

# Human digestive system

**Human digestive system**, the system used in the human body for the process of digestion. The human digestive system consists primarily of the digestive tract, or the series of structures and organs through which food and liquids pass during their processing into forms absorbable into the bloodstream. The system also consists of the structures through which wastes pass in the process of elimination and other organs that contribute juices necessary for the digestive process.

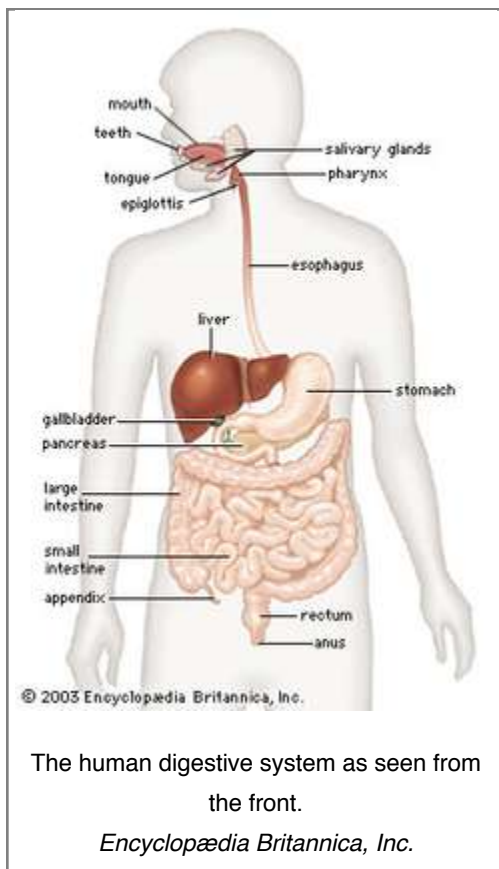
## TABLE OF CONTENTS

Introduction

Structures and functions of the human digestive system

Features of the gastrointestinal tract

Embryology and evolution of the vertebrate digestive system

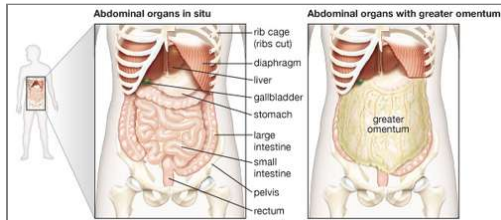


## Structures and functions of the human digestive system

The digestive tract begins at the lips and ends at the anus. It consists of the mouth, or oral cavity, with its teeth, for grinding the food, and its tongue, which serves to knead food and mix it with saliva; the throat, or pharynx; the esophagus; the stomach; the small intestine, consisting of the duodenum, the jejunum, and the ileum; and the large intestine, consisting of the cecum, a closed-end sac connecting with the ileum, the ascending colon, the transverse colon, the descending colon, and the sigmoid colon, which terminates in the rectum. Glands contributing digestive juices include the salivary glands, the gastric glands in the stomach lining, the pancreas, and the liver and its adjuncts—the gallbladder and bile ducts.

All of these organs and glands contribute to the physical and chemical breaking down of ingested food and to the eventual elimination of nondigestible wastes. Their structures and functions are described step

by step in this section.



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The abdominal organs are supported and protected by the bones of the pelvis and ribcage and are covered by the greater omentum, a fold of peritoneum that consists mainly of fat.

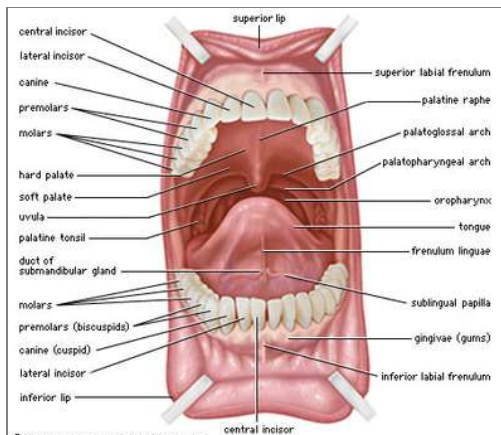
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## Mouth and oral structures

Little digestion of food actually takes place in the mouth. However, through the process of mastication, or chewing, food is prepared in the mouth for transport through the upper digestive tract into the stomach and small intestine, where the principal digestive processes take place.

Chewing is the first mechanical process to which food is subjected. Movements of the lower jaw in chewing are brought about by the muscles of mastication (the masseter, the temporal, the

medial and lateral pterygoids, and the buccinator). The sensitivity of the periodontal membrane that surrounds and supports the teeth, rather than the power of the muscles of mastication, determines the force of the bite.



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Anterior view of the oral cavity.

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Mastication is not essential for adequate digestion. Chewing does aid digestion, however, by reducing food to small particles and mixing it with the saliva secreted by the salivary glands. The saliva lubricates and moistens dry food, while chewing distributes the saliva throughout the food mass. The movement of the tongue against the hard palate and the cheeks helps to form a rounded mass, or bolus, of food.

## The lips and cheeks

The lips, two fleshy folds that surround the mouth, are composed externally of skin and internally of mucous membrane, or mucosa. The mucosa is rich in mucus-secreting glands, which together with saliva ensure adequate lubrication for the purposes of speech and mastication.

The cheeks, the sides of the mouth, are continuous with the lips and have a similar structure. A distinct fat pad is found in the subcutaneous tissue (the tissue beneath the skin) of the cheek; this pad is especially large in infants and is known as the

sucking pad. On the inner surface of each cheek, opposite the second upper molar tooth, is a slight elevation that marks the opening of the parotid duct, leading from the parotid salivary gland, which is located in front of the ear. Just behind this gland are four to five mucus-secreting glands, the ducts of which open opposite the last molar tooth.

## **The roof of the mouth**

The roof of the mouth is concave and is formed by the hard and soft palate. The hard palate is formed by the horizontal portions of the two palatine bones and the palatine portions of the maxillae, or upper jaws. The hard palate is covered by a thick, somewhat pale mucous membrane that is continuous with that of the gums and is bound to the upper jaw and palate bones by firm fibrous tissue. The soft palate is continuous with the hard palate in front. Posteriorly it is continuous with the mucous membrane covering the floor of the nasal cavity. The soft palate is composed of a strong, thin, fibrous sheet, the palatine aponeurosis, and the glossopalatine and pharyngopalatine muscles. A small projection called the uvula hangs free from the posterior of the soft palate.

## **The floor of the mouth**

The floor of the mouth can be seen only when the tongue is raised. In the midline is a prominent, elevated fold of mucous membrane (frenulum linguae) that binds each lip to the gums, and on each side of this is a slight fold called a sublingual papilla, from which the ducts of the submandibular salivary glands open. Running outward and backward from each sublingual papilla is a ridge (the plica sublingualis) that marks the upper edge of the sublingual (under the tongue) salivary gland and onto which most of the ducts of that gland open.

## **The gums**

The gums consist of mucous membranes connected by thick fibrous tissue to the membrane surrounding the bones of the jaw. The gum membrane rises to form a collar around the base of the crown (exposed portion) of each tooth. Rich in blood vessels, the gum tissues receive branches from the alveolar arteries; these vessels, called alveolar because of their relationship to the alveoli dentales, or tooth sockets, also supply the teeth and the spongy bone of the upper and lower jaws, in which the teeth are lodged.

## The teeth

The teeth are hard, white structures found in the mouth. Usually used for mastication, the teeth of different vertebrate species are sometimes specialized. The teeth of snakes, for example, are very thin and sharp and usually curve backward; they function in capturing prey but not in chewing, because snakes swallow their food whole. The teeth of carnivorous mammals, such as cats and dogs, are more pointed than those of primates, including humans; the canines are long, and the premolars lack flat grinding surfaces, being more adapted to cutting and shearing (often the more posterior molars are lost). On the other hand, herbivores such as cows and horses have very large, flat premolars and molars with complex ridges and cusps; the canines are often totally absent. Sharp pointed teeth, poorly adapted for chewing, generally characterize meat eaters such as snakes, dogs, and cats; and broad, flat teeth, well adapted for chewing, characterize herbivores. The differences in the shapes of teeth are functional adaptations. Few animals can digest cellulose, yet the plant cells used as food by herbivores are enclosed in cellulose cell walls that must be broken down before the cell contents can be exposed to the action of digestive enzymes. By contrast, the animal cells in meat are not encased in nondigestible matter and can be acted upon directly by digestive enzymes. Consequently, chewing is not so essential for carnivores as it is for herbivores. Humans, who are omnivores (eaters of plants and animal tissue), have teeth that belong, functionally and structurally, somewhere between the extremes of specialization attained by the teeth of carnivores and herbivores.

Each tooth consists of a crown and one or more roots. The crown is the functional part of the tooth that is visible above the gum. The root is the unseen portion that supports and fastens the tooth in the jawbone. The shapes of the crowns and the roots vary in different parts of the mouth and from one animal to another. The teeth on one side of the jaw are essentially a mirror image of those located on the opposite side. The upper teeth differ from the lower and are complementary to them. Humans normally have two sets of teeth during their lifetime. The first set, known as the deciduous, milk, or primary dentition, is acquired gradually between the ages of six months and two years. As the jaws grow and expand, these teeth are replaced one by one by the teeth of the secondary set. There are five deciduous teeth and eight permanent teeth in each quarter of the mouth, resulting in a total of 32 permanent teeth to succeed the 20 deciduous ones.

## The tongue

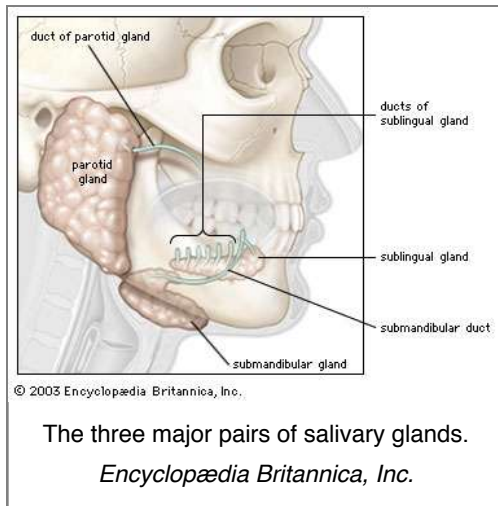
The tongue, a muscular organ located on the floor of the mouth, is an extremely mobile structure and is an important accessory organ in such motor functions as speech, chewing, and swallowing. In conjunction with the cheeks, it is able to guide and maintain food between the upper and lower teeth until mastication is complete. The motility of the tongue aids in creating a negative pressure within the oral cavity and thus enables infants to suckle. Especially important as a peripheral sense organ, the tongue contains groups of specialized epithelial cells, known as taste buds, that carry stimuli from the oral cavity to the central nervous system. Furthermore, the tongue's glands produce some of the saliva necessary for swallowing.

The tongue consists of a mass of interwoven striated (striped) muscles interspersed with fat. The mucous membrane that covers the tongue varies in different regions. The tongue is attached to the lower jaw, the hyoid bone (a U-shaped bone between the lower jaw and the larynx), the skull, the soft palate, and the pharynx by its extrinsic muscles. It is bound to the floor of the mouth and to the epiglottis (a plate of cartilage that serves as a lid for the larynx) by folds of mucous membrane.

## Salivary glands

Food is tasted and mixed with saliva that is secreted by several sets of glands. Besides the many minute glands that secrete saliva, there are three major pairs of salivary glands: the parotid, the submandibular, and the sublingual glands. The parotid glands, the largest of the pairs, are located at the side of the face, below and in front of each ear. The parotid glands are enclosed in sheaths that limit the extent of their swelling when inflamed, as in mumps. The submandibular glands, which are rounded in shape, lie near the inner side of the lower jawbone, in front of the sternomastoid muscle (the prominent muscle of the jaw). The sublingual glands lie directly under the mucous membrane covering the floor of the mouth beneath the tongue.

The salivary glands are of the type called racemose, from the Latin *racemosus* ("full of clusters"), because of the clusterlike arrangement of their secreting cells in rounded sacs, called acini, attached to freely branching systems of ducts. The walls of the acini surround a small central cavity known as an alveolus. In the walls of the acini are pyramidal secreting cells and some flat, star-shaped contractile cells called myoepithelial, or basket, cells. The latter cells are thought to contract, like the similar myoepithelial cells of the breast, which by their contraction expel milk from the milk



ducts.

The secreting cells may be of the serous or the mucous type. The latter type secretes mucin, the chief constituent of mucus; the former, a watery fluid containing the enzyme amylase. The secreting cells of the parotid glands are of the serous type; those of the submandibular glands, of both serous and mucous types, with the serous cells outnumbering the mucous cells by four to one. The acini of the sublingual glands are

composed primarily of mucous cells.

The salivary glands are controlled by the two divisions of the autonomic nervous system, the sympathetic and the parasympathetic. The parasympathetic nerve supply regulates secretion by the acinar cells and causes the blood vessels to dilate. Functions regulated by the sympathetic nerves include secretion by the acinar cells, constriction of blood vessels, and, presumably, contraction of the myoepithelial cells. Normally secretion of saliva is constant, regardless of the presence of food in the mouth. The amount of saliva secreted in 24 hours usually amounts to 1–1.5 litres. When something touches the gums, the tongue, or some region of the mouth lining, or when chewing occurs, the amount of saliva secreted increases. The stimulating substance need not be food—dry sand in the mouth or even moving the jaws and tongue when the mouth is empty increases the salivary flow. This coupling of direct stimulation to the oral mucosa with increased salivation is known as the unconditioned salivary reflex. When an individual learns that a particular sight, sound, smell, or other stimulus is regularly associated with food, that stimulus alone may suffice to stimulate increased salivary flow. This response is known as the conditioned salivary reflex.

## Saliva

Saliva dissolves some of the chewed food and acts as a lubricant, facilitating passage through the subsequent portions of the digestive tract. Saliva also contains a starch-digesting enzyme called amylase (ptyalin), which initiates the process of enzymatic hydrolysis; it splits starch (a polysaccharide containing many sugar molecules bound in a continuous chain) into molecules of the double sugar maltose. Many carnivores, such as dogs and cats, have no amylase in their saliva; therefore, their natural diet

contains very little starch. Substances must be in solution for the taste buds to be stimulated; saliva provides the solvent for food materials.

The composition of saliva varies, but its principal components are water, inorganic ions similar to those commonly found in blood plasma, and a number of organic constituents, including salivary proteins, free amino acids, and the enzymes lysozyme and amylase. Although saliva is slightly acidic, the bicarbonates and phosphates contained within it serve as buffers and maintain the pH, or hydrogen ion concentration, of saliva relatively constant under ordinary conditions.

