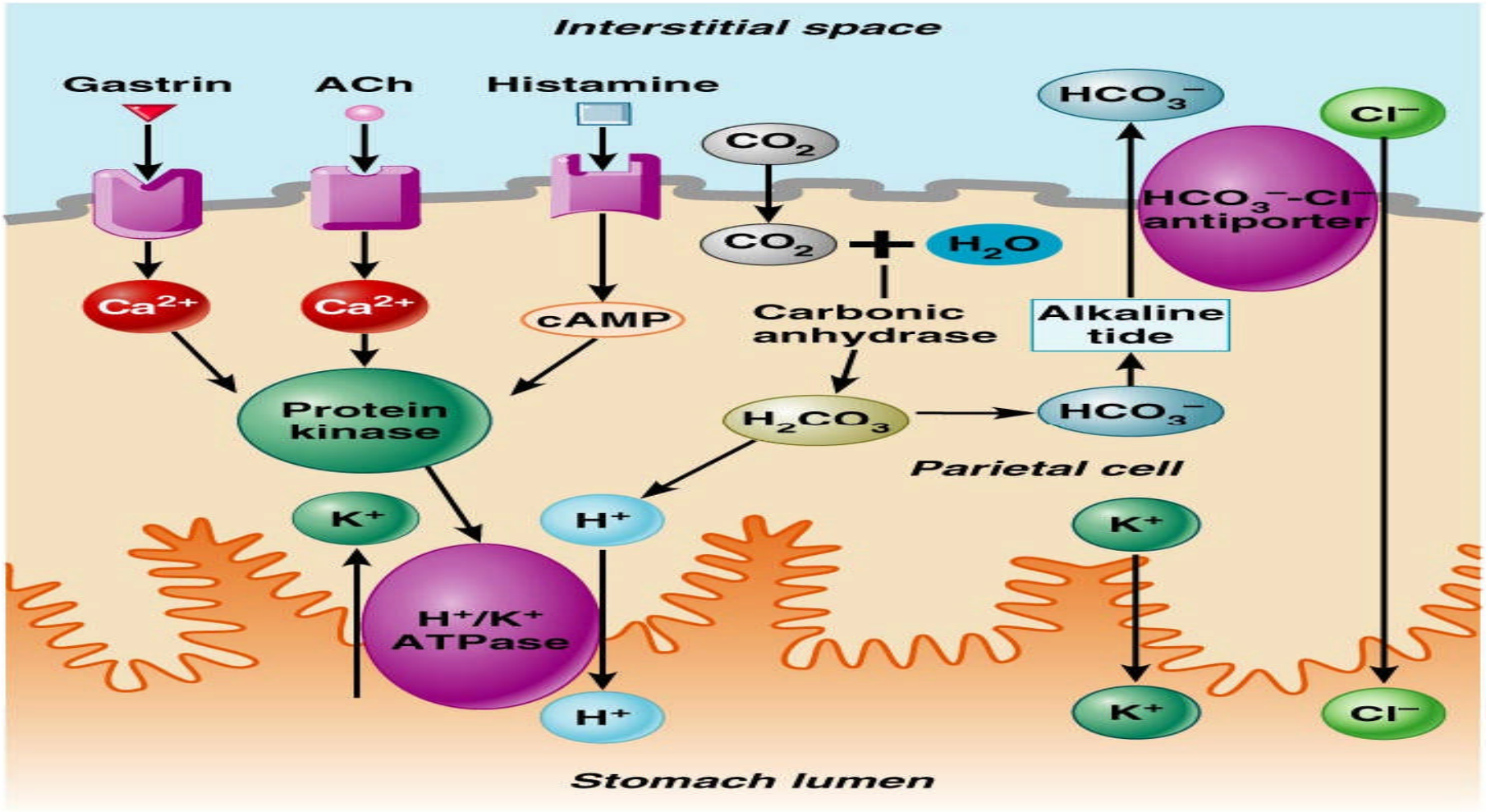
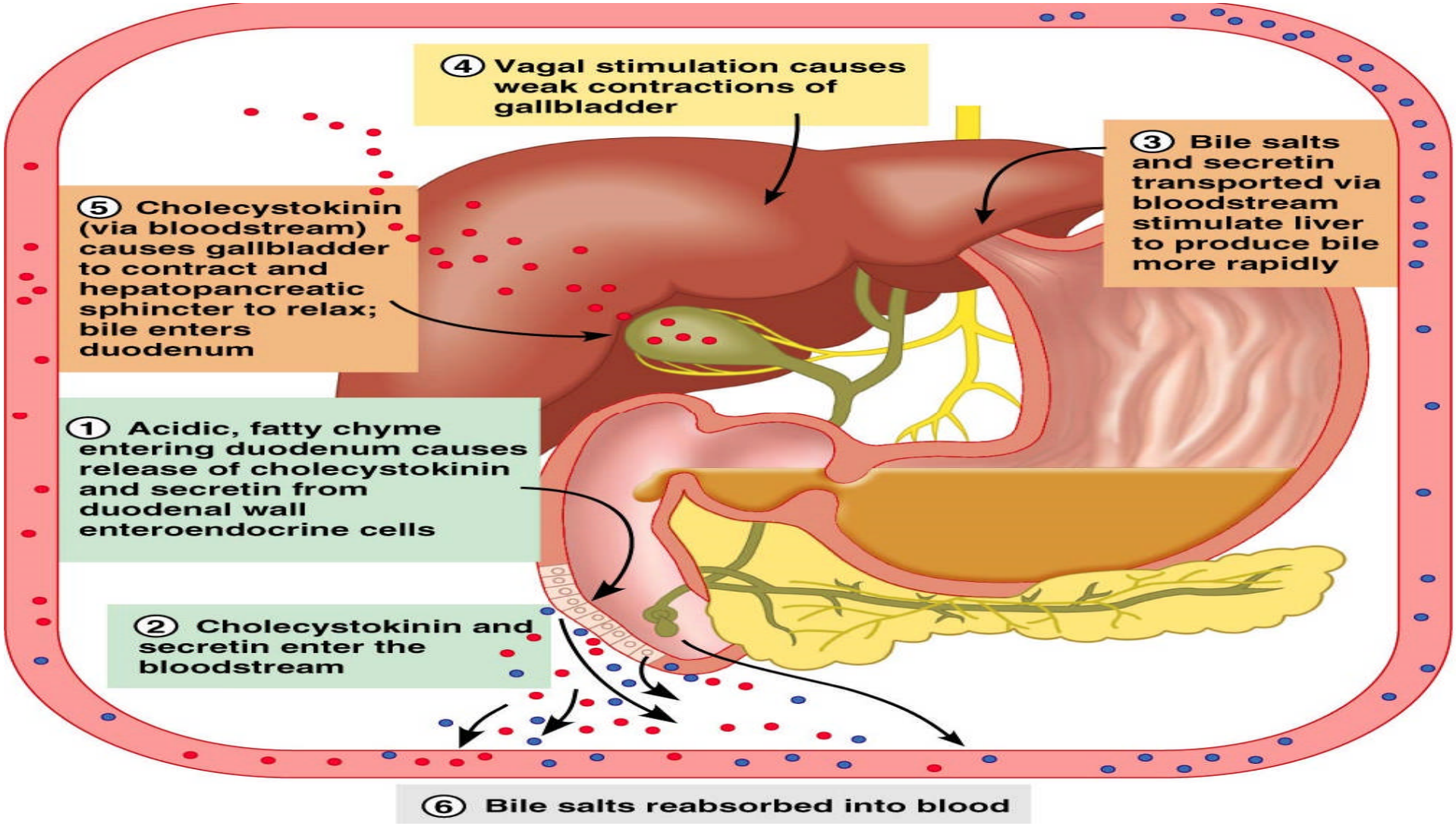
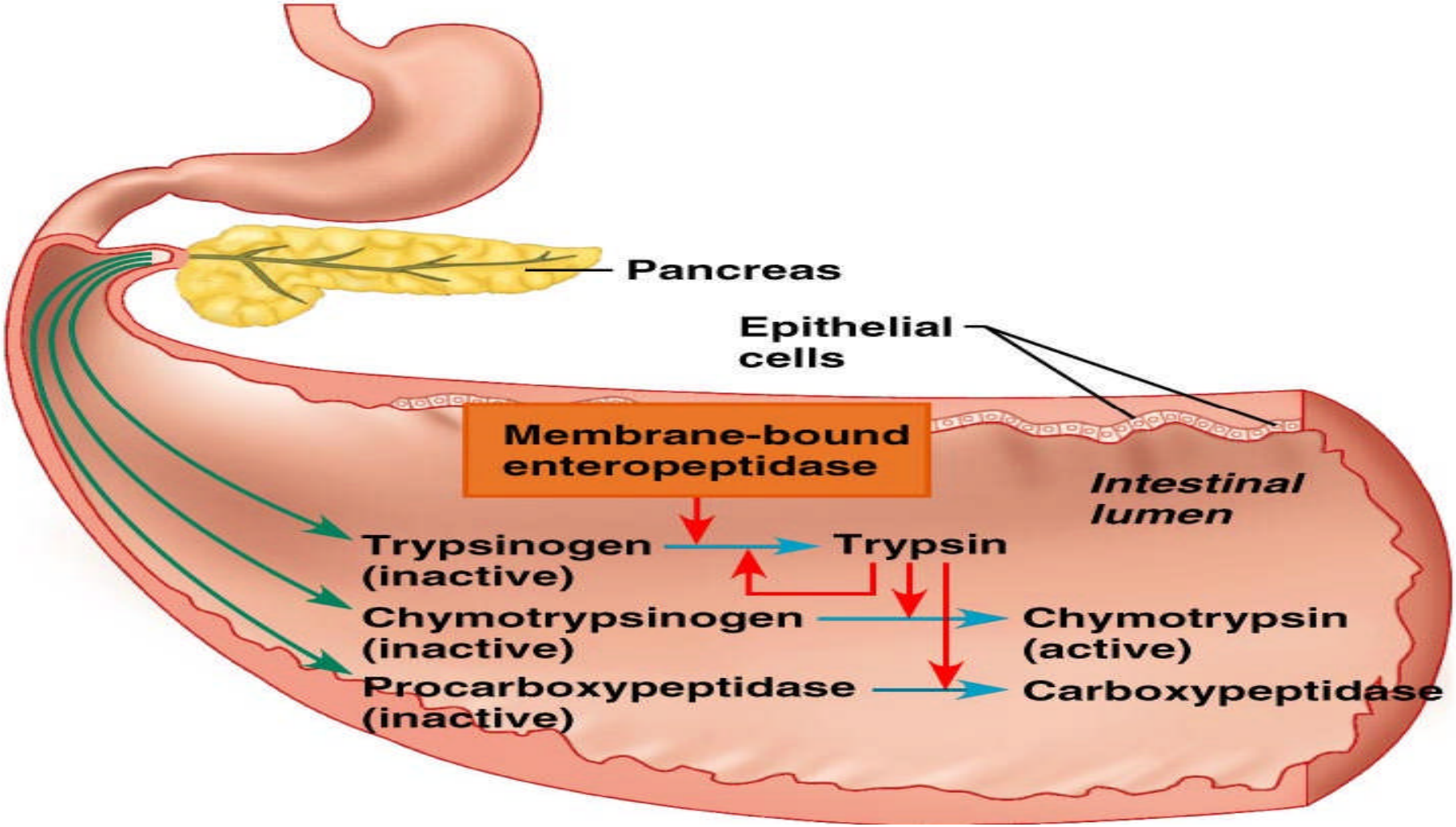
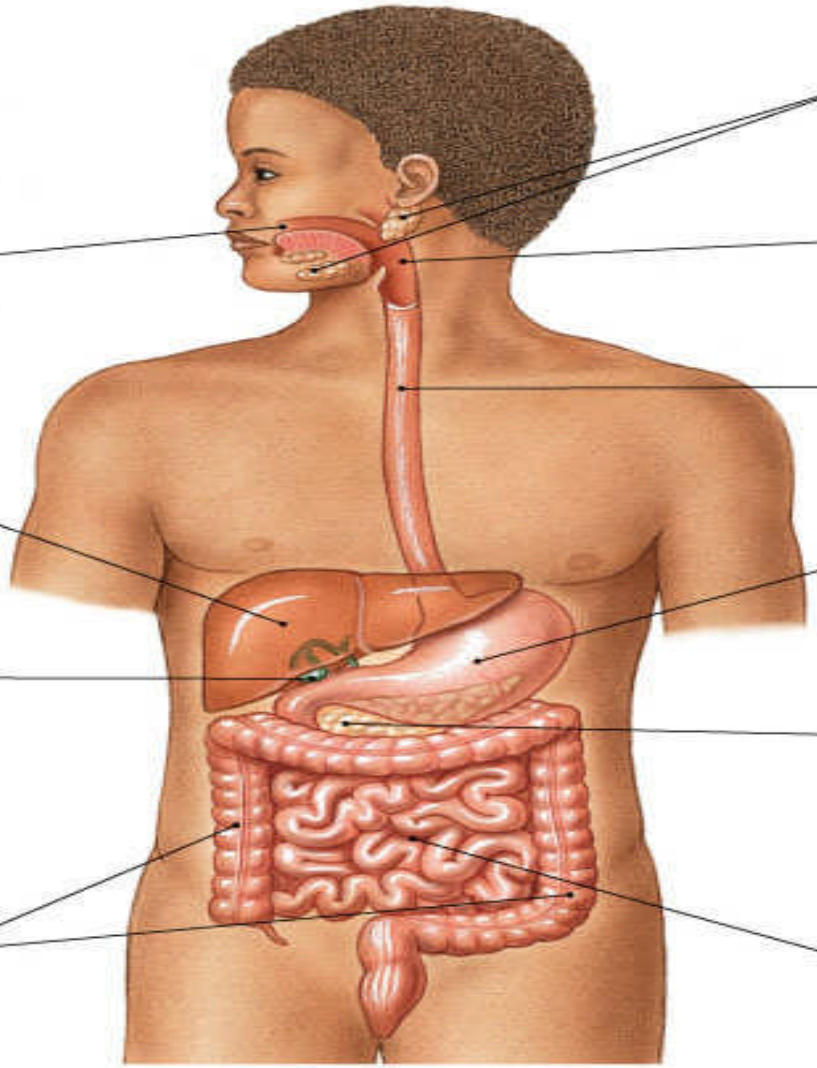

