DIGESTION

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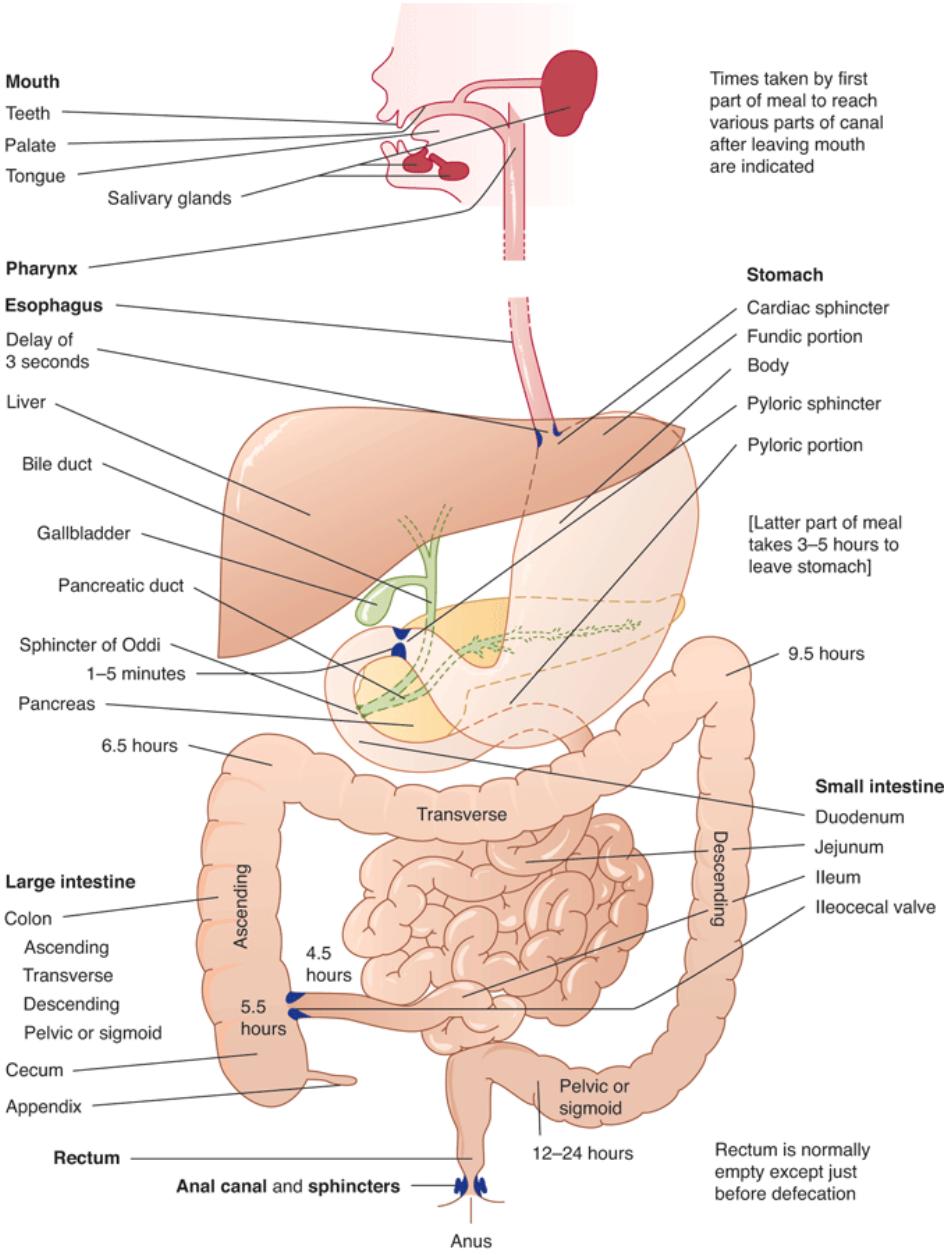


Progress of food along the alimentary canal. Food undergoes mechanical as well as chemical changes to render it suitable for absorption and assimilation.