The concentrations of bicarbonate, chloride, potassium, and sodium in saliva are directly related to the rate of their flow. There is also a direct relation between bicarbonate concentration and the partial pressure of carbon dioxide in the blood. The concentration of chloride in the blood varies from 5 millimoles per litre at low flow rates to 70 millimoles per litre when the flow rate is high. The sodium concentrations in similar circumstances vary from 5 millimoles per litre to 100 millimoles per litre. The concentration of potassium in the blood is often higher than that in the blood plasma, up to 20 millimoles per litre, which accounts for the sharp and metallic taste of saliva when flow is brisk.

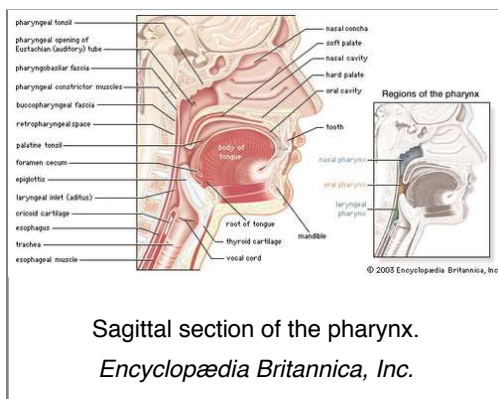
The constant flow of saliva keeps the oral cavity and teeth moist and comparatively free from food residues, sloughed epithelial cells, and foreign particles. By removing material that may serve as culture media, saliva inhibits the growth of bacteria. Saliva serves a protective function, for the enzyme lysozyme has the ability to lyse, or dissolve, certain bacteria. The secretion of saliva also provides a mechanism whereby certain organic and inorganic substances can be excreted from the body, including mercury, lead, potassium iodide, bromide, morphine, ethyl alcohol, and certain antibiotics such as penicillin, streptomycin, and chlortetracycline.

Although saliva is not essential to life, its absence results in a number of inconveniences, including dryness of the oral mucous membrane, poor oral hygiene because of bacterial overgrowth, a greatly diminished sense of taste, and difficulties with speech.

## **Pharynx**

The pharynx, or throat, is the passageway leading from the mouth and nose to the esophagus and larynx. The pharynx permits the passage of swallowed solids and

liquids into the esophagus, or gullet, and conducts air to and from the trachea, or windpipe, during respiration. The pharynx also connects on either side with the cavity of the middle ear by way of the Eustachian tube and provides for equalization of air pressure on the eardrum membrane, which separates the cavity of the middle ear from the external ear canal. The pharynx has roughly the form of a flattened funnel. It is attached to the surrounding structures but is loose enough to permit gliding of the pharyngeal wall against them in the movements of swallowing. The principal muscles of the pharynx, involved in the mechanics of swallowing, are the three pharyngeal constrictors, which overlap each other slightly and form the primary musculature of the side and rear pharyngeal walls.



There are three main divisions of the pharynx: the oral pharynx, the nasal pharynx, and the laryngeal pharynx. The latter two are airways, whereas the oral pharynx is shared by both the respiratory and digestive tracts. On either side of the opening between the mouth cavity and the oral pharynx is a palatine tonsil, so called because of its proximity to the palate. Each palatine tonsil is located between two vertical folds of mucous membrane

called the glossopalatine arches. The nasal pharynx, above, is separated from the oral pharynx by the soft palate. Another pair of tonsils are located on the roof of the nasal pharynx. The pharyngeal tonsils, also known as the adenoids, are part of the body's immune system. When the pharyngeal tonsils become grossly swollen (which occurs often during childhood) they occlude the airway. The laryngeal pharynx and the lower part of the oral pharynx are hidden by the root of the tongue.

The first stage of deglutition, or swallowing, consists of passage of the bolus into the pharynx and is initiated voluntarily. The front part of the tongue is retracted and depressed, mastication ceases, respiration is inhibited, and the back portion of the tongue is elevated and retracted against the hard palate. This action, produced by the strong muscles of the tongue, forces the bolus from the mouth into the pharynx. Entry of the bolus into the nasal pharynx is prevented by the elevation of the soft palate against the posterior pharyngeal wall. As the bolus is forced into the pharynx, the larynx moves upward and forward under the base of the tongue. The superior pharyngeal constrictor muscles contract, initiating a rapid pharyngeal peristaltic, or squeezing, contraction that moves down the pharynx, propelling the bolus in front of



it. The walls and structures of the lower pharynx are elevated to engulf the oncoming mass of food. The epiglottis, a lidlike covering that protects the entrance to the larynx, diverts the bolus to the pharynx. The cricopharyngeal muscle, or upper esophageal sphincter, which has kept the esophagus closed until this point, relaxes as the bolus approaches and allows it to enter the upper esophagus. The pharyngeal peristaltic contraction continues into the esophagus and becomes the primary esophageal peristaltic contraction.

## Esophagus

The esophagus, which passes food from the pharynx to the stomach, is about 25 cm (10 inches) in length; the width varies from 1.5 to 2 cm (about 1 inch). The esophagus lies behind the trachea and heart and in front of the spinal column; it passes through the diaphragm before entering the stomach.

The esophagus contains four layers—the mucosa, submucosa, muscularis, and tunica adventitia. The mucosa is made up of stratified squamous epithelium containing numerous mucous glands. The submucosa is a thick, loose fibrous layer connecting the mucosa to the muscularis. Together the mucosa and submucosa form long longitudinal folds, so that a cross section of the esophagus opening would be star-shaped. The muscularis is composed of an inner layer, in which the fibres are circular, and an outer layer of longitudinal fibres. Both muscle groups are wound around and along the alimentary tract, but the inner one has a very tight spiral, so that the windings are virtually circular, whereas the outer one has a very slowly unwinding spiral that is virtually longitudinal. The outer layer of the esophagus, the tunica adventitia, is composed of loose fibrous tissue that connects the esophagus with neighbouring structures. Except during the act of swallowing, the esophagus is normally empty, and its lumen, or channel, is essentially closed by the longitudinal folds of the mucosal and submucosal layers.

The upper third of the esophagus is composed of striated (voluntary) muscle. The middle third is a mixture of striated and smooth (involuntary) muscle, and the lower third consists only of smooth muscle. The esophagus has two sphincters, circular muscles that act like drawstrings in closing channels. Both sphincters normally remain closed except during the act of swallowing. The upper esophageal sphincter is located at the level of the cricoid cartilage (a single ringlike cartilage forming the lower part of the larynx wall). This sphincter is called the cricopharyngeus muscle. The lower esophageal sphincter encircles the 3 to 4 cm of the esophagus that pass

through an opening in the diaphragm called the diaphragmatic hiatus. The lower esophageal sphincter is maintained in tension at all times, except in response to a descending contraction wave, at which point it relaxes momentarily to allow the release of gas (belching) or vomiting. The lower esophageal sphincter has an important role, therefore, in protecting the esophagus from the reflux of gastric contents with changes in body position or with alterations of intragastric pressure.

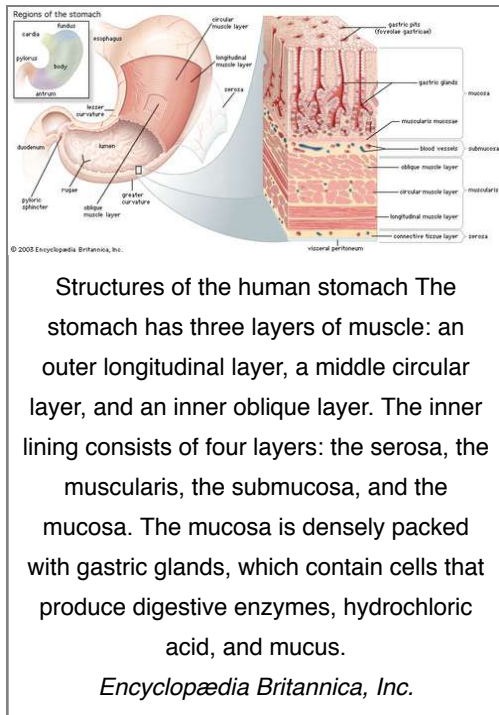
Transport through the esophagus is accomplished by the primary esophageal peristaltic contractions, which, as noted above, originate in the pharynx. These contractions are produced by an advancing peristaltic wave that creates a pressure gradient and sweeps the bolus ahead of it. Transport of material through the esophagus takes approximately 10 seconds. When the bolus arrives at the junction with the stomach, the lower esophageal sphincter relaxes and the bolus enters the stomach. If the bolus is too large, or if the peristaltic contraction is too weak, the bolus may become arrested in the middle or lower esophagus. When this occurs, secondary peristaltic contractions originate around the bolus in response to the local distension of the esophageal wall and propel the bolus into the stomach.

When a liquid is swallowed, its transport through the esophagus depends somewhat on the position of the body and the effects of gravity. When swallowed in a horizontal or head-down position, liquids are handled in the same manner as solids, with the liquid moving immediately ahead of the advancing peristaltic contraction. (The high pressures and strong contractions of the esophageal peristaltic wave make it possible for animals with very long necks, such as the giraffe, to transport liquids through the esophagus for many feet.) When the body is in the upright position, however, liquids enter the esophagus and fall by gravity to the lower end; there they await the arrival of the peristaltic contraction and the opening of the lower esophageal sphincter (8 to 10 seconds) before being emptied into the stomach.

## **Stomach**

### **Anatomy**

The stomach receives ingested food and liquids from the esophagus and retains them for grinding and mixing with gastric juice so that food particles are smaller and more soluble. The main functions of the stomach are to commence the digestion of carbohydrates and proteins, to convert the meal into chyme, and to discharge the chyme into the small intestine periodically as the physical and chemical condition of



the mixture is rendered suitable for the next phase of digestion. The stomach is located in the left upper part of the abdomen immediately below the diaphragm. In front of the stomach are the liver, part of the diaphragm, and the anterior abdominal wall. Behind it are the pancreas, the left kidney, the left adrenal gland, the spleen, and the colon. The stomach is more or less concave on its right side, convex on its left. The concave border is called the lesser curvature; the convex border, the greater curvature. When the stomach is empty, its mucosal lining is thrown into numerous longitudinal folds, known as rugae; these tend to disappear when the stomach is distended.

The cardia is the opening from the esophagus into the stomach. The uppermost part of the stomach, located above the entrance of the esophagus, is the fundus. The fundus adapts to the varying volume of ingested food by relaxing its muscular wall; it frequently contains a gas bubble, especially after a meal. The largest part of the stomach is known simply as the body; it serves primarily as a reservoir for ingested food and liquids. The antrum, the lowermost part of the stomach, is somewhat funnel-shaped, with its wide end joining the lower part of the body and its narrow end connecting with the pyloric canal, which empties into the duodenum (the upper division of the small intestine). The pyloric portion of the stomach (antrum plus pyloric canal) tends to curve to the right and slightly upward and backward and thus gives the stomach its J-shaped appearance. The pylorus, the narrowest portion of the stomach, is the outlet from the stomach into the duodenum. It is approximately 2 cm (almost 1 inch) in diameter and is surrounded by thick loops of smooth muscle.

The muscles of the stomach wall are arranged in three layers, or coats. The external coat, called the longitudinal muscle layer, is continuous with the longitudinal muscle coat of the esophagus. Longitudinal muscle fibres are divided at the cardia into two broad strips. The one on the right, the stronger, spreads out to cover the lesser curvature and the adjacent posterior and anterior walls of the stomach. Longitudinal fibres on the left radiate from the esophagus over the dome of the fundus to cover the greater curvature and continue on to the pylorus, where they join the longitudinal

fibres coming down over the lesser curvature. The longitudinal layer continues on into the duodenum, forming the longitudinal muscle of the small intestine.

The middle, or circular muscular layer, the strongest of the three muscular layers, completely covers the stomach. The circular fibres of this coat are best developed in the lower portion of the stomach, particularly over the antrum and pylorus. At the pyloric end of the stomach, the circular muscle layer becomes greatly thickened to form the pyloric sphincter. This muscular ring is slightly separated from the circular muscle of the duodenum by connective tissue.

The innermost layer of smooth muscle, called the oblique muscular layer, is strongest in the region of the fundus and progressively weaker as it approaches the pylorus.

The stomach is capable of dilating to accommodate more than one litre (about one quart) of food or liquids without increasing pressure on the stomach. This receptive relaxation of the upper part of the stomach to accommodate a meal is partly due to a neural reflex that is triggered when hydrochloric acid comes into contact with the mucosa of the antrum, possibly through the release of the hormone known as vasoactive intestinal peptide. The distension of the body of the stomach by food activates a neural reflex that initiates the muscle activity of the antrum.

## **Blood and nerve supply**

Many branches of the celiac trunk bring arterial blood to the stomach. The celiac trunk is a short, wide artery that branches from the abdominal portion of the aorta, the main vessel conveying arterial blood from the heart to the systemic circulation. Blood from the stomach is returned to the venous system through the portal vein, which carries the blood to the liver.

The nerve supply to the stomach is provided by both the parasympathetic and sympathetic divisions of the autonomic nervous system. The parasympathetic nerve fibres are carried in the vagus, or 10th cranial, nerve. As the vagus nerve passes through the opening in the diaphragm together with the esophagus, branches of the right vagus nerve spread over the posterior part of the stomach, while the left vagus nerve supplies the anterior part. Sympathetic branches from a nerve network called the celiac, or solar, plexus accompany the arteries of the stomach into the muscular wall.

## Stomach contractions

Three types of motor activity of the stomach have been observed. The first is a small contraction wave of the stomach wall that originates in the upper part of the stomach and slowly moves down over the organ toward the pyloric sphincter. This type of contraction produces a slight indentation of the stomach wall. Retrograde waves frequently sweep from the pyloric sphincter to the antrum and up to its junction with the body of the stomach, which results in a back-and-forth movement of the gastric contents that has a mixing and crushing effect. The second type of motor activity is also a contracting wave, but it is peristaltic in nature. The contraction originates in the upper part of the stomach as well and is slowly propagated over the organ toward the pyloric sphincter. This type of gastric contraction produces a deep indentation in the wall of the stomach. As the peristaltic wave approaches the antrum, the indentation completely obstructs the stomach lumen, or cavity, and thus compartmentalizes it. The contracting wave then moves over the antrum, propelling the material ahead of it through the pyloric sphincter into the duodenum. This type of contraction serves as a pumping mechanism for emptying the contents of the gastric antrum through the pyloric sphincter. Both the mixing and the peristaltic contractions of the stomach occur at a constant rate of three contractions per minute when recorded from the gastric antrum. A wave of peristalsis sweeps along the lower half of the stomach and along the entire intestine to the proximal colon at two-hour intervals after meals. These peristaltic waves can be halted by eating and can be induced by the hormone motilin.