Sight, smell, taste, thought of food
Central nervous system
Long reflexes
Afferent impulses
Efferent impulses
Chemoreceptors, osmoreceptors, or mechanoreceptors
Local (enteric) nerve plexus
Effectors: Smooth muscle or gland
Short reflexes
Response: Change in contractile or secretory activity
Gastrointestinal wall (site of short reflexes)
Stimulus
Lumen of the alimentary canal


Stimulatory Events
Inhibitory Events
Cephalic phase
1 Sight and thought of food
2 Stimulation of taste and smell receptors
Cerebral cortex
conditioned reflex
Hypothalamus and medulla oblongata
Vagus nerve
Lack of stimulatory impulses to parasym-pathetic center
Cerebral cortex
1 Loss of appetite, depression
Gastric phase
1 Stomach distension activates stretch receptors
Vagovagal reflexes
Medulla
Vagus nerve
Local reflexes
2 Food chemicals (especially peptides and caffeine) and rising pH activate chemoreceptors
G cells
Gastrin release to blood
Gastrin secretion declines
G cells
1 Excessive acidity (pH < 2) in stomach
Overrides parasym-pathetic controls
Sympathetic nervous system (SNS) activation
2 Emotional upset
Stomach secretory activity
Entero-gastric reflex
Local reflexes
1 Distension of duodenum; presence of fatty, acidic, hypertonic chyme, and/or irritants in the duodenum
Vagal nuclei in medulla
Pyloric sphincter
Intestinal phase
1 Presence of low pH, partially digested foods, fats, or hypertonic solution in duodenum when stomach begins to empty
Intestinal (enteric) gastrin release to blood
Brief effect
Release of intestinal hormones (secretin, cholecystokinin, vasoactive intestinal peptide)
2 Distension; presence of fatty, acidic, partially digested food in the duodenum
Key:
Stimulate
Inhibit




④ Vagal stimulation causes weak contractions of gallbladder
③ Bile salts and secretin transported via bloodstream stimulate liver to produce bile more rapidly
⑤ Cholecystokinin (via bloodstream) causes gallbladder to contract and hepatopancreatic sphincter to relax; bile enters duodenum
① Acidic, fatty chyme entering duodenum causes release of cholecystokinin and secretin from duodenal wall enteroendocrine cells
② Cholecystokinin and secretin enter the bloodstream
⑥ Bile salts reabsorbed into blood


Pancreas
Epithelial cells
Membrane-bound enteropeptidase
Intestinal lumen
Trypsinogen (inactive)
Trypsin
Chymotrypsinogen (inactive)
Chymotrypsin (active)
Procarboxypeptidase (inactive)
Carboxypeptidase



ORAL CAVITY, TEETH, TONGUE
Mechanical processing, moistening, mixing with salivary secretions

LIVER
Secretion of bile (important for lipid digestion), storage of nutrients, many other vital functions

GALLBLADDER
Storage and concentration of bile

LARGE INTESTINE
Dehydration and compaction of indigestible materials in preparation for elimination

SALIVARY GLANDS
Secretion of lubricating fluid containing enzymes that break down carbohydrates

PHARYNX
Pharyngeal muscles propel materials into the esophagus

ESOPHAGUS
Transport of materials to the stomach

STOMACH
Chemical breakdown of materials via acid and enzymes; mechanical processing through muscular contractions

PANCREAS
Exocrine cells secrete buffers and digestive enzymes; endocrine cells secrete hormones

SMALL INTESTINE
Enzymatic digestion and absorption of water, organic substrates, vitamins, and ions

- Are divided into classes by targets:
  - carbohydrases:
    - break bonds between simple sugars
  - proteases:
    - break bonds between amino acids
  - lipases:
    - separate fatty acids from glycerides

Movement of digestive materials

- Visceral smooth muscle shows rhythmic cycles of activity
  - Pacemaker cells
- Peristalsis
  - Waves that move a bolus
- Segmentation
  - Churn and fragment a bolus

The Swallowing Process

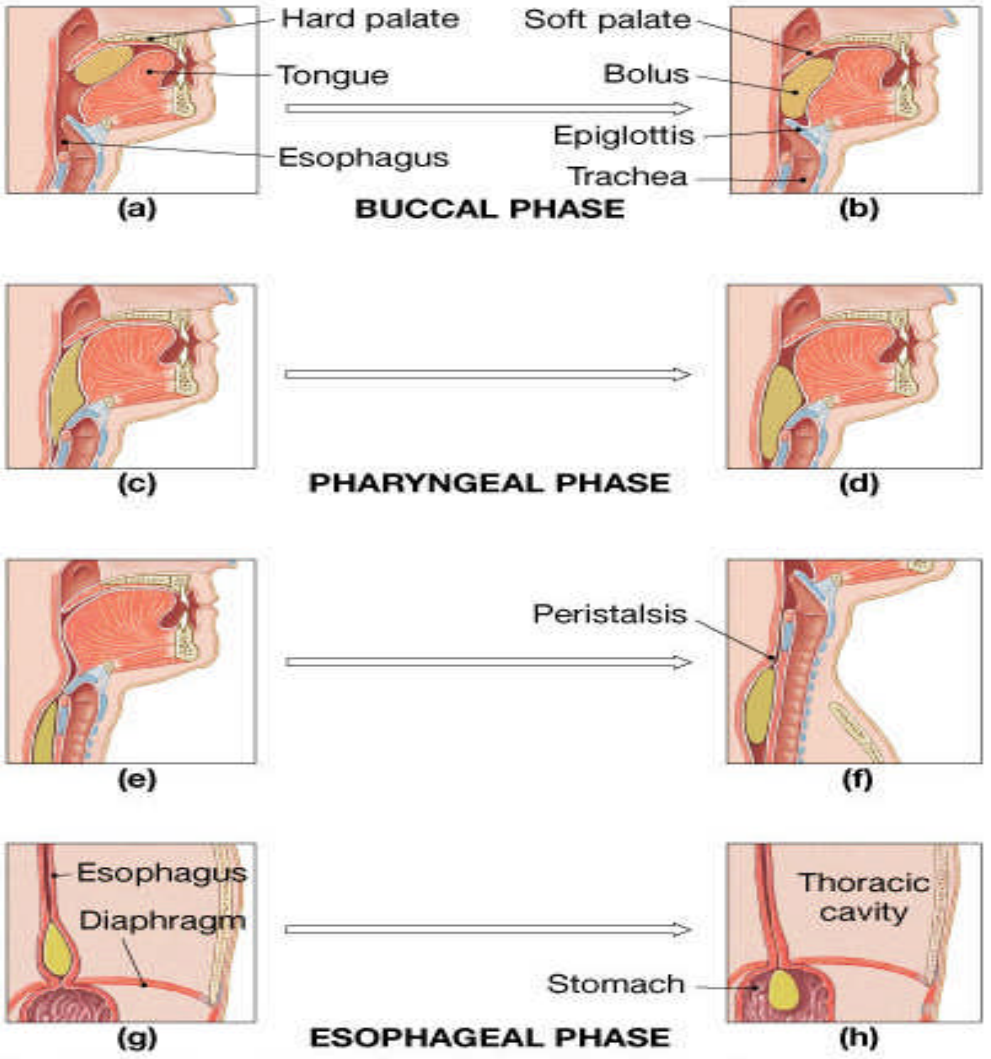
•Deglutition (swallowing)

•Involves the **coordinated activity of the tongue, soft palate, pharynx, esophagus and 22 separate muscle groups**

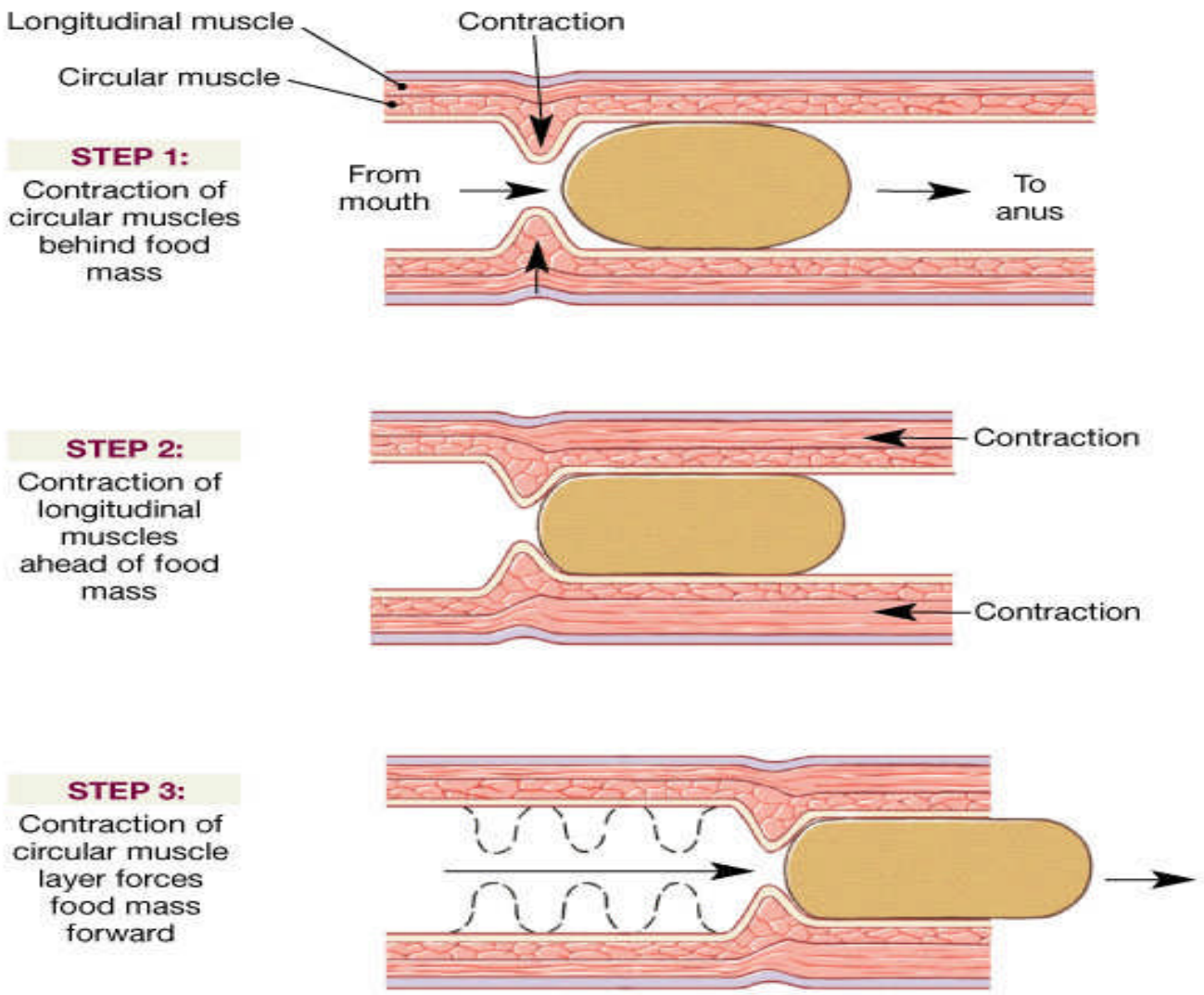
•**Buccal phase** - bolus is forced into the oropharynx