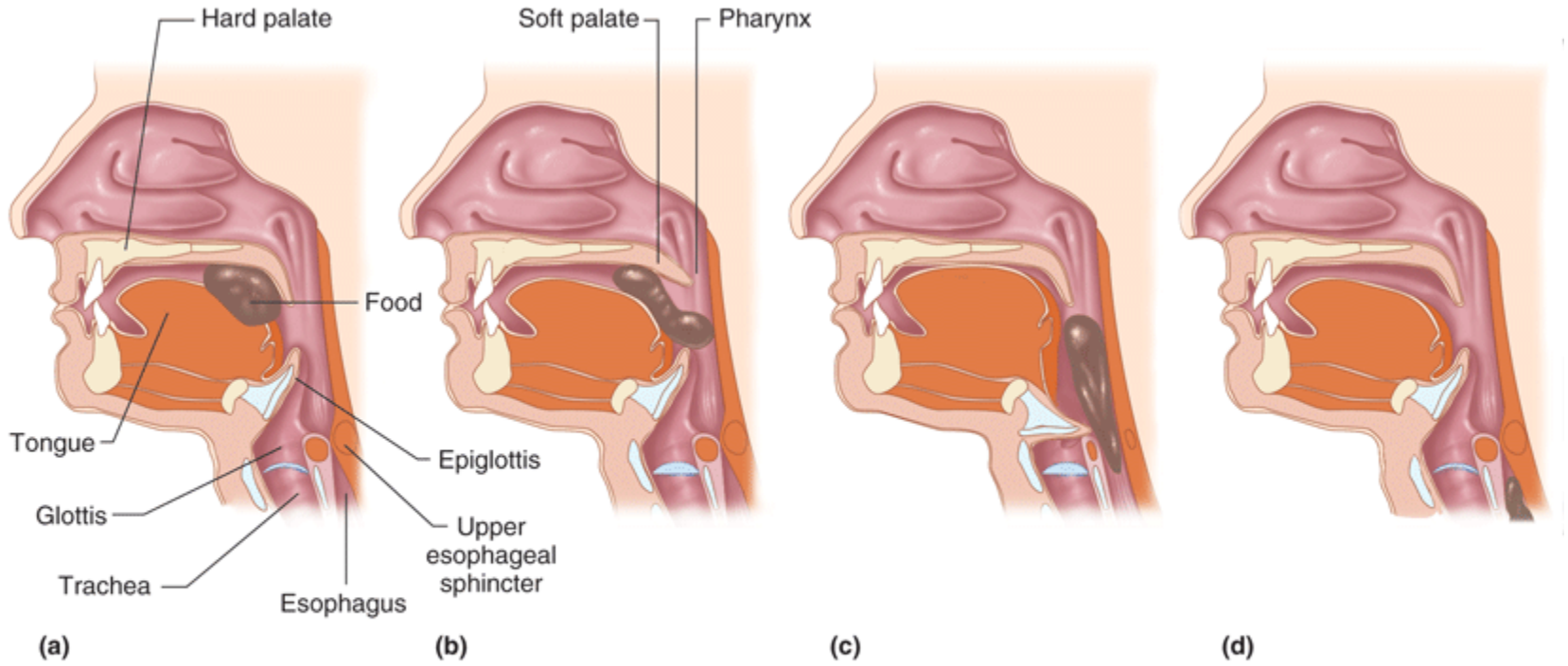
(Redrawn, with permission, from Mackenna BR, Callander R. *Illustrated Physiology*, 6th ed. Churchill Livingstone, 1997.)

Fig. 13-1 Accessed 08/01/2010

Digestion

- Swallowing is coordinated in the medulla.
- In swallowing, a food bolus is pushed to the posterior pharynx by the tongue.
- The soft palate moves upward to prevent reflux into nasal cavities.
- The palatopharyngeal folds narrow to create a small passageway for passage of food.
- The vocal cords tighten and the larynx moves upward, causing the epiglottis to swing backward over the opening to the larynx. (The glottis closes to prevent passage into the trachea.)

Swallowing



Fig/ 28-3 Accessed 03/01/2010

Digestion

- Digestion begins in the mouth with mechanical breakdown of the food (mastication).
- The salivary glands produce 1.5L saliva daily.
- In low flow states, saliva is hypotonic relative to plasma. Na^+ and Cl^- are high; K^+ levels are low.
- In high flow states, saliva is isotonic. Na^+ and Cl^- levels are low while K^+ is high.
- pH is between 6-7.