The third type of gastric motor activity is best described as a tonic, or sustained, contraction of all the stomach muscles. The tonic contraction decreases the size of the stomach lumen, as all parts of the gastric wall seem to contract simultaneously. This activity accounts for the stomach's ability to accommodate itself to varying volumes of gastric content. The tonic contraction is independent of the other two types of contractions; however, mixing contractions and peristaltic contractions normally occur simultaneously with the tonic contraction. As food is broken down, smaller particles flow through the pyloric sphincter, which opens momentarily as a peristaltic wave descends through the antrum toward it. This permits "sampling" of the gastric contents by the duodenum.

## Gastric mucosa

The inner surface of the stomach is lined by a mucous membrane known as the

gastric mucosa. The mucosa is always covered by a layer of thick mucus that is secreted by tall columnar epithelial cells. Gastric mucus is a glycoprotein that serves two purposes: the lubrication of food masses in order to facilitate movement within the stomach and the formation of a protective layer over the lining epithelium of the stomach cavity. This protective layer is a defense mechanism the stomach has against being digested by its own protein-lyzing enzymes, and it is facilitated by the secretion of bicarbonate into the surface layer from the underlying mucosa. The acidity, or hydrogen ion concentration, of the mucous layer measures pH7 (neutral) at the area immediately adjacent to the epithelium and becomes more acidic (pH2) at the luminal level. When the gastric mucus is removed from the surface epithelium, small pits, called foveolae gastricae, may be observed with a magnifying glass. There are approximately 90 to 100 gastric pits per square millimetre (58,000 to 65,000 per square inch) of surface epithelium. Three to seven individual gastric glands empty their secretions into each gastric pit. Beneath the gastric mucosa is a thin layer of smooth muscle called the muscularis mucosae, and below this, in turn, is loose connective tissue, the submucosa, which attaches the gastric mucosa to the muscles in the walls of the stomach.

The gastric mucosa contains six different types of cells. In addition to the tall columnar surface epithelial cells mentioned above, there are five common cell types found in the various gastric glands.

(1) Mucoïd cells secrete gastric mucus and are common to all types of gastric glands. Mucoïd cells are the main cell type found in the gastric glands in the cardiac and pyloric areas of the stomach. The necks of the glands in the body and fundic parts of the stomach are lined with mucoïd cells.

(2) Zymogenic, or chief, cells are located predominantly in gastric glands in the body and fundic portions of the stomach. These cells secrete pepsinogen, from which the proteolytic (protein-digesting) enzyme pepsin is formed. There are two varieties of pepsinogen, known as pepsinogen I and pepsinogen II. Both are produced in the mucoïd and zymogenic cells in the glands of the body of the stomach, but the mucoïd glands located elsewhere in the stomach produce only pepsinogen II. Those stimuli that cause gastric acid secretion—in particular, vagal nerve stimulation—also promote the secretion of the pepsinogens.

(3) Gastrin cells, also called G cells, are located throughout the antrum. These endocrine cells secrete the acid-stimulating hormone gastrin as a response to lowered acidity of the gastric contents when food enters the stomach and gastric

distention. Gastrin then enters the bloodstream and is carried in the circulation to the mucosa of the body of the stomach, where it binds to receptor sites on the outer membrane of the parietal cells (described below). The gastrin-receptor complex that is formed triggers an energy-consuming reaction moderated by the presence of the enzyme ATPase, bound to the membrane that leads to the production and secretion of hydrogen ions in the parietal cells.

(4) Parietal, or oxyntic, cells, found in the glands of the body and fundic portions of the stomach, secrete hydrogen ions that combine with chloride ions to form hydrochloric acid (HCl). The acid that is produced drains into the lumen of the gland and then passes through to the stomach. This process occurs only when one or more types of receptors on the outer membrane of the parietal cell are bound to histamine, gastrin, or acetylcholine. Prostaglandins, hormonelike substances that are present in virtually all tissues and body fluids, inhibit the secretion of hydrochloric acid. The drugs omeprazole (Losec™ or Prilosec™) and lansoprazole (Prevacid™) also inhibit acid secretion by the parietal cells and are used as treatments for peptic ulcer. Parietal cells produce most of the water found in gastric juice; they also produce glycoproteins called intrinsic factor, which are essential to the maturation of red blood cells, vitamin B<sub>12</sub> absorption, and the health of certain cells in the central and peripheral nervous systems.

(5) Endocrine cells called enterochromaffin-like cells because of their staining characteristics are scattered throughout the body of the stomach. Enterochromaffin-like cells secrete several substances, including the hormone serotonin.

## Gastric secretion

The gastric mucosa secretes 1.2 to 1.5 litres of gastric juice per day. Gastric juice renders food particles soluble, initiates digestion (particularly of proteins), and converts the gastric contents to a semiliquid mass called chyme, thus preparing it for further digestion in the small intestine. Gastric juice is a variable mixture of water, hydrochloric acid, electrolytes (sodium, potassium, calcium, phosphate, sulfate, and bicarbonate), and organic substances (mucus, pepsins, and protein). This juice is highly acidic because of its hydrochloric acid content, and it is rich in enzymes. As noted above, the stomach walls are protected from digestive juices by the membrane on the surface of the epithelial cells bordering the lumen of the stomach; this membrane is rich in lipoproteins, which are resistant to attack by acid. The gastric juice of some mammals (e.g., calves) contains the enzyme rennin, which clumps milk proteins and thus takes them out of solution and makes them more susceptible to

the action of a proteolytic enzyme.

The process of gastric secretion can be divided into three phases (cephalic, gastric, and intestinal) that depend upon the primary mechanisms that cause the gastric mucosa to secrete gastric juice. The phases of gastric secretion overlap, and there is an interrelation and some interdependence between the neural and humoral pathways.

The cephalic phase of gastric secretion occurs in response to stimuli received by the senses—that is, taste, smell, sight, and sound. This phase of gastric secretion is entirely reflex in origin and is mediated by the vagus (10th cranial) nerve. Gastric juice is secreted in response to vagal stimulation, either directly by electrical impulses or indirectly by stimuli received through the senses. Ivan Petrovich Pavlov, the Russian physiologist, originally demonstrated this method of gastric secretion in a now-famous experiment with dogs.

The gastric phase is mediated by the vagus nerve and by the release of gastrin. The acidity of the gastric contents after a meal is buffered by proteins so that overall it remains around pH3 (acidic) for approximately 90 minutes. Acid continues to be secreted during the gastric phase in response to distension and to the peptides and amino acids that are liberated from protein as digestion proceeds. The chemical action of free amino acids and peptides excites the liberation of gastrin from the antrum into the circulation. Thus, there are mechanical, chemical, and hormonal factors contributing to the gastric secretory response to eating. This phase continues until the food has left the stomach.

The intestinal phase is not fully understood, because of a complex stimulatory and inhibitor process. Amino acids and small peptides that promote gastric acid secretion are infused into the circulation, however, at the same time chyme inhibits acid secretion. The secretion of gastric acid is an important inhibitor of gastrin release. If the pH of the antral contents falls below 2.5, gastrin is not released. Some of the hormones that are released from the small intestine by products of digestion (especially fat), in particular glucagon and secretin, also suppress acid secretion.

## **Absorption and emptying**

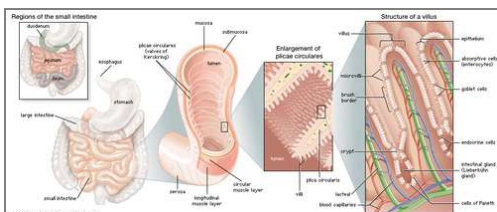
Although the stomach absorbs few of the products of digestion, it can absorb many other substances, including glucose and other simple sugars, amino acids, and some fat-soluble substances. The pH of the gastric contents determines whether some



substances are absorbed. At a low pH, for example, the environment is acidic and aspirin is absorbed from the stomach almost as rapidly as water, but, as the pH of the stomach rises and the environment becomes more basic, aspirin is absorbed more slowly. Water moves freely from the gastric contents across the gastric mucosa into the blood. The net absorption of water from the stomach is small, however, because water moves just as easily from the blood across the gastric mucosa to the lumen of the stomach. The absorption of water and alcohol can be slowed if the stomach contains foodstuffs and especially fats, probably because gastric emptying is delayed by fats, and most water in any situation is absorbed from the small intestine.

The rate of emptying of the stomach depends upon the physical and chemical composition of the meal. Fluids empty more rapidly than solids, carbohydrates more rapidly than proteins, and proteins more rapidly than fats. When food particles are sufficiently reduced in size and are nearly soluble and when receptors in the duodenal bulb (the area of attachment between the duodenum and the stomach) have a fluidity and a hydrogen ion concentration of a certain level, the duodenal bulb and the second part of the duodenum relax, allowing emptying of the stomach to start. During a duodenal contraction, the pressure in the duodenal bulb rises higher than that in the antrum. The pylorus prevents reflux into the stomach by shutting. The vagus nerve has an important role in the control of emptying, but there is some indication that the sympathetic division of the autonomic nervous system is also involved. Several of the peptide hormones of the digestive tract also have an effect on intragastric pressure and gastric movements, but their role in physiological circumstances is unclear.

## Small intestine



**Structures of the small intestine** The inner wall of the small intestine is covered by numerous folds of mucous membrane called plicae circulares. The surface of these folds contains tiny projections called villi and microvilli, which further increase the total area for absorption. Absorbed nutrients are

The small intestine is the principal organ of the digestive tract. The primary functions of the small intestine are mixing and transporting of intraluminal contents, production of enzymes and other constituents essential for digestion, and absorption of nutrients. Most of the processes that solubilize carbohydrates, proteins, and fats and reduce them to relatively simple organic compounds occur in the small intestine.

moved into circulation by blood capillaries and lacteals, or lymph channels.  
*Encyclopædia Britannica, Inc.*

## Anatomy

The small intestine, which is 670 to 760 cm (22 to 25 feet) in length and 3 to 4 cm (about 2 inches) in diameter, is the longest part of the digestive tract. It begins at the pylorus, the juncture with the stomach, and ends at the ileocecal valve, the juncture with the colon. The main functional segments of the small intestine are the duodenum, the jejunum, and the ileum.

The duodenum is 23 to 28 cm (9 to 11 inches) long and forms a C-shaped curve that encircles the head of the pancreas. Unlike the rest of the small intestine, it is retroperitoneal (that is, it is behind the peritoneum, the membrane lining the abdominal wall). Its first segment, known as the duodenal bulb, is the widest part of the small intestine. It is horizontal, passing backward and to the right from the pylorus, and lies somewhat behind the wide end of the gallbladder. The second part of the duodenum runs vertically downward in front of the hilum of the right kidney (the point of entrance or exit for blood vessels, nerves, and the ureters); it is into this part through the duodenal papilla (papilla of Vater) that the pancreatic juice and bile flow. The third part of the duodenum runs horizontally to the left in front of the aorta and the inferior vena cava (the principal channel for return to the heart of venous blood from the lower part of the body and the legs), while the fourth part ascends to the left side of the second lumbar vertebra (at the level of the small of the back), then bends sharply downward and forward to join the second part of the small intestine, the jejunum. An acute angle, called the duodenojejunal flexure, is formed by the suspension of this part of the small intestine by the ligament of Treitz.

The jejunum forms the upper two-fifths of the rest of the small intestine; it, like the ileum, has numerous convolutions and is attached to the posterior abdominal wall by the mesentery, an extensive fold of serous-secreting membrane. The ileum is the remaining three-fifths of the small intestine, though there is no absolute point at which the jejunum ends and the ileum begins. In broad terms, the jejunum occupies the upper and left part of the abdomen below the subcostal plane (that is, at the level of the 10th rib), while the ileum is located in the lower and right part. At its termination the ileum opens into the large intestine.

The arrangement of the muscular coats of the small intestine is uniform throughout the length of the organ. The inner, circular layer is thicker than the outer, longitudinal layer. The outermost layer of the small intestine is lined by the peritoneum.

## Blood and nerve supply

The superior mesenteric artery (a branch of the abdominal aorta) and the superior pancreaticoduodenal artery (a branch of the hepatic artery) supply the small intestine with blood. These vessels run between layers of the mesentery, the membrane that connects the intestines with the wall of the abdominal cavity, and give off large branches that form a row of connecting arches from which branches arise to enter the wall of the small bowel. The blood from the intestine is returned by means of the superior mesenteric vein, which, with the splenic vein, forms the portal vein, which drains into the liver.

The small intestine has both sympathetic and parasympathetic innervation. The vagus nerve provides parasympathetic innervation. Sympathetic innervation is provided by branches from the superior mesenteric plexus, a nerve network underneath the solar plexus that follows the blood vessels into the small intestine and finally terminates in the Auerbach plexus, which is located between the circular and longitudinal muscle coats, and the Meissner plexus, which is located in the submucosa. Numerous fibrils, both adrenergic (sympathetic) and cholinergic (parasympathetic), connect these two plexuses.

## Contractions and motility

The contractions of the circular and longitudinal muscles are regulated by electrical impulses that begin with the passage of calcium ions into the muscle cell. The duodenal pacemaker sends electrical impulses down the small intestine at a rate of 11 cycles per minute in the duodenum, gradually decreasing to 8 cycles per minute in the ileum. These electrical changes are propagated in the longitudinal muscle layer of the wall of the small intestine. Occurring simultaneously with the slow-wave electrical activity may be fast, spikelike electrical charges. This type of electrical activity originates in the circular muscle layer of the intestinal wall and occurs when the circular layer contracts to form a segmenting contraction. The depolarization of the muscle cell membranes, or an excess of positive charges on the inside of the cell, causes the myofibrils (the contracting components of the myofilaments that constitute the muscle tissues) to contract. The rate of these contractions is governed by the rate of depolarization of the muscle cell membrane. The two spiral muscle layers then contract, causing the motor activity that permits the mixing and transporting of the food in the small intestine.

The primary purposes of the movements of the small intestine are to provide mixing and transport of intraluminal contents. A characteristic of small intestine motility is the inherent ability of the smooth muscle constituting the wall of the intestine to contract spontaneously and rhythmically. This phenomenon is independent of any extrinsic nerve supply to the small intestine. In the myenteric plexus (a network of nerve fibres in the wall of the intestine), there are several other messenger substances and receptors capable of modulating smooth muscle activity, including somatostatin, serotonin (5-hydroxytryptamine), and the enkephalins. With at least seven such substances in and around the smooth muscle, there is some confusion as to their respective roles. The contractions of the small intestine create pressure gradients from one adjacent segment of the organ to another. The pressure gradients, in turn, are primarily responsible for transport within the small intestine. Two types of motor activity have been recognized: segmenting contractions and peristaltic contractions.

