

Digestion in the small intestine

Approximately 1500 ml of fluid is secreted by the walls of the small intestine from the blood into the lumen each day. One of the reasons for water movement into the lumen (secretion) is that the intestinal epithelium at the base of the villi secretes a number of mineral ions, notably sodium, chloride, and bicarbonate ions into the lumen, and water follows by osmosis. These secretions, along with mucus, lubricate the surface of the intestinal tract and help protect the epithelial cells from excessive damage by the digestive enzymes in the lumen. Some damage to these cells still occurs, however and the intestinal epithelium has one of the highest cell renewal rates of any tissue in the body. Chloride is the primary ion determining the magnitude of fluid secretion. Various hormonal and paracrine signals—as well as certain bacterial toxins— can increase the opening frequency of chloride channels and thus increase fluid secretion. As stated earlier, water movement into the lumen also occurs when the chyme entering the small intestine from the stomach is hypertonic because of a high concentration of solutes in the meal and because digestion breaks down large molecules into many more small molecules. This hypertonicity causes the osmotic movement of water from the isotonic plasma into the intestinal lumen.

Normally, virtually all of the fluid secreted by the small intestine is absorbed back into the blood. In addition, a much larger volume of fluid, which includes salivary, gastric, hepatic, and pancreatic secretions, as well as ingested water, is simultaneously absorbed from the intestinal lumen into the blood. Thus, overall there is a large net absorption of water from the small intestine. Absorption is achieved by the transport of ions, primarily sodium, from the intestinal lumen into the blood, with water following by osmosis.

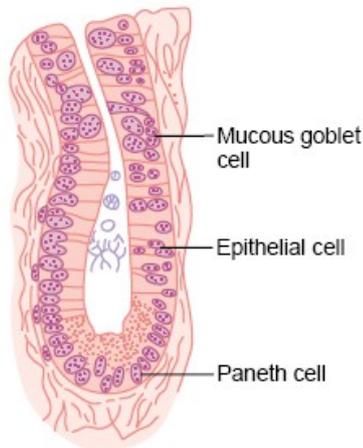
An extensive array of compound mucous glands, called Brunner's glands, is located in the wall of the first few centimeters of the duodenum, mainly between the pylorus of the stomach and the papilla of Vater where pancreatic secretion and bile empty into the duodenum. These glands secrete large amounts of alkaline mucus in response to

- (1) tactile or irritating stimuli on the duodenal mucosa;
- (2) vagal stimulation, which causes increased Brunner's glands secretion concurrently with increase in stomach secretion; and
- (3) gastrointestinal hormones, especially secretin.

The function of the mucus secreted by Brunner's glands is to protect the duodenal wall from digestion by the highly acid gastric juice emptying from the stomach. In addition, the mucus contains a large excess of bicarbonate ions, which add to the bicarbonate ions from pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach. Brunner's glands are inhibited by sympathetic stimulation; therefore, such stimulation in very excitable persons is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the gastrointestinal tract to be the site of peptic ulcers in about 50 per cent of ulcer patients.

Located over the entire surface of the small intestine are small pits called crypts of Lieberkühn, one of which is illustrated in Figure 1. These crypts lie between the intestinal villi. The surfaces of both the crypts and the villi are covered by an epithelium composed of two types of cells: (1) a moderate number of goblet cells, which secrete mucus that lubricates and protects the intestinal surfaces, and (2) a large number of enterocytes, which, in the crypts, secrete large quantities of water and electrolytes and, over the surfaces of adjacent villi, reabsorb the water and electrolytes along with end products of digestion. The intestinal secretions are formed by the enterocytes of the crypts at a rate of about 1800 ml/day. These secretions are almost pure extracellular fluid and have a slightly alkaline pH in the range of 7.5 to 8.0. The secretions also are rapidly reabsorbed by the villi. This flow of fluid from the crypts into the villi supplies a watery vehicle for absorption of substances from chyme when it

comes in contact with the villi. Thus, the primary function of the small intestine is to absorb nutrients and their digestive products into the blood.



The exact mechanism that controls the marked secretion of watery fluid by the crypts of Lieberkuhn is not known. It is believed to involve at least two active secretory processes: (1) active secretion of chloride ions into the crypts and (2) active secretion of bicarbonate ions. The secretion of both of these ions causes electrical drag as well as positively charged sodium ions through the membrane and into the secreted fluid. Finally, all these ions together cause osmotic movement of water. The enterocytes of the mucosa, especially those that cover the villi, do contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium.

Figure 1 A crypt of Lieberkuhn

These enzymes are the following: (1) several peptidases for splitting small peptides into amino acids, (2) four enzymes—sucrase, maltase, isomaltase and lactase—for splitting disaccharides into monosaccharides, and (3) small amounts of intestinal lipase for splitting neutral fats into glycerol and fatty acids. The epithelial cells deep in the crypts of Lieberkuhn continually undergo mitosis and new cells migrate along the basement membrane upward out of the crypts toward the tips of the villi, thus continually replacing the villus epithelium and also forming new digestive enzymes. As the villus cells age, they are finally shed into the intestinal secretions. The life cycle of an intestinal epithelial cell is about 5 days. This rapid growth of new cells also allows rapid repair of excoriations that occur in the mucosa.

Regulation of small intestine secretion

By far the most important means for regulating small intestine secretion are local enteric nervous reflexes, especially reflexes initiated by tactile or irritative stimuli from the chyme in the intestines.

Movements of the small intestine

The movements of the small intestine, can be divided into mixing contractions and propulsive contractions. To a great extent, this separation is artificial because essentially all movements of the small intestine cause at least some degree of both mixing and propulsion.

Mixing Contractions (Segmentation Contraction)

When a portion of the small intestine becomes distended with chyme, stretching of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine and lasting a fraction of a minute. Each contracting segment is only a few centimeters long and the contraction lasts a few seconds. The chyme in the lumen of a contracting segment is forced both up and down the intestine. This rhythmical contraction and relaxation of the intestine, known as segmentation, produces a continuous division and subdivision of the intestinal contents, thoroughly mixing the chyme in the lumen and bringing it into contact with the intestinal wall. That is, they divide the intestine into spaced segments that have the appearance of a chain of sausages. As one set of segmentation contractions relaxes, a new set often begins, but the contractions this time occur mainly at new points between the previous contractions. Therefore, the segmentation contractions “chop” the chyme two to three times per minute, in this way promoting progressive mixing of the food with secretions of the small intestine. These segmenting movements are initiated by electrical activity generated by pacemaker cells in or associated with the circular smooth-muscle layer. Like the slow waves in the stomach, this intestinal basic electrical rhythm produces oscillations in the smooth

muscle membrane potential that, if threshold is reached, trigger action potentials that increase muscle contraction.

The maximum frequency of the segmentation contractions in the small intestine is determined by the frequency of electrical slow waves in the intestinal wall, which is the basic electrical rhythm. Because this frequency normally is not over 12 per minute in the duodenum and proximal jejunum, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this occurs only under extreme conditions of stimulation. In the terminal ileum, the maximum frequency is usually 8 to 9 contractions per minute. The segmentation contractions become exceedingly weak when the excitatory activity of the enteric nervous system is blocked by the drug atropine. Therefore, even though it is the slow waves in the smooth muscle itself that cause the segmentation contractions, these contractions are not effective without background excitation mainly from the myenteric nerve plexus. The intensity of segmentation can be altered by hormones the enteric nervous system and autonomic nerves; parasympathetic activity increases the force of contraction and sympathetic stimulation decreases it. Thus, cephalic phase stimuli, including emotional states, can alter intestinal motility. As is true for the stomach, these inputs produce changes in the force of smooth-muscle contraction but do not significantly change the frequencies of the basic electrical rhythms. After most of a meal has been absorbed, the segmenting contractions cease and are replaced by a pattern of peristaltic activity known as the migrating motility complex. Beginning in the lower portion of the stomach, repeated waves of peristaltic activity travel about 2 ft along the small intestine and then die out. This short segment of peristaltic activity slowly migrates down the small intestine, taking about 2 h to reach the large intestine. By the time the migrating motility complex reaches the end of the ileum, new waves are beginning in the stomach, and the process is repeated. The migrating motility complex moves any undigested material still remaining in the small intestine into the large intestine and also prevents bacteria from remaining in the small intestine long enough to grow and multiply excessively. In diseases in which there is an aberrant migrating motility complex, bacterial overgrowth in the small intestine can become a major problem. Upon the arrival of a meal in the stomach, the migrating motility complex rapidly ceases in the intestine and is replaced by segmentation.

Propulsive movements peristalsis in the small intestine. Chyme is propelled through the small intestine by peristaltic waves. These can occur in any part of the small intestine and they move toward the anus at a velocity of 0.5 to 2.0 cm/sec, faster in the proximal intestine and slower in the terminal intestine. They normally are very weak and usually die out after traveling only 3 to 5 centimeters, very rarely farther than 10 centimeters, so that forward movement of the chyme is very slow, so slow in fact that net movement along the small intestine normally averages only 1 cm/min. This means that 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.

