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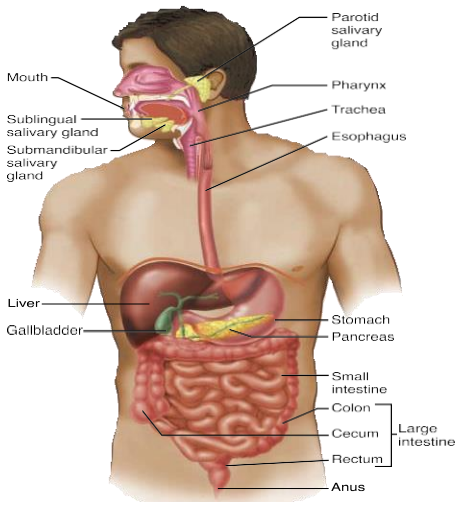
Gastrointestinal Physiology

The alimentary tract provides the body with a continual supply of water, electrolytes, vitamins, and nutrients. To achieve this requires :

1. Movement of food through the alimentary tract.
2. Secretion of digestive juices and digestion of the food.
3. Absorption of water, various electrolytes, vitamins, and digestive products.
4. Circulation of blood through the gastrointestinal organs to carry away the absorbed substances.
5. Control of all these functions by local, nervous, and hormonal systems.

Figure 1 shows the entire alimentary tract. Each part is adapted to its specific functions: some to simple passage of food, such as the esophagus; others to temporary storage of food, such as the stomach; and others to digestion and absorption, such as the small intestine.



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The adult gastrointestinal tract is a tube approximately 9 m (30 feet) in length, running through the body from mouth to **anus.** The lumen of the tract is continuous with the external environment, which means that its contents are technically outside the body. This fact is relevant to understanding some of the tract's properties. For example, the large intestine is colonized by billions of bacteria, most of which are harmless and even beneficial in this location. However, if the same bacteria enter the internal environment, as may happen, for example, if a portion of the large intestine is perforated, they may cause a severe infection.

Most food enters the gastrointestinal tract as large particles containing macromolecules, such as proteins and polysaccharides, which are unable to cross the intestinal epithelium. Before ingested food can be absorbed, therefore, it must be dissolved and broken down into small molecules (*Small nutrients such as vitamins and minerals do not need to be broken down and can cross the epithelium intact*.)

This dissolving and breaking-down process is called **digestion** and is accomplished by the action of hydrochloric acid in the stomach, bile from liver, and a variety of digestive enzymes released by the system's exocrine glands. Each of these substances is released into the lumen of the GI tract

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through the process of **secretion.** In addition, some digestive enzymes are located on the luminal membranes of the intestinal epithelium. The molecules produced by digestion, along with water and small nutrients that **do not require digestion**, then move from the lumen of the gastrointestinal tract across a layer of epithelial cells and enter the blood or lymph. This process is called **absorption.**

While digestion, secretion, and absorption are taking place, contractions of smooth muscles in the gastrointestinal tract wall **serve two functions**:

1. They mix the luminal contents with the various secretions
2. They move the contents through the tract from mouth to anus.These contractions are referred to as the **motility** of the gastrointestinal tract.

In some cases, muscular movements travel in a wave- like fashion in one direction along the length of a part of the tract, a process called **peristalsis.** The functions of the digestive system can be described in terms of these four major processes—**digestion**, **secretion**, **absorption**, and **motility** (**Figure 2**)—and the mechanisms controlling them.

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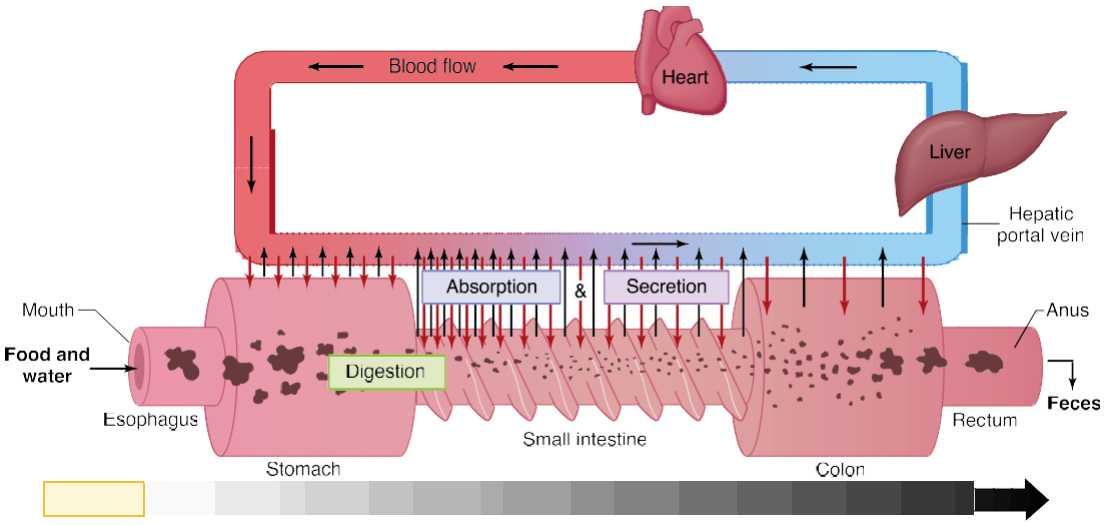

Figure 2: Four major processes the gastrointestinal tract carries out: digestion, secretion, absorption, and motility.

Small amounts of certain metabolic end products are excreted via the gastrointestinal tract, primarily by way of the bile. This represents a minor function of the GI tract in healthy individuals—**elimination.** In fact, the lungs and kidneys are usually responsible for the elimination of most of the body's waste products. The material known as **feces** leaves the system at the end of the gastrointestinal tract. Feces consist almost entirely of bacteria and ingested material that was neither digested nor absorbed, that is, material that was never actually absorbed into the internal environment.

General Principles of Gastrointestinal Motility

Figure 3 shows a typical cross section of the intestinal wall, including the following layers from outer surface inward:

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(1) The serosa

(2) A longitudinal smooth muscle layer

(3) A circular smooth muscle layer

(4) The submucosa

(5) The mucosa.

In addition, sparse bundles of smooth muscle fibers, the *mucosal muscle,* lie in the deeper layers of the mucosa. The motor functions of the gut are performed by the different layers of smooth muscle.

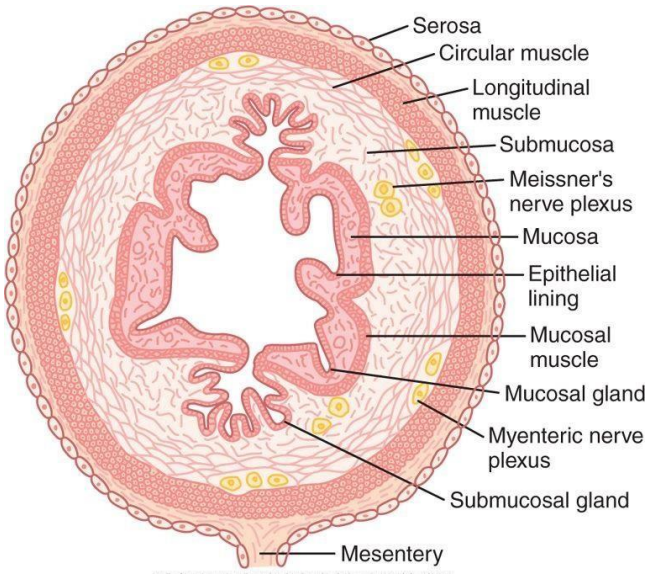

Figure 3: *Typical cross section of the gut.*

From the mid-esophagus to the anus, the wall of the gastrointestinal tract has the general structure illustrated in **Figure 3 & 4**. Most of the luminal (inside) surface is highly convoluted, a feature that greatly increases the surface area available for absorption. From the stomach on, this surface is covered by a single layer of epithelial cells linked together along the edges of their

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luminal surfaces by **tight junctions**.