The predominant motor action of the small intestine is the segmenting contraction, which is a localized circumferential contraction, principally of the circular muscle of the intestinal wall. Segmenting contractions mix, separate, and churn the intestinal chyme. The contraction involves only a short segment of the intestinal wall, less than 1 to 2 cm (about 1 inch), and constricts the lumen, tending to divide its contents. As the chyme moves from the duodenum to the ileum, there is a gradual decrease in the number of segmenting contractions. This has been described as the "gradient" of small intestine motility. Although segmenting contractions usually occur in an irregular manner, they can occur in a regular or rhythmic pattern and at a maximum rate for that particular site of the small intestine (rhythmic segmentation). Rhythmic segmentation may occur only in a localized segment of small intestine, or it may occur in a progressive manner, with each subsequent segmenting contraction occurring slightly below the preceding one (progressive segmentation).

A peristaltic contraction may be defined as an advancing ring, or wave, of contraction that passes along a segment of the gastrointestinal tract. It normally occurs only over a short segment (approximately every 6 cm) and moves at a rate of about 1 or 2 cm per minute. This type of motor activity in the small intestine results in the transport of intraluminal contents downward, usually one segment at a time.

When an inflammatory condition of the small bowel exists, or when irritating substances are present in the intraluminal contents, a peristaltic contraction may travel over a considerable distance of the small intestine; this is called the peristaltic

rush. Diarrhea due to common infections is frequently associated with peristaltic rushes. Most cathartics produce their diarrheic effect by irritating the intestinal mucosa or by increasing the contents, particularly with fluid.

## Absorption

Although the small intestine is only 3 to 4 cm in diameter and approximately 7 metres in length, it has been estimated that its total absorptive surface area is approximately 4,500 square metres (5,400 square yards). This enormous absorptive surface is provided by the unique structure of the mucosa, which is arranged in concentric folds that have the appearance of transverse ridges. These folds, known as plicae circulares, are approximately 5 to 6 cm (2 inches) long and about 3 mm (0.1 inch) thick. Plicae circulares are present throughout the small intestine except in the first portion, or bulb, of the duodenum, which is usually flat and smooth, except for a few longitudinal folds. Also called valves of Kerckring, the plicae circulares are largest in the lower part of the duodenum and in the upper part of the jejunum. They become smaller and finally disappear in the lower part of the ileum. The folds usually run one-half to two-thirds of the way around the intestinal wall; occasionally, a single fold may spiral the wall for three or four complete turns. It has been estimated that the small intestine contains approximately 800 plicae circulares and that they increase the surface area of the lining of the small bowel by five to eight times the outer surface area.

Another feature of the mucosa that greatly multiplies its surface area is that of tiny projections called villi. The villi usually vary from 0.5 to 1 mm in height. Their diameters vary from approximately one-eighth to one-third their height. The villi are covered by a single layer of tall columnar cells called goblet cells because of their rough resemblance to empty goblets after they have discharged their contents. Goblet cells are found scattered among the surface epithelial cells covering the villi and are a source of mucin, the chief constituent of mucus.

At the base of the mucosal villi are depressions called intestinal glands, or Lieberkühn's glands. The cells that line these glands continue up and over the surface of the villi. In the bottom of the glands, epithelial cells called cells of Paneth are filled with alpha granules, or eosinophilic granules, so called because they take up the rose-coloured stain eosin. Though they may contain lysozyme, an enzyme toxic to bacteria, and immunoglobins, their precise function is uncertain.

There are three other cell types in the Lieberkühn's glands: undifferentiated cells,

which have the potential to undergo changes for the purpose of replacing losses of any cell type; the goblet cells mentioned above; and endocrine cells, which are described below. The main functions of the undifferentiated cells in these glands are cell renewal and secretion. Undifferentiated cells have an average life of 72 hours before becoming exhausted and being cast off.

The appearance and shape of the villi vary in different levels of the small intestine. In the duodenum the villi are closely packed, large, and frequently leaflike in shape. In the jejunum the individual villus measures between 350 and 600  $\mu\text{m}$  in height (there are about 25,000  $\mu\text{m}$  in an inch) and has a diameter of 110 to 135  $\mu\text{m}$ . The inner structure of the individual villus consists of loose connective tissue containing a rich network of blood vessels, a central lacteal (or channel for lymph), smooth muscle fibres, and scattered cells of various types. The smooth muscle cells surround the central lacteal and provide for the pumping action required to initiate the flow of lymph out of the villus. A small central arteriole (minute artery) branches at the tip of the villus to form a capillary network; the capillaries, in turn, empty into a collecting venule that runs to the bottom of the villus.

A remarkable feature of the mucosa villi is the rough, specialized surface of the epithelial cells. This plasma membrane, known as the brush border, is thicker and richer in proteins and lipids than is the plasma membrane on the epithelial cells at the side and base of the villus. Water and solutes pass through pores in the surface epithelium of the mucosa by active transport and solvent drag; i.e., solutes are carried in a moving stream of water that causes an increased concentration of solute on the side of the membrane from which the water had originally come. The size of the pores is different in the ileum from in the jejunum; this difference accounts for the various rates of absorption of water at the two sites. The enterocytes are joined near their apex by a contact zone known as a "tight junction." These junctions are believed to have pores that are closed in the resting state and dilated when absorption is required. The brush border is fused to a layer of glycoprotein, known as the "fuzzy coat," where certain nutrients are partly digested. It consists of individual microvilli approximately 0.1  $\mu\text{m}$  in diameter and 1  $\mu\text{m}$  in height; each epithelial cell may have as many as 1,000 microvilli. The microvilli play an important role in the digestion and absorption of intestinal contents by enlarging the absorbing surface approximately 25 times. They also secrete the enzymes disaccharidase and peptidase that hydrolyze disaccharides and polypeptides to monosaccharides and dipeptides to amino acids, respectively. Molecular receptors for specific substances are found on the microvilli surfaces at

different levels in the small intestine. This may account for the selective absorption of particular substances at particular sites—for example, intrinsic-factor-bound vitamin B<sub>12</sub> in the terminal ileum. Such receptors may also explain the selective absorption of iron and calcium in the duodenum and upper jejunum. Furthermore, there are transport proteins in the microvillus membrane associated with the passage of sodium ions, D-glucose, and amino acids.

Actin is found in the core of the microvillus, and myosin is found in the brush border; because contractility is a function of these proteins, the microvilli have motor activity that presumably initiates the stirring and mixing actions within the lumen of the small intestine.

Beneath the mucosa of the small intestine, as beneath that of the stomach, are the muscularis and the submucosa. The submucosa consists of loose connective tissue and contains many blood vessels and lymphatics. Brunner's glands, located in the submucosa of the duodenum, are composed of acini (round sacs) and tubules that are twisting and have multiple branching. These glands empty into the base of Lieberkühn's glands in the duodenum. Their exact function is not known, but they do secrete a clear fluid that contains mucus, bicarbonate, and a relatively weak proteolytic (protein-splitting) enzyme. In the submucosa of the jejunum, solitary nodules (lumps) of lymphatic tissue are located. There is more lymphatic tissue in the ileum, in aggregates of nodules known as Peyer patches.

## Secretions

There are many sources of digestive secretions into the small intestine. Secretions into the small intestine are controlled by nerves, including the vagus, and hormones. The most effective stimuli for secretion are local mechanical or chemical stimulations of the intestinal mucous membrane. Such stimuli always are present in the intestine in the form of chyme and food particles. The gastric chyme that is emptied into the duodenum contains gastric secretions that will continue their digestive processes for a short time in the small intestine. One of the major sources of digestive secretion is the pancreas, a large gland that produces both digestive enzymes and hormones. The pancreas empties its secretions into the duodenum through the major pancreatic duct (duct of Wirsung) in the duodenal papilla (papilla of Vater) and the accessory pancreatic duct a few centimetres away from it. Pancreatic juice contains enzymes that digest proteins, fats, and carbohydrates. Secretions of the liver are delivered to the duodenum by the common bile duct via the gallbladder and are also received

through the duodenal papilla.

The composition of the succus entericus, the mixture of substances secreted into the small intestine, varies somewhat in different parts of the intestine. Except in the duodenum, the quantity of the fluid secreted is minimal, even under conditions of stimulation. In the duodenum, for example, where the Brunner's glands are located, the secretion contains more mucus. In general, the secretion of the small intestine is a thin, colourless or slightly straw-coloured fluid, containing flecks of mucus, water, inorganic salts, and organic material. The inorganic salts are those commonly present in other body fluids, with the bicarbonate concentration higher than it is in blood. Aside from mucus, the organic matter consists of cellular debris and enzymes, including a pepsinlike protease (from the duodenum only), an amylase, a lipase, at least two peptidases, sucrase, maltase, enterokinase, alkaline phosphatase, nucleophosphatases, and nucleocytases.

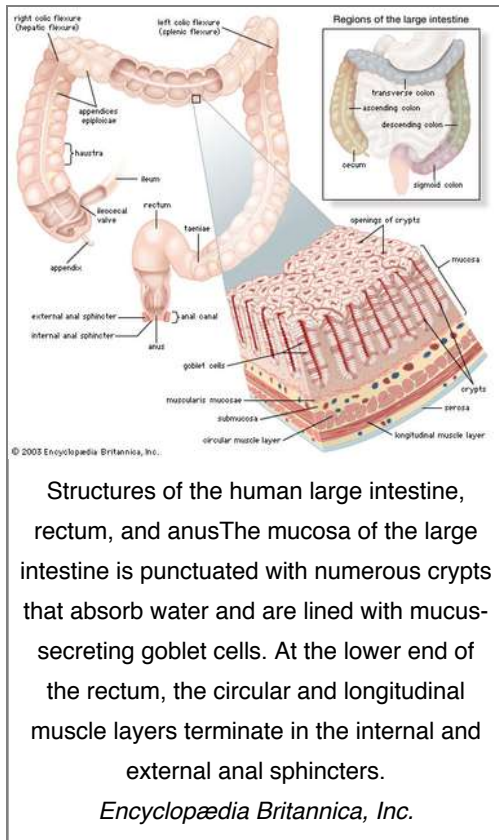
## Large intestine

The large intestine, or colon, serves as a reservoir for the liquids emptied into it from the small intestine. It has a much larger diameter than the small intestine (approximately 2.5 cm, or 1 inch, as opposed to 6 cm, or 3 inches, in the large intestine), but at 150 cm (5 feet), it is less than one-quarter the length of the small intestine. The primary functions of the colon are to absorb water; to maintain osmolality, or level of solutes, of the blood by excreting and absorbing electrolytes (substances, such as sodium and chloride, that in solution take on an electrical charge) from the chyme; and to store fecal material until it can be evacuated by defecation. The large intestine also secretes mucus, which aids in lubricating the intestinal contents and facilitates their transport through the bowel. Each day approximately 1.5 to 2 litres (about 2 quarts) of chyme pass through the ileocecal valve that separates the small and large intestines. The chyme is reduced by absorption in the colon to around 150 ml (5 fluid ounces). The residual indigestible matter, together with sloughed-off mucosal cells, dead bacteria, and food residues not digested by bacteria, constitute the feces.

The colon also contains large numbers of bacteria that synthesize niacin (nicotinic acid), thiamin (vitamin B<sub>1</sub>) and vitamin K, vitamins that are essential to several metabolic activities as well as to the function of the central nervous system.

## Anatomy





The large intestine can be divided into the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. The cecum, the first part of the large intestine, is a sac with a closed end that occupies the right iliac fossa, the hollow of the inner side of the ilium (the upper part of the hipbone). Guarding the opening of the ileum (the terminal portion of the small intestine) into the cecum is the ileocecal valve. The circular muscle fibres of the ileum and those of the cecum combine to form the circular sphincter muscle of the ileocecal valve.

The ascending colon extends up from the cecum at the level of the ileocecal valve to the bend in the colon called the hepatic flexure, which is located beneath and behind the right lobe of the liver; behind, it is in contact with the rear

abdominal wall and the right kidney. The ascending colon is covered by peritoneum except on its posterior surface.

The transverse colon is variable in position, depending largely on the distention of the stomach, but usually is located in the subcostal plane—that is, at the level of the 10th rib. On the left side of the abdomen, it ascends to the bend called the splenic flexure, which may make an indentation in the spleen. The transverse colon is bound to the diaphragm opposite the 11th rib by a fold of peritoneum.

The descending colon passes down and in front of the left kidney and the left side of the posterior abdominal wall to the iliac crest (the upper border of the hipbone). The descending colon is more likely than the ascending colon to be surrounded by peritoneum.

The sigmoid colon is commonly divided into iliac and pelvic parts. The iliac colon stretches from the crest of the ilium, or upper border of the hipbone, to the inner border of the psoas muscle, which lies in the left iliac fossa. Like the descending colon, the iliac colon is usually covered by peritoneum. The pelvic colon lies in the true pelvis (lower part of the pelvis) and forms one or two loops, reaching across to the right side

of the pelvis and then bending back and, at the midline, turning sharply downward to the point where it becomes the rectum.

The layers that make up the wall of the colon are similar in some respects to those of the small intestine; there are distinct differences, however. The external aspect of the colon differs markedly from that of the small intestine because of features known as the taeniae, haustra, and appendices epiploicae. The taeniae are three long bands of longitudinal muscle fibres, about 1 cm in width, that are approximately equally spaced around the circumference of the colon. Between the thick bands of the taeniae, there is a thin coating of longitudinal muscle fibres. Because the taeniae are slightly shorter than the large intestine, the intestinal wall constricts and forms circular furrows of varying depths called haustra, or sacculations. The appendices epiploicae are collections of fatty tissue beneath the covering membrane. On the ascending and descending colon, they are usually found in two rows, whereas on the transverse colon they form one row.

The inner surface of the colon has many crypts that are lined with mucous glands and numerous goblet cells, and it lacks the villi and plicae circulares characteristic of the small intestine. It contains many solitary lymphatic nodules but no Peyer patches. Characteristic of the colonic mucosa are deep tubular pits, increasing in depth toward the rectum.

The inner layer of muscle of the large intestine is wound in a tight spiral around the colon, so that contraction results in compartmentalization of the lumen and its contents. The spiral of the outer layer, on the other hand, follows a loose undulating course, and contraction of this muscle causes the contents of the colon to shift forward and backward. The bulk of the contents, in particular the amount of undigested fibre, influences these muscular activities.

## **Blood and nerve supply**

The arterial blood supply to the large intestine is supplied by branches of the superior and inferior mesenteric arteries (both of which are branches of the abdominal aorta) and the hypogastric branch of the internal iliac artery (which supplies blood to the pelvic walls and viscera, the genital organs, the buttocks, and the inside of the thighs). The vessels form a continuous row of arches from which vessels arise to enter the large intestine. Venous blood is drained from the colon from branches that form venous arches similar to those of the arteries. These eventually drain into the superior

and inferior mesenteric veins, which ultimately join with the splenic vein to form the portal vein.

The innervation of the large intestine is similar to that of the small intestine.