•**Pharyngeal-esophageal phase** - controlled by the medulla and lower pons - all routes except into the digestive tract are sealed off

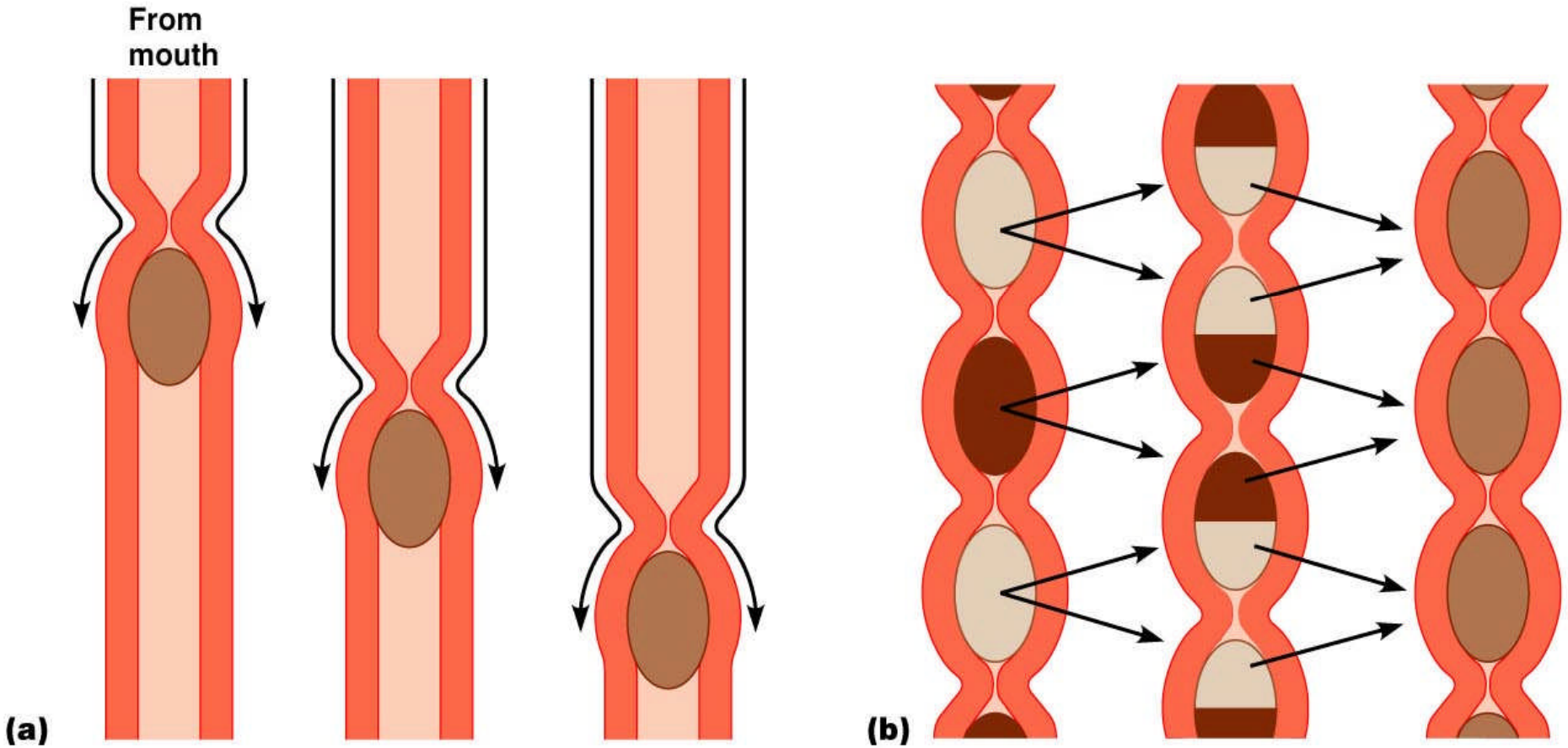
•**Peristalsis** moves food through the pharynx to the esophagus



Peristalsis



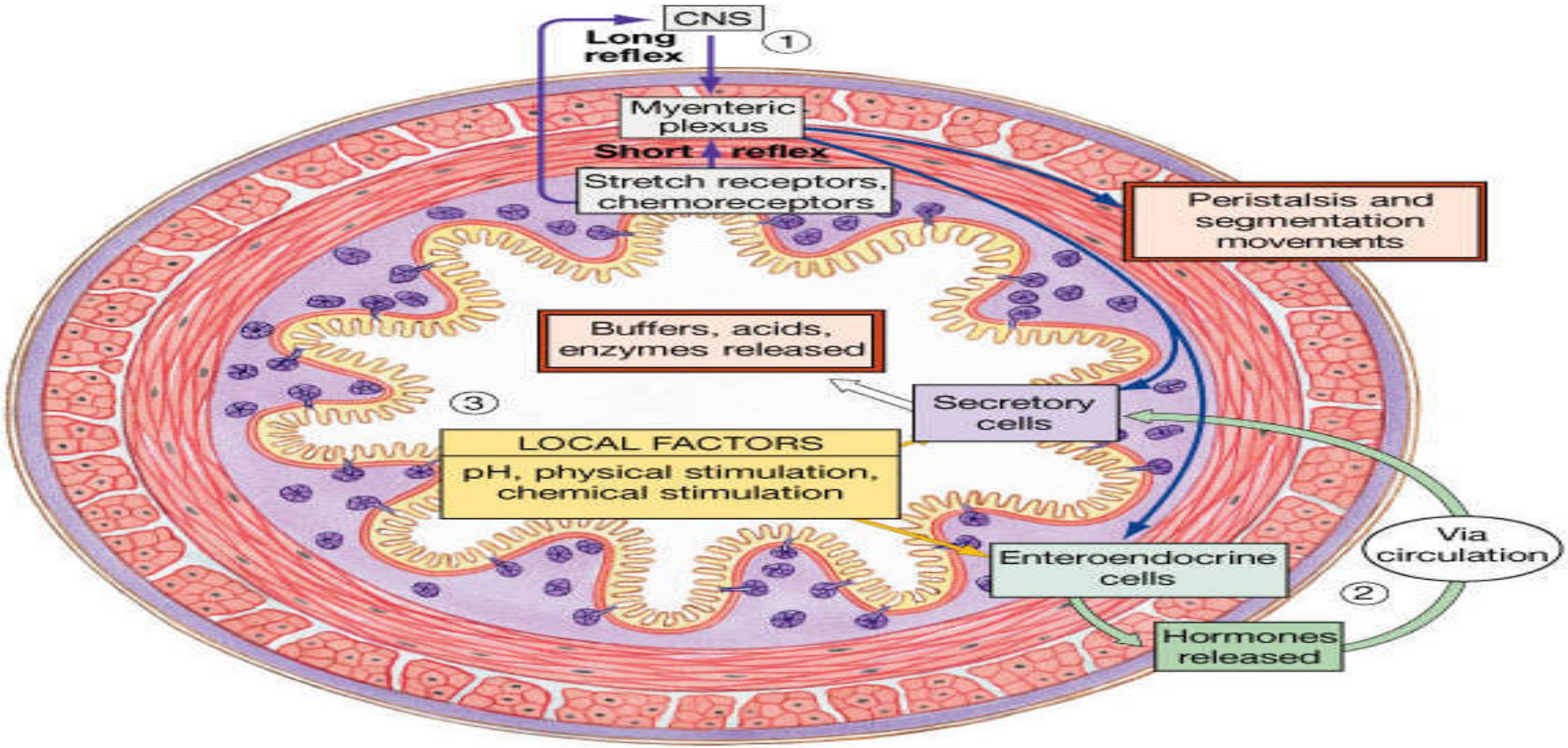
Peristalsis and Segmentation



Control of the digestive system

- Movement of materials along the digestive tract is controlled by:
  - Neural mechanisms
    - Parasympathetic and local reflexes
  - Hormonal mechanisms
    - Enhance or inhibit smooth muscle contraction
  - Local mechanisms
    - Coordinate response to changes in pH or chemical stimuli

The Regulation of Digestive Activities



Functions of Saliva

Moistens ingested food and helps turn it into a semisolid bolus that is more easily swallowed.

Moistens and cleanses the oral cavity structures.

First step in chemical digestion occurs when amylase in saliva begins to break down carbohydrates.

Contains antibodies and an antibacterial element called lysozyme that help inhibit bacterial growth in the oral cavity.

Watery medium into which food molecules are dissolved so taste receptors can be stimulated.

Salivary glands – what is their function?

- Two main purposes:
- 1. secrete saliva – chemical digestion
- 2. solvent – dissolves food – so can taste cleanses mouth and teeth

Esophagus

- Function – food passageway
- Location – from pharynx→stomach
- 1. passes thru mediastinum
- 2. behind the trachea
- 3. moves through diaphragm
- Esophageal sphincter – distal end of esophagus prevents regurgitation of food

Stomach

- J shaped
- Can hold about a liter

Functions:

- 1. receives food
- 2. mixes food with gastric juice
- 3. moves food to small intestine

Mixing in the Stomach

- Chyme – semifluid made by mixing food with digestive juices.