Control of peristalsis by nervous and hormonal signals. Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum causing stretch of the duodenal wall, but also by a so-called gastroenteric reflex that is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine. In addition to the nervous signals that may affect small intestinal peristalsis, several hormonal factors also affect peristalsis: gastrin, CCK, insulin, motilin, and serotonin, all of which enhance intestinal motility and are secreted during various phases of food processing. Conversely, secretin and glucagon inhibit small intestinal motility. The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the

chyme along the intestine; and this process intensifies as additional chyme enters the duodenum. On reaching the ileocecal valve, the chyme is sometimes blocked for several hours until the person eats another meal; at that time, a gastroileal reflex intensifies peristalsis in the ileum and forces the remaining chyme through the ileocecal valve into the cecum of the large intestine.

A rise in the plasma concentration of a candidate intestinal hormone, motilin, is thought to initiate the migrating motility complex. The mechanisms of motilin action and the control of its release have not been determined. The contractile activity in various regions of the small intestine can be altered by reflexes initiated at different points along the gastrointestinal tract. For example, segmentation intensity in the ileum increases during periods of gastric emptying, and this is known as the gastroileal reflex. Large distensions of the intestine, injury to the intestinal wall, and various bacterial infections in the intestine lead to a complete cessation of motility, the intestino-intestinal reflex.

Propulsive effect of the segmentation movements. The segmentation movements, although lasting for only a few seconds at a time, often also travel 1 centimeter or so in the anal direction and during that time help propel the food down the intestine.

Peristaltic rush. Although peristalsis in the small intestine is normally weak, intense irritation of the intestinal mucosa, as occurs in some severe cases of infectious diarrhea, can cause both powerful and rapid peristalsis, called the peristaltic rush. This is initiated partly by nervous reflexes that involve the autonomic nervous system and brain stem and partly by intrinsic enhancement of the myenteric plexus reflexes within the gut wall itself. The powerful peristaltic contractions travel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme and excessive distention.

The muscularis mucosae can cause short folds to appear in the intestinal mucosa. In addition, individual fibers from this muscle extend into the intestinal villi and cause them to contract intermittently. The mucosal folds increase the surface area exposed to the chyme, thereby increasing absorption. Also, contractions of the villi—shortening, elongating, and shortening again—“milk” the villi, so that lymph flows freely from the central lacteals of the villi into the lymphatic system. These mucosal and villous contractions are initiated mainly by local nervous reflexes in the submucosal nerve plexus that occur in response to chyme in the small intestine.

Function of the ileocecal valve

A principal function of the ileocecal valve is to prevent backflow of fecal contents from the colon into the small intestine. The ileocecal valve itself protrudes into the lumen of the cecum and therefore is forcefully closed when excess pressure builds up in the cecum and tries to push cecal contents backward against the valve lips. The valve usually can resist reverse pressure of at least 50 to 60 centimeters of water. In addition, the wall of the ileum for several centimeters immediately upstream from the ileocecal valve has a thickened circular muscle called the ileocecal sphincter. This sphincter normally remains mildly constricted and slows emptying of ileal contents into the cecum. However, immediately after a meal, a gastroileal reflex intensifies peristalsis in the ileum, and emptying of ileal contents into the cecum proceeds. Resistance to emptying at the ileocecal valve prolongs the stay of chyme in the ileum and thereby facilitates absorption. Normally, only 1500 to 2000 milliliters of chyme empty into the cecum each day. The degree of contraction of the ileocecal sphincter and the intensity of peristalsis in the terminal ileum are controlled significantly by reflexes from the cecum. When the cecum is distended, contraction of the ileocecal sphincter becomes intensified and ileal peristalsis is inhibited, both of which greatly delay emptying of additional chyme into the cecum from the ileum. Also, any irritant in the cecum delays emptying. For

instance, when a person has an inflamed appendix, the irritation of this vestigial remnant of the cecum can cause such intense spasm of the ileocecal sphincter and partial paralysis of the ileum that these effects together block emptying of the ileum into the cecum. The reflexes from the cecum to the ileocecal sphincter and ileum are mediated both by way of the myenteric plexus in the gut wall itself and of the extrinsic autonomic nerves, especially by way of the prevertebral sympathetic ganglia.

Large Intestine

The large intestine is a tube 2.5 in. in diameter and about 4 ft long. Its first portion, the cecum, forms a blind-ended pouch from which extends the appendix, a small fingerlike projection having no known essential function. The colon consists of three relatively straight segments—the ascending, transverse and descending portions. The terminal portion of the descending colon is S-shaped, forming the sigmoid colon, which empties into a relatively straight segment of the large intestine, the rectum, which ends at the anus. Although the large intestine has a greater diameter than the small intestine, its epithelial surface area is far less, since the large intestine is about half as long as the small intestine, its surface is not convoluted, and its mucosa lacks villi. The secretions of the large intestine are scanty, lack digestive enzymes and consist mostly of mucus and fluid containing bicarbonate and potassium ions. The primary function of the large intestine is to store and concentrate fecal material before defecation.

Chyme enters the cecum through the ileocecal sphincter. This sphincter is normally closed, but after a meal, when the gastroileal reflex increases ileal contractions, it relaxes each time the terminal portion of the ileum contracts, allowing chyme to enter the large intestine. Distension of the large intestine, on the other hand, produces a reflex contraction of the sphincter, preventing fecal material from moving back into the small intestine. About 1500 ml of chyme enters the large intestine from the small intestine each day. This material is derived largely from the secretions of the lower small intestine since most of the ingested food has been absorbed before reaching the large intestine. Fluid absorption by the large intestine normally accounts for only a small fraction of the fluid entering the gastrointestinal tract each day. The primary absorptive process in the large intestine is the active transport of sodium from lumen to blood, with the accompanying osmotic absorption of water. If fecal material remains in the large intestine for a long time, almost all the water is absorbed, leaving behind hard fecal pellets. There is normally a net movement of potassium from blood into the large intestine lumen, and severe depletion of total-body potassium can result when large volumes of fluid are excreted in the feces. There is also a net movement of bicarbonate ions into the lumen, and loss of this bicarbonate (a base) in patients with prolonged diarrhea can cause the blood to become acidic. The large intestine also absorbs some of the products formed by the bacteria inhabiting this region. Undigested polysaccharides (fiber) are metabolized to short-chain fatty acids by bacteria in the large intestine and absorbed by passive diffusion. The bicarbonate secreted by the large intestine helps to neutralize the increased acidity resulting from the formation of these fatty acids.

These bacteria also produce small amounts of vitamins, especially vitamin K, that can be absorbed into the blood. Although this source of vitamins generally provides only a small part of the normal daily requirement, it may make a significant contribution when dietary vitamin intake is low. An individual who depends on absorption of vitamins formed by bacteria in the large intestine may become vitamin deficient if treated with antibiotics that inhibit other species of bacteria as well as the disease-causing bacteria. Other bacterial products include gas (flatus), which is a mixture of nitrogen and carbon dioxide, with small amounts of the inflammable gases hydrogen, methane and hydrogen sulfide. Bacterial

fermentation of undigested polysaccharides produces these gases in the colon (except for nitrogen, which is derived from swallowed air), at the rate of about 400 to 700 ml/day. Certain foods (beans, for example) contain large amounts of carbohydrates that cannot be digested by intestinal enzymes but are readily metabolized by bacteria in the large intestine, producing large amounts of gas.

The mucosa of the large intestine, like that of the small intestine, has many crypts of Lieberkühn; however, unlike the small intestine, there are no villi. The epithelial cells contain almost no enzymes; they consist mainly of mucous cells that secrete only mucus. This mucus contains moderate amounts of bicarbonate ions secreted by a few non-mucus-secreting epithelial cells. The rate of secretion of mucus is regulated principally by direct, tactile stimulation of the epithelial cells lining the large intestine and by local nervous reflexes to the mucous cells in the crypts of Lieberkühn. Stimulation of the pelvic nerves from the spinal cord, which carry parasympathetic innervation to the distal one half to two thirds of the large intestine, also can cause marked increase in mucus secretion. During extreme parasympathetic stimulation, often caused by emotional disturbances, so much mucus can occasionally be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30 minutes; this mucus often contains little or no fecal material. Mucus in the large intestine protects the intestinal wall against excoriation, but in addition, it provides an adherent medium for holding fecal matter together. Furthermore, it protects the intestinal wall from the great amount of bacterial activity that takes place inside the feces, and, finally, the mucus plus the alkalinity of the secretion (pH of 8.0 caused by large amounts of sodium bicarbonate) provides a barrier to keep acids formed in the feces from attacking the intestinal wall.

Whenever a segment of the large intestine becomes intensely irritated, as occurs when bacterial infection becomes rampant during enteritis, the mucosa secretes extra large quantities of water and electrolytes in addition to the normal viscid alkaline mucus. This acts to dilute the irritating factors and to cause rapid movement of the feces toward the anus. The result is diarrhea, with loss of large quantities of water and electrolytes. But the diarrhea also washes away irritant factors, which promotes earlier recovery from the disease than might otherwise occur.

Movements of the colon

The principal functions of the colon are (1) absorption of water and electrolytes from the chyme to form solid feces and (2) storage of fecal matter until it can be expelled. The proximal half of the colon, is concerned principally with absorption and the distal half with storage. Because intense colon wall movements are not required for these functions, the movements of the colon are normally very sluggish. Yet in a sluggish manner, the movements still have characteristics similar to those of the small intestine and can be divided once again into mixing movements and propulsive movements.