## **Contractions and motility**

Local contractions and retrograde propulsions ensure mixing of the contents and good contact with the mucosa. Colonic motility is stimulated by mastication and by the presence of fat, unabsorbed bile salts, bile acids, and the peptide hormones gastrin and cholecystokinin. The hormones secretin, glucagon, and vasoactive intestinal peptide act to suppress motility. The electrical activity of the muscles of the colon is more complex than that of the small intestine. Variations from the basic rhythmic movements of the colon are present in the lower (distal) half of the colon and in the rectum. Slow-wave activity that produces contractions from the ascending colon to the descending colon occurs at the rate of 11 cycles per minute, and slow-wave activity in the sigmoid colon and rectum occurs at 6 cycles per minute. Local contractions migrate distally in the colon at the rate of 4 cm (1.6 inches) per second. Retrograde, or reverse, movements occur mainly in the upper (proximal) colon.

## **Rectum and anus**

The rectum, which is a continuation of the sigmoid colon, begins in front of the midsacrum (the sacrum is the triangular bone near the base of the spine and between the two hipbones). It ends in a dilated portion called the rectal ampulla, which in front is in contact with the rear surface of the prostate in the male and with the posterior vaginal wall in the female. Posteriorly, the rectal ampulla is in front of the tip of the coccyx (the small bone at the very base of the spine).

At the end of the pelvic colon, the mesocolon, the fold of peritoneum that attaches the colon to the rear wall of the abdomen and pelvis, ceases, and the rectum is then covered by peritoneum only at its sides and in front; lower down, the rectum gradually loses the covering on its sides until only the front is covered. About 7.5 cm (3 inches) from the anus, the anterior peritoneal covering is also folded back onto the bladder and the prostate or the vagina.

Near the termination of the sigmoid colon and the beginning of the rectum, the colonic taeniae spread out to form a wide external longitudinal muscle coat. At the

lower end of the rectum, muscle fibres of the longitudinal and circular coats tend to intermix. The internal circular muscle coat terminates in the thick rounded internal anal sphincter muscle. The smooth muscle fibres of the external longitudinal muscle coat of the rectum terminate by interweaving with striated muscle fibres of the levator ani, or pelvic diaphragm, a broad muscle that forms the floor of the pelvis. A second sphincter, the external anal sphincter, is composed of striated muscle and is divided into three parts known as the subcutaneous, superficial, and deep external sphincters. Thus, the internal sphincter is composed of smooth muscle and is innervated by the autonomic nervous system, while the external sphincters are of striated muscle and have somatic (voluntary) innervation provided by nerves called the pudendal nerves.

The mucosal lining of the rectum is similar to that of the sigmoid colon but becomes thicker and better supplied with blood vessels, particularly in the lower rectum. Arterial blood is supplied to the rectum and anus by branches from the inferior mesenteric artery and the right and left internal iliac arteries. Venous drainage from the anal canal and rectum is provided by a rich network of veins called the internal and external hemorrhoidal veins.

Two to three large crescentlike folds known as rectal valves are located in the rectal ampulla. These valves are caused by an invagination, or infolding, of the circular muscle and submucosa. The columnar epithelium of the rectal mucosa, innervated by the autonomic nervous system, changes to the stratified squamous (scalelike) type, innervated by the peripheral nerves, in the lower rectum a few centimetres above the pectinate line, which is the junction between the squamous mucous membrane of the lower rectum and the skin lining the lower portion of the anal canal.

Once or twice in 24 hours, a mass peristaltic movement shifts the accumulated feces onward from the descending and sigmoid sectors of the colon. The rectum is normally empty, but when it is filled with gas, liquids, or solids to the extent that the intraluminal pressure is raised to a certain level, the impulse to defecate occurs.

The musculus puborectalis forms a sling around the junction of the rectum with the anal canal and is maintained in a constant state of tension. This results in an angulation of the lower rectum so that the lumen of the rectum and the lumen of the anal canal are not in continuity, a feature essential to continence. Continuity is restored between the lumina of the two sectors when the sling of muscle relaxes, and

the longitudinal muscles of the distal and pelvic colon contract. The resulting shortening of the distal colon tends to elevate the pelvic colon and obliterates the angle that it normally makes with the rectum. The straightening and shortening of the passage facilitates evacuation.

The act of defecation is preceded by a voluntary effort, which, in turn, probably gives rise to stimuli that magnify the visceral reflexes, although these originate primarily in the distension of the rectum. Centres that control defecation reflexes are found in the hypothalamus of the brain, in two regions of the spinal cord, and in the ganglionic plexus of the intestine. As the result of these reflexes, the internal anal sphincter relaxes.

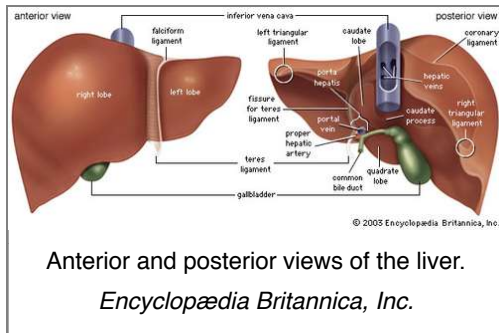
## Liver

The liver is not only the largest gland in the body but also the most complex in function. The major functions of the liver are to participate in the metabolism of protein, carbohydrates, and fat; to synthesize cholesterol and bile acids; to initiate the formation of bile; to engage in the transport of bilirubin; to metabolize and transport certain drugs; and to control transport and storage of carbohydrates.

## Gross anatomy

The liver lies under the lower right rib cage and occupies much of the upper right quadrant of the abdomen, with a portion extending into the upper left quadrant. The organ weighs from 1.2 to 1.6 kg (2.6 to 3.5 pounds) and is somewhat larger in men than in women. Its greatest horizontal measurement ranges from 20 to 22 cm (approximately 8 inches); vertically, it extends 15 to 18 cm, and in thickness it ranges from 10 to 13 cm. The liver is divided into two unequal lobes: a large right lobe and a smaller left lobe. The left lobe is separated on its anterior (frontal) surface by the dense falciform (sickle-shaped) ligament that connects the liver to the undersurface of the diaphragm. On the inferior surface of the liver, the right and left lobes are separated by a groove containing the teres ligament, which runs to the navel. Two small lobes, the caudate and the quadrate, occupy a portion of the inferior surface of the right lobe. The entire liver, except for a small portion that abuts the right leaf of the diaphragm, is enveloped in a capsule of tissue that is continuous with the parietal peritoneum that lines the abdominopelvic walls and diaphragm.

The major blood vessels enter the liver on its inferior surface in a centrally placed



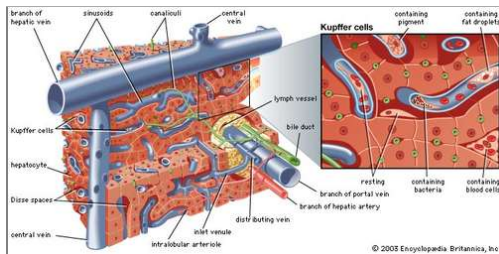
groove called the porta hepatis, which anatomically separates the quadrate and caudate lobes. The liver has two sources of blood supply: fully oxygenated blood from the hepatic artery, which is a major branch of the celiac axis (the main artery that crosses the abdomen) after its emergence from the abdominal aorta; and partially oxygenated blood from the large portal

vein, which in turn receives all venous blood from the spleen, pancreas, gallbladder, lower esophagus, and the remainder of the gastrointestinal tract, including the stomach, small intestine, large intestine, and upper portion of the rectum. The portal vein is formed by the juncture of the splenic vein with the superior mesenteric vein. At the porta hepatis the portal vein divides into two large branches, each going to one of the major lobes of the liver. The porta hepatis is also the exit point for the hepatic ducts. These channels are the final pathway for a network of smaller bile ductules interspersed throughout the liver that serve to carry newly formed bile from liver cells to the small intestine via the biliary tract.

## Microscopic anatomy

The microscopic anatomy of the liver reveals a uniform structure of clusters of cells called lobules, where the vital functions of the liver are carried out. Each lobule, measuring about one millimetre in diameter, consists of numerous cords of rectangular liver cells, or hepatocytes, that radiate from central veins, or terminal hepatic venules, toward a thin layer of connective tissue that separates the lobule from other neighbouring lobules. The cords of liver cells are one cell thick and are separated from one another on several surfaces by spaces called sinusoids, or hepatic capillaries. Sinusoids are lined by thin endothelial cells that have openings through which fingerlike projections (microvilli) of the hepatocytes extend, allowing direct accessibility of the hepatocyte to the bloodstream in the sinusoids. The other major cell of the liver, the Kupffer cell, adheres to the wall of the sinusoid and projects into its lumen. It functions as a phagocyte (a cell that engulfs and destroys foreign material or other cells). Small spaces (Disse spaces) are present in places between the hepatocyte and the sinusoidal endothelium, probably for the transport of lymph. On neighbouring surfaces the hepatocytes are bound to one another by dense, tight junctions. These are perforated by small channels, called canaliculi, that are the terminal outposts of the biliary system, receiving bile from the hepatocyte. They

eventually join with other canaliculi, forming progressively larger bile ducts that eventually emerge from the porta hepatis as the hepatic duct.



Microscopic structure of the liver Liver cells, or hepatocytes, have direct access to the liver's blood supply through small capillaries called sinusoids. Hepatocytes carry out many metabolic functions, including the production of bile. Kupffer cells line the liver's vascular system; they play a role in blood formation and the destruction of cellular debris.

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Hepatocytes occupy about 80 percent of the volume of the liver, and their cytoplasm (the area surrounding the nucleus) contains many mitochondria, which provide the energy needed for the many synthetic and metabolic functions of the liver cell. The cytoplasm also contains a series of long tubules, called the endoplasmic reticulum, which provides many enzymes essential to liver function. Some of the membranes of the endoplasmic reticulum appear granular, or rough, owing to the presence of ribosomes, which are responsible for forming specific polypeptide (protein) chains after having had the amino group removed (deamination) and having been converted into glucose through a process called

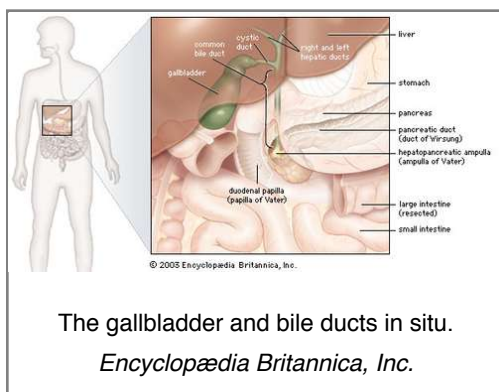
gluconeogenesis. The ammonia released from gluconeogenesis is converted to urea in the hepatocyte by way of the urea cycle. The nonribosomal, or smooth, endoplasmic reticulum is where cytochromes (combinations of heme from hemoglobin with various proteins) and certain enzymes undertake the important hepatic functions of drug and hormonal metabolism and also cholesterol synthesis. Hepatocytes also conjugate with carbohydrate components of bilirubin and other fat-soluble metabolic and foreign compounds and thereby are made soluble in water. Bilirubin is the product of hemoglobin metabolism that is formed in the bone marrow and the lymphatic tissue and is carried to the liver after becoming bound to plasma albumin. It is released at the hepatocytic sinusoidal membrane and is transported to the smooth endoplasmic reticulum, where it is conjugated with one or two molecules of glucuronic acid and thereby becomes soluble in water and excretable in bile. The Golgi apparatus, a series of tubular structures between the endoplasmic reticulum and the canaliculus, acts as a transport station for newly made proteins and other hepatocytic products before they are conveyed to other parts of the cell or out of the cell entirely. Lysosomes, another important cytoplasmic constituent, are responsible for the intracellular storage of pigments, such as iron or copper, and for the digestion of certain contents, such as glycogen or foreign particles. The nucleus of the hepatocyte guides replication of the cell and transmits genetic material in the form of

messenger ribonucleic acid (mRNA) from deoxyribonucleic acid (DNA) to organelles located in the cytoplasm.

## Biliary tract

### Anatomy

The biliary tract begins with the appearance of two large ducts, the right and left hepatic ducts, at the porta hepatis, a groove that separates two lobes on the right side of the liver. Just below the porta hepatis, these 1- to 2-cm (about half-inch) ducts join to form the hepatic duct, which proceeds for another 2 to 3 cm and is joined by the cystic duct, leading from the gallbladder. The resulting common bile duct progresses downward through the head of the pancreas. There it is usually joined by the main pancreatic duct (duct of Wirsung) at a slightly dilated area called the hepatopancreatic ampulla (ampulla of Vater), which lies in the wall of the inner curve of the descending duodenum, and terminates in the lumen of the duodenum at a 2- to 3-cm elevation called the duodenal papilla (papilla of Vater).



The common bile duct averages about 10 cm in length, and flow of bile from its lower end into the intestine is controlled by the muscular action of the hepatopancreatic sphincter (sphincter of Oddi), located in the duodenal papilla. The cystic duct varies from 2 to 3 cm in length and terminates in the gallbladder, a saccular structure with a capacity of about 50 ml (about 1.5 fluid ounces). Throughout its length, the cystic duct is

lined by a spiral mucosal elevation, called the valvula spiralis (valve of Heister).

Normally, the gallbladder lies partially embedded on the undersurface of the right lobe of the liver.

### Bile

The primary digestive function of bile is to aid in the dispersion and digestion of fat in the lumen of the small intestine. Bile is formed initially in the hepatocyte (liver cell), and the rate of formation is dependent primarily on the rate at which bile acids are secreted into the bile channels, or canaliculi. A portion of the bile flow, however, is related to factors other than the secretion of bile acids; in particular, it appears to be



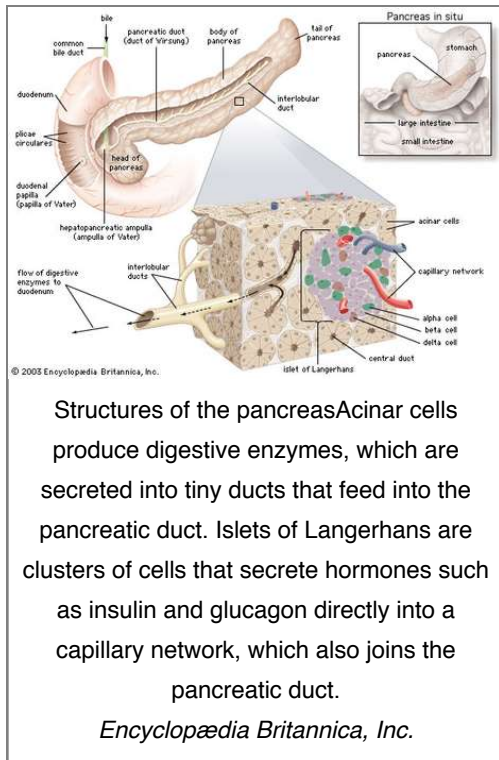
dependent on the secretion of sodium from the hepatocyte and is also partially governed by the action of intestinal hormones such as secretin, cholecystokinin (CCK), and gastrin. The total bile acid pool at any one time measures about 3 grams (about 0.1 ounce), almost all of which is contained at rest in the gallbladder. In its passage through the biliary tract, hepatic bile is concentrated to as little as one-tenth of its original volume by the selective reabsorption of water, chloride, and bicarbonate. This concentration process takes place largely in the gallbladder, and, as a result, bile from this organ is much thicker in density and darker in colour (owing to the concentration of pigments) than is bile emerging from the liver. Distension of the duodenum, particularly by a meal containing fat, provokes the secretion of CCK, a hormone that causes contractions of the muscular layer in the wall of the gallbladder.