1. pushed toward small intestine
2. water moves right through
3. Movement thru fastest to slowest: carbs→proteins→fats (4-6hrs for fats)

TABLE 15.4 HORMONES OF THE DIGESTIVE TRACT

HORMONE	SOURCE	FUNCTION
Gastrin	Gastric cells, in response to food	Causes gastric glands to increase their secretory activity
Cholecystokinin	Intestinal wall cells, in response to proteins and fats in the small intestine	Causes gastric glands to decrease their secretory activity and inhibits gastric motility; stimulates pancreas to secrete fluid with a high digestive enzyme concentration; stimulates gallbladder to contract and release bile
Secretin	Cells in the duodenal wall, in response to acidic chyme entering the small intestine	Stimulates pancreas to secrete fluid with a high bicarbonate ion concentration

Important actions of GI hormones

Action	**Gastrin**	**CCK**	**Secretin**	**GIP**	
Acid secretion	S		I		I
Pancreatic HCO_3^- secretion	S	S			
Pancreatic enzyme secretion	S				
Bile HCO_3^-			S		
Gallbladder contraction		S			
Gastric emptying		I			
Mucosal growth	S				
Pancreatic growth	S	S			

S = stimulates; I = inhibits

Additional GI hormones

Hormones are produced by enteroendocrine cells in the GI tract in stomach, small and large intestine

Motilin	increases intestinal motility
Serotonin	increases intestinal motility
Substance P	increases intestinal motility
Vasoactive intestinal peptide (VIP)	neurotransmitter for intestinal smooth muscle stimulates secretion of water and ions
Neurotensin	decreases intestinal motility increases blood flow to ileum

Additional GI hormones (cont.)

	stimulate hepatic glycogenolysis
Glucagon **Entero-glucagon**	
	stimulates hepatic glycogenolysis
Glicentin (glucagon-like substance)	
	local inhibition of other endocrine cells
Somatostatin	(e.g. G-cells)
Urogastrone	inhibits secretion of HCl
(Epidermal Growth Factor)	increases epithelial growth
Histamine	increases secretion of HCl

- **GASTRIN** stimulates exocrine glands in stomach to release gastric juice
- Acids (chyme) from stomach, fatty acids in duodenum stimulate release of **SECRETIN**
  - Stimulates secretion of alkali (bicarbonate ions) from pancreas
    - Neutralises acidity from intestinal contents
    - When pH reaches neutrality, secretion of secretin is inhibited
  - Inhibits gastric gland secretion
- Acidic chyme from stomach, fat, amino acids in **duodenum** stimulate release of **CHOLECYSTOKININ-PANCREOZYMIN CCK-PZ**
  - Activates smooth muscle contraction/emptying of gall bladder (to release bile)
  - Triggers secretion of enzymes from pancreas
  - Stimulates Medulla oblongata which give a satiety signal
  - Once molecules stimulating CCK are digested → CCK inhibited again
- **SOMATOSTATIN**
  - Acts on stomach, duodenum, pancreas
  - Inhibits release of gastrin, secretin, and CCK-PZ

- Cardia – mucus, endocrine and undifferentiated cells
- Fundus & body – oxyntic glands
  - Parietal, chief, endocrine, mucus neck, undifferentiated cells
- Antrum & pylorus – pyloric glands
  - Endocrine, mucus neck, G-cells

- Endocrine cells
  - G cells – secrete gastrin
- Paracrine cells
  - D cells – secrete somatostatin
  - Enterochromaffin-like (ECL) cells – secrete histamine

Parietal Cell

- Stimulated by histamine, gastrin, acetylcholine
- Inhibited by somatosatin, prostaglandins

Somatostatin

- Secreted by D cells
- Stimulated by CCK
- Effects H^+ secretion via inhibitory effects on oxyntic ECL cells and pyloric G cells
- D cell in pylorus stimulated by acid

CCK

- Produced by duodenal endocrine cells in response to dietary fatty acids and amino acids
- In vitro stimulates parietal cells
- In vivo inhibits acid production through D cells

Secretin

- Produced by duodenal S cells in response to H^+
- Inhibits gastric acid secretion, stimulates pancreatic HCO_3^- production

Pepsinogens

- Pepsins cleave peptide bonds formed by phenylalanine and tyrosine
- PG secretion stimulated by acetylcholine analogs, histamine, gastrin, secretin
- Inhibited by somatostatin

Intrinsic Factor

- Secreted by parietal cells
- Binds cobalamin(B_{12}) to facilitate absorption
- 2 cobalamin binding proteins – IF/R
- Initially binds to cobalamin R in acidic stomach then is cleaved in duodenum and binds to IF
- Attaches to ileal mucosa
- B_{12} malabsorption may result from IF deficiency, achlorhydria or hypochlorhydria, bacterial overgrowth, pancreatic insufficiency, ileal receptor defect, ileal disease, ileal resection

Inhibition of Gastric Secretion

- Important for protection of duodenum
- **Gastric pH < 3 ---> gastric D cells release somatostatin which inhibits gastrin release**
- Acid in duodenum ---> **secretin & CCK---> inhibits gastric secretion and motility**
- Acid, fats, hyper-osmotic solutions in the duodenum ---> release of enterogastrones ---> inhibit gastric motility and secretion
-
- Gastric Inhibitory Peptide (GIP) from duodenum ---> **inhibits parietal cell function**
-

- **Inhibitors of Gastric Secretion**
  - **GIP**
  - **CCK**
  - **Secretin**

INTESTINAL PHYSIOLOGY

Main Functions of Small Intestine

Digestion - various enzymes:

- 1. peptidases – protein digestion
- 2. *sucrase*, maltase and lactase – sugar digestion
- 3. *lipase* – fat digestion

Absorption – performed by villi (small fingerlike projections)

Release of waste to large intestine

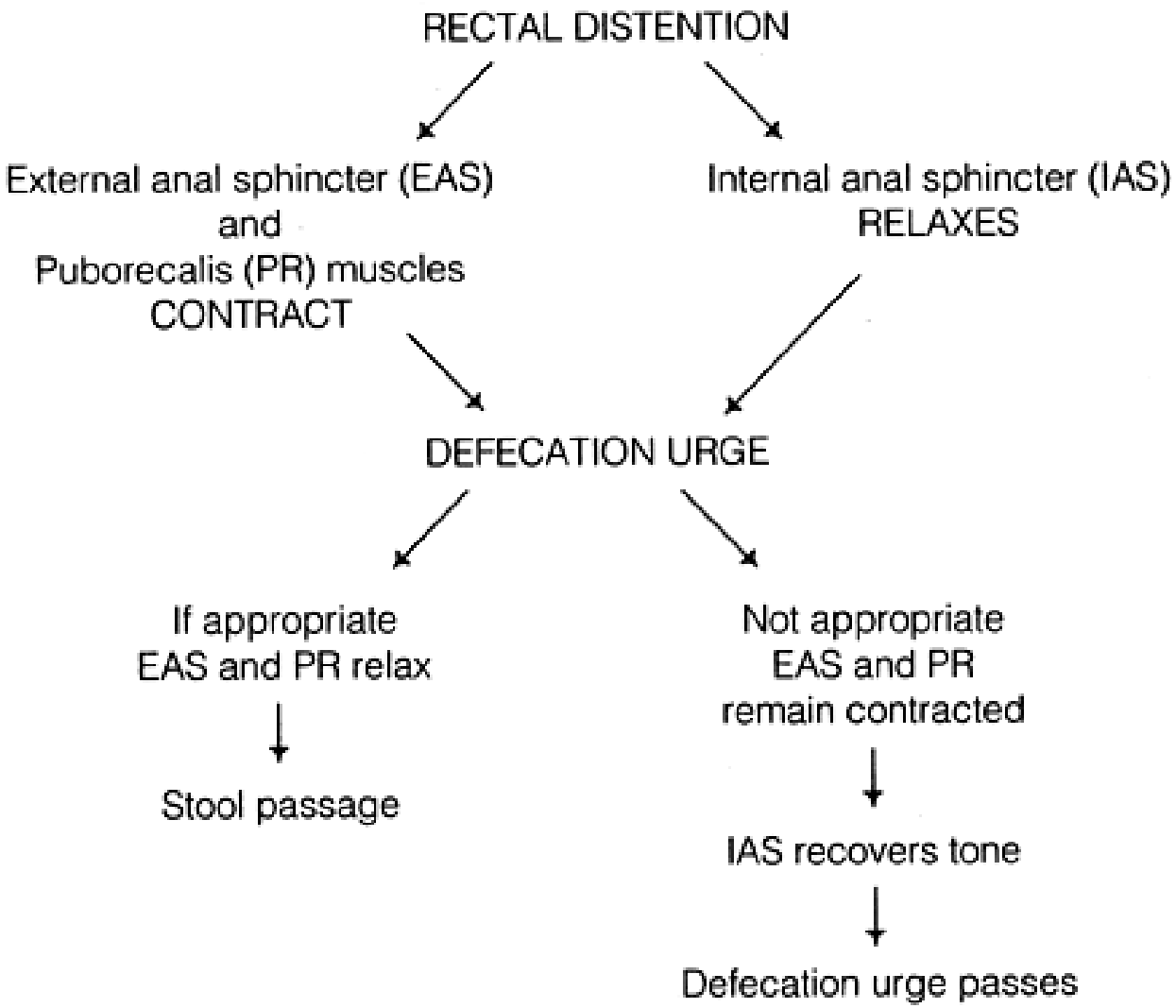
Functions of Large Intestine

- Absorbs water and electrolytes
- Contain intestinal flora (bacteria) – break down some of the molecules not broken down in the small intestine

a. Bacteria use the materials for energy they make certain vitamins like K, thiamine, riboflavin and B12 – absorbed through intestine wall

Defecation

- Presence of food in the stomach:
  - Activates the gastrocolic reflex
  - Initiates peristalsis that forces contents toward the rectum
- Distension of rectal walls caused by feces:
  - Stimulates contraction of the rectal walls
  - Relaxes the internal anal sphincter
- Voluntary signals stimulate relaxation of the external anal sphincter and defecation occurs


RECTAL DISTENTION
External anal sphincter (EAS)
and
Puborecalis (PR) muscles
CONTRACT
Internal anal sphincter (IAS)
RELAXES
DEFECATION URGE
If appropriate
EAS and PR relax
Stool passage
Not appropriate
EAS and PR
remain contracted
IAS recovers tone
Defecation urge passes

Defecation cycle,

- is normally a combination of both voluntary and involuntary processes.
- The defecation cycle is the interval of time between the completion of one bowel movement, and the completion of the following bowel movement.
- At the start of the cycle, the rectum ampulla (anatomically also: *ampulla recti*) acts as a temporary storage facility for the unneeded material.
- As additional fecal material enters the rectum, the rectal walls expand.
- A sufficient increase in fecal material in the rectum causes stretch receptors from the nervous system located in the rectal walls to trigger the contraction of rectal muscles, relaxation of the internal anal sphincter and an initial contraction of the skeletal muscle of the external sphincter.
- The relaxation of the internal anal sphincter causes a signal to be sent to the brain indicating an urge to defecate.

If this urge is not acted upon, the material in the rectum is often returned to the colon by reverse peristalsis where more water is absorbed, thus temporarily reducing pressure and stretching within the rectum.

The additional fecal material is stored in the colon until the next mass 'peristaltic' movement of the transverse and descending colon.
If defecation is delayed for a prolonged period the fecal matter may harden, resulting in constipation.
Once the voluntary signal to defecate is sent back from the brain, the final phase of the cycle begins.
The rectum now contracts and shortens in peristaltic waves, thus forcing fecal material out of the rectum and out through the anal canal.
The internal and external anal sphincters along with the puborectalis muscle allow the feces to be passed by pulling the anus up over the exiting feces in shortening and contracting actions.

Defecation is normally assisted by taking a deep breath and trying to expel this air against a closed glottis (Valsalva maneuver).
This contraction of expiratory chest muscles, diaphragm, abdominal wall muscles, and pelvic diaphragm exert pressure on the digestive tract.
Ventilation at this point temporarily ceases as the lungs push the chest diaphragm down in order to exert the pressure.

Cardiovascular aspects

During defecation, the thoracic blood pressure rises, and as a reflex response the amount of blood pumped by the heart decreases.
Death has been known to occur in cases where defecation causes the blood pressure to rise enough to cause the rupture of an aneurysm or to dislodge blood clots
Also, in release of the Valsalva maneuver blood pressure falls, this coupled often with standing up quickly to leave the toilet results in a common incidence of blackouts in this situation.

Neurological aspects

•When defecating, the external sphincter muscles relax.

•The anal and urethal sphincter muscles are closely linked, and experiments by Dr. Harrison Weed at the Ohio State University Medical Center have shown that they can only be contracted together, not individually, and that they both show relaxation during urination This explains why defecation is frequently accompanied by urination, and why urination is frequently accompanied by flatulence.

•Defecation may be involuntary or under voluntary control.

•Young children learn voluntary control through the process of toilet training.

•Once trained, loss of control causing fecal incontinence may be caused by physical injury (such as damage to the anal sphincter that may result from an episiotomy), intense fright, excessive pressure placed upon the abdomen, inflammatory bowel disease, impaired water absorption in the colon and psychologicalor neurological factors.