In the same manner that segmentation movements occur in the small intestine, large circular constrictions occur in the large intestine. At each of these constrictions, about 2.5 centimeters of the circular muscle contracts, sometimes constricting the lumen of the colon almost to occlusion. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the teniae coli, contracts. These combined contractions of the circular and longitudinal strips of muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called haustrations. Each haustration usually reaches peak intensity in about 30 seconds and then disappears during the next 60 seconds. They also at times move slowly toward the anus during contraction, especially in the cecum and ascending colon, and thereby provide a minor amount of forward propulsion of the colonic contents. After another few minutes, new haustral contractions occur in other areas

nearby. Therefore, the fecal material in the large intestine is slowly dug into and rolled over in much the same manner that one spades the earth. In this way, all the fecal material is gradually exposed to the mucosal surface of the large intestine and fluid and dissolved substances are progressively absorbed until only 80 to 200 milliliters of feces are expelled each day. Contractions of the circular smooth muscle in the large intestine produce a segmentation motion with a rhythm considerably slower (one every 30 min) than that in the small intestine. Because of the slow propulsion of the large intestine contents, material entering the large intestine from the small intestine remains for about 18 to 24 h. This provides time for bacteria to grow and multiply. Three to four times a day, generally following a meal, a wave of intense contraction, known as a mass movement, spreads rapidly over the transverse segment of the large intestine toward the rectum. This usually coincides with the gastroileal reflex. Unlike a peristaltic wave, in which the smooth muscle at each point relaxes after the wave of contraction has passed, the smooth muscle of the large intestine remains contracted for some time after a mass movement.

Much of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions, requiring as many as 8 to 15 hours to move the chyme from the ileocecal valve through the colon, while the chyme itself becomes fecal in quality, a semisolid slush instead of semifluid. From the cecum to the sigmoid, mass movements can, for many minutes at a time, take over the propulsive role. These movements usually occur only one to three times each day, in many people especially for about 15 minutes during the first hour after eating breakfast. A mass movement is a modified type of peristalsis characterized by the following sequence of events: First, a constrictive ring occurs in response to a distended or irritated point in the colon, usually in the transverse colon. Then, rapidly, the 20 or more centimeters of colon distal to the constrictive ring lose their haustrations and instead contract as a unit, propelling the fecal material in this segment en masse further down the colon. The contraction develops progressively more force for about 30 seconds, and relaxation occurs during the next 2 to 3 minutes. Then, another mass movement occurs, this time perhaps farther along the colon. A series of mass movements usually persists for 10 to 30 minutes. Then they cease but return perhaps a half day later. When they have forced a mass of feces into the rectum, the desire for defecation is felt.

Appearance of mass movements after meals is facilitated by gastrocolic and duodenocolic reflexes. These reflexes result from distention of the stomach and duodenum. They occur either not at all or hardly at all when the extrinsic autonomic nerves to the colon have been removed; therefore, the reflexes almost certainly are transmitted by way of the autonomic nervous system. Irritation in the colon can also initiate intense mass movements. For instance, a person who has an ulcerated condition of the colon mucosa (ulcerative colitis) frequently has mass movements that persist almost all the time.

Defecation

The anus, the exit from the rectum, is normally closed by the internal anal sphincter, which is composed of smooth muscle, and the external anal sphincter, which is composed of skeletal muscle under voluntary control. The sudden distension of the walls of the rectum produced by the mass movement of fecal material into it initiates the neurally mediated defecation reflex. Most of the time, the rectum is empty of feces. This results partly from the fact that a weak functional sphincter exists about 20 centimeters from the anus at the juncture between the sigmoid colon and the rectum. There is also a sharp angulation here that contributes additional resistance to filling of the rectum. When a mass movement forces feces into the rectum, the desire for defecation occurs immediately, including reflex contraction of the rectum and relaxation of the anal sphincters. Continual dribble of fecal matter through the anus is prevented by tonic constriction of (1) an internal anal sphincter, a several-centimeters-

long thickening of the circular smooth muscle that lies immediately inside the anus, and (2) an external anal sphincter, composed of striated voluntary muscle that both surrounds the internal sphincter and extends distal to it. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore is under voluntary, conscious or at least subconscious control; subconsciously, the external sphincter is usually kept continuously constricted unless conscious signals inhibit the constriction.

Ordinarily, defecation is initiated by defecation reflexes. One of these reflexes is an intrinsic reflex mediated by the local enteric nervous system in the rectal wall. When feces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus; if the external anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs. The intrinsic myenteric defecation reflex functioning by itself normally is relatively weak. To be effective in causing defecation, it usually must be fortified by another type of defecation reflex, a parasympathetic defecation reflex that involves the sacral segments of the spinal cord, shown in Figure 2. When the nerve endings in the rectum are stimulated, signals are transmitted first into the spinal cord and then reflexly back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the pelvic nerves. These parasympathetic signals greatly intensify the peristaltic waves as well as relax the internal anal sphincter, thus converting the intrinsic myenteric defecation reflex from a weak effort into a powerful process of defecation that is sometimes effective in emptying the large bowel all the way from the splenic flexure of the colon to the anus.

Defecation signals entering the spinal cord initiate other effects, such as taking a deep breath, closure of the glottis, and contraction of the abdominal wall muscles to force the fecal contents of the colon downward and at the same time cause the pelvic floor to relax downward and pull outward on the anal ring to evaginate the feces. When it becomes convenient for the person to defecate, the defecation reflexes can purposely be activated by taking a deep breath to move the diaphragm downward and then contracting the abdominal muscles to increase the pressure in the abdomen, thus forcing fecal contents into the rectum to cause new reflexes. Reflexes initiated in this way are almost never as effective as those that arise naturally, for which reason people who too often inhibit their natural reflexes are likely to become severely constipated. In newborn babies and in some people with transected spinal cords, the defecation reflexes cause automatic emptying of the lower bowel at inconvenient times during the day because of lack of conscious control exercised through voluntary contraction or relaxation of the external anal sphincter.

The conscious urge to defecate, mediated by mechanoreceptors, accompanies distension of the rectum. The reflex response consists of a contraction of the rectum, relaxation of the internal anal sphincter, but contraction of the external anal sphincter (initially), and increased peristaltic activity in the sigmoid colon. Eventually, a pressure is reached in the rectum that triggers reflex relaxation of the external anal sphincter, allowing the feces to be expelled. Brain centers can, however, via descending pathways to somatic nerves to the external anal sphincter, override the reflex signals that eventually would relax the sphincter, thereby keeping the external sphincter closed and allowing a person to delay defecation. In this case, the prolonged distension of the rectum initiates a reverse peristalsis, driving the rectal contents back into the sigmoid colon. The urge to defecate then subsides until the next mass movement again propels more feces into the rectum, increasing its volume and again initiating the defecation reflex. Voluntary control of the external anal sphincter is learned during childhood. Spinal-cord damage can lead to a loss of voluntary control over defecation. Defecation is normally assisted by a deep inspiration, followed by closure of the

glottis and contraction of the abdominal and thoracic muscles, producing an increase in abdominal pressure that is transmitted to the contents of the large intestine and rectum. This maneuver (termed the Valsalva maneuver) also causes a rise in intrathoracic pressure, which leads to a transient rise in blood pressure followed by a fall in pressure as the venous return to the heart is decreased. The cardiovascular changes resulting from excessive strain during defecation may precipitate a stroke or heart attack, especially in constipated elderly individuals with cardiovascular disease.

Several other important nervous reflexes also can affect the overall degree of bowel activity. They are the peritoneointestinal reflex, reointestinal reflex, and vesicointestinal reflex. The peritoneointestinal reflex results from irritation of the peritoneum; it strongly inhibits the excitatory enteric nerves and thereby can cause intestinal paralysis, especially in patients with peritonitis. The reointestinal and vesicointestinal reflexes inhibit intestinal activity as a result of kidney or bladder irritation.

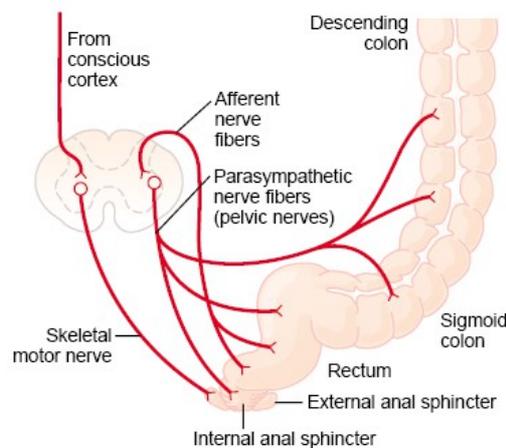
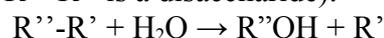


Figure 2 The pathways of the defecation reflex

Digestion and absorption in the gastrointestinal tract

The major foods on which the body lives (with the exception of small quantities of substances such as vitamins and minerals) can be classified as carbohydrates, fats, and proteins. They generally cannot be absorbed in their natural forms through the gastrointestinal mucosa and, for this reason, are useless as nutrients without preliminary digestion.