Just below the epithelium is the **lamina propria,** which is a layer of loose connective tissue through which pass small blood vessels, nerve fibers, and lymphatic vessels. The lamina propria is separated from underlying tissues by the **muscularis mucosa,** which is a thin layer of smooth muscle that may be involved in the movement of villi, described subsequently. The combination of these three layers(the epithelium, lamina propria, and muscularis mucosa)is called the **mucosa** (see Figure 4).

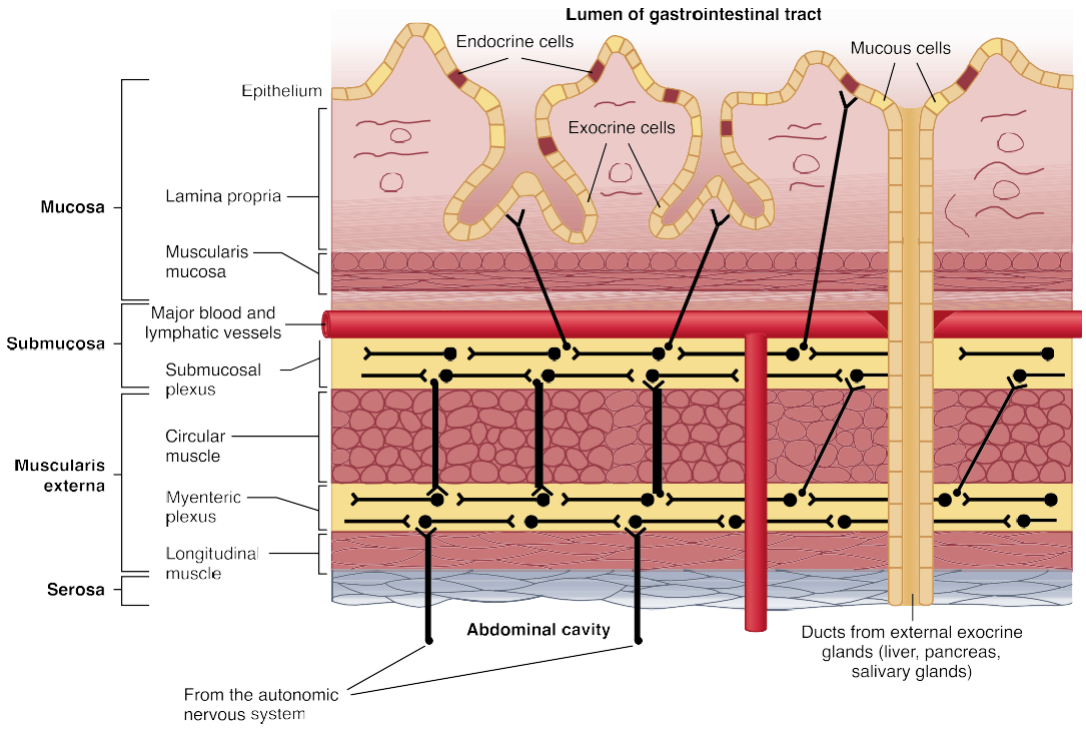

Figure 4: *Structure of the gastrointestinal wall in longitudinal section.*

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Beneath the mucosa is the **submucosa,** which is a second connective-tissue layer. This layer also contains a network of neurons (the **submucosal plexus)** and blood and lymphatic vessels whose branches penetrate into both the overlying mucosa and the underlying layers of smooth muscle called the **muscularis externa.** Contractions of these muscles provide the forces for moving and mixing the gastrointestinal contents. Except for the stomach, which has three layers, the muscularis externa has two layers:

(1) Relatively thick inner layer of **circular muscle,** whose fibers are oriented in a circular pattern around the tube so that contraction produces a narrowing of the lumen.

(2) thinner outer layer of **longitudinal muscle,** whose contraction shortens the tube. Between these two muscle layers is a second network of neurons known as the **myenteric plexus.**

There are neurons projecting from the submucosal plexus to the single layer of cells on the luminal surface as well as to the myenteric plexus. The myenteric plexus is innervated by nerves from the autonomic nervous system and has neurons that project to the submucosal plexus.

Finally, surrounding the outer surface of the tube is a thin layer of connective tissue called the **serosa.** Thin sheets of connective tissue connect

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the serosa to the abdominal wall and support the gastrointestinal tract in the abdominal cavity.

The macro- and microscopic structure of the wall of the small intestine is shown in **Figure 5**. The **circular folds** (mucosa and submucosa) are covered with fingerlike projections called **villi.** The surface of each villus is covered with a layer of epithelial cells whose surface membranes form small projections called **microvilli.**

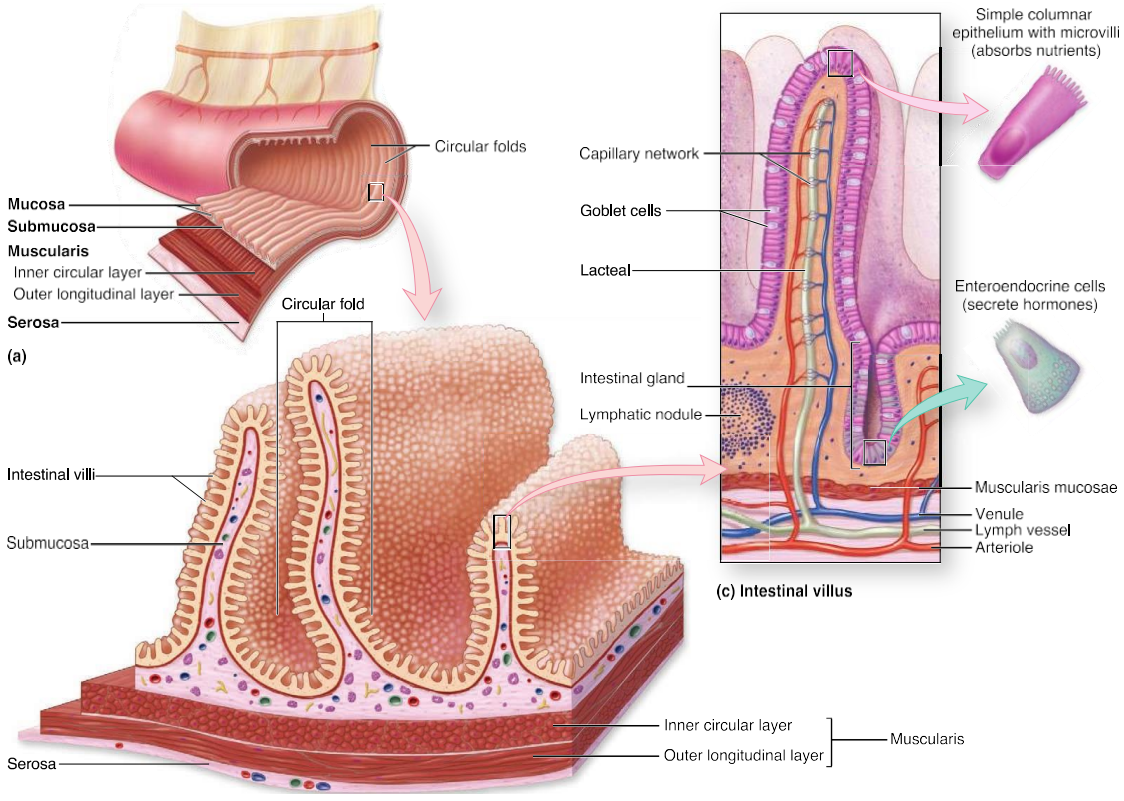

Figure 5: *Microscopic structure of the small-intestine wall demonstrates increased surface area.*