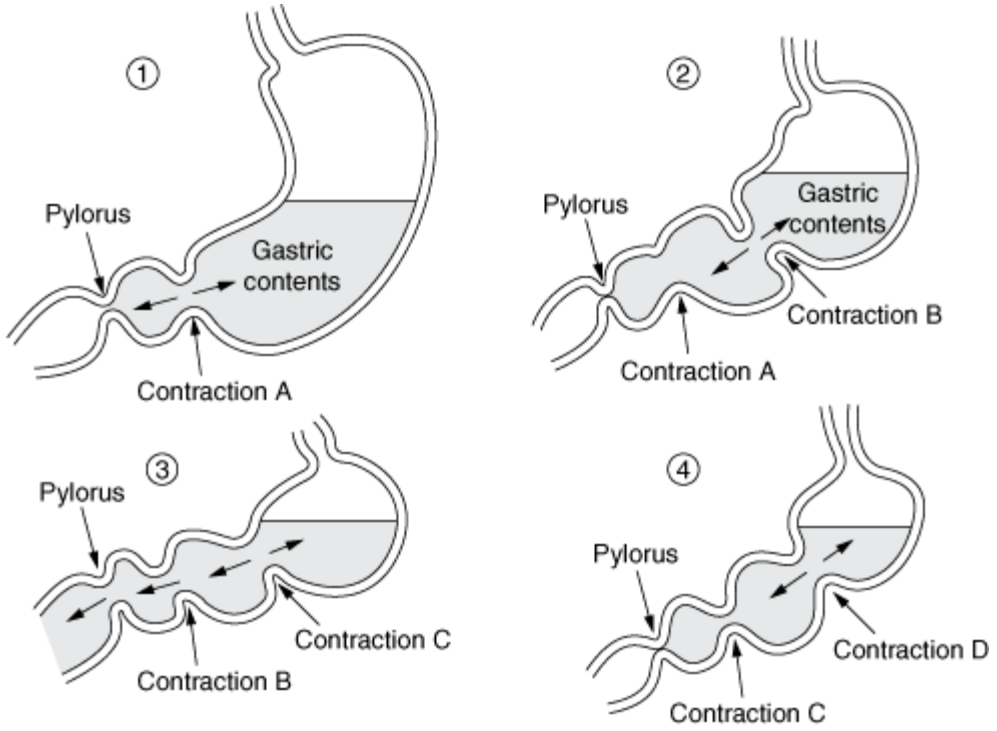
Digestion

- An increase in watery saliva is mediated by CN VII and CN IX from the superior and inferior salivatory nuclei in the brain stem via muscarinic receptors (parasympathetic).
- An increase in viscous saliva is mediated via the T1-T3 nerves of the superior cervical ganglion via β-adrenergic receptors (sympathetic).
- Contains ptyalin (α-amylase). Begins digestion of carbohydrates by hydrolyzing α-1,4 bonds. Inactivated by low gastric pH.
- Lingual lipase begins breakdown of lipids. It can cleave fatty acids from all three positions on a triglyceride (in contrast to pancreatic lipase).

Digestion

- The upper esophageal sphincter relaxes (resting pressure is 100 torr).
- Peristalsis directs food to the stomach.
- The lower esophageal sphincter relaxes (resting pressure, 20).
- Proximal stomach receptively relaxes. Vagal control.
- The stomach contracts 3-5/minute. Vagal stimulation increases; sympathetic stimulation (celiac plexus) decreases contractions.

Gastric motility



Gastric pacemaker at midpoint of wall of greater curvature

Fig. 8-5 Accessed 02/01/2010

Digestion

- Hypotonic or hypertonic food, low duodenal pH delay gastric emptying as does the release of cholecystokinin in response to a lipid meal.
- Gastrin is released in response to stomach distention. Later, to presence of protein in the duodenum.
- As the food passes into the intestine, secretin, somatostatin, gastric inhibitory peptide, and vasoactive intestinal peptide inhibit gastric secretion.