Hydrolysis of carbohydrates. Almost all the carbohydrates of the diet are either large polysaccharides or disaccharides, which are combinations of monosaccharides bound to one another by condensation. This means that a hydrogen ion (H^+) has been removed from one of the monosaccharides, and a hydroxyl ion (OH^-) has been removed from the next one. The two monosaccharides then combine with each other at these sites of removal, and the hydrogen and hydroxyl ions combine to form water (H_2O). When carbohydrates are digested, the above process is reversed and the carbohydrates are converted into monosaccharides. Specific enzymes in the digestive juices of the gastrointestinal tract return the hydrogen and hydroxyl ions from water to the polysaccharides and thereby separate the monosaccharides from each other. This process, under an action of some digestive enzyme called hydrolysis, is the following (in which $R''-R'$ is a disaccharide):



Hydrolysis of fats. Almost the entire fat portion of the diet consists of triglycerides (neutral fats), which are combinations of three fatty acid molecules condensed with a single glycerol molecule. During condensation, three molecules of water are removed. Digestion of

the triglycerides consists of the reverse process: the fat-digesting enzymes return three molecules of water to the triglyceride molecule and thereby split the fatty acid molecules away from the glycerol. The digestive process is one of hydrolysis.

Hydrolysis of proteins. Proteins are formed from multiple amino acids that are bound together by peptide linkages. At each linkage, a hydroxyl ion has been removed from one amino acid and a hydrogen ion has been removed from the succeeding one; thus, the successive amino acids in the protein chain are also bound together by condensation, and digestion occurs by the reverse effect: hydrolysis. That is, the proteolytic enzymes return hydrogen and hydroxyl ions from water molecules to the protein molecules to split them into their constituent amino acids.

Therefore, the chemistry of digestion is simple because, in the case of all three major types of food, the same basic process of hydrolysis is involved. The only difference lies in the types of enzymes required to promote the hydrolysis reactions for each type of food. All the digestive enzymes are proteins.

Digestion of carbohydrates (carbohydrate foods of the diet). Only three major sources of carbohydrates exist in the normal human diet. They are sucrose, which is the disaccharide known popularly as cane sugar; lactose, which is a disaccharide found in milk; and starches, which are large polysaccharides present in almost all nonanimal foods, particularly in potatoes and the different types of grains. Other carbohydrates ingested to a slight extent are amylose, glycogen, alcohol, lactic acid, pyruvic acid, pectins, dextrans, and minor quantities of carbohydrate derivatives in meats. The diet also contains a large amount of cellulose, which is a carbohydrate. However, no enzymes capable of hydrolyzing cellulose are secreted in the human digestive tract. Consequently, cellulose cannot be considered a food for humans.

When food is chewed, it is mixed with saliva, which contains the digestive enzyme ptyalin (an alpha-amylase) secreted mainly by the parotid glands. This enzyme hydrolyzes starch into the disaccharide maltose and other small polymers of glucose that contain three to nine glucose molecules. However, the food remains in the mouth only a short time, so that probably not more than 5 per cent of all the starches will have become hydrolyzed by the time the food is swallowed. However, starch digestion sometimes continues in the body and fundus of the stomach for as long as 1 hour before the food becomes mixed with the stomach secretions. Then activity of the salivary amylase is blocked by acid of the gastric secretions because the amylase is essentially nonactive as an enzyme once the pH of the medium falls below about 4.0. Pancreatic secretion, like saliva, contains a large quantity of alpha-amylase that is almost identical in its function with the alpha-amylase of saliva but is several times as powerful. Therefore, within 15 to 30 minutes after the chyme empties from the stomach into the duodenum and mixes with pancreatic juice, virtually all the carbohydrates will have become digested. In general, the carbohydrates are almost totally converted into maltose and/or other very small glucose polymers before passing beyond the duodenum or upper jejunum.

The enterocytes lining the villi of the small intestine contain four enzymes (lactase, sucrase, maltase, and alpha-dextrinase), which are capable of splitting the disaccharides lactose, sucrose, and maltose, plus other small glucose polymers, into their constituent monosaccharides. These enzymes are located in the enterocytes covering the intestinal microvilli brush border, so that the disaccharides are digested as they come in contact with these enterocytes. Lactose splits into a molecule of galactose and a molecule of glucose. Sucrose splits into a molecule of fructose and a molecule of glucose. Maltose and other small glucose polymers all split into multiple molecules of glucose. Thus, the final products of carbohydrate digestion are all monosaccharides. They are all water soluble and are absorbed immediately into the portal blood. In the ordinary diet, which contains far more starches than

intercellular connective tissue of meats; therefore, for the digestive enzymes of the digestive tract to penetrate meats and digest the other meat proteins, it is first necessary that the collagen fibers be digested. Consequently, in persons who lack pepsin in the stomach juices, the ingested meats are less well penetrated by the other digestive enzymes and, therefore, may be poorly digested. Pepsin only initiates the process of protein digestion, usually providing only 10 to 20 % of the total protein digestion to convert the protein to proteoses, peptones, and a few polypeptides. This splitting of proteins occurs as a result of hydrolysis at the peptide linkages between amino acids.

Most protein digestion occurs in the upper small intestine, in the duodenum and jejunum, under the influence of proteolytic enzymes from pancreatic secretion. Immediately on entering the small intestine from the stomach, the partial breakdown products of the protein foods are attacked by major proteolytic pancreatic enzymes: trypsin, chymotrypsin, carboxypolypeptidase and proelastase. Both trypsin and chymotrypsin split protein molecules into small polypeptides; carboxypolypeptidase then cleaves individual amino acids from the carboxyl ends of the polypeptides. Proelastase, in turn, is converted into elastase, which then digests elastin fibers that partially hold meats together. Only a small percentage of the proteins are digested all the way to their constituent amino acids by the pancreatic juices. Most remain as dipeptides and tripeptides.

The last digestive stage of the proteins in the intestinal lumen is achieved by the enterocytes that line the villi of the small intestine, mainly in the duodenum and jejunum. These cells have a brush border that consists of hundreds of microvilli projecting from the surface of each cell. In the membrane of each of these microvilli are multiple peptidases that protrude through the membranes to the exterior, where they come in contact with the intestinal fluids. Two types of peptidase enzymes are especially important, aminopolypeptidase and several dipeptidases. They succeed in splitting the remaining larger polypeptides into tripeptides and dipeptides and a few into amino acids. Both the amino acids plus the dipeptides and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.

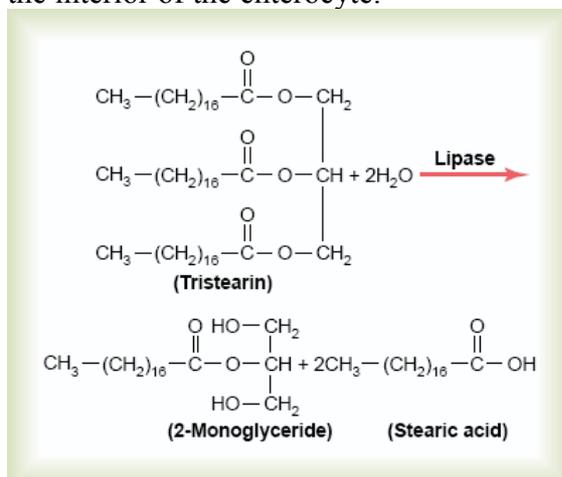


Figure 5 Digestion of neutral fat

Finally, inside the cytosol of the enterocyte are multiple other peptidases that are specific for the remaining types of linkages between amino acids. Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage to form single amino acids; these then pass on through to the other side of the enterocyte and thence into the blood. More than 99% of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides and very, very rare absorption of whole protein molecules.

Digestion of fats (the diet). By far the most abundant fats of the diet are the neutral fats, also known as triglycerides, each molecule of which is composed of a glycerol nucleus and three fatty acid side chains. Neutral fat is a major constituent in food of animal origin but much, much less so in food of plant origin. In the usual diet are also small quantities of phospholipids, cholesterol, and cholesterol esters. The phospholipids and cholesterol esters contain fatty acid and therefore can be considered fats themselves. Cholesterol, however, is a sterol compound that contains no fatty acid, but it does exhibit some of the physical and chemical characteristics of fats; plus, it is derived from fats and is metabolized similarly to fats. Therefore, cholesterol is considered, from a dietary point of view, a fat.