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The center of each intestinal villus is occupied by both a single, blind-ended lymphatic vessel and a capillary network. The absorbed nutrients enter the blood capillaries. The venous drainage from the small intestine(as well as from the large intestine, pancreas, and portions of the stomach) does not empty directly into the vena cava but passes first, via the **hepatic portal vein,** to the liver. (The term **hepatic** refers to the liver.) There it flows through a second capillary network before leaving the liver to return to the heart. Because of this portal circulation, material that is absorbed into the intestinal capillaries, in contrast to the lacteals (A **lacteal** is a lymphatic capillary that absorbs dietary fats in the villi of the small intestine.), can be processed by the liver before entering the general circulation. This is important because the liver contains enzymes that can metabolize (detoxify) harmful compounds that may have been ingested, thereby preventing them from entering the circulation.

General Functions of the Gastrointestinal

Digestion begins with chewing in the **mouth** where large pieces of food are broken up into smaller particles that we can swallow. **Saliva** secreted by three pairs of exocrine **salivary glands** located in the head, drains into the mouth through a series of short ducts. Saliva, which contains mucus, moistens and lubricates the food particles before swallowing. It also contains

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the enzyme **amylase,** which partially digests polysaccharides (complex sugars) described later. A third function of saliva is to dissolve some of the food molecules. Only in the dissolved state can these molecules react with chemoreceptors in the mouth, giving rise to the sensation of taste. Finally, saliva has antibacterial properties.

Table 1: Functions of the Gastrointestinal Organs

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

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The next segments of the tract, the **pharynx** and **esophagus,** do not contribute to digestion but provide the pathway for ingested materials to reach the stomach. The muscles in the walls of these segments control swallowing.

The **stomach** is a saclike organ located between the esophagus and the small intestine. Its functions are to store, dissolve, and partially digest the macromolecules in food and to regulate the rate at which the contents of the stomach empty into the small intestine. The acidic environment in the **gastric** (adjective for "stomach") lumen alters the ionization of polar molecules, leading to denaturation of protein.

Polysaccharides and fat are major food components that are not dissolved to a significant extent by acid. The low pH also kills most of the bacteria that enter along with food. This process is not completely effective, and some bacteria survive to colonize and multiply in the gastrointestinal tract, particularly the large intestine.

The digestive actions of the stomach reduce food particles to a solution known as **chyme,** which contains molecular fragments of proteins and polysaccharides; droplets of fat; and salt, water, and various other small molecules ingested in the food. Virtually none of these molecules, except water, can cross the epithelium of the gastric wall, and thus little absorption

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of organic nutrients occurs in the stomach.

Most absorption and digestion occur in the next section of the tract, the **small intestine,** a tube about 2.4 cm in diameter and 3 m in length, which leads from the stomach to the **large intestine.** (The small intestine is almost twice as long if removed from the abdomen because the muscular wall loses its tone.) Hydrolytic enzymes in the small intestine break down molecules of intact or partially digested carbohydrates, fats, proteins, and nucleic acids into monosaccharides, fatty acids, amino acids, and nucleotides. Some of these enzymes are on the luminal surface of the intestinal lining cells, whereas others are secreted by the pancreas and enter the intestinal lumen. The products of digestion are absorbed across the epithelial cells and enter the blood and/or lymph. Vitamins, minerals, and water, which do not require enzymatic digestion, are also absorbed in the small intestine.

The small intestine is divided into three segments: An initial short segment, the **duodenum,** is followed by the **jejunum** and then by the longest segment, the **ileum.** Normally, most of the chyme entering from the stomach is digested and absorbed in the **first quarter of the small intestine** in the duodenum and jejunum. Therefore, the small intestine has a very large reserve for the absorption of most nutrients; removal of portions of the small

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intestine as a treatment for disease does not necessarily result in nutritional deficiencies, depending on which part of the intestine is removed.

Two major organs—the pancreas and liver—secrete substances that flow via ducts into the duodenum. The **pancreas,** an elongated gland located behind the stomach, has both endocrine and exocrine functions, but only the latter are directly involved in gastrointestinal function.

The exocrine portion of the pancreas secretes digestive enzymes and a fluid rich in HCO_3^+. The high acidity of the chyme coming from the stomach would inactivate the pancreatic enzymes in the small intestine if the acid were not neutralized by the $HCO3^+$ in the pancreatic fluid.

The **liver,** a large organ located in the upper-right portion of the abdomen, has a variety of functions. We will be concerned in our lectures primarily with the liver's exocrine functions that are directly related to the secretion of **bile.** Bile contains HCO_3^+, cholesterol, phospholipids, bile pigments, a number of organic wastes, and—most important—a group of substances collectively termed **bile salts.** The HCO_3^+, like that from the pancreas, helps neutralize acid from the stomach, whereas the bile salts solubilize dietary fat. These fats would otherwise be insoluble in water, and their solubilization

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increases the rates at which they are digested and absorbed.

Bile is secreted by the **liver** into small ducts that join to form the common hepatic duct. Between meals, secreted bile is stored in the **gallbladder,** a small sac underneath the liver that branches from the common hepatic duct. The gallbladder concentrates the organic molecules in bile by absorbing some salts and water. During a meal, the smooth muscles in the gallbladder wall contract, causing a concentrated bile solution to be injected into the duodenum via the **common bile duct**, an extension of the common hepatic duct.

In the small intestine, monosaccharides and amino acids are absorbed by specific transporter-mediated processes in the plasma membranes of the intestinal epithelial cells, whereas fatty acids enter these cells primarily by diffusion. Most mineral ions are actively absorbed by transporters, and water diffuses passively down osmotic gradients.

The motility of the small intestine, brought about by the smooth muscles in its walls,

(1) Mixes the luminal contents with the various secretions.

(2) Brings the contents into contact with the epithelial surface where absorption takes place.

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(3) Slowly advances the luminal material toward the large intestine, the next segment of the alimentary canal.

Because most substances are absorbed in the small intestine, only a small amount of water, salts, and undigested material passes on to the large intestine. The large intestine temporarily stores the undigested material (some of which is metabolized by bacteria) and concentrates it by absorbing salts and water. Contractions of the **rectum,** the final segment of the large intestine, and relaxation of associated sphincter muscles expel the feces in a process called **defecation.**

The average adult consumes about 500–800 g of food and 1200 mL of water per day, but this is only a fraction of the material entering the lumen of the gastrointestinal tract. An additional 7000 mL of fluid from salivary glands, gastric glands, pancreas, liver, and intestinal glands is secreted into the tract each day. Of the approximately 8 L of fluid entering the tract, 99% is absorbed; only about 100 mL is normally lost in the feces. This small amount of fluid loss represents only 4% of the total fluids lost from the body each day. Most fluid loss is via the kidneys and respiratory system. Almost all the salts in the secreted fluids are also reabsorbed into the blood. Moreover, the secreted digestive enzymes are themselves digested, and the resulting amino acids are absorbed into the blood.

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Finally, a critical component in the control of gastrointestinal functions is the role of the central nervous system. The CNS receives information from the GI tract (afferent input) and has a vital influence on GI function (efferent output).