•The loss of voluntary control of defecation is experienced frequently by those undergoing a terminal illness

Feces

- Makeup: water, undigested food, electrolytes, mucous, shed intestinal cells, and bacteria
- 75% water
- Odor – usually a result of bacterial action

LIVER PHYSIOLOGY

- The functions of the liver are so numerous and important that we cannot live without it.
- It produces heparin, prothrombin, and thrombin.
- Its Kupffer's cells phagocytose bacteria and worn-out blood cells.
- It stores excess carbohydrates as glycogen. It stores copper, iron, and vitamins A, D, E, and K.

It stores or transforms poisons into less harmful substances.

It produces bile salts that emulsify or break down fats.

Liver Functions:

- Helps in the break down of carbohydrates
- Maintains blood sugar level
- Breaks down fatty acids – lipoproteins, cholesterol and phospholipids
- Breaks down amino acids
- Stores glycogen, iron and Vitamins A,D, B12
- Breaks down old and damaged RBC
- Removes toxins
- Secretes bile

Hepatocytes' functions include:

•Production of bile
•Processing bloodborne nutrients
•Storage of fat-soluble vitamins
•Detoxification
•Secreted bile flows between hepatocytes toward bile ducts in portal triads

Metabolic function

- **Carbohydrate metabolism**
  - **Gluconeogenesis**
  - **Glycogenolysis and glycogenesis**
- **Hormone metabolism**
- **Lipid Metabolism**
  - **Synthesis of fatty acids, cholesterol, lipoproteins**
  - **Ketogenesis**
- **Drug Metabolism**
- **Protein Metabolism**
  - **Synthesis of plasma proteins**
  - **Urea synthesis**

Storage function

- **Glycogen**
- **All fat-soluble vitamins (A, D, E, K) and some**
- **water soluble vitamins (B12)**
- **Iron**

Protection

Detoxification – converts noxious or insoluble compounds into less toxic or more water soluble forms

Kupffer cells ingest bacteria or other foreign material from blood

Liver Tests:

- Aminotransferases (AST/ALT)
- Alkaline Phosphatase
- Gammaglutamly Transpeptidase (GGTP)
- Bilirubin
- Total Protein/Albumin/Globulin
- Prothrombin Time (INR)

- Aminotransferases
  - **enzymes that leak when liver cells damaged**
  - **AST = aspartate aminotransferase**
  - **ALT = alanine aminotransferase**
  - **– ALT = more specific for liver disease**
  - **AST:ALT ratio: >2:1 alcoholic liver disease**
  - **pyridoxine (B6) = coenzyme in synthesis**
  - **– B6 deficiency: inhibits ALT>AST**
  - **Alcohol causes mitochondrial injury**
  - **– AST: cytosol & mitochondria**

- Alkaline Phosphatase (ALP)
  - **enzyme found in many body tissues**
  - **>80% in liver and bone**
  - **component of cells lining bile ducts**
  - **↑ ALP synthesis by liver in cholestasis**
  - **ALP >3-5X: cholestatic disease**
  - **doesn't differentiate intra/extrahepatic**
  - **t½ = 7d ∴↑ after several days**

Transaminases

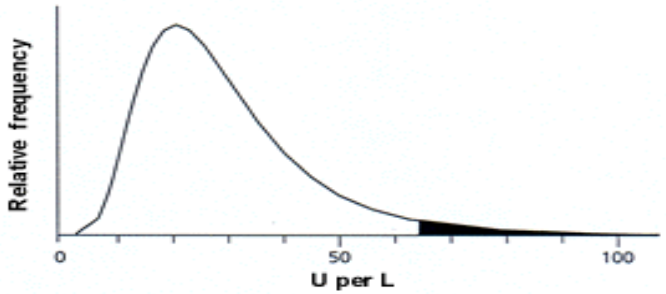
AST made in cytosol and mitochondria. ALT in cytosol only.
AST (aspartate aminotransferase) = SGOT
ALT (alanine aminotransferase) = SGPT

ALT is present in other tissues but just in lower levels

- Located in hepatocytes
  - Released after hepatocellular injury
- 2 Forms
  - AST
    - Non-specific to liver: heart, skeletal muscle, blood
  - ALT
    - More specific: elevated in myopathies

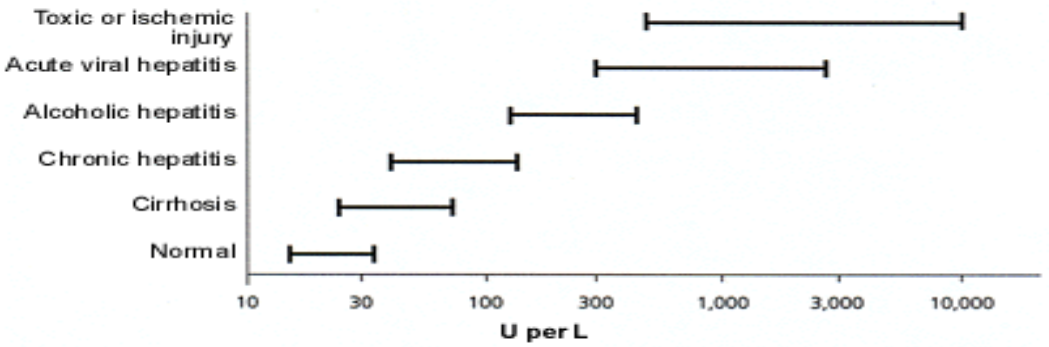
Transaminases

- May not be elevated in chronic liver disease
  - HCV- apoptosis
  - Cirrhosis
- Minimal ALT elevations (<1.5 X normal)
  - Race/Gender
  - Obesity
  - Muscle injury



Transaminases

- Mild elevations – more to come
- Marked elevations
  - Acute toxic injury- ie tylenol, ischemia
  - Acute viral disease
  - Alcoholic hepatitis

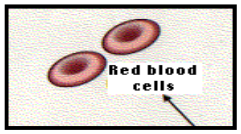


Transaminases

- AST:ALT ratio
  - Elevated in alcoholic disease
    - 2:1
    - If AST > 500 consider other cause
  - No alcohol use suggests cirrhosis

Extravascular Pathway for RBC Destruction

(Liver, Bone marrow,
& Spleen)