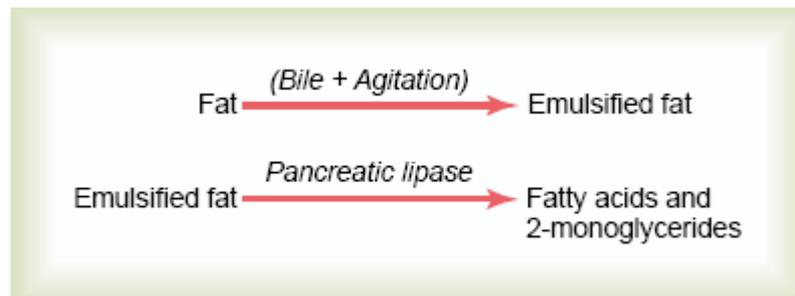


Figure 6 Digestion of fats

The first step in fat digestion is physically to break the fat globules into very small sizes so that the water-soluble digestive enzymes can act on the globule surfaces. This process is called emulsification of the fat, and it begins by agitation in the stomach to mix the fat with the products of stomach digestion. Then, most of the emulsification occurs in the duodenum under the influence of bile, the secretion from the liver that does not contain any digestive enzymes. However, bile does contain a large quantity of bile salts as well as the phospholipid lecithin. Both of these, but especially the lecithin, are extremely important for emulsification of the fat. The polar parts (the points where ionization occurs in water) of the bile salts and lecithin molecules are highly soluble in water, whereas most of the remaining portions of their molecules are highly soluble in fat. Therefore, the fat-soluble portions of these liver secretions dissolve in the surface layer of the fat globules, with the polar portions projecting. The polar projections, in turn, are soluble in the surrounding watery fluids, which greatly decreases the interfacial tension of the fat and makes it soluble as well. When the interfacial tension of a globule of nonmiscible fluid is low, this nonmiscible fluid, on agitation, can be broken up into many very minute particles far more easily than it can when the interfacial tension is great. Consequently, a major function of the bile salts and lecithin, especially the lecithin, in the bile is to make the fat globules readily fragmentable by agitation with the water in the small bowel. This action is the same as that of many detergents that are widely used in household cleaners for removing grease. Each time the diameters of the fat globules are significantly decreased as a result of agitation in the small intestine, the total surface area of the fat increases manyfold. Because the average diameter of the fat particles in the intestine after emulsification has occurred is less than 1 micrometer, this represents an increase of as much as 1000-fold in total surface areas of the fats caused by the emulsification process. The lipase enzymes are water-soluble compounds and can attack the fat globules only on their surfaces.

By far the most important enzyme for digestion of the triglycerides is pancreatic lipase, present in enormous quantities in pancreatic juice, enough to digest within 1 minute all triglycerides that it can reach. In addition, the enterocytes of the small intestine contain still more lipase, known as enteric lipase, but this is usually not needed.

Most of the triglycerides of the diet are split by pancreatic lipase into free fatty acids and 2-monoglycerides. The hydrolysis of triglycerides is a highly reversible process;

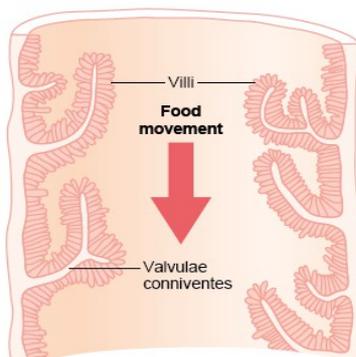
therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion. But the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed. This occurs in the following way. Bile salts, when in high enough concentration in water, have the propensity to form micelles, which are small spherical, cylindrical globules 3 to 6 nanometers in diameter composed of 20 to 40 molecules of bile salt. These develop because each bile salt molecule is composed of a sterol nucleus that is highly fat-soluble and a polar group that is highly water-soluble. The sterol nucleus encompasses the fat digestate, forming a small fat globule in the middle of a resulting micelle, with polar groups of bile salts projecting outward to cover the surface of the micelle. Because these polar groups are negatively charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids and to remain in stable solution until the fat is absorbed into the blood. The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells. There the monoglycerides and free fatty acids are absorbed into the blood, but the bile salts themselves are released back into the chyme to be used again and again for this “ferrying” process.

Most cholesterol in the diet is in the form of cholesterol esters, which are combinations of free cholesterol and one molecule of fatty acid. Phospholipids also contain fatty acid within their molecules. Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids—the enzyme cholesterol ester hydrolase to hydrolyze the cholesterol ester, and phospholipase A2 to hydrolyze the phospholipid. The bile salt micelles play the same role in “ferrying” free cholesterol and phospholipid molecule digestates that they play in “ferrying” monoglycerides and free fatty acids.

Basic principles of gastrointestinal absorption

The total quantity of fluid that must be absorbed each day by the intestines is equal to the ingested fluid (about 1.5 liters) plus that secreted in the various gastrointestinal secretions (about 7 liters). This comes to a total of 8 to 9 liters. All but about 1.5 liters of this is absorbed in the small intestine, leaving only 1.5 liters to pass through the ileocecal valve into the colon each day. The stomach is a poor absorptive area of the gastrointestinal tract because it lacks the typical villus type of absorptive membrane, and also because the junctions between the epithelial cells are tight junctions. Only a few highly lipid-soluble substances, such as alcohol and some drugs like aspirin, can be absorbed in small quantities.

Figure 7 demonstrates the absorptive surface of the small intestinal mucosa, showing many folds called valvulae conniventes (or folds of Kerckring), which increase the surface area of the absorptive mucosa about threefold. These folds extend circularly most of the way around the intestine and are especially well developed in the duodenum and jejunum, where they often protrude as much as 8 millimeters into the lumen. Also located on the epithelial



surface of the small intestine all the way down to the ileocecal valve are literally millions of small villi. The villi lie so close to one another in the upper small intestine that they touch in most areas, but their distribution is less profuse in the distal small intestine. The presence of villi on the mucosal surface enhances the total absorptive area another 10-fold. Finally, each intestinal epithelial cell on each villus is characterized by a brush border, consisting of as many as 1000 microvilli 1 micrometer in length and 0.1 micrometer in diameter

protruding into the intestinal chyme. This increases the surface area exposed to the intestinal materials at least another 20-fold.

Figure 7 Longitudinal section of the small intestine

Thus, the combination of the folds of Kerckring, the villi, and the microvilli increases the total absorptive area of the mucosa perhaps 1000-fold. Figure shows in longitudinal section the general organization of the villus, emphasizing (1) the advantageous arrangement of the vascular system for absorption of fluid and dissolved material into the portal blood and (2) the arrangement of the “central lacteal” lymph vessel for absorption into the lymph.

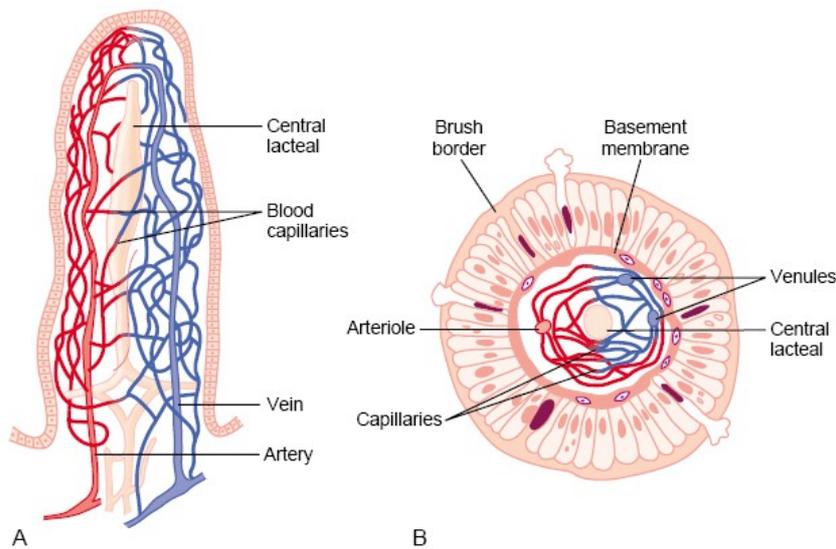


Figure 8 Functional organization of the villus

Figure 8 shows a cross section of the villus, and many small pinocytotic vesicles, which are pinched-off portions of infolded enterocyte membrane forming vesicles of absorbed fluids that have been entrapped. Small amounts of substances are absorbed by this physical process of pinocytosis. Extending from the epithelial cell body into each microvillus of the brush border are multiple actin filaments that contract rhythmically to cause continual movement of the microvilli, keeping them constantly exposed to new quantities of intestinal fluid.

Absorption in the small intestine

Absorption from the small intestine each day consists of several hundred grams of carbohydrates, 100 or more grams of fat, 50 to 100 grams of amino acids, 50 to 100 grams of ions, and 7 to 8 liters of water. The absorptive capacity of the normal small intestine is far greater than this: as much as several kilograms of carbohydrates per day, 500 grams of fat per day, 500 to 700 grams of proteins per day, and 20 or more liters of water per day. The large intestine can absorb still additional water and ions, although very few nutrients.

Water is transported through the intestinal membrane entirely by diffusion. Furthermore, this diffusion obeys the usual laws of osmosis. Therefore, when the chyme is dilute enough, water is absorbed through the intestinal mucosa into the blood of the villi almost entirely by osmosis. Conversely, water can also be transported in the opposite direction—from plasma into the chyme. This occurs especially when hyperosmotic solutions are discharged from the stomach into the duodenum. Within minutes, sufficient water usually will be transferred by osmosis to make the chyme isosmotic with the plasma.