Gastric emptying

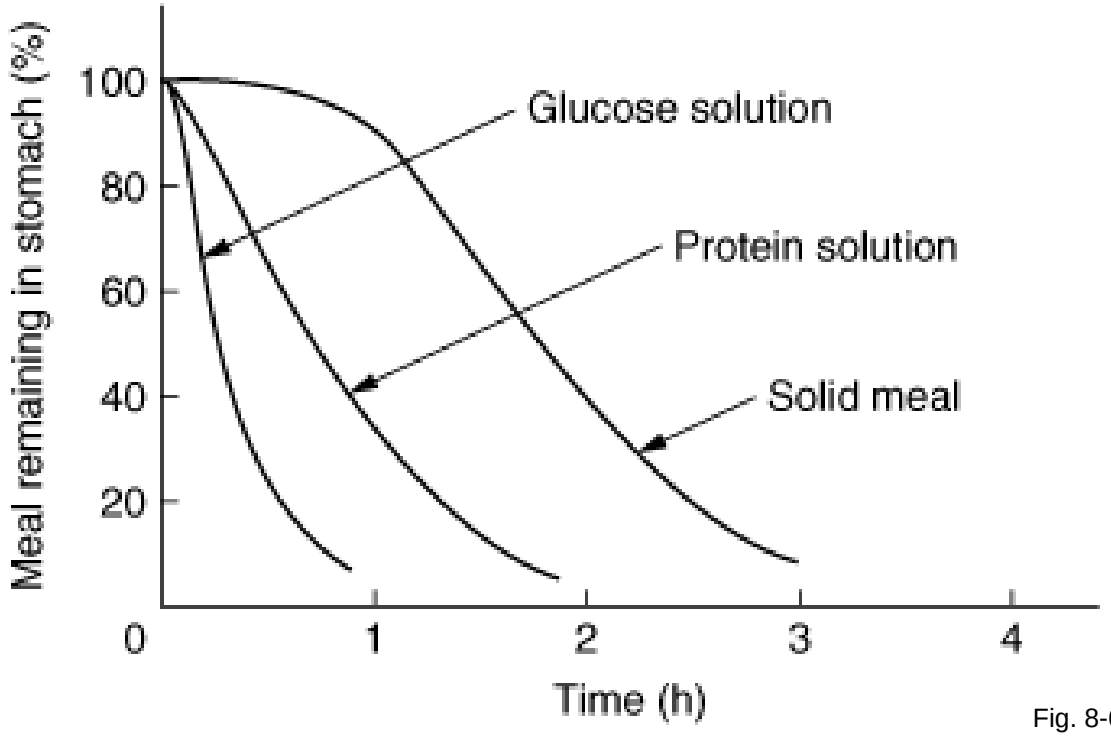


Fig. 8-6 Accessed 02/01/2010

Source: Barrett KE: *Gastrointestinal Physiology*:
http://www.accessmedicine.com

Enteric nervous system

- The enteric nervous system extends from the mid-region of the esophagus to the anal canal.
- The dorsal nucleus of the vagus provides the pre-ganglionic parasympathetic supply to the gut with the exception of distal colon and anus. That is derived from the pelvic-splanchnic nerves (S2-4). Intramural ganglion cells are located in both intramural plexes.
- Acetylcholine is the principal excitatory transmitter with substance P; GABA, nitric oxide, VIP inhibit.

Enteric nervous system

- In the myenteric plexus, inhibitory and excitatory nerves control the function of the circular and longitudinal muscle layers. There are also ascending and descending interneurons that relay information through the myenteric plexus along the length of the gastrointestinal tract. Cell bodies of primary afferent neurons responding to specific chemical characteristics of the lumen, or to stretch, have cell bodies in myenteric ganglia.

Enteric nervous system

- In the submucosal plexus, secreto-motor neurons regulate the secretion of fluid and electrolytes and contractions of the muscularis mucosa. “Mechanosensitive" nerves have their cell bodies in the submucosal plexus.
- Every 90-120 minutes while fasting, the stomach and small intestine contract in sequence (migrating motility complex, mediated by motilin, produced by enterochromaffin cells).