Aside from inorganic ions (sodium, potassium, calcium, magnesium, chloride, and bicarbonate), bile contains protein and bilirubin; the latter is responsible for its golden colour in dilute solutions and dark amber colour in concentrate. It is richest, however, in bile acids (derived from cholesterol in the hepatocyte), phospholipids (largely phosphatidyl choline, or lecithin), and cholesterol. Cholesterol is a four-ringed sterol that is absorbed from the diet or synthesized by the liver and the intestinal lining. Normally not soluble in watery secretions, cholesterol is carried in a colloidal solution in bile in the form of mixed aggregates of complexes containing bile acids and lecithin. In the absence of adequate amounts of lecithin and bile acids, cholesterol crystallizes. The liver synthesizes two types of primary bile acid from cholesterol, called chenodeoxycholic acid and cholic acid. In the lower intestine bacterial action removes one of the hydroxyl groups (dehydroxylation) from cholic acid, changing it to deoxycholic acid. This secondary bile acid appears in bile because it is absorbed from the intestine and recirculated to the liver. Chenodeoxycholic acid is also dehydroxylated in the intestine, becoming lithocholic acid, a small amount of which is also reabsorbed and appears in normal bile.

## **Pancreas**

The pancreas is a long, narrow gland that is situated transversely across the upper abdomen, behind the stomach and the spleen. The midportion of the pancreas lies against the vertebral column, the abdominal aorta, and the inferior vena cava.

The pancreas is both an exocrine (ductal) and endocrine (ductless) gland. The exocrine tissue, called acinar tissue, produces important digestive enzyme precursors that are transmitted into the small intestine, while the endocrine tissue (contained in the islets



of Langerhans) produces at least two hormones (insulin and glucagon) that are important in the regulation of carbohydrate metabolism. Two other hormones produced by the pancreas, vasoactive intestinal polypeptide and somatostatin, are pivotal elements in the control of intestinal secretion and motility.

Individual acinar cells have the shape of a truncated pyramid, arranged in groups around a central ductal lumen. These central ducts empty into progressively larger intercalated and collecting ducts that eventually join the pancreatic duct (duct of Wirsung). The pancreatic duct in turn enters the hepatopancreatic ampulla (ampulla of Vater) of the duodenum, where, in

about 80 percent of instances, it is joined by the common bile duct. Occasionally the junction with the common bile duct is proximal to the ampulla, and in a few cases the pancreatic duct and the common bile duct join the duodenum separately.

## Acinar cells

The acinar cells constitute more than 95 percent of the cellular population of the exocrine pancreas. They produce a variety of digestive proteins, or enzymes, involved principally with the degradation of dietary proteins (proteases), fats (lipases), and carbohydrates (amylases) in the intestine. Other protein secretions include a trypsin inhibitor, a so-called "stone protein" that keeps calcium in solution, and various serum proteins, including albumin and immunoglobulins.

In the acinar cells almost all enzymatic proteins are synthesized on ribosomes from amino acids carried to the pancreas by the bloodstream. Enzyme precursors are conjugated in the Golgi apparatus and then concentrated into membrane-wrapped zymogen granules, which are stored in the cytoplasm before secretion. Enzymatic secretion is mediated by stimulants such as secretin, a hormone released from the duodenum by the introduction of gastric acid, cholecystikinin (CCK), released by the presence of dietary fat, amino acids, hydrochloric acid, and acetylcholine, which is produced as a response to the sensory aspects of feeding and to the physical effects of chewing and swallowing. Upon binding of specific receptor sites on the acinar

membrane with CCK or acetylcholine, the zymogen granules migrate to the apex of the acinar cell, where they are extruded into the central ductal lumen. Binding of vasoactive intestinal polypeptide or secretin to acinar receptors causes increased production of bicarbonate, sodium, water, and enzymes by acinar cells and small ductal cells. Bicarbonate is secreted in exchange for chloride, and sodium is exchanged for hydrogen, with a resultant increased acidity of the blood leaving the actively secreting pancreas. Binding of CCK causes production of bicarbonate and enzymes by the acinar cells.

In the absence of CCK and acetylcholine, as in fasting subjects or in patients being fed intravenously, the synthesis of zymogen by the acinar cells is markedly reduced. Pancreatic atrophy also occurs after removal of the pituitary gland, probably owing to the absence of growth hormone. Thus, CCK, acetylcholine, and growth hormone are pancreatotrophic, or pancreas-feeding, hormones. The pancreas itself also appears to secrete an as-yet-unidentified hormone that is trophic, or nutritive, to the liver.

## Islet cells

There are at least three types of islet cells, designated alpha (or A), beta (or B), and delta (or D), which constitute about 2 percent of the total pancreatic mass. Islet cells are about 20 to 35 percent alpha, 60 to 75 percent beta, and 5 percent delta. Alpha cell granules contain only glucagon, whose release leads to the breakdown of glycogen in the liver and elevation of the level of blood glucose, while beta cell granules contain insulin, whose effects are the opposite of glucagon. Delta cell granules contain somatostatin, whose effects inhibit the release of glucagon and insulin.

Harvey J. Dworken Nicholas Carr Hightower William Sircus

## Features of the gastrointestinal tract

### General features of digestion and absorption

There are four means by which digestive products are absorbed: active transport, passive diffusion, facilitated diffusion, and endocytosis.

Active transport involves the movement of a substance across the membrane of the absorbing cell against an electrical or chemical gradient. It is carrier-mediated; that is, the substance is temporarily bound to another substance that transports it across the cell membrane, where it is released. This process requires energy and is at risk of

competitive inhibition by other substances; that is, other substances with a similar molecular structure can compete for the binding site on the carrier. Passive diffusion requires neither energy nor a carrier; the substance merely passes along a simple concentration gradient from an area of high concentration of the substance to an area of low concentration until a state of equilibrium exists on either side of the membrane. Facilitated diffusion also requires no energy, but it involves a carrier, or protein molecule located on the outside of the cell membrane that binds the substance and carries it into the cell. The carrier may be competitively inhibited. Endocytosis takes place when the material to be absorbed, on reaching the cell membrane, is engulfed into the cell interior.

Absorption of food by the small intestine occurs principally in the middle section, or jejunum; however, the duodenum, although the shortest portion of the small intestine, has an extremely important role. The duodenum receives not only chyme saturated with gastric acid but pancreatic and liver secretions as well. It is in the duodenum that the intestinal contents are rendered isotonic with the blood plasma; i.e., the pressures and volumes of the intestinal contents are the same as those of the blood plasma, so that the cells on either side of the barrier will neither gain nor lose water.

Bicarbonate secreted by the pancreas neutralizes the acid secreted by the stomach. This brings the intestinal contents to the optimal pH, allowing the various digestive enzymes to act on their substrates at peak efficiency. A number of important gastrointestinal hormones regulate gastric emptying, gastric secretion, pancreatic secretion, and contraction of the gallbladder. These hormones, along with neural impulses from the autonomic nervous system, provide for autoregulatory mechanisms for normal digestive processes.

Most salts and minerals, as well as water, are readily absorbed from all portions of the small intestine. Sodium is absorbed by an active process, the necessary metabolic energy being provided by the epithelial cells of the mucosa of the small intestine. Sodium is moved from the lumen of the intestine across the mucosa against a concentration gradient (i.e., a progressive increase in the concentration of sodium) and an electrochemical gradient (i.e., a gradual increase in the concentration of charged ions). Sodium ions are absorbed more readily from the jejunum than from other parts of the small intestine. Chloride is readily absorbed in the small intestine, probably as a consequence of sodium absorption.

Potassium is absorbed at about 5 percent of the rate of sodium. It is thought that potassium moves across the intestinal mucosa passively or by facilitated diffusion as a consequence of water absorption. The absorption of water appears to be secondary to the absorption of electrolytes (substances that dissociate into ions in a solution). Water absorption occurs throughout the small intestine, though chiefly in the jejunum. Water moves freely across the intestinal mucosa both ways, but it tends to move in the direction of the hypertonic solution (the solution into which a net flow of water occurs) and away from the hypotonic solution (one from which a net flow of water occurs). Thus, if the contents of the lumen are hypotonic, water moves rapidly from the lumen to the blood. If the contents of the intestinal lumen are hypertonic, water moves more rapidly from the blood into the lumen. This two-way movement of water tends to maintain the intestinal contents in an isotonic state.

## **Digestion and absorption of specific nutrients**

### **Carbohydrates**

Carbohydrates are absorbed as monosaccharides (simple sugars such as glucose, fructose, and galactose that cannot be further broken down by hydrolysis) or as disaccharides (carbohydrates such as sucrose, lactose, maltose, and dextrin that can be hydrolyzed to two monosaccharides). These simpler molecules, however, must be obtained by the breaking down of polysaccharides, complex carbohydrates that contain many monosaccharides. Chief among these is amylose, a starch that accounts for 20 percent of dietary carbohydrate. Amylose consists of a straight chain of glucose molecules bound to their neighbours by oxygen links. The bulk of the starch is amylopectin, which has a branch chain linked in after every 25 molecules of glucose on the main chain.

Only a small amount of starch is digested by salivary amylase; most is rapidly digested in the duodenum by pancreatic amylase. But even this enzyme has little effect on the branch chains of amylopectin and even less on the linkages in cellulose molecules. This accounts for the inability of humans to break down cellulose. There are several forms of amylase in pancreatic juice whose function is to hydrolyze complex carbohydrates to disaccharides and trisaccharides and amylopectins to dextrans. In the brush border (comprising ultrafine microvilli) and the surface membrane of the epithelial enterocytes are the disaccharidase enzymes, lactase, maltase, sucrase, and trehalase, which hydrolyze maltose and the dextrans to the monosaccharides glucose, galactose, and fructose.

Glucose, which is one of the two monosaccharide components of table sugar (sucrose) and milk sugar (lactose), is combined with phosphate in the liver cell and is either transported to peripheral tissues for metabolic purposes or stored in the hepatocyte as glycogen, a complex polysaccharide. Specific enzyme systems are present in the hepatocyte for these conversions, as well as for the translation of other dietary monosaccharides (fructose from sucrose and galactose from lactose) into glucose. The hepatocyte (liver cell) is also able to convert certain amino acids and products of glucose metabolism (pyruvate and lactate) into glucose through gluconeogenesis.

Fructose appears to be absorbed by simple diffusion, but glucose and galactose are transported by an energy-using process, probably binding to a specific protein carrier with attached sodium ions; the sugar is released inside the enterocyte, sodium is pumped out, and the sugars then diffuse into the circulation down a concentration gradient.

## Proteins

The digestion of protein entails breaking the complex molecule first into peptides, each having a number of amino acids, and second into individual amino acids. The pepsins are enzymes secreted by the stomach in the presence of acid that breaks down proteins (proteolysis). The pepsins account for about 10 to 15 percent of protein digestion. They are most active in the first hour of digestion, and their ability to break down protein is restricted by the necessity for an acidic environment with a pH between 1.8 and 3.5. The trypsins (proteolytic enzymes secreted by the pancreas) are much more powerful than pepsins, so the greater part of protein digestion occurs in the duodenum and upper jejunum. Therefore, even after total removal of the stomach, protein digestion usually is not impaired.

Pancreatic secretion contains inactive protease precursors that become enzymatically active after interacting with another enzyme, enterokinase, which is secreted from the microvillous component of the enterocytes in the duodenal and jejunal mucosa. Trypsinogen is activated in the intestine by enterokinase, which is liberated from duodenal lining cells by the interaction of bile acids and CCK. This activation of trypsinogen to trypsin is initiated by the cleavage from it of six terminal amino acid residues. The other proteases are activated by free trypsin. The net effect of these proteases is to reduce dietary proteins to small polypeptide chains of two to six amino acids and to single amino acids. Trypsin activates the other pancreatic proteases,

including chymotrypsin and elastase. Trypsin, chymotrypsin, and elastase are known as endopeptidases and are responsible for the initial breakdown of the protein chains to peptides by hydrolysis. The next step, the breakdown of these peptides to smaller molecules and then to individual amino acids, is brought about by the enzymic activity of carboxypeptidases, which are also secreted by the pancreas.

Peptidase activity commences outside the enterocytes (in the mucus and brush border) and continues inside the cell. A different peptidase appears to be involved in each stage of the breakdown of protein to amino acids. Likewise, the transport of different peptides involves different mechanisms. Dipeptides (peptides that release two amino acids on hydrolysis) and tripeptides (peptides that release three amino acids) are moved from the surface brush border into the cell by an energy-requiring process involving a carrier protein. Small peptides with few amino acids are absorbed directly as such. The greater part of the breakdown of peptides to amino acids takes place within the enterocyte. Curiously, small peptides are absorbed more rapidly than amino acids, and, indeed, the precise details of the mechanism for absorption of amino acids are largely unknown. It is known that some amino acids have a specific individual transport system while others share one.

Amino acids may be classified into groups, depending upon their optical rotatory characteristics (i.e., whether they rotate polarized light to the left, or *levo*, or to the right, or *dextro*) and in terms of reactivity, or acidity (pH). Levorotatory amino acids are absorbed extremely rapidly—much more rapidly than are dextrorotatory amino acids. In fact, levorotatory amino acids are absorbed almost as quickly as they are released from protein or peptide. Neutral amino acids have certain structural requirements for active transport, and if these specific structural arrangements are disturbed, active transport will not occur. Basic amino acids, which have a pH above 7, are transported at about 5 to 10 percent of the rate of neutral levorotatory amino acids.

## Fats

Almost all dietary fat is stored as triglycerides. Solubility in water is necessary in order for fat to be transferred from the lumen of the intestine to the absorptive cells. Many factors, such as the length of the fatty acid chains of the triglycerides, play an important role in determining this solubility. Triglycerides have three long chains of fatty acids (LCFA) attached to a glycerol framework, and they are insoluble in water. The remainder are medium-chain triglycerides (MCT), which can be absorbed intact by the mucosa of the small intestine. Lipases, which include phospholipase, esterase,

colipase, and lipase, function to reduce MCTs to free monoglycerides and medium-chain fatty acids (MCFA), which are more soluble in water than the LCFAs and move quickly through the cells and pass into the portal circulation and then to the liver. Lipases require the presence of bile acids in the intestinal lumen for the formation of micellar solutions of fat prior to optimal digestion.