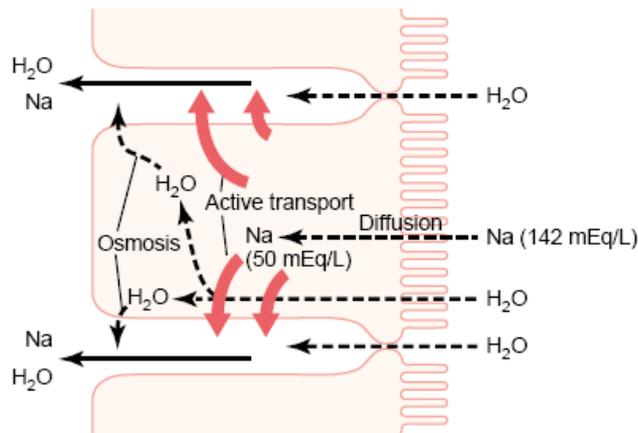


Figure 9 Absorption of sodium and water

Twenty to 30 grams of sodium are secreted in the intestinal secretions each day. In addition, the average person eats 5 to 8 grams of sodium each day. Therefore, to prevent net loss of sodium into the feces, the intestines must absorb 25 to 35 grams of sodium each day, which is equal to about one seventh of all the sodium present in the body. Whenever significant amounts of intestinal secretions are lost to the exterior, as in extreme diarrhea, the sodium reserves of the body can sometimes be depleted to lethal levels within hours. Normally, however, less than 0.5 per cent of the intestinal sodium is lost in the feces each day because it is rapidly absorbed through the intestinal mucosa. Sodium also plays an important role in helping to absorb sugars and amino acids. The basic mechanism of sodium absorption from the intestine is shown in Figure. The motive power for sodium absorption is provided by active transport of sodium from inside the epithelial cells through the basal and side walls of these cells into paracellular spaces. This is demonstrated by the heavy red arrows in Figure 65–8. This active transport obeys the usual laws of active transport: it requires energy, and the energy process is catalyzed by appropriate adenosine triphosphatase enzymes in the cell membrane. Part of the sodium is absorbed along with chloride ions; in fact, the negatively charged chloride ions are mainly passively “dragged” by the positive electrical charges of the sodium ions. Active transport of sodium through the basolateral membranes of the cell reduces the sodium concentration inside the cell to a low value (about 50 mEq/L). Because the sodium concentration in the chyme is normally about 142 mEq/L (that is, about equal to that in plasma), sodium moves down this steep electrochemical gradient from the chyme through the brush border of the epithelial cell into the epithelial cell cytoplasm. This provides still more sodium ions to be transported by the epithelial cells into the paracellular spaces.

The next step in the transport process is osmosis of water into the paracellular spaces. This occurs because a large osmotic gradient has been created by the elevated concentration of ions in the paracellular space. Much of this osmosis occurs through the tight junctions between the apical borders of the epithelial cells, but much also occurs through the cells themselves. And osmotic movement of water creates flow of fluid into and through the paracellular spaces and, finally, into the circulating blood of the villus. When a person becomes dehydrated, large amounts of aldosterone almost always are secreted by the cortices of the adrenal glands. Within 1 to 3 hours this aldosterone causes increased activation of the enzyme and transport mechanisms for all aspects of sodium absorption by the intestinal epithelium. And the increased sodium absorption in turn causes secondary increases in absorption of chloride ions, water, and some other substances. This effect of aldosterone is especially important in the colon because it allows virtually no loss of sodium chloride in the feces and also little water loss. Thus, the function of aldosterone in the intestinal tract is the

same as that achieved by aldosterone in the renal tubules, which also serves to conserve sodium chloride and water in the body when a person becomes dehydrated.

In the upper part of the small intestine, chloride ion absorption is rapid and occurs mainly by diffusion— that is, absorption of sodium ions through the epithelium creates electronegativity in the chyme and electropositivity in the paracellular spaces between the epithelial cells. Then chloride ions move along this electrical gradient to “follow” the sodium ions.

Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine because large amounts of bicarbonate ions have been secreted into the duodenum in both pancreatic secretion and bile. The bicarbonate ion is absorbed in an indirect way as follows: when sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium. These hydrogen ions in turn combine with the bicarbonate ions to form carbonic acid (H_2CO_3), which then dissociates to form water and carbon dioxide. The water remains as part of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired through the lungs. Thus, this is so-called “active absorption of bicarbonate ions.” It is the same mechanism that occurs in the tubules of the kidneys.

The epithelial cells on the surfaces of the villi in the ileum as well as on all surfaces of the large intestine have a special capability of secreting bicarbonate ions in exchange for absorption of chloride ions. This is important because it provides alkaline bicarbonate ions that neutralize acid products formed by bacteria in the large intestine.

Deep in the spaces between the intestinal epithelial folds are immature epithelial cells that continually divide to form new epithelial cells. These in turn spread outward over the luminal surfaces of the intestines. While still in the deep folds, the epithelial cells secrete sodium chloride and water into the intestinal lumen. This secretion in turn is reabsorbed by the older epithelial cells outside the folds, thus providing flow of water for absorbing intestinal digestates. The toxins of cholera and of some other types of diarrheal bacteria can stimulate the fold secretion so greatly that this secretion often becomes much greater than can be reabsorbed, thus sometimes causing loss of 5 to 10 liters of water and sodium chloride as diarrhea each day. Within 1 to 5 days, many severely affected patients die from this loss of fluid alone. Extreme diarrheal secretion is initiated by entry of a subunit of cholera toxin into the epithelial cells. This stimulates formation of excess cyclic adenosine monophosphate, which opens tremendous numbers of chloride channels, allowing chloride ions to flow rapidly from inside the cell into the intestinal crypts. In turn, this is believed to activate a sodium pump that pumps sodium ions into the crypts to go along with the chloride ions. Finally, all this extra sodium chloride causes extreme osmosis of water from the blood, thus providing rapid flow of fluid along with the salt. All this excess fluid washes away most of the bacteria and is of value in combating the disease, but too much of a good thing can be lethal because of serious dehydration of the whole body that might ensue. In most instances, the life of a cholera victim can be saved by administration of tremendous amounts of sodium chloride solution to make up for the loss.

Calcium ions are actively absorbed into the blood especially from the duodenum and the amount of calcium ion absorption is very exactly controlled to supply exactly the daily need of the body for calcium. One important factor controlling calcium absorption is parathyroid hormone secreted by the parathyroid glands, and another is vitamin D. Parathyroid hormone activates vitamin D and the activated vitamin D in turn greatly enhances calcium absorption. Iron ions are also actively absorbed from the small intestine. Potassium, magnesium, phosphate, and probably still other ions can also be actively absorbed through the intestinal mucosa. In general, the monovalent ions are absorbed with ease and in great quantities. Conversely, bivalent ions are normally absorbed in only small amounts; for

example, maximum absorption of calcium ions is only 1/50 as great as the normal absorption of sodium ions.

Essentially all the carbohydrates in the food are absorbed in the form of monosaccharides; only a small fraction are absorbed as disaccharides and almost none as larger carbohydrate compounds. By far the most abundant of the absorbed monosaccharides is glucose, usually accounting for more than 80 per cent of carbohydrate calories absorbed. The reason for this is that glucose is the final digestion product of our most abundant carbohydrate food, the starches. The remaining 20 per cent of absorbed monosaccharides are composed almost entirely of galactose and fructose, the galactose derived from milk and the fructose as one of the monosaccharides digested from cane sugar.

In the absence of sodium transport through the intestinal membrane, virtually no glucose can be absorbed. The reason is that glucose absorption occurs in a cotransport mode with active transport of sodium. There are two stages in the transport of sodium through the intestinal membrane. First is active transport of sodium ions through the basolateral membranes of the intestinal epithelial cells into the blood, thereby depleting sodium inside the epithelial cells. Second, decrease of sodium inside the cells causes sodium from the intestinal lumen to move through the brush border of the epithelial cells to the cell interiors by a process of facilitated diffusion. That is, a sodium ion combines with a transport protein, but the transport protein will not transport the sodium to the interior of the cell until the protein itself also combines with some other appropriate substance such as glucose. Fortunately, intestinal glucose also combines simultaneously with the same transport protein and then both the sodium ion and glucose molecule are transported together to the interior of the cell. Thus, the low concentration of sodium inside the cell literally “drags” sodium to the interior of the cell and along with it the glucose at the same time. Once inside the epithelial cell, other transport proteins and enzymes cause facilitated diffusion of the glucose through the cell’s basolateral membrane into the paracellular space and from there into the blood.

Galactose is transported by almost exactly the same mechanism as glucose. Conversely, fructose transport does not occur by the sodium co-transport mechanism. Instead, fructose is transported by facilitated diffusion all the way through the intestinal epithelium but not coupled with sodium transport. Much of the fructose, on entering the cell, becomes phosphorylated, then converted to glucose, and finally transported in the form of glucose the rest of the way into the blood. Because fructose is not co-transported with sodium, its overall rate of transport is only about one half that of glucose or galactose.