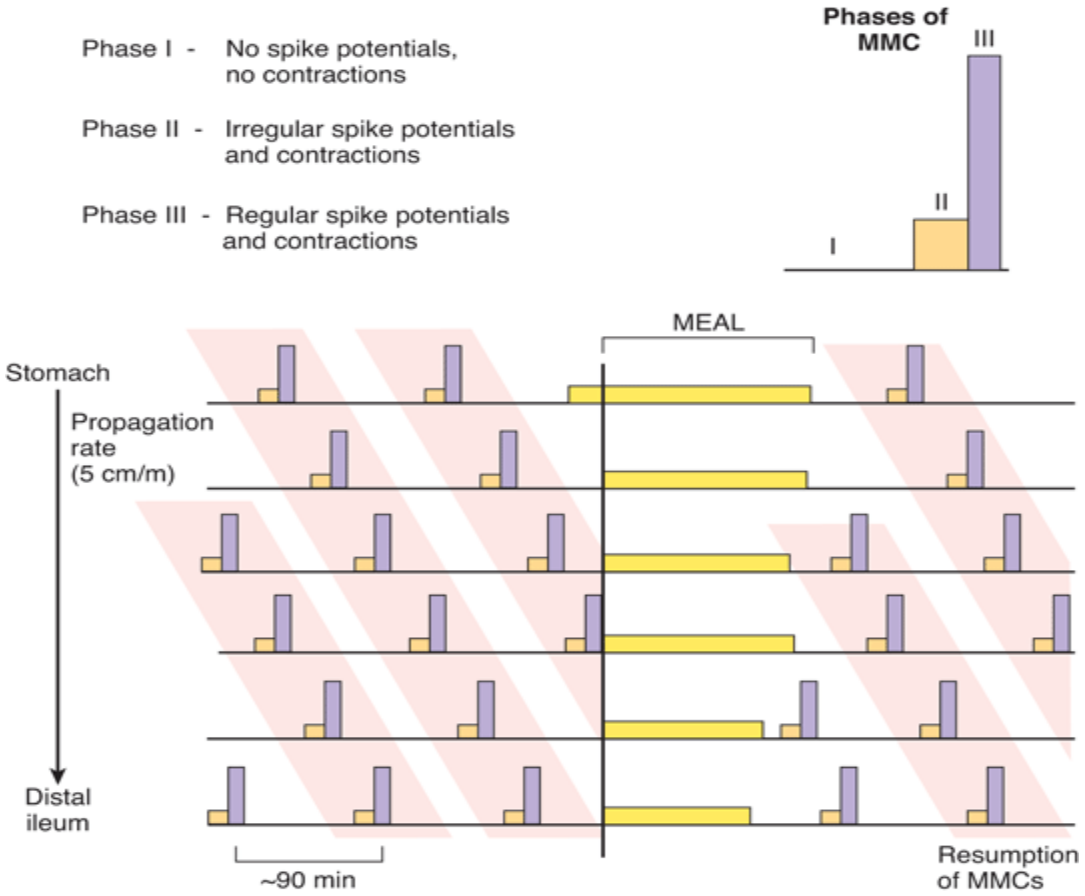
Enteric nervous system

- Postganglionic fibers of the myenteric plexus initiate peristaltic waves by simultaneously causing the gut to contract and by inhibiting neurons distally leading to relaxation.
- Parasympathetic ganglion cells in Meissner's plexus (and in the pancreas) cause glandular secretion.
- Parasympathetic ganglion cells in the wall of the gall bladder causes expulsion of bile.
- The colonic phase after a meal lasts 2 hours. May stimulate stooling.

Enteric nervous system

- Pre-ganglionic sympathetic nerves originate in the lateral horn cells. They terminate in the pre-vertebral splanchnic ganglia within the abdomen. Post-ganglionic fibers supply intestinal smooth muscle and blood vessels (β2 receptors).
- Intrinsic visceral afferent neurons are bipolar. Some participate in local reflex arcs; others project to the splanchnic ganglia.
- Visceral afferents reaching the CNS have their unipolar somas in a nodose ganglion of the vagus and in posterior root ganglia at spinal levels. Nociceptive.

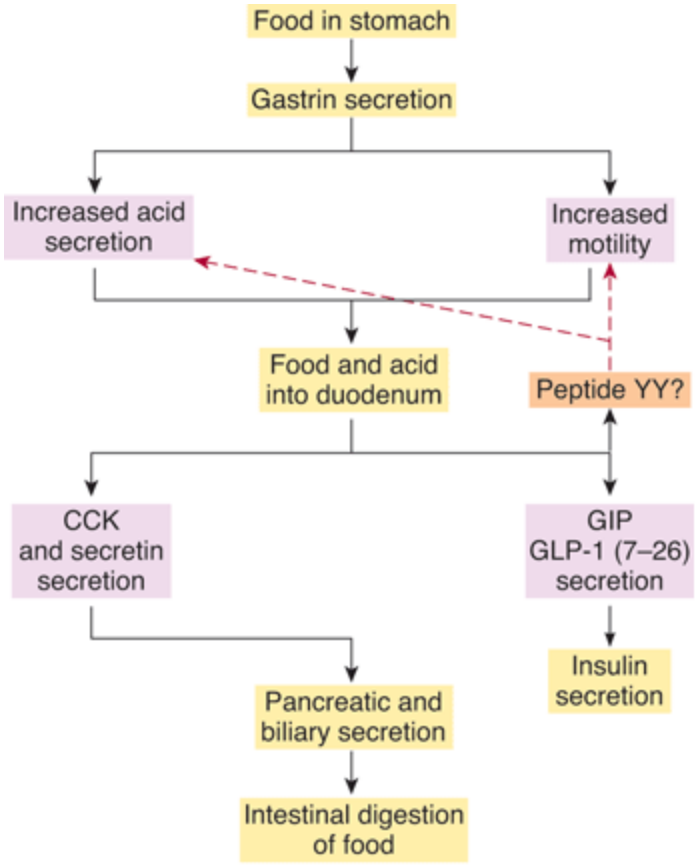
Migrating motor complexes



(Reproduced with permission from Chang EB, Sitrin MD, Black DD: *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott-Raven, 1996.)

Fig. 26-24 Accessed 02/01/2010

Neurohormonal control of digestion



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 26-23 Accessed 02/01/2010

Digestive hormones

- Gastrin is produced by G cells in the antrum of the stomach as well as in pancreatic islets. Gastrin stimulates enterochromaffin-like cells to secrete histamine; chief cells to produce pepsinogen; parietal cells to produce acid.
- Cholecystokinin is produced by I cells in the duodenum and jejunum. It stimulates pancreatic enzyme secretion, gallbladder contraction, and relaxation of the sphincter of Oddi. Secretin inhibits.
- Cholecystokinin serves to coordinate nutrient delivery to match intestinal capacity.

Digestive hormones

- Somatostatin is produced by D cells in the duodenum and intestinal mucosa as well as in pancreatic islets (δ cells). Inhibits gastric acid and pepsiongen secrtion, pancreatic and small intestine fluid secretion, gallbladder contraction, insulin and glucagon release. Inhibited by vagal action.
- Gastric inhibitory peptide is produced by K cells of the duodenum and jejunum. Stimulates insulin release; inhibits gastric acid secretion.