Long-chain fatty acids attached to the triglycerides are attacked by the pancreatic enzyme lipase. Two of the three fatty acid chains are split off, leaving one attached to the glycerol (forming a monoglyceride). In the presence of excess levels of bile salts, however, this activity of pancreatic lipase is inhibited. A lipase may be present in gastric juice, but it is not capable of digesting MCFAs and LCFAs, and the proportion of small-chain fatty acids in food is small. Thus, little digestion occurs in the stomach. Another pancreatic enzyme, colipase, binds to the bile salts, leaving lipase available to attack the triglycerides. The monoglycerides that result from these splitting processes combine into a complex called a micelle. The micelle permits fat components to be soluble in water. Because bile salts have a hydrophobic, or water-repelling region, and a hydrophilic, or water-attracting region, the micelle is formed with bile salts arranged around the outside with hydrophobic ends facing inside and hydrophobic fatty acids, monoglycerides, phospholipids, and cholesterol, as well as the fat-soluble vitamins A, D, E, and K, in the centre.

There is a layer of fluid overlying the surface cells of the mucosa of the small intestine known as the "unstirred" layer. It is across this layer that the micelles must pass to reach the cell membranes. The rate of diffusion through the unstirred layer is determined by the thickness of the layer and the gradient in concentrations of the various elements of the transport system from the lumen of the intestine to the cell membrane. Underneath the unstirred layer is a glycoprotein layer known as the "fuzzy coat," which mainly comprises mucus. Beneath the fuzz is the brush border on the surface of the cell membrane. It has a double layer of lipid that is easily penetrated by the fatty acids and monoglycerides that are soluble in lipids. Once the micelle has passed through the fuzzy coat and the brush border, it enters the cells of the tissues that line the intestine. The micelle disintegrates, the bile salts diffuse back into the lumen, and a carrier protein picks up the fatty acids and the monoglycerides and transports them to the endoplasmic reticulum, a tubular structure rich in enzymes, in the cell interior. At this site the triglyceride is synthesized again under the influence of an enzyme catalyst called acyltransferase.



The triglycerides pass to the membrane of another tubular structure, known as the Golgi apparatus, where they are packaged into vesicles (chylomicrons). These vesicles are spheres with an outer coating of phospholipids and a small amount of apoprotein, while the interior is entirely triglyceride except for a small quantity of cholesterol. The chylomicrons migrate to the cell membrane, pass through it, and are attracted into the fine branches of the lymphatic system, the lacteals. From there the chylomicrons pass to the thoracic duct. The whole process of absorption, from the formation of micelles to the movement out of the cells and into the lacteals, takes between 10 and 15 minutes.

The medium-chain triglycerides are broken down to medium-chain fatty acids by pancreatic lipase. Medium-chain fatty acids are soluble in water and readily enter the micelles. Ultimately, after moving across the membrane of the enterocyte, they pass into the capillary tributaries of the portal vein and then to the liver.

The liver metabolizes fat by converting stored fatty acids to their energy-releasing form, acetylcoenzyme A (acetyl CoA), when hepatic glucose and glycogen stores are exhausted or unavailable for metabolic purposes (as in diabetic ketoacidosis). The liver also plays a role in the formation of storage fats (triglycerides) whenever carbohydrates, protein, or fat exceeds the requirements of tissues for glucose or the needs of the liver for glycogen. Furthermore, the liver synthesizes cell membrane components (phospholipids) and proteins (lipoproteins) that carry lipids (fats and cholesterol) in the blood.

## **Fat-soluble vitamins**

Fat-soluble vitamins pass with the chylomicrons into the lymphatic system. Vitamin A, first presenting as the precursor beta-carotene, is cleaved to form retinol, which is then recombined with fatty acids before entering the chylomicron. Vitamins D and D<sub>3</sub> diffuse passively into the chylomicron. The absence of bile salts from the intestine, which occurs in jaundice due to obstruction of the biliary tract, severely impairs vitamin K absorption and blood clotting, with risk of hemorrhage. Vitamin E, a mixture of oils known as tocopherols, is present in eggs and is synthesized by such plants as soybeans, corn (maize), and wheat. It passes through the enterocyte with the other lipids of the micelle and is ultimately stored in the liver.

## **Calcium**

Calcium is required for the construction of bone; it forms part of the substance cementing together the walls of adjacent cells; and it is vital in the responsiveness to stimuli of muscle and nerve cells, which determines their excitability. The main sources of calcium are milk and milk products; meat, in which it is bound to proteins; and vegetables, in which it is bound to phytates (phytic acid) and oxalates (the salt of oxalic acid).

The absorption of calcium is influenced by conditions within the lumen of the small intestine. The acid secretion from the stomach converts the calcium to a salt, which is absorbed primarily in the duodenum. Unabsorbed calcium is precipitated in the ileum and is excreted in the feces. Lactose, the sugar of milk, aids calcium absorption, whereas excess fatty acid and high concentrations of magnesium and oxalates interfere with it.

Calcium is absorbed across the brush border of the enterocyte cell membrane by a mechanism that requires energy. Vitamin D is essential to this process, and, when it is deficient, the active transport of calcium stops. Parathyroid hormone (parathormone) and growth hormone from the pituitary gland also influence calcium absorption. An average diet contains 1,200 mg of calcium, one-third of which is absorbed. In the passage of the blood through the kidney, 99 percent of the circulating calcium is reabsorbed. Thus, in kidney failure as well as in malabsorption states, excessive losses of calcium occur. In calcium deficiency, calcium is resorbed from the bone, which thereby weakens and softens the skeletal structure.

## Magnesium

An average diet contains around 300 mg of magnesium, of which two-thirds is absorbed. Half of the absorbed magnesium is excreted by the kidneys, which can regulate the amount within a range of 1 to 150 millimoles per day. This control is subject to the influences of the parathyroid hormone parathormone and the thyroid hormone calcitonin. Magnesium is important to neuromuscular transmission. It is also an important cofactor in the enzymic processes that form the matrix of bone and in the synthesis of nucleic acid. Magnesium deficiency can result from the overuse of diuretics and from chronic renal failure, chronic alcoholism, uncontrolled diabetes mellitus, and intestinal malabsorption.

Magnesium has an inverse relationship with calcium. Thus, if food is deficient in magnesium, more of the calcium in the food is absorbed. If the blood level of

magnesium is low, calcium is mobilized from bone. The treatment of hypocalcemia due to malabsorption includes administration of magnesium supplements.

## Hematinics

Hematinics are substances that are essential to the proper formation of the components of blood. Examples of hematinics include folic acid, vitamin B<sub>12</sub>, and iron. In addition, vitamin D, which helps maintain the health of bones—the reservoirs of new blood cells—may also have a role in protecting hemoglobin and in stimulating the formation of new blood cells.

## Folic acid

Folic acid (pteroylglutamic acid) is necessary for the synthesis of nucleic acids and for cell replication. Folic acid deficiency results in an impaired maturation of red blood cells (erythrocytes). Foliates are synthesized by bacteria and plants and are hydrolyzed to folic acid in the intestine. Milk and fruit are the main sources of folic acid, providing on average 500 micrograms daily. Folic acid is stored in the liver.

The hydrolysis of the folates, a necessary step to absorption, takes place on the brush borders of jejunal enterocytes and is completed on lysosomes (structures within the cell that contain various hydrolytic enzymes and are part of the intracellular digestive system). When hydrolysis of folates is disturbed, anemia develops. This process is interfered with by certain drugs, especially phenytoin, used in the management of epilepsy, and by the long-term use of sulfonamides in the suppression of disease. A methyl group is added to pteroylglutamic acid in the enterohepatic circulation in the liver and is excreted in the bile. Approximately 100 micrograms are utilized each day. The method of absorption is uncertain.

## Vitamin B<sub>12</sub>

Vitamin B<sub>12</sub>, also called cobalamin because it contains cobalt, is essential to the formation of blood cells. It is a coenzyme that assists the enzymes responsible for moving folate into the cell interior. Vitamin B<sub>12</sub> is a product of bacterial metabolism. Although bacteria in the colon also produce vitamin B<sub>12</sub>, it cannot be absorbed at that site. Vitamin B<sub>12</sub> occurs in a bound form in food and is liberated by proteolytic activity in the stomach and small intestine. It then binds with intrinsic factor (IF), a glycoprotein produced by the same parietal cells that form hydrochloric acid. Intrinsic

factor is essential to transport, and the B<sub>12</sub> protein complex, known as transcobalamin II, is necessary to transfer the vitamin from the intestine to the rest of the body. Once the IF is attached, further proteolytic digestion of the bound vitamin is prevented. Absorption is confined to the distal 100 cm of ileum, especially the last 20 cm, where the complex binds to receptors in the brush border of the enterocytes. The process is slow; it takes three hours from its presentation in food to its appearance in the peripheral blood via the enterohepatic circulation and hepatic veins. The daily requirement of vitamin B<sub>12</sub> is one microgram. Vitamin B<sub>12</sub> is stored primarily in the liver.

## Iron

Iron is necessary for the synthesis of hemoglobin, the oxygen-carrying compound of the red blood cells. It also has an important role as a cofactor in intracellular metabolism. The main dietary sources are meat, eggs, nuts, and seeds. The average daily diet contains approximately 20 mg of iron; humans are unable to excrete iron that has been absorbed in excess of the daily requirement of 1 mg.

The acid in the stomach prevents the formation of insoluble complexes, as does vitamin C. Some amino acids from dietary protein stabilize the iron in low molecular weight complexes. Phosphates and phytates of vegetable origin, some food additives, and the inhibition of acid secretion impede the absorption of iron. Iron is almost wholly absorbed in the duodenum by a process that involves metabolic activity requiring energy. Most of the iron remains trapped in the surface enterocytes and is lost when the cells die and are shed into the intestine. The amount of iron lost seems to be related in some way to the state of the body's iron stores, although this can be overcome if very large doses of iron are taken orally. Alcohol in the stomach and duodenum increases the rate of absorption. Transport of the iron from the enterocyte is achieved by binding to a carrier, a plasma protein called transferrin. From the intestine it passes into the portal circulation and the liver. When the loss of iron is increased, as in excessive menstruation and in bleeding disorders, the rate of absorption is stepped up from less than 1 mg per day to 1.5 mg or more.

## Vitamin D

Vitamin D is essentially a hormone and is available from two sources. First, under the influence of photosynthesis made possible by ultraviolet rays from the Sun, a sterol compound from the liver (dehydrocholesterol) is converted to vitamin D<sub>3</sub>. This

supplies enough vitamin D<sub>3</sub> for human needs. In the absence of exposure to sunlight, dietary supplements become necessary. Eggs, liver, fortified bread, and milk are the main sources of vitamin D. Deficiency of vitamin D occurs when there is lack of sunlight and inadequate vitamin D in the diet. It may also result from disease or after resection of the small intestine, which may cause malabsorption. In these circumstances softening of bone (osteomalacia) and rickets may occur.

In the jejunum vitamin D is incorporated along with bile salts and fatty acids into the micelles, and, subsequently, as the provitamin D<sub>1</sub>, vitamin D is absorbed in the ileum and then passes into the circulation via the portal vein. A specific bloodborne protein, an alpha-1-globulin, carries it to the liver, where the process of chemical change to the active hormone begins by hydroxylation to cholecalciferol. The derivatives are conveyed from the liver to various tissues, including the skin, bone, and parathyroid glands. In the intestine vitamin D influences the permeability of the brush borders of the enterocytes to calcium.

Vitamin D levels can influence hemoglobin production in the body. For example, persons with low levels of vitamin D may develop anemia, and hemoglobin levels in these individuals can be increased by vitamin D supplements. Although the mechanism by which vitamin D influences hemoglobin production is unclear, research has suggested that it may protect the oxygen-carrying molecule via a protective anti-inflammatory action. Vitamin D has also been shown to augment the production of red blood cells in the presence of erythropoietin, a hormone produced primarily in the kidneys that influences the rate of red cell production.

## Intestinal gas

The movement of gas through the intestines produces the gurgling sounds known as borborygmi. In the resting state there are usually about 200 ml of gas in the gastrointestinal tract. Its composition varies: between 20 and 90 percent is nitrogen, up to 10 percent is oxygen, up to 50 percent is hydrogen, up to 10 percent is methane, and between 10 and 30 percent is carbon dioxide. Most of the air that people swallow, while talking and eating in particular, is either regurgitated (as in belching) or absorbed in the stomach. Anxiety or eating quickly induces frequent swallowing of air with consequent belching or increased rectal flatus. Although some of the carbon dioxide in the small intestine is due to the interaction of hydrogen ions of gastric acid with bicarbonate, some is generated in the jejunum by the degradation of dietary triglycerides to fatty acids. High levels of carbon dioxide in rectal flatus reflect bacterial

activity in the colon. Methane cannot be produced by any cell and is entirely the result of bacteria's acting on fermentable dietary residues in the colon, although there appears to be a familial factor involved in this, as not everyone can generate methane. In the colon bacterial production of hydrogen is markedly elevated when the diet contains an excess of vegetable saccharides. This is particularly noticeable after consuming beans, for example. Gas is more often responsible for the buoyancy of stools than is excessive residual fat in malabsorption states.

The gradient between the partial pressures (or the pressure exerted by each gas in a mixture of gases) of particular gases in the intestinal lumen and the partial pressures of gases in the circulating blood determines the direction of movement of gases. Thus, because oxygen tends to be in low pressure in the colon, it diffuses out from the blood into the intestine. The diffusion of nitrogen from the blood into the intestine occurs because a gradient is established by the carbon dioxide, methane, and hydrogen that result from metabolic activities of the commensal bacteria; the partial pressure contributed by nitrogen in the colon is lowered, stimulating nitrogen to enter the intestine from the blood. In areas where lactase, the enzyme that breaks down lactose (milk sugar), is missing from the group of disaccharidases of the small intestine, lactose passes into the colon undigested. In a lactase-deficient person, the unhydrolyzed lactose enters the colon, where the amount of lactose normally present in a glass of milk is capable of liberating, after bacterial fermentation, the equivalent of two to four cups (500–1,000 ml) of gas (hydrogen). About 15 percent of the gas diffuses back into the blood, with the rest passing as flatus.

Hydrogen generated in the colon is partly absorbed, passes in the circulating blood to the lungs, and diffuses into the respiratory passages, where its presence can be easily determined. The time taken for hydrogen to appear in the breath after ingestion of a standard load of glucose or lactose is used to determine whether the upper area of the gastrointestinal tract is colonized by bacteria. Hydrogen that appears within 30 minutes of the ingestion of the sugar load suggests heavy colonization of the small intestine.