Digestion and Absorption

The process of absorption illustrates the general principle of physiology that controlled exchange of materials occurs between compartments (in this case, from the lumen of the GI tract to the blood and lymph) and across cellular membranes (of the cells lining the GI tract).

Carbohydrates

The average daily intake of carbohydrates is about 250 to 300 g per day in a typical diet. This represents about half the average daily intake of calories. About two-thirds of this carbohydrate is the plant polysaccharide starch, and most of the remainder consists of the disaccharides sucrose (table sugar) and lactose (milk sugar) (**Table 1**). Only small amounts of monosaccharides are normally present in the diet. Cellulose and certain other complex polysaccharides found in vegetable matter(referred to as **fiber**)are not broken down by the enzymes in the small intestine and pass on to the large

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intestine, where they are partially metabolized by bacteria.

Class	Examples	Composed Of:
Polysaccharides	Starch	Glucose
	Cellulose	Glucose
	Glycogen	Glucose
Disaccharides	Sucrose	Glucose–fructose
	Lactose	Glucose–galactose
	Maltose	Glucose–glucose
Monosaccharides	Glucose	
	Fructose	
	Galactose	

Table 1: *Carbohydrates in Food*

The digestion of starch by salivary amylase begins in the mouth but accounts for only a small fraction of total starch digestion. It continues very briefly in the upper part of the stomach before gastric acid inactivates the amylase. Most (~95% or more) starch digestion is completed in the small intestine by pancreatic amylase (**Figure 1**). The products of both salivary and pancreatic amylase are the disaccharide maltose and a mixture of short, branched chains of glucose molecules. These products, along with ingested sucrose and lactose, are broken down into monosaccharides—glucose, galactose, and fructose—by enzymes located on the luminal membranes of the small-intestine epithelial cells (brush border). These monosaccharides are then transported across the intestinal epithelium into the blood. Fructose enters the epithelial cells by facilitated diffusion via a glucose transporter (GLUT), whereas glucose and galactose undergo secondary active transport coupled

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to Na via the sodium–glucose cotransporter (SGLT). These monosaccharides then leave the epithelial cells and enter the interstitial fluid (fluid in spaces around the cells) by way of facilitated diffusion via GLUT proteins in the basolateral membranes of the epithelial cells. From there, the monosaccharides diffuse into the blood through capillary pores. Most ingested carbohydrates are digested and absorbed within the first 20% of the small intestine.

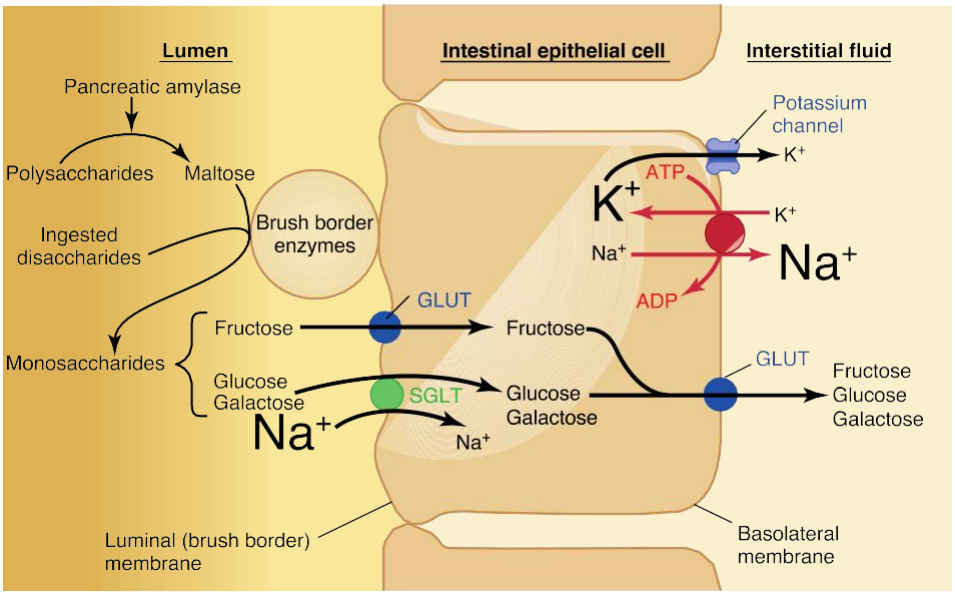

Figure 1: Carbohydrate digestion and sugar absorption in the small intestine.

Protein

A healthy adult requires only 40 to 50 g of protein per day to supply essential amino acids and replace the nitrogen contained in amino acids that are converted to urea. A typical American diet contains about 60 to 90 g of

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protein per day. This represents about one-sixth of the average daily caloric intake. In addition, a large amount of protein, in the form of enzymes and mucus, is secreted into the gastrointestinal tract or enters it via the disintegration of epithelial cells. Regardless of the source, most of the protein in the lumen is broken down into dipeptides, tripeptides, and amino acids, all of which are absorbed by the small intestine.

Proteins are first partially broken down to peptide fragments in the stomach by **pepsin** that, as you will learn, is produced from a precursor **pepsinogen.** Further breakdown is completed in the small intestine by **trypsin** and **chymotrypsin,** the major proteases secreted by the pancreas. These fragments can be absorbed or are further digested to free amino acids by **carboxypeptidases** from the pancreas and **aminopeptidases,** located on the luminal membranes of the small intestine epithelial cells (**Figure 2**). These last two enzymes split off amino acids from the carboxyl and amino ends of peptide chains, respectively. At least 20 different peptidases are located on the luminal membrane of the epithelial cells, with various specificities for the peptide bonds they attack.

Most of the products of protein digestion are absorbed as short chains of two or three amino acids by a secondary active transport coupled to the H

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gradient (see Figure 2). The absorption of small peptides contrasts with carbohydrate absorption, in which molecules larger than monosaccharides are not absorbed. Free amino acids, by contrast, enter the epithelial cells by secondary active transport coupled to Na. There are many different amino acid transporters that are specific for the different amino acids, but only one transporter is shown in Figure 2 for simplicity.

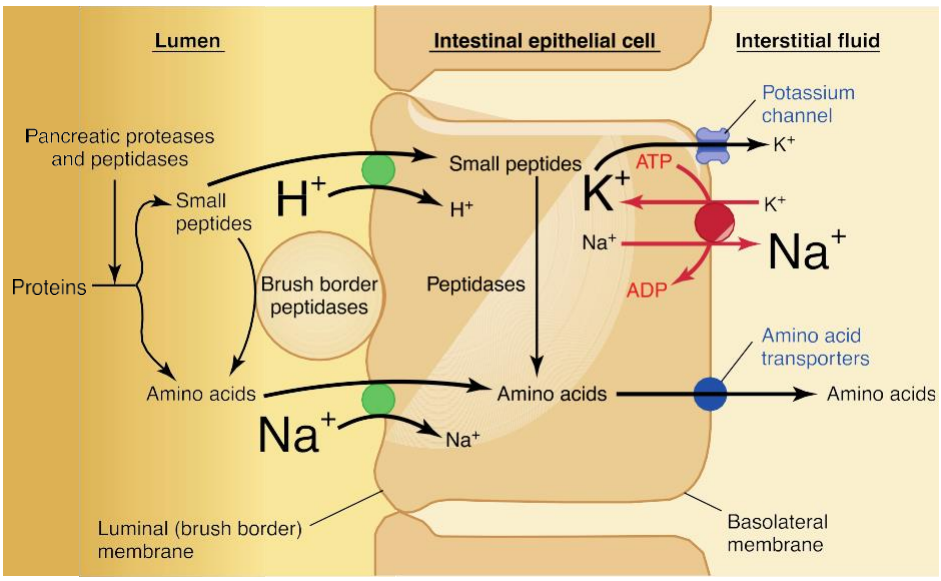

Figure 2: *Protein digestion and peptide and amino acid absorption in the small intestine.*

Within the cytosol of the epithelial cell, the dipeptides and tripeptides are hydrolyzed to amino acids; these, along with free amino acids that entered the cells, then leave the cell and enter the interstitial fluid through facilitated-diffusion transporters in the basolateral membranes. As with carbohydrates, protein digestion and absorption are largely completed in the upper portion

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of the small intestine.