Most proteins, after digestion, are absorbed through the luminal membranes of the intestinal epithelial cells in the form of dipeptides, tripeptides, and a few free amino acids. The energy for most of this transport is supplied by a sodium co-transport mechanism in the same way that sodium co-transport of glucose occurs. That is, most peptide or amino acid molecules bind in the cell’s microvillus membrane with a specific transport protein that requires sodium binding before transport can occur. After binding, the sodium ion then moves down its electrochemical gradient to the interior of the cell and pulls the amino acid or peptide along with it. This is called co-transport (or secondary active transport) of the amino acids and peptides. A few amino acids do not require this sodium co-transport mechanism but instead are transported by special membrane transport proteins in the same way that fructose is transported, by facilitated diffusion. At least five types of transport proteins for transporting amino acids and peptides have been found in the luminal membranes of intestinal epithelial cells. This multiplicity of transport proteins is required because of the diverse binding properties of different amino acids and peptides.

When fats are digested to form monoglycerides and free fatty acids, both of these digestive end products first become dissolved in the central lipid portions of bile micelles. Because the molecular dimensions of these micelles are only 3 to 6 nanometers in diameter,

and because of their highly charged exterior, they are soluble in chyme. In this form, the monoglycerides and free fatty acids are carried to the surfaces of the microvilli of the intestinal cell brush border and then penetrate into the recesses among the moving, agitating microvilli. Here, both the monoglycerides and fatty acids diffuse immediately out of the micelles and into the interior of the epithelial cells, which is possible because the lipids are also soluble in the epithelial cell membrane. This leaves the bile micelles still in the chyme, where they function again and again to help absorb still more monoglycerides and fatty acids. Thus, the micelles perform a “ferrying” function that is highly important for fat absorption. In the presence of an abundance of bile micelles, about 97 per cent of the fat is absorbed; in the absence of the bile micelles, only 40 to 50 per cent can be absorbed. After entering the epithelial cell, the fatty acids and monoglycerides are taken up by the cell’s smooth endoplasmic reticulum; here, they are mainly used to form new triglycerides that are subsequently released in the form of chylomicrons through the base of the epithelial cell, to flow upward through the thoracic lymph duct and empty into the circulating blood.

Small quantities of short- and medium-chain fatty acids, such as those from butterfat, are absorbed directly into the portal blood rather than being converted into triglycerides and absorbed by way of the lymphatics. The cause of this difference between short- and long-chain fatty acid absorption is that the short-chain fatty acids are more water-soluble and mostly are not reconverted into triglycerides by the endoplasmic reticulum. This allows direct diffusion of these short-chain fatty acids from the intestinal epithelial cells directly into the capillary blood of the intestinal villi.

Formation of Feces

About 1500 milliliters of chyme normally pass through the ileocecal valve into the large intestine each day. Most of the water and electrolytes in this chyme are absorbed in the colon, usually leaving less than 100 milliliters of fluid to be excreted in the feces. Also, essentially all the ions are absorbed, leaving only 1 to 5 milliequivalents each of sodium and chloride ions to be lost in the feces. Most of the absorption in the large intestine occurs in the proximal one half of the colon, giving this portion the name absorbing colon, whereas the distal colon functions principally for feces storage until a propitious time for feces excretion and is therefore called the storage colon.

The mucosa of the large intestine, like that of the small intestine, has a high capability for active absorption of sodium, and the electrical potential gradient created by absorption of the sodium causes chloride absorption as well. The tight junctions between the epithelial cells of the large intestinal epithelium are much tighter than those of the small intestine. This prevents significant amounts of back-diffusion of ions through these junctions, thus allowing the large intestinal mucosa to absorb sodium ions far more completely—that is, against a much higher concentration gradient—than can occur in the small intestine. This is especially true when large quantities of aldosterone are available because aldosterone greatly enhances sodium transport capability. In addition, as occurs in the distal portion of the small intestine, the mucosa of the large intestine secretes bicarbonate ions while it simultaneously absorbs an equal number of chloride ions in an exchange transport process that has already been described. The bicarbonate helps neutralize the acidic end products of bacterial action in the large intestine. Absorption of sodium and chloride ions creates an osmotic gradient across the large intestinal mucosa, which in turn causes absorption of water.

The large intestine can absorb a maximum of 5 to 8 liters of fluid and electrolytes each day. When the total quantity entering the large intestine through the ileocecal valve or by way of large intestine secretion exceeds this amount, the excess appears in the feces as diarrhea. As noted earlier in the chapter, toxins from cholera or certain other bacterial infections often cause the crypts in the terminal ileum and in the large intestine to secrete 10 or more liters of

fluid each day, leading to severe and sometimes lethal diarrhea. Numerous bacteria, especially colon bacilli, are present even normally in the absorbing colon. They are capable of digesting small amounts of cellulose, in this way providing a few calories of extra nutrition for the body. In herbivorous animals, this source of energy is significant, although it is of negligible importance in human beings. Other substances formed as a result of bacterial activity are vitamin K, vitamin B12, thiamine, riboflavin, and various gases that contribute to flatus in the colon, especially carbon dioxide, hydrogen gas, and methane. The bacteria-formed vitamin K is especially important because the amount of this vitamin in the daily ingested foods is normally insufficient to maintain adequate blood coagulation.

Composition of the Feces. The feces normally are about three-fourths water and one-fourth solid matter that itself is composed of about 30 per cent dead bacteria, 10 to 20 per cent fat, 10 to 20 per cent inorganic matter, 2 to 3 per cent protein, and 30 per cent undigested roughage from the food and dried constituents of digestive juices, such as bile pigment and sloughed epithelial cells. The brown color of feces is caused by stercobilin and urobilin, derivatives of bilirubin. The odor is caused principally by products of bacterial action; these products vary from one person to another, depending on each person's colonic bacterial flora and on the type of food eaten. The actual odoriferous products include indole, skatole, mercaptans, and hydrogen sulfide.

Regulation of food intake and energy storage

Stability of the body's total mass and composition over long periods requires that energy intake match energy expenditure. Only about 27 percent of the energy ingested normally reaches the functional systems of the cells, and much of this is eventually converted to heat, which is generated as a result of protein metabolism, muscle activity, and activities of the various organs and tissues of the body. Excess energy intake is stored mainly as fat, whereas a deficit of energy intake causes loss of total body mass until energy expenditure eventually equals energy intake or death occurs. Although there is considerable variability in the amount of energy storage (i.e., fat mass) in different individuals, maintenance of an adequate energy supply is necessary for survival. Therefore, the body is endowed with powerful physiologic control systems that help maintain adequate energy intake. Deficits of energy stores, for example, rapidly activate multiple mechanisms that cause hunger and drive a person to seek food. In athletes and laborers, energy expenditure for the high level of muscle activity may be as high as 6000 to 7000 Calories per day, compared with only about 2000 Calories per day for sedentary individuals. Thus, a large energy expenditure associated with physical work usually stimulates equally large increases in caloric intake.

Maintenance of adequate energy supply in the body is so critical that there are multiple short-term and long-term control systems that regulate not only food intake but also energy expenditure and energy stores.

Neural centers regulate food intake

The sensation of hunger is associated with a craving for food and several other several physiologic effects, such as rhythmical contractions of the stomach and restlessness, which cause the person to search for an adequate food supply. A person's appetite is a desire for food, often of a particular type, and is useful in helping to choose the quality of the food to be eaten. If the quest for food is successful, the feeling of satiety occurs. Each of these feelings is influenced by environmental and cultural factors, as well as by physiologic controls that influence specific centers of the brain, especially the hypothalamus.

The Hypothalamus contains hunger and satiety centers. Several neuronal centers of the hypothalamus participate in the control of food intake. The lateral nuclei of the hypothalamus serve as a feeding center and stimulation of this area causes an animal to eat voraciously (hyperphagia). Conversely, destruction of the lateral hypothalamus causes lack of desire for food and progressive inanition, a condition characterized by marked weight loss, muscle weakness, and decreased metabolism. The lateral hypothalamic feeding center operates by exciting the motor drives to search for food. The ventromedial nuclei of the hypothalamus serve as the satiety center. This center is believed to give a sense of nutritional satisfaction that inhibits the feeding center. Electrical stimulation of this region can cause complete satiety, and even in the presence of highly appetizing food, the animal refuses to eat (aphagia). Conversely, destruction of the ventromedial nuclei causes voracious and continued eating until the animal becomes extremely obese, sometimes as large as four times normal.

The paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus also play a major role in regulating food intake. For example, lesions of the paraventricular nuclei often cause excessive eating, whereas lesions of the dorsomedial nuclei usually depress eating behavior. The arcuate nuclei are the sites in the hypothalamus where multiple hormones released from the gastrointestinal tract and adipose tissue converge to regulate food intake as well as energy expenditure. There is much chemical cross-talk among the neurons on the hypothalamus, and together, these centers coordinate the processes that control eating behavior and the perception of satiety. These nuclei of the hypothalamus also influence the secretion of several hormones that are important in regulating energy balance and metabolism,

including those from the thyroid and adrenal glands, as well as the pancreatic islet cells. The hypothalamus receives neural signals from the gastrointestinal tract that provide sensory information about stomach filling, chemical signals from nutrients in the blood (glucose, amino acids, and fatty acids) that signify satiety, signals from gastrointestinal hormones, signals from hormones released by adipose tissue, and signals from the cerebral cortex (sight, smell, and taste) that influence feeding behavior. Some of these inputs to the hypothalamus are shown in Figure 10. The hypothalamic feeding and satiety centers have a high density of receptors for neurotransmitters and hormones that influence feeding behavior. A few of the many substances that have been shown to alter appetite and feeding behavior in experimental studies are listed in [Table 1](#) and are generally categorized as (1) orexigenic substances that stimulate feeding, or (2) anorexigenic substances that inhibit feeding.