## **Hormones of the gastrointestinal tract**

### **Production and secretion of peptides**

Control of the activity of the specialized cells in the digestive system that are concerned with motor and secretory functions depends upon signals received at their

cell membranes. These signals originate in either endocrine or nerve cells and are carried to the target cell by amino or peptide “messenger” molecules. When secreted, these substances either diffuse into the tissue spaces around the cells and affect target cells in the vicinity or are taken up in the circulating blood and delivered to target cells some distance away. In both circumstances the messengers are hormones, but those exerting their effect locally are called paracrine; those exerting their effect at a distance are called endocrine.

Peptides are composed of a number of amino acids strung together in a chain. The amino acids occur in an ordered sequence that is peculiar to each peptide. The biological activity of the peptide (i.e., the ability to stimulate the target cells) may reside in only a fraction of the chain—for example, in a four- or five-amino-acid sequence. In other instances the entire chain must be intact to achieve this purpose. For example, delta (D) cells, which produce a hormone known as somatostatin, are dispersed throughout the whole gastrointestinal tract. Somatostatin has inhibiting effects on the production of acid in the stomach, the motor activity of the intestine, and the release of digestive enzymes from the pancreas. These effects are achieved by local diffusion of somatostatin from the D cells in the vicinity of the target tissue. On the other hand, gastrin, a hormone produced by the granular gastrin (G) cells in the mucosa of the gastric antrum (the lower part of the stomach), is secreted into the blood.

The hormone gastrin also exemplifies the biological capability of a fraction of the molecule. These fractions have a molecular structure that fits the receptor site on the membrane of the target cell and therefore can initiate the intracellular events in the production of the acid. The G cells of the antrum of the stomach primarily produce a messenger peptide with 17 amino acids in sequence, while those in the duodenum and jejunum of the small intestine primarily produce a messenger peptide with 34 amino acids. The shorter molecule is more potent. The chain can be cleaved to only four amino acids (the tetrapeptide), however, and (provided that the sequence remains the same as in the parent molecule and the fragment is the one at the amino terminal of the whole molecule) the cleaved amino acid chain retains biological activity, although it is less potent than the larger molecules of gastrin.

Certain messenger peptides have been found to originate not in endocrine cells but in neural elements within the gastrointestinal tract, to be released during electrical discharge within the nerves. For example, vasoactive intestinal peptide (VIP) released

from nerve terminals in the brain also is abundant in the nervous structures of the gut, including the submucosal and myenteric nerve plexuses. Occasionally VIP coexists with acetylcholine, the messenger molecule of the autonomic parasympathetic nervous system. The discharge of VIP brings about receptive relaxation of the esophageal and pyloric sphincters, modulates the long peristaltic movements in the intestine, and influences the secretion of electrolytes from the mucosa of the small intestine.

Eighteen different endocrine cells can be identified within the gastrointestinal tract, but it is probable that several of these and their particular peptides are evolutionary vestiges that functioned in other stages of human development, while others may represent different stages of maturation of the same endocrine cell.

Peptides that bind with target cell receptors and stimulate the cell to react are known as agonists. Others that fit the receptor but do not initiate intracellular events are known as antagonists. The ability of antagonists to occupy receptors and thereby deny access to an agonist is the basis of the treatment of peptic ulcer disease with histamine ( $H_2$ ) receptor blockers. By occupying the receptors on the parietal cells, antagonists deny histamine the opportunity to initiate the production of hydrochloric acid, one of the chief causative agents of peptic ulcers.

Similar events stimulate or suppress the production of the messenger peptides in their endocrine or neural cell of origin. For example, the discharge of granules of gastrin from the G cells occurs when a meal is consumed. While the concentration of hydrogen ions (the acidity) remains low because of the buffering effect of the food, the release of gastrin continues. As digestion proceeds and the stomach begins to empty, however, the acidity increases because of the diminishing neutralizing effect of the food. When the contents of the stomach in contact with the mucosa of the antrum reach a certain level of acidity (pH of 2.5 or less), the release of gastrin stops. Failure of this mechanism leads to inappropriate secretion of acid when the stomach is empty and may cause peptic ulcers in the duodenum. Some endocrine cells have microvilli on their surface that project into the lumen of the gland or into the main channel of the stomach or intestine. These cells probably have an ability to "sample" continuously the luminal contents in their vicinity.

When production and secretion of a peptide hormone is excessive, it induces an increase in the number of the target cells and may increase the size of the individual



cells. This is known as trophism and is similar to the increase in size of skeletal muscle in response to appropriate exercise (work hypertrophy). Such trophism is observed in certain disease states that involve the gastrointestinal hormones. Thus, when gastrin is secreted into the blood by a tumour of G cells (gastrinoma) of the pancreas, it is a continuous process because there is no mechanism at that site to inhibit the secretion; this brings about a massive increase in the number of parietal cells in the stomach and an overproduction of acid. This in turn overwhelms the defenses of the mucosa of the upper gastrointestinal tract against autodigestion and results in intractable and complicated peptic ulceration.

## Individual hormones

### Insulin

Insulin is secreted by the beta (B) cells of the pancreas in response to a rise in plasma glucose concentration and a fall in glucagon level. It stimulates the absorption of carbohydrates (glucose) into stores in muscle and adipose (fatty) tissue. Insulin is used in the treatment of diabetes mellitus.

### Glucagon

Glucagon is produced by pancreatic alpha (A) cells in response to a drop in plasma glucose concentration; the effects of glucagon are opposite to those of insulin. Glucagon stimulates the breakdown of glycogen and the production of new glucose (gluconeogenesis) in the liver. It also decreases the production of gastric and pancreatic secretions. Glucagon is used in the treatment of conditions in which the level of sugar in the blood is lowered.

### Somatostatin

Somatostatin is a peptide secreted by the delta (D) cells in response to eating, especially when fat enters the duodenum. It is an inhibitory modulator of the secretion of acid and pepsin and of the release of gastrin, insulin, and other intestinal hormones. It inhibits motility of the gallbladder and intestines and suppresses the secretion of lipase by the pancreas.

### Serotonin

Serotonin, or 5-hydroxytryptamine, is an amine that is formed from amino acid

5-hydroxytryptophan in the enterochromaffin cells (EC) and in other similar cells called enterochromaffin-like cells (ECL). These cells also secrete histamine and kinins, which likewise have important messenger functions in glandular secretions and on blood vessels. Serotonin acts in paracrine fashion. Both EC and ECL cells are widely distributed in the gastrointestinal tract.

## **Cholecystokinin**

Cholecystokinin, a peptide secreted by the I cells in response to the emptying of the stomach contents into the duodenum, causes contraction of the gallbladder with emptying of its contents, relaxation of the sphincter closing the end of the bile duct, and stimulation of the production of enzymes by the pancreas. Cholecystokinin increases intestinal peristalsis, and it is used in radiological examination of the gallbladder and in tests of pancreatic function.

## **Gastric inhibitory peptide**

Secreted by the K cells, gastric inhibitory peptide enhances insulin production in response to a high concentration of blood sugar, and it inhibits the absorption of water and electrolytes in the small intestine. The cell numbers are increased in persons with duodenal ulcer, chronic inflammation of the pancreas, and diabetes resulting from obesity.

## **Intestinal glucagon**

Secreted by the L cells in response to the presence of carbohydrate and triglycerides in the small intestine, intestinal glucagon (enteroglucagon) modulates intestinal motility and has a strong trophic influence on mucosal structures.

## **Motilin**

A high level of motilin in the blood stimulates the contraction of the fundus and antrum and accelerates gastric emptying. It contracts the gallbladder and increases the squeeze pressure of the lower esophageal sphincter. Motilin is secreted between meals.

## **Neurotensin**

Secreted by the N cells of the ileum in response to fat in the small intestine,

neurotensin modulates motility, relaxes the lower esophageal sphincter, and blocks the stimulation of acid and pepsin secretion by the vagus nerve.

## **Pancreatic polypeptide**

Special endocrine cells, "PP" cells, secrete pancreatic polypeptide in response to protein meals. Their function is intimately related to vagal and cholinergic activity. The level of pancreatic polypeptide is frequently raised in diabetes.

## **Secretin**

Secreted by the S cells of the duodenum in response to meals and to the presence of acid in the duodenum, secretin stimulates the production of bicarbonate by the pancreas.

## **Vasoactive intestinal peptide**

Secreted locally by endocrine cells or nerve endings, vasoactive intestinal peptide is located almost exclusively in nerves distributed throughout the gastrointestinal tract. It inhibits the release of gastrin and the secretion of acid, is a mild stimulant of bicarbonate secretion from the pancreas, and is a powerful stimulant of the secretion of water and electrolytes by the small and large intestines. It relaxes the sphincters and slows intestinal transit time. There is another group of peptide messengers that is found in quantity within the brain and in the nerves of the gastrointestinal tract. These include substance P, endorphins, enkephalins, and bombesin.

## **Substance P**

Present in significant amounts in the vagus nerves and the myenteric plexus, substance P stimulates saliva production, contraction of smooth muscle cells, and inflammatory responses in tissues, but it is uncertain whether it is anything other than an evolutionary vestige.

## **Endorphins and enkephalins**

Endorphins and enkephalins, each comprising five amino acids in the molecule, are present in the vagus nerves and the myenteric plexus. They have the properties of opiate (opium-derived) substances such as morphine; they bind to the same receptors and are neutralized by the opiate antagonist naloxone. There is no evidence that

endorphins and enkephalins are circulating hormones, but the enkephalins may have a physiological paracrine role in modulating smooth muscle activity in the gastrointestinal tract, and endorphins may serve in modulating the release of other peptides from endocrine cells in the digestive system.

## **Bombesin**

A peptide that is found in the intrinsic nerves of the gastrointestinal tract, bombesin stimulates the release of gastrin and pancreatic enzymes and causes contraction of the gallbladder. These functions may be secondary, however, to the release of cholecystokinin, a hormone secreted by the mucosa of the intestine that has similar effects. It is uncertain if bombesin has a physiological role or if it is an evolutionary vestige.

## **Prostaglandins**

Prostaglandins are hormonelike substances involved in the contraction and relaxation of the smooth muscle of the gastrointestinal tract. Prostaglandins are also able to protect the mucosa of the alimentary tract from injury by various insults (boiling water, alcohol, aspirin, bile acids, stress) by increasing the secretion of mucus and bicarbonate from the mucosa, which in turn stimulates the migration of cells to the surface for repair and replacement of the mucosal lining.

## **The gastrointestinal tract as an organ of immunity**

The body is continuously exposed to damage by viruses, bacteria, and parasites; ingested toxins and chemicals, including drugs and food additives; and foreign protein of plant origin. These insults are received by the skin, the respiratory system, and the digestive system, which constitute the interface between the sterile body interior and the environment.

The defense of the body is vested largely in the lymphatic system and its lymphocytes. A substantial part of the gastrointestinal tract is occupied by lymphoid tissue, which can be divided into three sectors. The first is represented by the pharyngeal tonsils, the appendix, and the large aggregates of nodules known as Peyer patches located at intervals throughout the small intestine. The second sector includes the lymphocytes and plasma cells that populate the basement membrane (lamina propria) of the small intestine, the area of loose connective tissue above the supporting tissue of the

mucosal lining extending into the villi. The third sector comprises lymphocytes that lie between the epithelial cells in the mucosa. The interaction between these cells of the lymphatic system and the threatening agent is the basis of defense in the gastrointestinal tract.

Lymphocytes are of two types, B and T, according to whether they originate in the bone marrow (B) or in the thymus gland (T), located in the chest. On leaving their tissue of origin, both types end up in the peripheral lymphoid structures. These include the peripheral lymph glands, the spleen, the lymph nodes in the mesentery of the intestine, the Peyer patches, and the spaces between the epithelial cells of the mucosa.

Lymphocytes are immature until they come into contact with antigens. If foreign material is recognized as such by T cells (T lymphocytes), the lymphocytes undergo a process of maturation in which they proliferate and divide into subclasses. The first subclass comprises the "helper" T cells, which are mediators of immune function. The second class consists of "suppressor" T cells, which modulate and control immune responses. The third class comprises the "killer" T cells, which are cytotoxic (i.e., they are able to destroy other cells). Most of the lymphocytes lying between the epithelial cells of the mucosa are killer T cells.

When B cells (B lymphocytes) recognize antigen, they also mature, changing to the form known as plasma cells. These cells elaborate a highly specialized protein material, immunoglobulin (Ig), which constitutes antibodies. There are five varieties of immunoglobulin: IgA, IgM, IgG, IgD, and IgE. B cells and plasma cells are found mainly in the cells in the spaces of the basement membrane. Another group of specialized cells are known as M cells. These are stretched over and around ordinary epithelial cells of the mucosa. The M cells package antigenic material into vesicles and move it through the cell and into the surrounding spaces.

Lymphocytes of the Peyer patches pass through lymph vessels to the nodes in the mesentery and then to the thoracic duct. This is the collecting channel in the abdomen, which passes up through the thorax to drain into the venous system at the junction of the left internal jugular and left subclavian veins. The various ramifications of the abdominal lymphatics all drain into the thoracic duct. From there the lymphocytes are carried back to the intestine as well as being dispersed to other organs. It is these migrated lymphocytes that come to populate the basement

membrane and to occupy the spaces between epithelial cells.

Most cells in the mesenteric nodes and the basement membrane are plasma cells that produce immunoglobulin of class IgA, while IgM and, to a lesser extent, IgE are produced by other cells, and IgG is formed by cells in the spleen and peripheral lymph nodes. The IgA of plasma cells is secreted into the lumen of the intestine, where it is known as "secretory IgA" and has a different molecular structure from that of the IgA circulating in the blood. When secreted, it is accompanied by a glycoprotein that is produced by the epithelial cells of the mucosa. This substance, when attached to the IgA molecule, protects it from digestion by protein-splitting enzymes. This IgA complex can adhere to virus and bacteria, interfering with their growth and diminishing their power to invade tissue. It is also capable of rendering toxic substances harmless.

Formed by B cells, IgE coats the surface of mast cells, which are specially adapted to deal with the allergic challenge posed by parasites and worms.

The newborn infant is protected by already-matured immunoglobulin with which the colostrum, the initial secretion of the lactating breast, is richly endowed. As time passes, the gastrointestinal tract of the infant is increasingly exposed to various insults, and the lymphocytes and other cells of the immune system become adapted to deal with these. In this way, the body also develops a tolerance to potentially offending substances. If invasion of tissue occurs despite these various defenses, then a generalized systemic immune reaction is marshaled. Some of the features of this reaction, such as fever and a massive increase in the white blood cells, are the evidence of illness.

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