Digestive hormones

- Secretin is produced by S cells in the crypts of Lieberkühn. It stimulates pancreatic bicarbonate secretion and production of bile by the liver.
- Vasoactive intestinal peptide is produced by enteric neurons and the pancreas. Vagal activation. Stimulates smooth muscle relaxation, intestinal water and pancreatic bicarbonate secretion. (G-protein coupled adenyl cyclase activation.)
- Pancreatic polypeptide is produced by F cells in the small intestine as well as in pancreatic islets. It inhibits the release of pancreatic secretions.

Acid production

- Gastrin (via cholesystekinin B receptor) increases adenyl cyclase to stimulate H^+ production by parietal cells.
- Vagal stimulation leads to acetylcholine release (muscarinic 3 receptor) and increases adenyl cyclase to stimulate H^+ production by parietal cells.
- Histamine (histamine 2 receptor) increases cAMP, stimulating H^+ production by parietal cells.

Acid production

- Secretion of hydrochloric acid by the parietal cells is an active process that uses ATP and takes place against a steep concentration gradient.
- The precursors of the exported protons are carbon dioxide and water. Carbon dioxide diffuses from the blood into the parietal cells.
- In a reaction catalyzed by carbonic anhydrase, carbon dioxide reacts with water to form H^+ and HCO_3^-.
- H^+ is transported into the gastric lumen in exchange for K^+ by a membrane-bound transport ATPase of the P type.

Digestion

- The remaining HCO_3^- is released into the interstitium thorugh an electically neutral antiport in in exchange for Cl^-, and from there into the blood. The Cl^- follows the secreted H^+ into the gastric lumen.
- Hydrochloric acid activates pepsinogen and provides a pH for optimal enzyme function.
- Bile acids emulsify ingested water insoluble neutral fats, preventing coalescence in the bowel lumen, permitting hydrolysis by lipases.

Digestion

- Brunner's glands produce a heavy alkaline mucus to protect the duodenum from large amounts of acid. Under vagal and secretin control.
- Goblet cells in the small intestine produce mucus as well.
- The duodenum contracts 12/minute; the ileum, 8-9/minute.
- 7-8L fluid produced daily (saliva, stomach, bile and pancreas, small intestine). Converted to isotonic fluid in colon; colon absorbs up to 1L fluid daily. 150ml water lost daily in stool.
- Water-soluble vitamins are absorbed in the terminal jejunum.

Digestion

- Water is absorbed through passive diffusion. Aquaporins involved in cell entry in colon.
- Electroneutral absorption of Na^+ occurs in the absence of foodstuffs. Electrogenic absorption of sodium occurs with concomitant release of K^+ into circulation.
- Na^+ is actively transported into and out of the cell in the ileum and colon; in the presence of HCO_3^-, Na^+ is transported actively into cells in the jejunum.

Digestion

- Cl^- is passively absorbed and is secreted down an electrochemical gradient.
- K^+ is absorbed in the jejunum and ileum. It is secreted in the colon. If the K^+ concentration is >25mEq/L, K^+ will be absorbed in the colon.
- Glucose, galactose, amino acids, thiamine, folic acid, bile acids, Ca^{2+} and Fe^{2+} are transported actively.
- Fructose, riboflavin, and vitamin B12-intrinsic factor enter the cell through facilitated diffusion.

Carbohydrate digestion

- Salivary amylase randomly breaks down glucose at the 1-4 bond. It is denatured in the stomach. There is no net digestion in the stomach.
- Pancreatic amylase breaks down sugars further into monosaccharides and disaccharides.
- Monosaccharides are absorbed via specific transporters. Glucose and galactose compete for absorption via a Sodium dependent co-transporter (SGLT1). They move against a concentration gradient with Na^+ (secondary active transport). A glut 2 transporter moves the sugar into the extracellular fluid.

Carbohydrate digestion

- In the jejunum, fructose is absorbed. Diffusion is facilitated through the glut 5 transporter on the luminal surface; glut 2, basolaterally.
- Further degradation of disaccharides occurs in the small intestine (disaccharidases in luminal epithelium at the intestinal brush border).
- β-galactosidase (highest concentration in jejunum) breaks the galactose β1-4 bond of lactose and some oligosaccharides associated with glycolipids (specifically ceramide).
- Trehalase breaks glucose at the1-1 bond.

Carbohydrate digestion

- Sucrase-Isomaltase (highest concentration in jejunum) has two enzymatic sites: the sucrase-maltase site breaks glucose at the1-2 bond of sucrose and glucose, at the 1-4 of maltose; the isomaltase site breaks glucose at the 1-6 bond of isomaltose.
- Glucoamylase (highest concentration found in ileum) breaks glucose at the 1-4 bonds one at a time from the non-reducing end on starch, glycogen and the partial digestion products of amylase.
- Fiber passes through the system without being absorbed.