Phagocytosis & Lysis

Hemoglobin

Globin

Amino acids

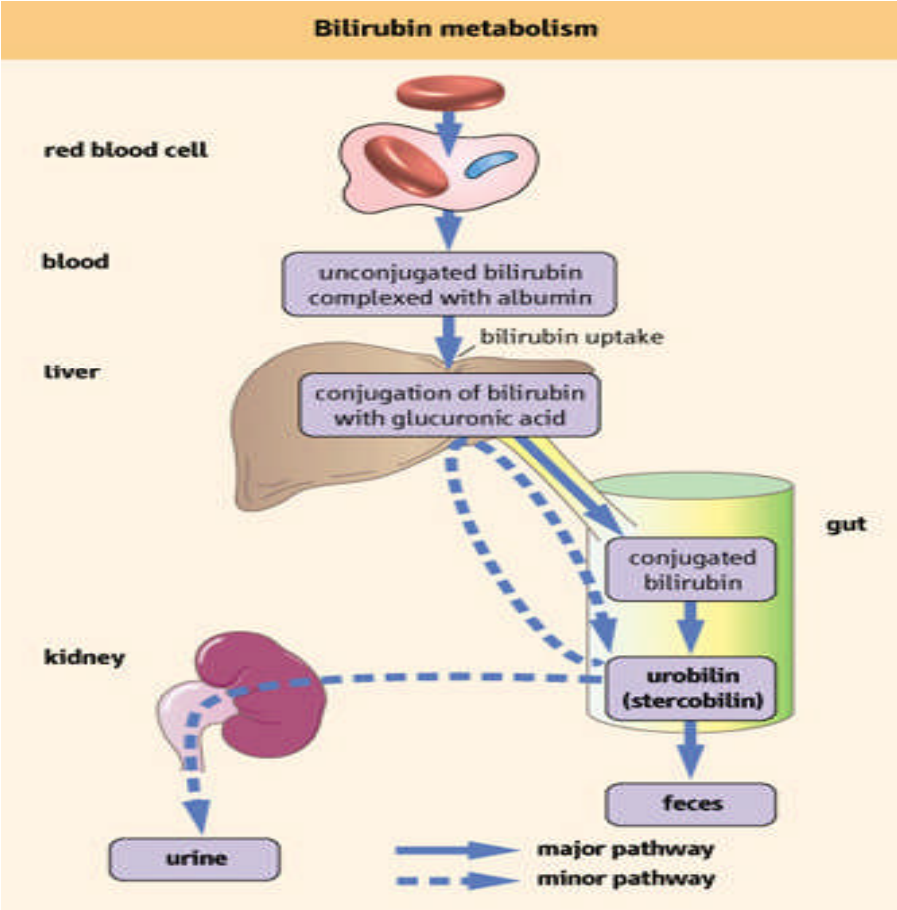
Amino acid pool

Heme → → **Bilirubin**

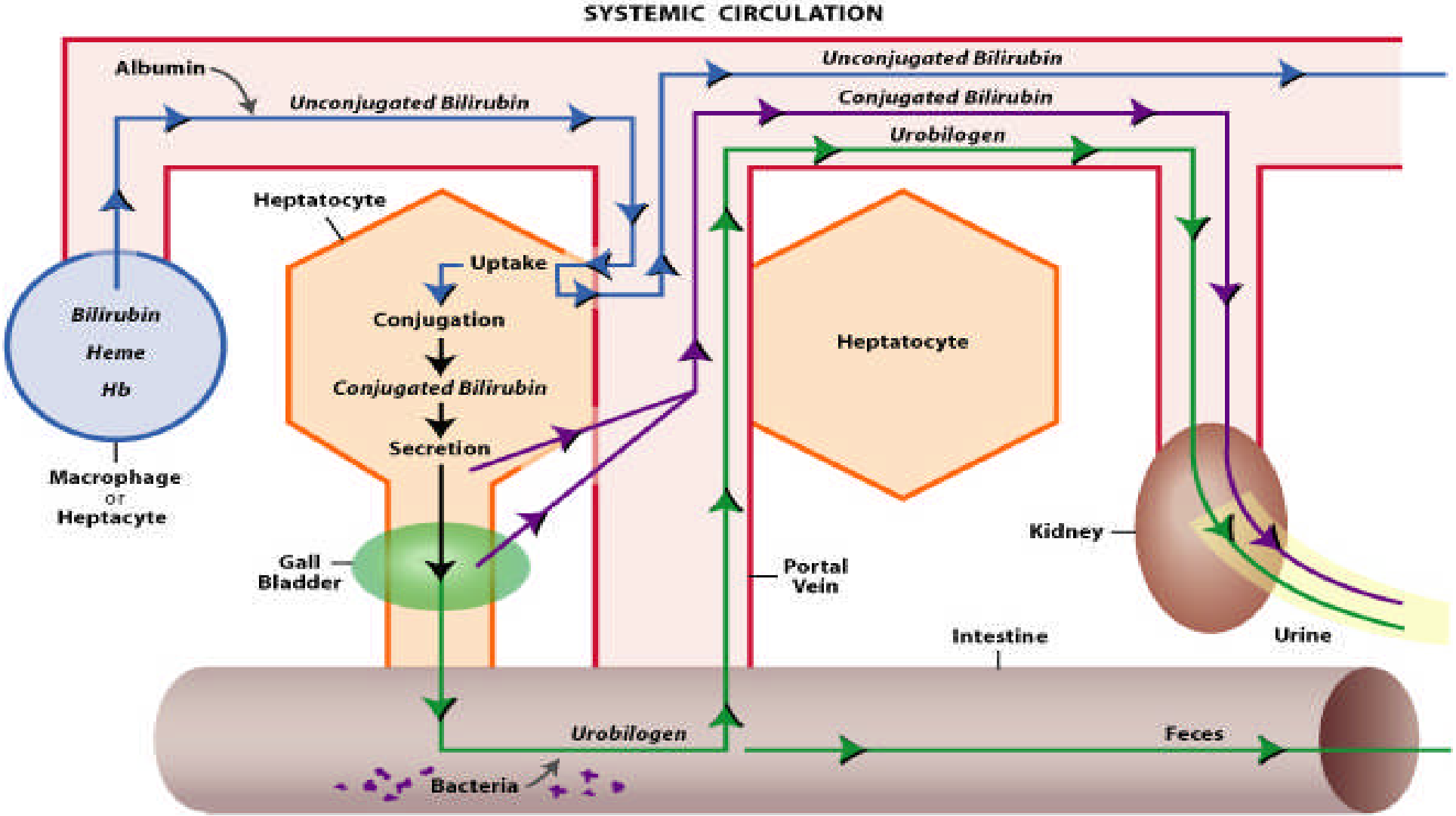
Fe^{2+}

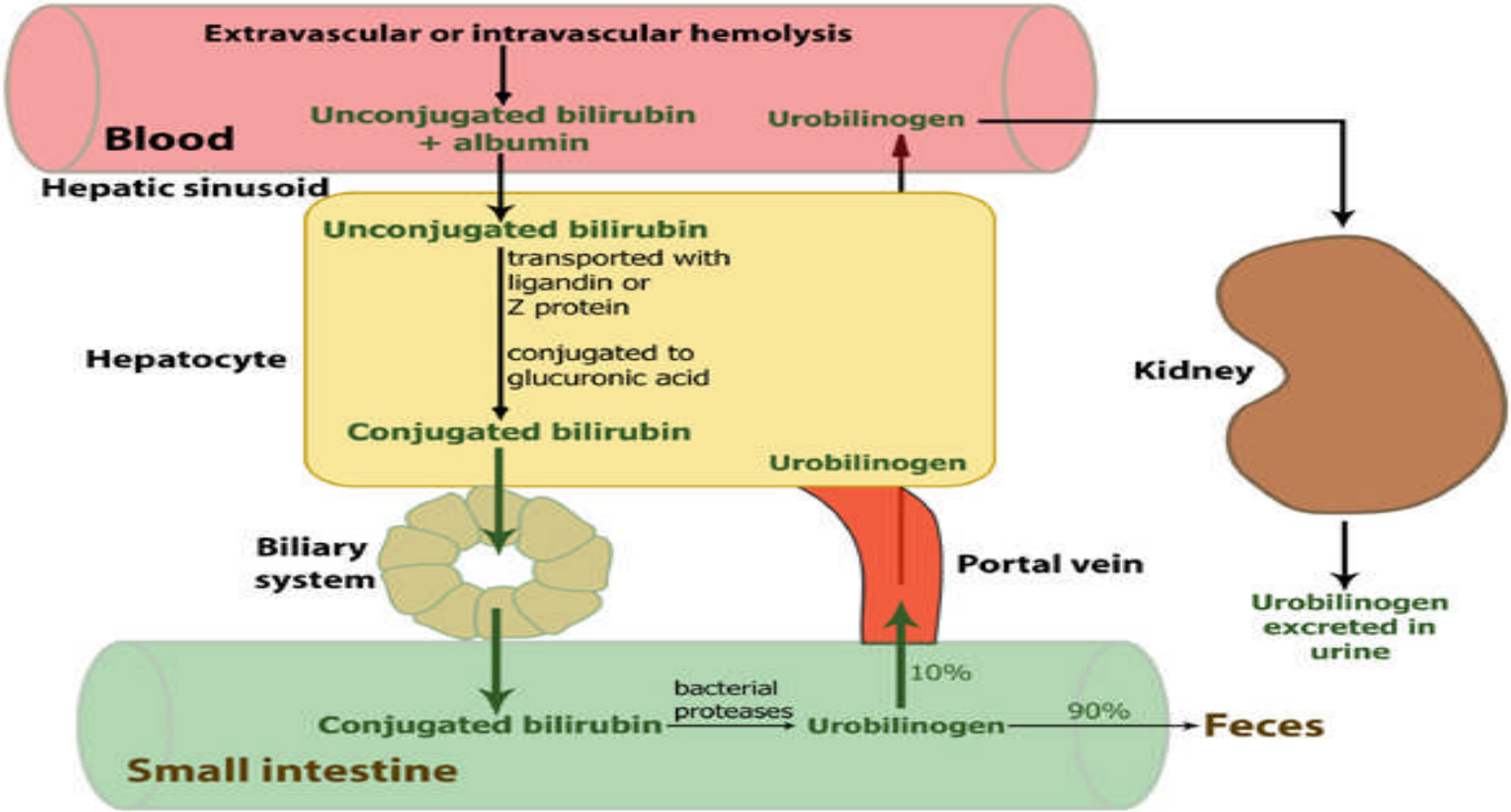
Excreted

NORMAL BILIRUBIN METABOLISM



- Uptake of bilirubin by the liver is mediated by a carrier protein (receptor)
- Uptake may be competitively inhibited by other organic anions
- On the smooth ER, bilirubin is conjugated with glucoronic acid, xylose, or ribose
- Glucoronic acid is the major conjugate - catalyzed by UDP glucuronyl tranferase
- "Conjugated" bilirubin is water soluble and is secreted by the hepatocytes into the biliary canaliculi
- Converted to stercobilinogen (urobilinogen) (colorless) by bacteria in the gut
- Oxidized to stercobilin which is colored
- Excreted in feces
- Some stercobilin may be re-adsorbed by the gut and re-excreted by either the liver or kidney


SYSTEMIC CIRCULATION
Albumin
Unconjugated Bilirubin
Unconjugated Bilirubin
Conjugated Bilirubin
Urobilogen
Heptatocyte
Uptake
Conjugation
Conjugated Bilirubin
Secretion
Bilirubin
Heme
Hb
Macrophage
or
Heptacyte
Heptatocyte
Gall
Bladder
Portal
Vein
Kidney
Urine
Intestine
Urobilogen
Feces
Bacteria


Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

The causes of jaundice

Type	Cause	Clinical example	Frequency
Prehepatic	hemolysis	autoimmune abnormal hemoglobin	uncommon depends on region
intrahepatic	infection	hepatitis A, B, C	common/very common
	chemical/drug	acetaminophen alcohol	common common
	genetic errors: bilirubin metabolism	Gilbert's syndrome Crigler–Najjar syndrome Dubin–Johnson syndrome Rotor's syndrome	1 in 20 very rare very rare very rare
	genetic errors: specific proteins	Wilson's disease α_1 antitrypsin	1 in 200 000 1 in 1000 with genotype
	autoimmune	chronic active hepatitis	uncommon/ rare
	neonatal	physiologic	very common
Posthepatic	intrahepatic bile ducts	drugs primary bilary cirrhosis cholangitis	common uncommon common
	extrahepatic bile ducts	gall stones pancreatic tumor cholangiocarcinoma	very common uncommon rare

Differential diagnosis of jaundice

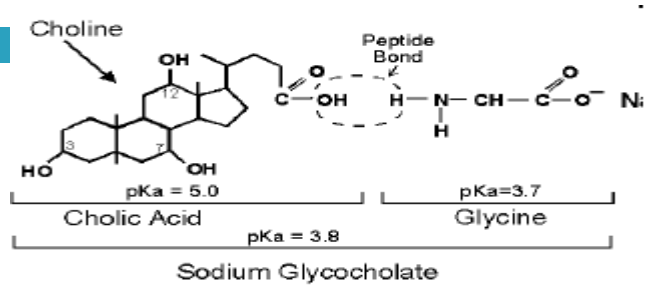
	Prehepatic	Intrahepatic	Posthepatic
conjugated bilirubin	absent	↑	↑
AST or ALT	normal	↑	normal
ALP	normal	normal	↑
urine bilirubin	absent	present	present
urine urobilinogen	present	present	absent

Bile

- Yellowish green liquid
- Make up: bile salts, bile pigments, cholesterol and electrolytes.
- Bile salts – breaks down fat into smaller molecules.

Components of Bile

- 50% Bile Acids (Cholic, chenodeoxycholic, deoxycholic, and lithocholic acid
  - Product of Cholesterol + 7a-Hydroxylase, most is recycled from distal ileum
  - Form micelles- amphipathic
  - pK= approx. 7 if unconjugated
  - conjugated to taurine or glycine- pK goes down, allows them to be soluble in the intestine ☺
- Phospholipids (lecithin)
  - solubilized by bile salts
- Cholesterol
- Bile pigments
  - bilirubin glucuronide



- **Composition of Bile** A yellow-green, alkaline solution containing bile salts, bile pigments, cholesterol, neutral fats, phospholipids, and electrolytes
- Bile salts are cholesterol derivatives that:
  - Emulsify fat
  - Facilitate fat and cholesterol absorption
  - Help solubilize cholesterol
- Enterohepatic circulation recycles bile salts
- The chief bile pigment is bilirubin, a waste product of heme

- Regulation of Bile Release Acidic, fatty chyme causes the duodenum to release:
  - Cholecystokinin(CCK) and secretin into the bloodstream
- Bile salts and secretin transported in blood stimulate the liver to produce bile
- Vagal stimulation causes weak contractions of the gallbladder
- **Cholecystokinin causes:**
  - **The gallbladder to contract**
  - **The hepatopancreatic sphincter to relax**
- As a result, bile enters the duodenum