Very small amounts of intact proteins are able to cross the intestinal epithelium and gain access to the interstitial fluid. They do so by a combination of endocytosis and exocytosis. The absorptive capacity for intact proteins is much greater in infants than in adults, and antibodies (proteins involved in the immunologic defense system of the body) secreted into the mother's milk can be absorbed by the infant, providing some immunity until the infant begins to produce his or her own antibodies.

Fat

The average daily intake of lipids is 70 to 100 g per day in a typical American diet, most of this in the form of fat (triglycerides). This represents about one-third of the average daily caloric intake. Triglyceride digestion occurs to a limited extent in the mouth and stomach, but it predominantly occurs in the small intestine. The major digestive enzyme in this process is pancreatic **lipase,** which catalyzes the splitting of bonds linking fatty acids to the first and third carbon atoms of glycerol, producing two free fatty acids and a monoglyceride as products:

The lipids in the ingested foods are insoluble in water and aggregate into large lipid droplets in the upper portion of the stomach. This is like a mixture

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of oil and vinegar after shaking. Because pancreatic lipase is a water-soluble enzyme, its digestive action in the small intestine can take place only at the *surface* of a lipid droplet. Therefore, if most of the ingested fat remained in large lipid droplets, the rate of triglyceride digestion would be very slow because of the small surface-area-to- volume ratio of these big fat droplets. The rate of digestion is, however, substantially increased by division of the large lipid droplets into many very small droplets, each about 1 mm in diameter, thereby increasing their surface area and accessibility to lipase action. This process is known as **emulsification,** and the resulting suspension of small lipid droplets is an emulsion.

The emulsification of fat requires

(1) Mechanical disruption of the large lipid droplets into smaller droplets

(2) An emulsifying agent, which acts to prevent the smaller droplets from re-aggregating back into large droplets.

The mechanical disruption is provided by the motility of the gastrointestinal tract, occurring in the lower portion of the stomach and in the small intestine, which grinds and mixes the luminal contents. Phospholipids in food, along with phospholipids and bile salts secreted in the bile, provide the emulsifying agents. Phospholipids are amphipathic molecules consisting of

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two nonpolar fatty acid chains attached to glycerol, a charged phosphate group located on glycerol's third carbon. Bile salts are formed from cholesterol in the liver and are also amphipathic. The nonpolar portions of the phospholipids and bile salts associate with the nonpolar interior of the lipid droplets, leaving the polar portions exposed at the water surface. There, they repel other lipid droplets that are similarly coated with these emulsifying agents, thereby preventing their re-aggregation into larger fat droplets.

Coating of the lipid droplets with these emulsifying agents, however, impairs the accessibility of the water-soluble lipase to its lipid substrate. To overcome this problem, the pancreas secretes a protein known as **colipase,** which is amphipathic and lodges on the lipid droplet surface. Colipase binds the lipase enzyme, holding it on the surface of the lipid droplet.

Although emulsification speeds up digestion, absorption of the water-insoluble products of the lipase reaction would still be very slow if it were not for a second action of the bile salts, the formation of **micelles,** which are similar in structure to emulsion droplets but much smaller—4 to 7 nm in diameter. Micelles consist of bile salts, fatty acids, monoglycerides, and phospholipids all clustered together with the polar ends of each molecule

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oriented toward the micelle's surface and the nonpolar portions forming the micelle's core. Also included in the core of the micelle are small amounts of fat-soluble vitamins and cholesterol.

Monoglycerides are resynthesized into triglycerides. This occurs in the smooth endoplasmic reticulum, where the enzymes for triglyceride synthesis are located. This process decreases the concentration of cytosolic free fatty acids and monoglycerides and thereby maintains a diffusion gradient for these molecules into the cell from the intestinal lumen. The resynthesized fat aggregates into small droplets coated with amphipathic proteins that perform an emulsifying function similar to that of bile salts.

The exit of these fat droplets from the cell follows the same pathway as a secreted protein. Vesicles containing the droplet pinch off the endoplasmic reticulum, are processed through the Golgi apparatus, and eventually fuse with the plasma membrane, releasing the fat droplet into the interstitial fluid. These 1-micron-diameter, extracellular fat droplets are known as **chylomicrons.** Chylomicrons contain not only triglycerides but other lipids (including phospholipids, cholesterol, and fat-soluble vitamins) that have been absorbed by the same process that led to fatty acid and monoglyceride movement into the epithelial cells of the small intestine.

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The chylomicrons released from the epithelial cells pass into lacteals—lymphatic vessels in the intestinal villi—rather than into the blood capillaries. The chylomicrons cannot enter the blood capillaries because the basement membrane (an extracellular glycoprotein layer) at the outer surface of the capillary provides a barrier to the diffusion of large chylomicrons. In contrast, the lacteals have large pores between their endothelial cells that allow the chylomicrons to pass into the lymph. The lymph from the small intestine, as from every-where else in the body, eventually empties into systemic veins.

Vitamins

The fat-soluble vitamins (A, D, E, and K) follow the pathway for fat absorption described in the previous section. They are solubilized in micelles; thus, any interference with the secretion of bile or the action of bile salts in the intestine decreases the absorption of the fat-soluble vitamins, a pathological condition called ***malabsorption.***

The water-soluble vitamins are absorbed by diffusion or mediated transport. The exception, vitamin B_{12} (cyanocobalamin), is a very large, charged molecule. To be absorbed, vitamin B_{12} must first bind to a protein known as **intrinsic factor,** which is secreted by the acid-secreting cells in the stomach.

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Intrinsic factor with bound vitamin B_{12} then binds to specific sites on the epithelial cells in the lower portion of the ileum, where vitamin B_{12} is absorbed by endocytosis. Vitamin B_{12} is required for erythrocyte formation, and deficiencies result in ***pernicious anemia.*** This form of anemia may occur when the stomach either has been removed (for example, to treat ulcers or gastric cancer) or fails to secrete intrinsic factor (often due to autoimmune destruction of acid-producing cells). Because the absorption of vitamin B_{12} occurs in the lower part of the ileum, removal or dysfunction of this segment due to disease can also result in pernicious anemia. Although healthy individuals can absorb oral vitamin B_{12}, it is not very effective in patients with pernicious anemia because of the absence of intrinsic factor. Therefore, the treatment of pernicious anemia usually requires injections of vitamin B_{12}.

Water and Minerals

Water is the most abundant substance in chyme. Approximately 8000 mL of ingested and secreted water enters the small intestine each day, but only 1500 mL passes on to the large intestine because 80% of the fluid is absorbed in the small intestine. Small amounts of water are absorbed in the stomach, but the stomach has a much smaller surface area available for

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diffusion and lacks the solute-absorbing mechanisms that create the osmotic gradients necessary for net water absorption. The epithelial membranes of the small intestine are very permeable to water, and net water diffusion occurs across the epithelium whenever a water concentration difference is established by the active absorption of solutes.