Protein digestion

- There is no digestion in the mouth. Proteins are denatured in the stomach by acid. Pepsin cleaves the N-terminal of aromatic amino acids.
- Bicarbonate from the pancreas neutralizes stomach secretions in the small intestine.
- Trypsinogen is converted by enteropeptidase to trypsin. The pancreas exocrine cells also contain trypsin inhibitor to protect itself from free trypsin.
- Trypsin cuts the C-terminal of Basic amino acids.
- Chymotrypsinogen is activated by trypsin. Chymotrypsin cuts the C-terminal of aromatic amino acids.

Protein digestion

- Procarboxypeptidase is activated by trypsin. Carboxypeptidase cuts the C-terminal amino acid one at a time.
- Amino peptidase cuts the N-terminal amino acid one at a time.
- Proelastase is also activated by trypsin.
- Proteins are further hydrolyzed to amino acids in the intestinal lumen.
- Individual amino acid groups have group–specific amino acid transporters. Both secondary active transport and facilitated diffusion are mechanisms for cell entry.
- Plasma protein levels are generally constant.

Lipid digestion

- There is no net digestion of lipids in the mouth.
- Bile salts emulsify triacylglycerols in the small intestine.
- Lingual lipase removes fatty acids at positions 1,2,3 of triacylglycerols; gastric, pancreatic lipases cut off fatty acids at positions 1 and 3.
- The resulting 2-monoacylglycerols, cholesterol, and bile salts that form the micelle are absorbed in the ileum. (Bile salt absorption is a Na^+ dependent process).

Lipid digestion

- Fatty acids, monoglycerols and glycerol are formed through hydrolysis. Their resorption is not ATP-dependent.
- Short chain fatty acids and glycerol pass directly into the blood.
- Long chain fatty acids are resynthesized in mucosal cells by an ATP-dependent ligase and released into the lymph as chylomicrons.
- Triglycerides and cholesterol are packaged as chylomicrons and are released into the blood.

Absorption of lipids occurs in the small intestine

- Micelles contain:
- bile salts (synthesized by the liver)
- 2-monoacylglycerols (derived from dietary triacylglycerol breakdown)
- dietary free fatty acids > 12 carbons in length
- dietary cholesterol
- dietary fat soluble vitamins (A, D, E, K)
- Micelle components (except bile salts) are absorbed by intestinal epithelial cells in the duodenum and jejunum.
- Bile salts are absorbed in the ileum and return to the liver, which secretes them again (enterohepatic cycle).

Absorption of short and medium chain fatty acids

- Short (<6 C) and medium (6-12 C) fatty acids do not require bile salts for their absorption.
- They are not packaged into chylomicrons within intestinal epithelial cells.
- They diffuse across the cell membranes of the intestinal cells directly into the portal vein.
- They are transported in the blood bound to serum albumin instead of chylomicrons.

Clinical significance of the direct absorption of short chain fatty acids

- Patients with a deficiency of bile salt formation have a deficit in long chain fatty acid absorption
- Patients with a deficiency in lipoprotein lipase activity have a deficit in long chain fatty acid delivery to cells, especially muscle and heart cells.
- Short chain fatty acids are absorbed directly from the gut into the portal blood and transported on albumin, and supply the much needed energy source in both these patients

Iron absorption

- Iron crosses the brush border membrane of duodenal enterocytes via DMT1 after reduction of Fe^{3+} to the Fe^{2+} state by duodenal cytochrome B.
- Fe^{2+} then moves from the enterocyte into the circulation via a process requiring the basolateral iron exporter ferroportin and the iron oxidase hephaestin.
- In the circulation, Fe^{2+} binds to plasma transferrin for distribution to sites of iron utilization and storage.
- Fe^{2+} is returned to the circulation after export from macrophages that have degraded hemoglobin from senescent red cells.

Iron absorption

- The liver-derived peptide hepcidin represses basolateral iron transport in the gut as well as iron release from macrophages and other cells and serves as a central regulator of body iron traffic. Hepcidin responds to changes in body iron requirements by signals mediated by HFE, TfR2, and hemojuvelin. Heme is metabolized by heme oxygenase within the enterocytes, and the released iron then follows the same pathway.
- Mutations in the genes encoding HFE, TfR2, hemojuvelin, and hepcidin all lead to decreased hepcidin release and increased iron stores.

Vitamin B12 absorption

- Bound B12 is released from proteins during digestion and free B12 binds to haptocorrin proteins (transcobalamin I) released by salivary glands and gastric mucosa.
- In the duodenum and jejunum, digestion of haptocorrins releases B12 which then binds to “intrinsic factor”, a glycoprotein secreted in the stomach. Intrinsic factor binds to receptors in the ileum and is internalized.
- B12 then binds to transcobalamin II and is released to circulation. Transcobalamin II receptors on cells take up the B12.