Regulation of Bile Release

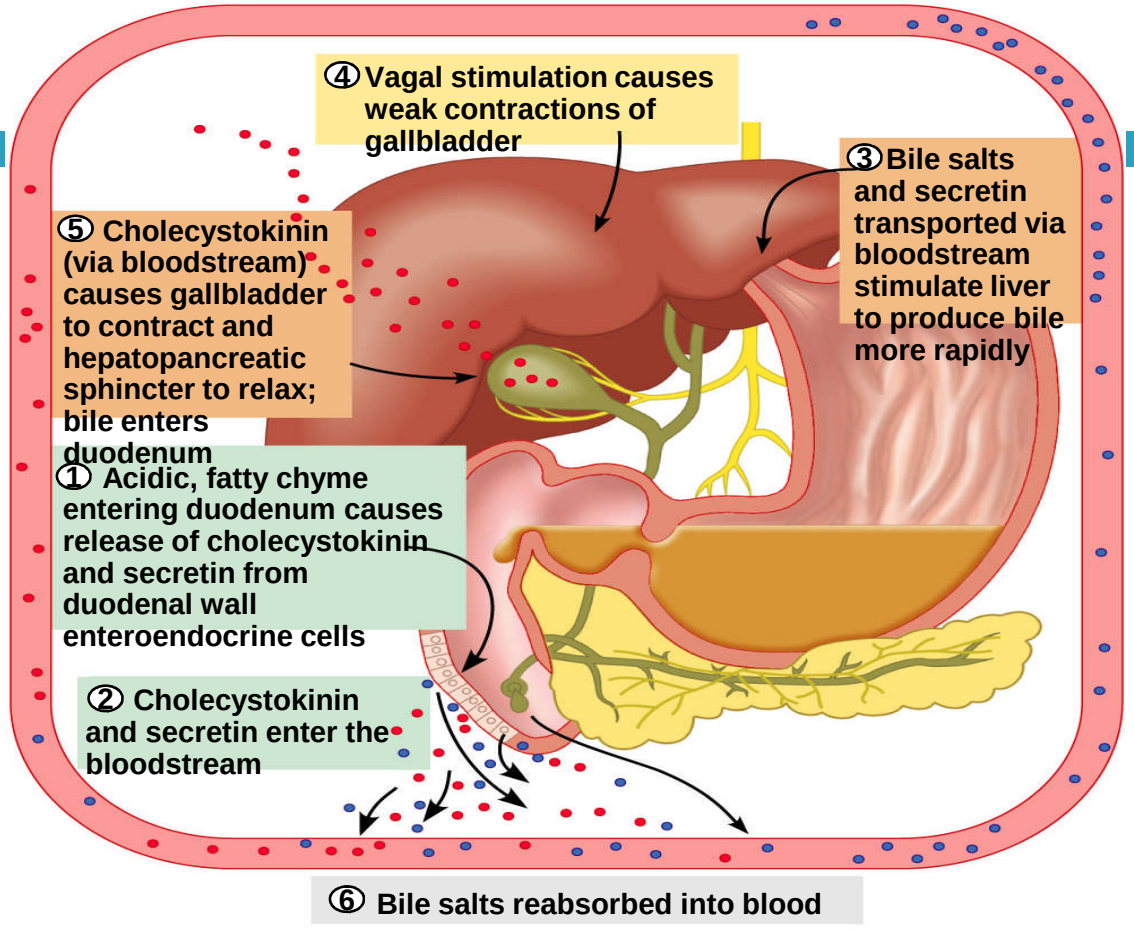


Figure 23.25

BILE

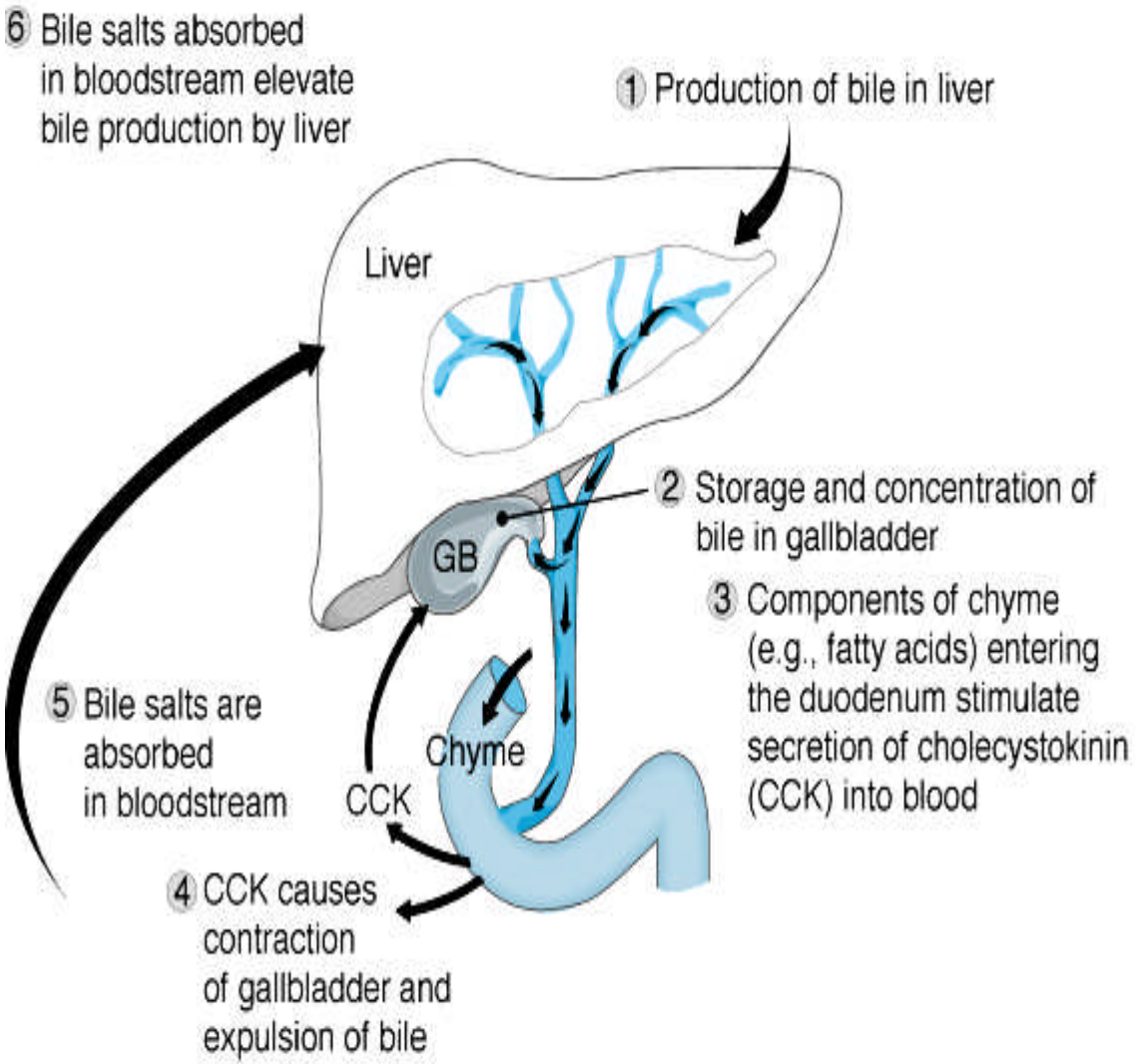
COMPONENTS:

- **BILE SALTS, (formed in the liver from cholesterol) are the most essential part of bile.**
- **BILE PIGMENTS-The pigment bilirubin (red) and biliverdin (green), derived from hemoglobin, give bile its greenish color because it secretes bile into ducts.**
- **CHOLESTEROL**
- **PHOSPHOLIPIDS**

FUNCTIONS OF BILE

1. It breaks down the fats that you eat so that your body can utilize them.
2. Bile is a very powerful antioxidant which helps to remove toxins from the liver.

hepatic artery and **hepatic portal vein**
drain through the
leaky liver sinusoids
⇓
The sinusoids drain into the **central vein**
⇓
Bile flows back through the bile canaliculi
into the bile duct
⇓
stored in the gallbladder
⇓
Cholecystokinin (CCK) is releases bile



Movement of bile

liver

⬇

common hepatic duct

⬇

gall bladder

⬇

cystic duct

⬇

bile duct

⬇

hepatopancreatic sphincter

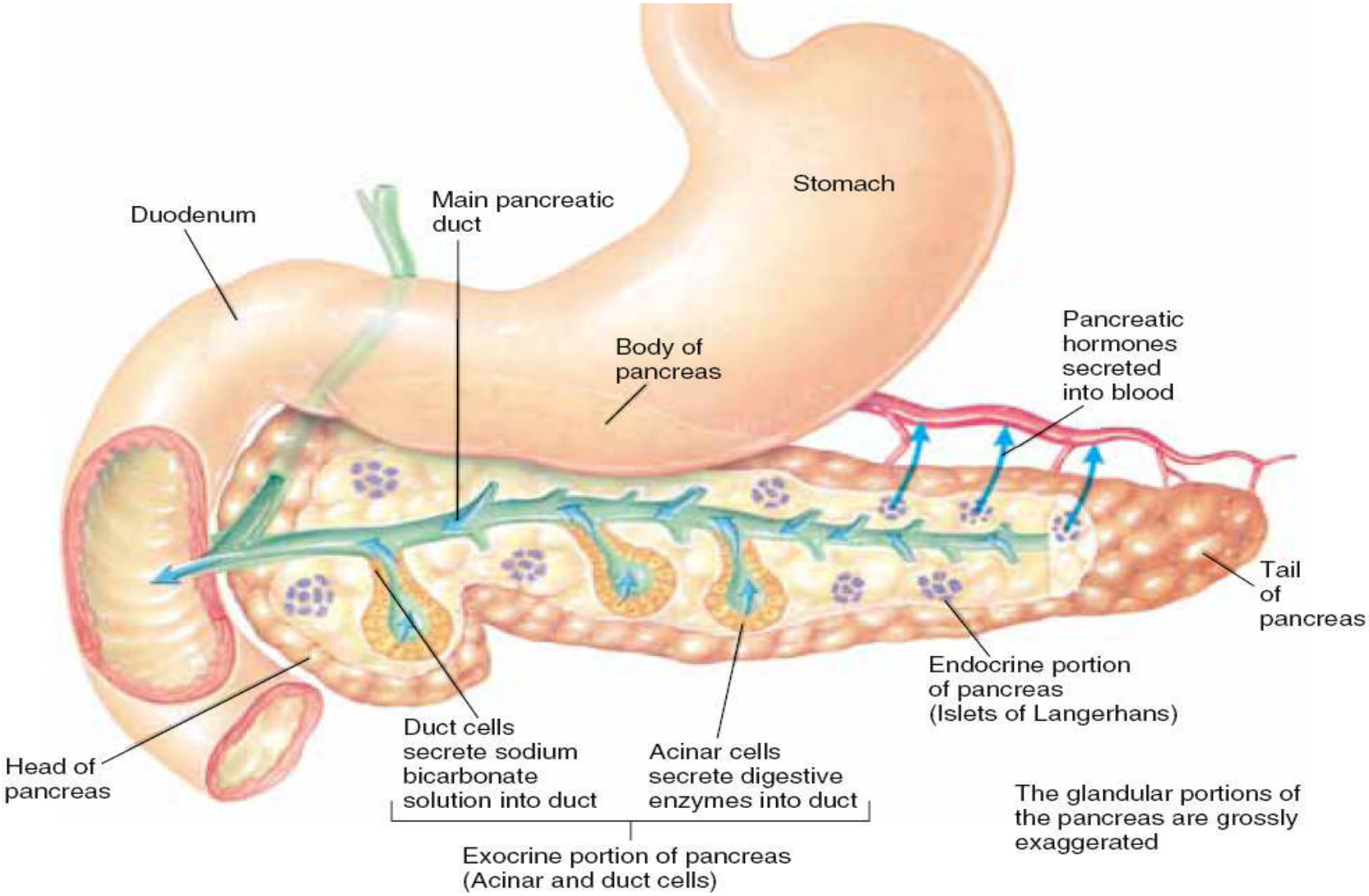
⬇

small intestine

Pancreatic juice is composed of two secretory products critical to proper digestion: digestive enzymes and bicarbonate.

The enzymes are synthesized and secreted from the exocrine acinar cells, whereas bicarbonate is secreted from the epithelial cells lining small pancreatic ducts.

PANCREATIC PHYSIOLOGY


Stomach
Duodenum
Main pancreatic duct
Body of pancreas
Pancreatic hormones secreted into blood
Tail of pancreas
Endocrine portion of pancreas (Islets of Langerhans)
Head of pancreas
Duct cells secrete sodium bicarbonate solution into duct
Acinar cells secrete digestive enzymes into duct
Exocrine portion of pancreas (Acinar and duct cells)
The glandular portions of the pancreas are grossly exaggerated

- The endocrine cells are the islets of Langerhans:
  - Alpha cells – Glucagon
  - Beta cells – Insulin
  - Both of above regulated by serum blood sugar.
  - Delta cells – Gastrin and other polypeptide hormones

Functions

Most (> 80%) of the cells in the pancreas are involved in the exocrine activity of the organ:

- The production and export of inactive precursors, known collectively as the zymogens, for twenty major digestive enzymes including proteases, lipases, nucleases, and amylase. The pancreas produces more protein per gram of tissue than any other organ.
- The secretion of a bicarbonate-rich alkaline fluid (1200 ml/day in humans) which functions to neutralize the acidic chyme produced in the stomach. The alkalinization is necessary for digestive enzyme activity.