Na accounts for much of the actively transported solute because it constitutes the most abundant solute in chyme. Na absorption is a primary active process—using the Na/K-ATPase pumps and is similar to that for renal tubular Na and water reabsorption. Chloride Cl and HCO_3 are absorbed with the Na and contribute another large fraction of the absorbed solute.

Other minerals present in smaller concentrations, such as potassium, magnesium, and calcium ions, are also absorbed, as are trace elements such as iron, zinc, and iodide.

ABSORPTION OF MINERALS

IRON

In adults, the amount of iron lost from the body is relatively small. The losses are generally unregulated, and total body stores of iron are regulated by changes in the rate at which it is absorbed from the intestine. Men lose

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about 0.6 mg/d, largely in the stools. Premenopausal women have a variable, larger loss averaging about twice this value because of the additional iron lost during menstruation. Most of the iron in the diet is in the ferric (Fe^{3+}) form, whereas it is the ferrous (Fe^{2+}) form that is absorbed. Fe^{3+} reductase activity is associated with the iron transporter in the brush borders of the enterocytes (**Figure 1**). Gastric secretions dissolve the iron and permit it to form soluble complexes with ascorbic acid and other substances that aid its reduction to the Fe^{2+} form.

Transport of Fe^{2+} into the enterocytes occurs via divalent metal transporter 1 **(DMT1)** (Figure 9). Some is stored in ferritin, and the remainder is transported out of the enterocytes by a basolateral transporter named **ferroportin 1.**

In the plasma, Fe^{2+} is converted to Fe^{3+} and bound to the iron transport protein **transferrin.** This protein has two iron-binding sites. Normally, transferrin is about 35% saturated with iron, and the normal plasma iron level is about 130 μg/dL (23 μmol/L) in men and 110 μg/dL (19 μmol/L) in women.

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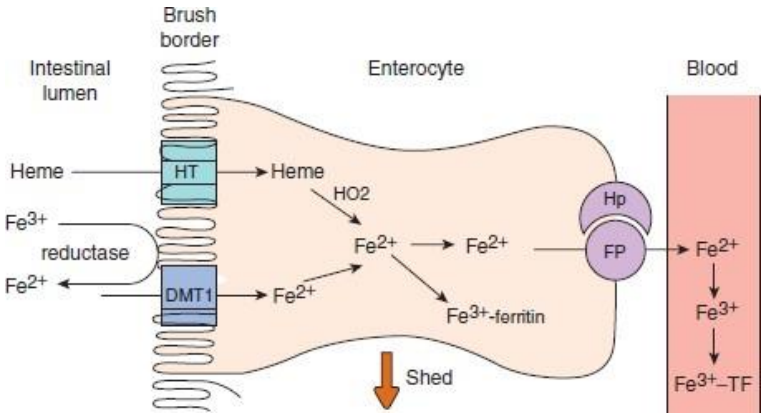

Figure 1: ***Absorption of iron.***

Regulation of Gastrointestinal Tract

Basic Principles

Gastrointestinal reflexes are initiated by a relatively small number of luminal stimuli:

(1) Distension of the wall by the volume of the luminal contents.

(2) chyme osmolarity (total solute concentration).

(3) chyme acidity.

(4)chyme concentrations of specific digestion products like monosaccharides, fatty acids, peptides, and amino acids.

These stimuli act on mechanoreceptors, osmoreceptors, and chemoreceptors located in the wall of the tract and trigger reflexes that influence the effectors—the muscle layers in the wall of the tract and the exocrine glands that secrete substances into its lumen.

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Neural Regulation

The gastrointestinal tract has its own local nervous system, a division of the autonomic nervous system known as the **enteric nervous system.** The cells in this system form two networks or plexuses of neurons, the myenteric plexus and the submucosal plexus. These neurons either synapse with other neurons within a given plexus or end near smooth muscles, glands, and epithelial cells. Many axons leave the myenteric plexus and synapse with neurons in the submucosal plexus, and vice versa, so that neural activity in one plexus influences the activity in the other. Moreover, stimulation at one point in the plexus can lead to impulses that are conducted both up and down the tract. For example, stimuli in the upper part of the small intestine may affect smooth muscle and gland activity in the stomach as well as in the lower part of the intestinal tract. In general, the myenteric plexus influences smooth muscle activity whereas the submucosal plexus influences secretory activity.

The enteric nervous system contains adrenergic and cholinergic neurons as well as neurons that release other neurotransmitters, such as nitric oxide, several neuropeptides, and ATP.

The effectors mentioned earlier—muscle cells and exocrine glands—are

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supplied by neurons that are part of the enteric nervous system. This permits neural reflexes that are completely within the tract—that is, independent of the CNS. In addition, nerve fibers from both the sympathetic and parasympathetic branches of the autonomic nervous system enter the intestinal tract and synapse with neurons in both plexuses. Via these pathways, the CNS can influence the motility and secretory activity of the gastrointestinal tract.

Thus, two types of neural-reflex arcs exist (**Figure**):

(1) **short reflexes** from receptors through the nerve plexuses to effector cells

(2) **long reflexes** from receptors in the tract to the CNS by way of afferent nerves, and back to the nerve plexuses and effector cells by way of autonomic nerve fibers.

Finally, it should be noted that not all neural reflexes are initiated by signals *within* the tract. Hunger, the sight or smell of food, and the emotional state of an individual can have significant effects on the gastrointestinal tract, effects that are mediated by the CNS via autonomic neurons.

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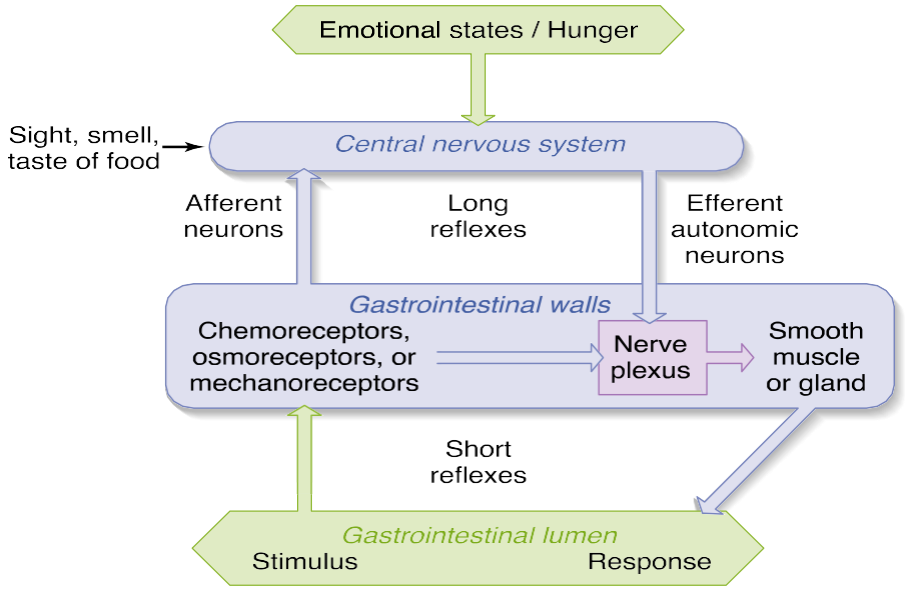

Figure 2: Long and short neural-reflex pathways activated by stimuli in the gastrointestinal tract.