Vitamin B12 absorption

- The liver takes up about 50% of vitamin B12 and can store 3-6 years worth of vitamin B12.
- Pernicious anemia is caused by the lack of intrinsic factor.
- Accumulation of methylmalonyl CoA blocks myelin formation by competitive inhibition of malonyl CoA carboxylase (key enzyme in folic acid synthesis) and by disrupting membrane structure through incorporation of methylmalonyl CoA producing branched fatty acids.

Movement across the cell membrane

- The membrane is a bi-layer of phospholipid in which are interspersed large globular protein molecules that protrude through the service. Channels through the structures of the protein molecules serve as pores.
- Diffusion across the membrane occurs as molecules migrate from a region of high concentration to one of low concentration as a result of random motion.
- The diffusion of water is called “osmosis”.

Movement across the cell membrane

- The rate of diffusion is related to the difference in electrical potential and chemical concentration across the membrane; the permeability of the membrane (lipid soluble substances favored); the surface area of the membrane.
- Diffusion is inversely related to the size of the solute.
- Large molecules such as glucose, water, and solvated ions pass through the membrane channels formed by glycoprotein molecules that extend through the membrane.

Movement across the cell membrane

- Glucose is transported from the lumen through the cell membrane through a **symport** by combining chemically with a carrier protein, the glucose transporter (glut), that penetrates through the membrane. Na^+ enters with the glucose.
- Glucose is then released into the cytosol.
- Glucose leaves the cell for the blood through a **uniport**. A Na^+-K^+-ATPase dependent pump at the blood interface maintains the cellular concentration of Na^+. (ATP on cytoplasmic side.)

Movement across the cell membrane

- This “facilitated” diffusion is a form of secondary active transport. While the rate of diffusion increases proportionally with the concentration of the diffusing substance, a transport maximum is reached in facilitated diffusion.
- Aquaporin-1 is a pore whose size only permits the entrance of hydronium ion (water), and is responsive to antidiuretic hormone (ADH).
- Tight junctions limit water flow.

Glucose transporters

Transporter	Location	
Glut 1	Red cell Cells with barrier function	High affinity for glucose
Glut 2	Liver Kidney Intestinal epithelium Pancreatic β-cell	High capacity Low affinity for glucose
Glut 3	Neurons	High affinity for glucose
Glut 4	Adipose tissue Skeletal and cardiac muscle	Insulin sensitive High affinity for glucose
Glut 5	Spermatozoa Intestinal epithelium Kidney	Fructose transporter Glucose resorption

Amino acid transporters

Transporter	Amino acids	
1	Acidic	(glutamine, aspartate as examples)
2	Basic	(arginine, lysine, ornithine as examples)
3	Neutral	(glycine, alanine)
4	Neutral and	(phenylalanine, tyrosine, tryptophan, branched amino acids)

The four amino acid transporters are found cells that have a barrier function.

Movement across the cell membrane

- Active transport differs from facilitated diffusion in that it can transport the substance even in the absence of or against an electrochemical gradient. High energy phosphate compounds provide the energy to drive that transport.
- The Na^+-K^+ transport pump causes the concentration of Na^+ inside the cell to become very low while simultaneously greatly increasing the intracellular K^+ concentration.
- Counter-transport is seen with Na^+- Ca^{2+} and Na^+-H^+. Both utilize the same carrier protein.

Movement across the cell membrane

- The Calcium pump transports Ca^{2+} outside of the cell membrane as well as into the organelles of the cell, maintaining a very low intracellular Ca^{2+} concentration. It is a P type pump in that the transporter undergoes covalent phosphorylation during the transport cycle. It is ATP dependent.
- The Hydrogen F type pump is found in mitochondria where the pump couples oxidation with ATP generation.
- The Hydrogen V type pump is found in lysozymes where protons are introduced. It is an ATP dependent pump.

Movement across the cell membrane

- Voltage gated ion channels:
- Sodium is the most important as it maintains polarization. Potassium and calcium ion channels are dependent upon potential generated when cell is depolarized.
- Ligand gated ion channels:
- Nicotine receptor for acetylcholine as an example (Na^+-K^+). Receptor binding induces conformational change in the ion channel.

Transporter defects

- Low absorption in the intestine may keep amino acid blood levels low. Amino acids are filtered by the glomerulus and are normally taken up again by transporters. If they are not, their level in the urine increases.
- In Hartnup disease, there is a defect in the neutral amino acid transporter. Pellagra-like symptoms as tryptophan needed to make NADH.
- In cystinuria there is a defect in the upatke of cystine, lysine, arginine, and ornithine. Cystine is water insoluble and can precipitate to form kidney stones.