The remainder of the cells are responsible for the production of hormones (predominantly insulin and glucagon) that are released into the blood stream (endocrine function). They are organized in the islets of Langerhans

- **Exocrine function** - Secretes pancreatic juice which breaks down all categories of foodstuff Water solution of enzymes and electrolytes (primarily HCO3-)
  - Neutralizes acid chyme
  - Provides optimal environment for pancreatic enzymes
- **Enzymes are released in inactive form and activated in the duodenum**
  - Examples include
    - Trypsinogen is activated to trypsin
    - Procarboxypeptidase is activated to carboxypeptidase
- **Active enzymes secreted**
  - Amylase, lipases, and nucleases
  - These enzymes require ions or bile for optimal activity
- **The pancreas also has an endocrine function - release of insulin and glucagon**
- Regulation of Pancreatic Secretion Secretin and CCK are released when fatty or acidic chyme enters the duodenum
- CCK and secretin enter the bloodstream
- Upon reaching the pancreas:
  - CCK induces the secretion of enzyme-rich pancreatic juice
  - Secretin causes secretion of bicarbonate-rich pancreatic juice
- Vagal stimulation also causes release of pancreatic juice

Pancreatic Secretions:

- **Hydrelatic**
  - HCO_3^- rich aqueous fluid
  - neutralizes stomach HCl
  - dilutes the chyme
- **Ecbolic**
  - enzyme rich secretion
  - Proteases - endopeptidases
  - **Trypsinogen ---> trypsin**
  - **Chymotrypsinogen --> chymotrypsin**
  - Proelastase --> elastase
  - Proteases - exopeptidases
  - Procarboxypeptidase --> carboxypeptidase
  - Proaminopeptidase --> aminopeptidase
  - **amylase**
  - **Lipases**
  - Ribonuclease
  - Deoxyribonuclease

Protease Activation

• Pancreatic secretion contains trypsinogen and trypsin inhibitor

• Enterokinase in intestine activates trypsin

• Trypsin inhibitor is diluted by chyme

Hormonal Regulation of Pancreatic Secretion

• Secretin

peptide hormone

pancreatic secretion rich in $HCO3^-$

• Cholecystokinin (CCK)

peptide hormone (33 amino acids)

pancreatic secretion rich in enzyme

Pancreatic Secretion:

- • **Cephalic Phase**
  Sight, taste, smell of food
  Release of ACh & gastrin in response to vagal stimulation
  Increased pancreatic flow, especially ecbolic
- • **Gastric Phase**
  Protein in chyme --> gastrin
  Gastric distention --> ACh from vagus
  Increased pancreatic secretion, esp. ecbolic
- • **Intestinal Phase**
  Acid in chyme --> secretin
  hydrelatic secretion
  Long chain fatty acids & amino acids and peptides in chyme
  CCK & vagovagal reflex
  ecbolic secretion
- **Bile from the Liver**

Bile Acids
Primary from cholesterol by addition of OH and COOH
Secondary formed in intestine by resident bacteria
conjugated to taurine or glycine
Bile Flow
Released as CCK causes contraction of gall bladder and relxation of Sphincter of Oddi
CCK (33 amino acid hormone) released in response to fatty acids and lipids in chyme

Pancreatic and Bile Secretions

- Acid in Duodenum activates Secretion of Secretin to initiate HCO_3^- secretion
- AA, Lipids stimulate Gastrin (quick response) and CCK (prolonged response) to initiate pancreatic enzyme secretion.
- CCK also causes GB contraction, Sphincter of Oddi relaxation, and increased Bile Salt excretion by the liver.

Physiology – Exocrine Pancreas

- Secretion of water and electrolytes originates in the centroacinar and intercalated duct cells
- Pancreatic enzymes originate in the acinar cells
- Final product is a colorless, odorless, and isosmotic **alkaline** fluid that contains digestive enzymes (amylase, lipase, and trypsinogen)

Physiology – Exocrine Pancreas

- 500 to 800 ml pancreatic fluid secreted per day
- Alkaline pH results from secreted bicarbonate which serves to neutralize gastric acid and regulate the pH of the intestine
- Enzymes digest carbohydrates, proteins, and fats

Bicarbonate Secretion

- Centroacinar cells and ductular epithelium secrete 20 mmol of bicarbonate per liter in the basal state
- Fluid (pH from 7.6 to 9.0) acts as a vehicle to carry inactive proteolytic enzymes to the duodenal lumen
- Sodium and potassium concentrations are constant and equal those of plasma
- Chloride secretion varies inversely with bicarbonate secretion

Bicarbonate Secretion

- Bicarbonate is formed from carbonic acid by the enzyme carbonic anhydrase
- Major stimulants

  Secretin, Cholecystokinin, Gastrin, Acetylcholine
- Major inhibitors

  Atropine, Somatostatin, Pancreatic polypeptide and Glucagon
- Secretin - released from the duodenal mucosa in response to a duodenal luminal pH < 3

Enzyme Secretion

- Acinar cells secrete isozymes
  - amylases, lipases, and proteases
- Major stimulants
  - Cholecystokinin, Acetylcholine, Secretin, VIP
- Synthesized in the endoplasmic reticulum of the acinar cells and are packaged in the zymogen granules
- Released from the acinar cells into the lumen of the acinus and then transported into the duodenal lumen, where the enzymes are activated.

Enzymes

- Amylase
  - only digestive enzyme secreted by the pancreas in an active form
  - functions optimally at a pH of 7
  - hydrolyzes starch and glycogen to glucose, maltose, maltotriose, and dextrins
- Lipase
  - function optimally at a pH of 7 to 9
  - emulsify and hydrolyze fat in the presence of bile salts

Enzymes of Pancreas

- Proteases
  - essential for protein digestion
  - secreted as proenzymes and require activation for proteolytic activity
  - duodenal enzyme, enterokinase, converts trypsinogen to trypsin
  - Trypsin, in turn, activates chymotrypsin, elastase, carboxypeptidase, and phospholipase
- Within the pancreas, enzyme activation is prevented by an antiproteolytic enzyme secreted by the acinar cells

Insulin

- Synthesized in the B cells of the islets of Langerhans
- 80% of the islet cell mass must be surgically removed before diabetes becomes clinically apparent
- Proinsulin, is transported from the endoplasmic reticulum to the Golgi complex where it is packaged into granules and cleaved into insulin and a residual connecting peptide, or C peptide

Insulin

- Major stimulants
  - Glucose, amino acids, glucagon, GIP, CCK, sulfonylurea compounds, β-Sympathetic fibers
- Major inhibitors
  - somatostatin, amylin, pancreastatin, α-sympathetic fibers

Glucagon

- Secreted by the A cells of the islet
- Glucagon elevates blood glucose levels through the stimulation of glycogenolysis and gluconeogenesis
- Major stimulants
  - Aminoacids, Cholinergic fibers, β-Sympathetic fibers
- Major inhibitors
  - Glucose, insulin, somatostatin, α-sympathetic fibers

Somatostatin

- Secreted by the D cells of the islet
- Inhibits the release of growth hormone
- Inhibits the release of almost all peptide hormones
- Inhibits gastric, pancreatic, and biliary secretion
- Used to treat both endocrine and exocrine disorders

To resume

TABLE 8–2. Summary of Gastrointestinal Hormones

Hormone	Hormone Family	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	Gastrin-CCK	G cells of the stomach	Small peptides and amino acids Distention of the stomach Vagal stimulation (GRP)	↑ Gastric H^+ secretion Stimulates growth of gastric mucosa
Cholecystokinin (CCK)	Gastrin-CCK	I cells of the duodenum and jejunum	Small peptides and amino acids Fatty acids	↑ Pancreatic enzyme secretion ↑ Pancreatic HCO_3^- secretion Stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi Stimulates growth of the exocrine pancreas and gallbladder Inhibits gastric emptying
Secretin	Secretin-glucagon	S cells of the duodenum	H^+ in the duodenum Fatty acids in the duodenum	↑ Pancreatic HCO_3^- secretion ↑ Biliary HCO_3^- secretion ↓ Gastric H^+ secretion Inhibits trophic effect of gastrin on gastric mucosa
Gastric inhibitory peptide (GIP)	Secretin-glucagon	Duodenum and jejunum	Fatty acids Amino acids Oral glucose	↑ Insulin secretion from pancreatic β cells ↓ Gastric H^+ secretion

Dr. Alzoghaibi presentation

TABLE 8–1. Neurotransmitters and Neuromodulators in the Enteric Nervous System

Substance	Source	Actions
Acetylcholine (ACh)	Cholinergic neurons	Contraction of smooth muscle in wall Relaxation of sphincters ↑ Salivary secretion ↑ Gastric secretion ↑ Pancreatic secretion
Norepinephrine (NE)	Adrenergic neurons	Relaxation of smooth muscle in wall Contraction of sphincters ↑ Salivary secretion
Vasoactive intestinal peptide (VIP)	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↑ Intestinal secretion ↑ Pancreatic secretion
Gastrin-releasing peptide (GRP) or bombesin	Neurons of gastric mucosa	↑ Gastrin secretion
Enkephalins (opiates)	Neurons of mucosa and smooth muscle	Contraction of smooth muscle ↓ Intestinal secretion
Neuropeptide Y	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↓ Intestinal secretion
Substance P	Cosecreted with ACh	Contraction of smooth muscle ↑ Salivary secretion

Regulation of Gastric Activity

1. Cephalic Phase
2. Gastric Phase
3. Intestinal Phase

1. CephalicPhase

a) Begins with smelling, thinking, taste about food
b) Stimulates the production of gastric juices

c) This is a short lived phase

2. Gastric Phase

a) Begins with arrival of food

b) Stimuli include

(1) Distension of the stomach

(2) Increase in pH of stomach contents

(3) Presence of undigested materials

c) Lasts about 3-4 hours

d) Main action is to release more products from chief cells and parietal cells

(1) Also increased muscle contractions to mix chyme

e) Neural response – stimulation by chemo and stretch receptors coordinate short reflexes and chief and parietal cell releases

f) Hormonal response – gastrin enters the capillaries at the stomach and stimulate chief and parietal cells

3. Intestinal Phase

a) Starts when chyme enters the small intestine

b) Small amounts of liquidy material is squirted into the small intestines

c) Lasts a long time

d) Primary action is to inhibit gastric acid and pepsinogen production, reduction of gastric mixing

e) Hormonal response – stimulation of CCK (cholecystokinin) and gastric inhibitory peptide (GIP)

f) Release of buffers in the small intestine to bring the pH back up

Enzymes of the Small Intestine

(1) Enterokinase – activates proenzymes secreted by the pancreas

(2) Gastrin, cholecystokinin and secretin

Intestinal Hormones

1. Enterocrinin – hormone stimulates the Submucosal glands

2. Secretin – cause an increase in the secretion of bile and buffers
a) Secondarily reduces gastric motility and secretory rates (to duodenum)

3. Cholecystokinin – accelerates the secretion of all digestive enzymes
a) Increase pancreatic enzymes
b) Push pancreatic secretions and bile into duodenum

4. Gastric Inhibitory Peptide
a) Inhibit gastric activity [Glucose dependent]
b) Activates the Submucosal glands
c) Works to make glucose go into the blood and target the fat cells

5. Gastrin – facilitates large amounts of protein enzymes to be released

Small Intestine

- **Mucosa**
- Absorptive cells
- Goblet cells -- mucous
- Enteroendocrine cells -- cholecystokinin (CCK), secretin
- GIP - glucose dependent insulinotropic peptide
- Somatostatin
- Intestinal crypts (Crypts of Lieberkühn)
-
- **Submucosa**
- Brunner's glands in duodenum - alkaline secretion
- Peyer's patches in ileum.
- 5. Surface area increasing structures - plicae circulares, villi, microvilli
- 6. Segmentation and Peristalsis

Main Functions of Small Intestine

Digestion - various enzymes:

- 1. peptidases – protein digestion
- 2. *sucrase*, maltase and lactase – sugar digestion
- 3. *lipase* – fat digestion

Absorption – performed by villi (small fingerlike projections)

Release of waste to large intestine

Liver Functions:

- Helps in the break down of carbohydrates
- Maintains blood sugar level
- Breaks down fatty acids – lipoproteins, cholesterol and phospholipids
- Breaks down amino acids
- Stores glycogen, iron and Vitamins A,D, B12
- Breaks down old and damaged RBC
- Removes toxins
- Secretes bile

Bile

- Yellowish green liquid
- Make up: bile salts, bile pigments, cholesterol and electrolytes.
- Bile salts – breaks down fat into smaller molecules.

Functions of Large Intestine

- Absorbs water and electrolytes
- Contain intestinal flora (bacteria) – break down some of the molecules not broken down in the small intestine

a. Bacteria use the materials for energy they make certain vitamins like K, thiamine, riboflavin and B12 – absorbed through intestine wall

Feces

- Makeup: water, undigested food, electrolytes, mucous, shed intestinal cells, and bacteria
- 75% water
- Odor – usually a result of bacterial action