Hormonal Regulation

The hormones that control the gastrointestinal system are secreted mainly by endocrine cells scattered throughout the epithelium of the stomach and small intestine. That is, these cells are not clustered into discrete organs like the thyroid or adrenal glands. One surface of each endocrine cell is exposed to the lumen of the gastrointestinal tract. At this surface, various chemical substances in the chyme stimulate the cell to release its hormones from the opposite side of the cell into the blood. The gastrointestinal hormones reach their target cells via the circulation.

The four best-understood gastrointestinal hormones are **secretin,**

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cholecystokinin (**CCK**), **gastrin,** and **glucose-dependent insulinotropic peptide** (**GIP**). **Table 1** summarizes the characteristics of these GI hormones and not only serves as a reference for future discussions but also illustrates the following generalizations:

(1) Each hormone participates in a feedback control system that regulates some aspect of the GI luminal environment,

(2) Most GI hormones affect more than one type of target cell.

CCK can illustrate these two generalizations. The presence of fatty acids and amino acids in the small intestine triggers CCK secretion from cells in the small intestine into the blood. Circulating CCK then stimulates the pancreas to increase the secretion of digestive enzymes and causes the sphincter of Oddi to relax. CCK also causes the gallbladder to contract, delivering to the intestine the bile salts required for micelle formation. As fatty acids and amino acids are absorbed, their concentrations in the lumen decrease, removing the signal for CCK release.

In many cases, a single effector cell contains receptors for more than one hormone, as well as receptors for neurotransmitters and paracrine agents (cell to cell communication). The result is a variety of inputs that can affect the cell's response. One such event is the phenomenon known as

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potentiation, which is exemplified by the interaction between secretin and CCK. Secretin strongly stimulates pancreatic $HCO3^{+}$ secretion, whereas CCK is a weak stimulus of $HCO3^{+}$secretion. Both hormones together, however, stimulate pancreatic HCO^{+} secretion more strongly than would be predicted by the sum of their individual stimulatory effects. This is because CCK amplifies the response to secretin.

Table 1: *Properties of Gastrointestinal Hormones*

	Gastrin	CCK	Secretin	GIP
Chemical class	Peptide	Peptide	Peptide	Peptide
Site of production	Antrum of stomach	Small intestine	Small intestine	Small intestine
Stimuli for hormone release	Amino acids, peptides in stomach; parasympathetic nerves	Amino acids, fatty acids in small intestine	Acid in small intestine	Glucose, fat in small intestine
Factors inhibiting hormone release	Acid in stomach; somatostatin			
		Target Organ Responses		
Stomach Acid secretion Motility	 Stimulates Stimulates	 Inhibits Inhibits	 Inhibits Inhibits	
Pancreas HCO_3^2 secretion Enzyme secretion Insulin secretion		 Potentiates secretin's actions Stimulates	 Stimulates Potentiates CCK's actions	 Stimulates
Liver (bile ducts) HCO_3^2 secretion		 Potentiates secretin's actions	 Stimulates	
Gallbladder Contraction		 Stimulates		
Sphincter of Oddi		Relaxes		
Small intestine Motility	 Stimulates ileum			
Large intestine	Stimulates mass movement			

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Phases of Gastrointestinal Control

The neural and hormonal control of the gastrointestinal system is, in large part, divisible يقسم into three phases—cephalic, gastric, and intestinal—according to where the stimulus is perceived.

The **cephalic** (from a Greek word for "head") **phase** is initiated when sensory receptors in the head are stimulated by sight, smell, taste, and chewing. Various emotional states can also initiate this phase. The efferent pathways for these reflexes are primarily mediated by parasympathetic fibers carried in the vagus nerves. These fibers activate neurons in the gastrointestinal nerve plexuses, which in turn affect secretory and contractile activity.

Four stimuli in the stomach initiate the reflexes that constitute the **gastric phase** of regulation: distension, acidity, amino acids, and peptides formed during the digestion of ingested protein. The responses to these stimuli are mediated by short and long neural reflexes and by release of the hormone gastrin.

Finally, the **intestinal phase** is initiated by stimuli in the intestinal tract: distension, acidity, osmolarity, and various digestive products. The intestinal phase is mediated by both short and long neural reflexes and by the

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gastrointestinal hormones secretin, CCK, and GIP, all of which are secreted by endocrine cells in the small intestine.

We reemphasize that each of these phases is named for the site at which the various stimuli initiate the reflex and not for the sites of effector activity.

Keeping in mind the neural and hormonal mechanisms available for regulating gastrointestinal activity, we can now examine the specific contractile and secretory processes that occur in each segment of the gastrointestinal system.

Mouth, Pharynx, and Esophagus

- **Chewing**

Chewing is controlled by the somatic nerves to the skeletal muscles of the mouth and jaw. In addition to the voluntary control of these muscles, rhythmic chewing motions are reflexively activated by the pressure of food against the gums, hard palate at the roof of the mouth, and tongue. Activation of these mechanoreceptors leads to reflexive inhibition of the muscles holding the jaw closed. The resulting relaxation of the jaw reduces the pressure on the various mechanoreceptors, leading to a new cycle of contraction and relaxation.

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Chewing prolongs the subjective pleasure of taste. Chewing also breaks up food particles, creating a bolus that is easier to swallow and, possibly, digest. Attempting to swallow a large particle of food can lead to choking if the particle lodges over the trachea, blocking the entry of air into the lungs.

- **Saliva**

There are three pairs of salivary glands—the parotid, sublingual, and submandibular glands (Figure 1 in lecture 1). The secretion of saliva is controlled by both sympathetic and parasympathetic neurons. Unlike their antagonistic activity in most organs, both systems stimulate salivary secretion, with the parasympathetic neurons producing the greater response. There is no hormonal regulation of salivary secretion. In the absence of ingested material, a low rate of salivary secretion keeps the mouth moist. The smell or sight of food induces a cephalic phase of salivary secretion. Salivary secretion can increase markedly in response to a meal. This reflex response is initiated by chemoreceptors (acidic fruit juices are particularly strong stimuli) and pressure receptors in the walls of the mouth and on the tongue.

Increased saliva secretion is accomplished by a large increase in blood flow to the salivary glands, which is mediated primarily by an increase in

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parasympathetic neural activity. The volume of saliva secreted per gram of tissue is the largest secretion of any of the body's exocrine glands. Overall, the three pairs of salivary glands that drain into the mouth supply 1000–1500 mL of saliva per day.

The saliva also has some antibacterial action, and patients with deficient salivation **(xerostomia)** have a higher than normal incidence of dental caries. The buffers in saliva help maintain the oral pH at about 7.0.

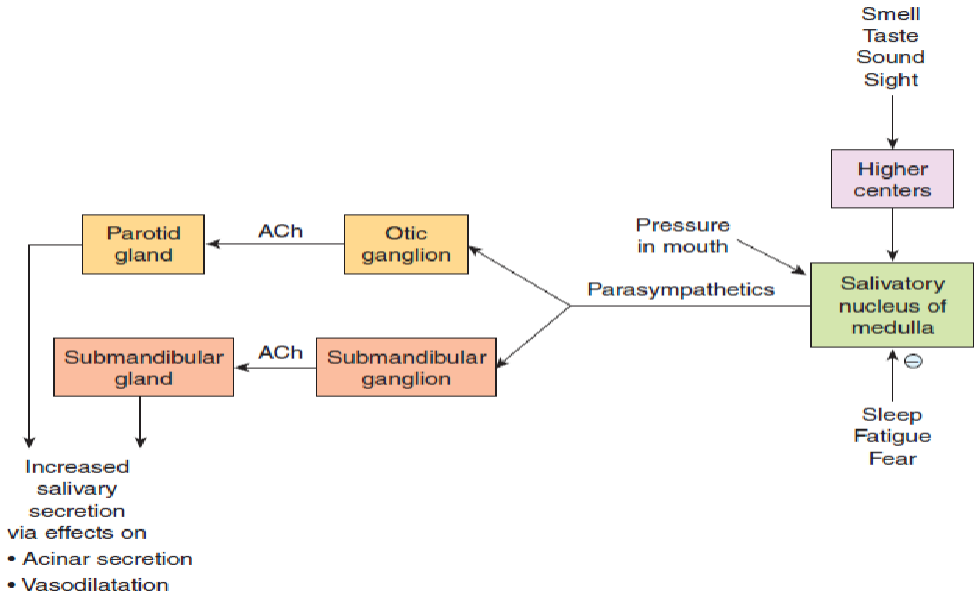

Figure 4: *Regulation of salivary secretion by the parasympathetic nervous system***.**

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- **Swallowing**

Swallowing is a complex reflex initiated when pressure receptors in the walls of the pharynx are stimulated by food or drink forced into the rear of the mouth by the tongue (**Figure 3a**). These receptors send afferent impulses to the **swallowing center** in the medulla oblongata of the brainstem. This center then elicits swallowing via efferent fibers to the muscles in the pharynx and esophagus as well as to the respiratory muscles.

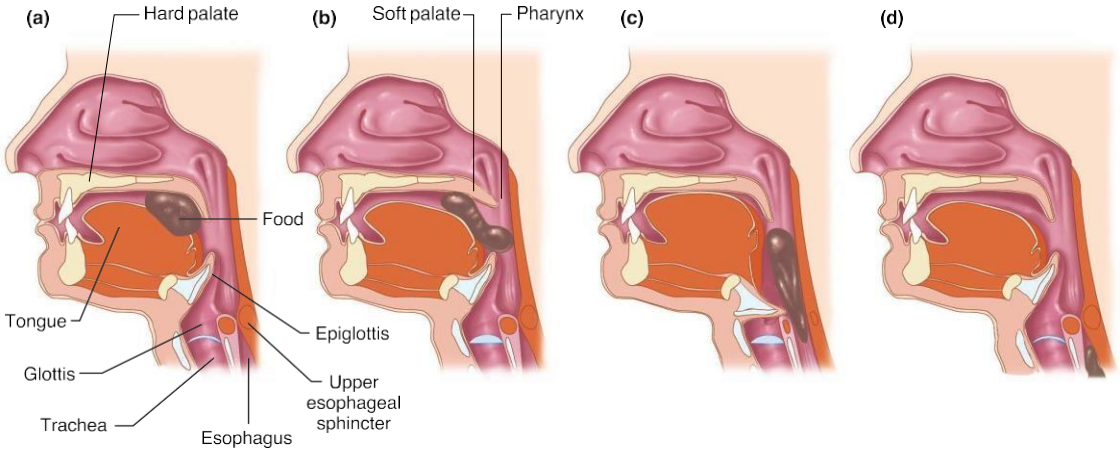

Figure 3: *Movements of food through the pharynx and upper esophagus during swallowing.*

As the ingested material moves into the pharynx, the soft palate elevates and lodges against the back wall of the pharynx, preventing food from entering the nasal cavity (**Figure 3b**). Impulses from the swallowing center inhibit respiration, raise the larynx, and close the **glottis** (the area around the vocal

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cords and the space between them), keeping food from moving into the trachea. As the tongue forces the food farther back into the pharynx, the food tilts a flap of tissue, the **epiglottis,** backward to cover the closed glottis (**Figure 3c**). This prevents **aspiration** of food, a potentially dangerous situation in which food travels down the trachea and can cause choking, or regurgitated stomach contents are allowed into the lungs causing damage.

The next stage of swallowing occurs in the esophagus (**Figure 3d**), the tube that passes through the thoracic cavity, penetrates the diaphragm (which separates the thoracic cavity from the abdominal cavity), and joins the stomach a few centimeters below the diaphragm. Skeletal muscle surrounds the upper third of the esophagus, and smooth muscle surrounds the lower two-thirds.

Both ends of the esophagus are normally closed by the contraction of **sphincter** muscles. A ring of skeletal muscle surrounds the esophagus just below the pharynx and forms the **upper esophageal sphincter** (see Figure 4), whereas the smooth muscle in the last portion of the esophagus forms the **lower esophageal sphincter** (**Figure 5**).

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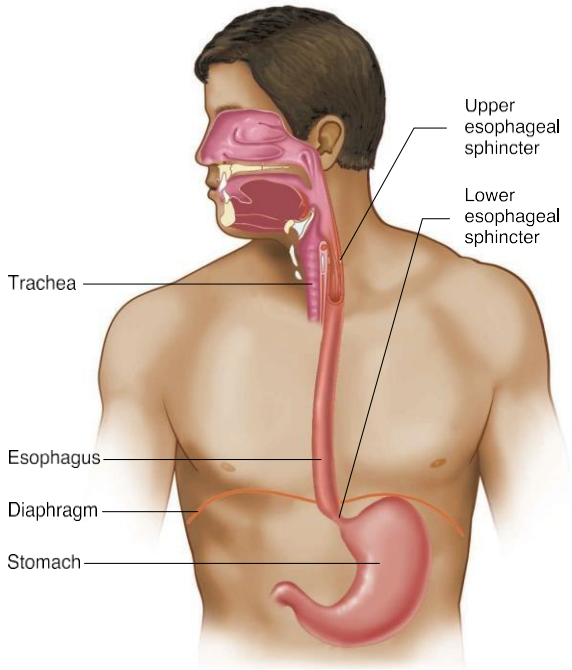

Figure 5: *Location of upper and lower esophageal sphincters.*

The act of swallowing is a neural and muscular reflex coordinated by a group of brainstem nuclei collectively called the swallowing center. Both skeletal and smooth muscles are involved, so the swallowing center must direct efferent activity in both somatic nerves (to skeletal muscle) and autonomic nerves (to smooth muscle).

The ability of the lower esophageal sphincter to maintain a barrier between the stomach and the esophagus when swallow- ing is not taking place is aided by the fact that the last portion of the esophagus lies below the diaphragm and is subject to the same abdominal pressures as the stomach. In other words, if the pressure in the abdominal cavity increases, for example, during cycles of respiration or contraction of the abdominal muscles, the

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pressures on both the gastric contents and the terminal segment of the esophagus are increased together. This prevents the formation of a pressure gradient between the stomach and esophagus that could force the stomach's contents into the esophagus.

During pregnancy, the growth of the fetus not only increases the pressure on the abdominal contents but also can push the terminal segment of the esophagus through the diaphragm into the thoracic cavity. The sphincter is therefore no longer assisted by changes in abdominal pressure. Consequently, during the last half of pregnancy, increased abdominal pressure tends to force some of the gastric contents up into the esophagus (***gastroesophageal reflux***). The **hydrochloric acid** from the stomach irritates the esophageal walls, producing pain known as ***heartburn*** (because the pain appears to be located in the area of the heart). Heartburn often subsides in the last weeks of pregnancy prior to delivery, as the uterus descends lower into the pelvis, decreasing the pressure on the stomach.

Gastroesophageal reflux and the pain of heartburn also occur in the absence of pregnancy. Some people have less efficient lower esophageal sphincters, resulting in repeated episodes of gastric contents refluxing into the esophagus. In extreme cases, ulceration, scarring, obstruction, or

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perforations (holes) of the lower esophagus may occur. Gastroesophageal reflux can also occur after a large meal, which can sufficiently increase the pressure in the stomach to force acid into the esophagus.