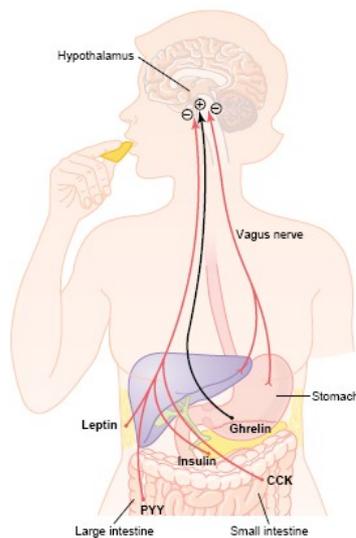


Figure 10 Feedback mechanisms for control of food intake

There are two distinct types of neurons in the arcuate nuclei of the hypothalamus that are especially important as controllers of both appetite and energy expenditure: (1) proopiomelanocortin (POMC) neurons that produce a melanocyte-stimulating hormone (α -MSH) together with cocaine- and amphetamine-related transcript (CART), and (2) neurons that produce the orexigenic substances neuropeptide Y (NPY) and a gut-related protein (AGRP). Activation of the POMC neurons decreases food intake and increases energy expenditure, whereas activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure. These neurons appear to be the major targets for the actions of several hormones that regulate appetite, including leptin, insulin, cholecystokinin (CCK), and ghrelin. In fact, the neurons of the arcuate nuclei appear to be a site of convergence of many of the nervous and peripheral signals that regulate energy stores.

Table 1

Neurotransmitters and Hormones That Influence Feeding and Satiety Centers in the Hypothalamus

Decrease Feeding (Anorexigenic)	Increase Feeding (Orexigenic)
α -Melanocyte-stimulating hormone (α -MSH)	Neuropeptide Y (NPY)
Leptin	Agouti-related protein (AGRP)
Serotonin	Melanin-concentrating hormone (MCH)
Norepinephrine	Orexins A and B
Corticotropin-releasing hormone	Endorphins
Insulin	Galanin (GAL)
Cholecystokinin (CCK)	Amino acids (glutamate and γ -aminobutyric acid)
Glucagon-like peptide (GLP)	Cortisol
Cocaine- and amphetamine-regulated transcript (CART)	Ghrelin
Peptide YY (PYY)	

The POMC neurons release α -MSH, which then acts on melanocortin receptors found especially in neurons of the paraventricular nuclei. Although there are at least five subtypes of melanocortin receptor (MCR), MCR-3 and MCR-4 are especially important in regulating food intake and energy balance. Activation of these receptors reduces food intake while increasing energy expenditure. Conversely, inhibition of MCR-3 and MCR-4 greatly increases food intake and decreases energy expenditure. The effect of MCR activation to increase energy

expenditure appears to be mediated, at least in part, by activation of neuronal pathways that project from the paraventricular nuclei to the nucleus tractus solitarius and stimulate sympathetic nervous system activity.

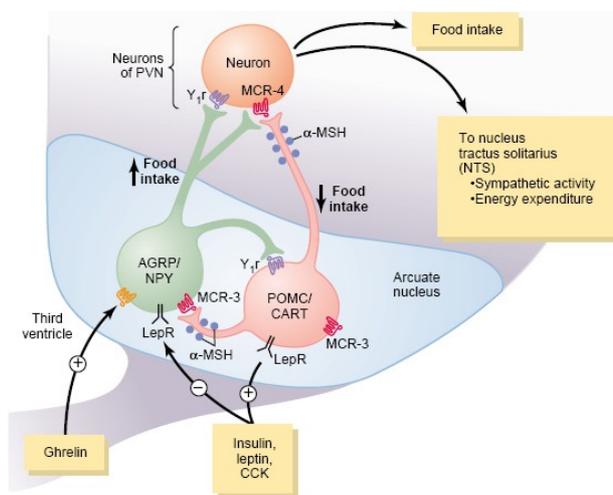


Figure 11 Control of energy balance

The hypothalamic melanocortin system plays a powerful role in regulating energy stores of the body, and defective signaling of the melanocortin pathway is associated with extreme obesity. In fact, mutations of MCR-4 represent the most common known monogenic (single-gene) cause of human obesity, and some studies suggest that MCR-4 mutations may account for as much as 5 to 6 percent of early-onset severe obesity in children. In contrast, excessive activation of the melanocortin system reduces appetite. Some studies suggest that this activation may play a role in causing the anorexia associated with severe infections or cancer tumors. AGRP released from the orexigenic neurons of the hypothalamus is a natural antagonist of MCR-3 and MCR-4 and probably increases feeding by inhibiting the effects of α-MSH to stimulate melanocortin receptors (Figure 11). Although the role of AGRP in normal physiologic control of food intake is unclear, excessive formation of AGRP in mice and humans, due to gene mutations, is associated with excessive feeding and obesity.

NPY is also released from orexigenic neurons of the arcuate nuclei. When energy stores of the body are low, orexigenic neurons are activated to release NPY, which stimulates appetite. At the same time, firing of the POMC neurons is reduced, thereby decreasing the activity of the melanocortin pathway and further stimulating appetite.

Another aspect of feeding is the mechanical act of the feeding process itself. If the brain is sectioned below the hypothalamus but above the mesencephalon, the animal can still perform the basic mechanical features of the feeding process. It can salivate, lick its lips, chew food, and swallow. Therefore, the actual mechanics of feeding are controlled by centers in the brain stem. The function of the other centers in feeding, then, is to control the quantity of food intake and to excite these centers of feeding mechanics to activity. Neural centers higher than the hypothalamus also play important roles in the control of feeding, particularly in the control of appetite. These centers include the amygdala and the prefrontal cortex, which are closely coupled with the hypothalamus. Destructive lesions in the amygdala have demonstrated that some of its areas increase feeding, whereas others inhibit feeding. In addition, stimulation of some areas of the amygdala elicits the mechanical act of feeding. An important effect of destruction of the amygdala on both sides of the brain is a “psychic blindness” in the choice of foods. In other words, the animal (and presumably the human

being as well) loses or at least partially loses the appetite control that determines the type and quality of food it eats.

Factors that regulate quantity of food intake

Regulation of the quantity of food intake can be divided into short-term regulation, which is concerned primarily with preventing overeating at each meal, and long-term regulation, which is concerned primarily with maintenance of normal quantities of energy stores in the body.

1.Short-Term regulation of food intake

It is important that the person not overeat and that he or she eat an amount of food that approximates nutritional needs. The following are several types of rapid feedback signals that are important for these purposes.

Gastrointestinal filling inhibits feeding.

When the gastrointestinal tract becomes distended, especially the stomach and the duodenum, stretch inhibitory signals are transmitted mainly by way of the vagi to suppress the feeding center, thereby reducing the desire for food.

- Cholecystokinin is released mainly in response to fat entering the duodenum and has direct effect on the feeding centers to reduce subsequent eating. Studies in experimental animals suggest that CCK may decrease feeding mainly by activation of the melanocortin pathway in the hypothalamus.
- Peptide YY (PYY) is secreted from the entire gastrointestinal tract, but especially from the ileum and colon. Food intake stimulates release of PYY, with blood concentrations rising to peak levels 1 to 2 hours after ingesting a meal. These peak levels of PYY are influenced by the number of calories ingested and the composition of the food, with higher levels of PYY observed after meals with a high fat content. Although injections of PYY into mice have been shown to decrease food intake for 12 hours or more, the importance of this gastrointestinal hormone in regulating appetite in humans is still unclear. For reasons that are not entirely understood, the presence of food in the intestines stimulates them to secrete glucagon-like peptide, which in turn enhances glucose-dependent insulin production and secretion from the pancreas. Glucagon-like peptide and insulin both tend to suppress appetite. Thus, eating a meal stimulates the release of several gastrointestinal hormones that may induce satiety and reduce further intake of food.
- Ghrelin—a gastrointestinal hormone—increases feeding. Ghrelin is a hormone released mainly by the oxyntic cells of the stomach but also, to a much less extent, by the intestine. Blood levels of ghrelin rise during fasting, peak just before eating, and then fall rapidly after a meal, suggesting a possible role in stimulating feeding. Also, administration of ghrelin increases food intake in experimental animals, further supporting the possibility that it may be an orexigenic hormone. However, its physiologic role in humans is still uncertain.
- Oral receptors meter food intake.

When an animal with an esophageal fistula is fed large quantities of food, even though this food is immediately lost again to the exterior, the degree of hunger is decreased after a reasonable quantity of food has passed through the mouth. This effect occurs despite the fact that the gastrointestinal tract does not become the least bit filled. Therefore, it is postulated that various “oral factors” related to feeding, such as chewing, salivation, swallowing, and tasting, “meter” the food as it passes through the mouth, and after a certain amount has passed, the hypothalamic feeding center becomes inhibited. However, the inhibition caused by this metering mechanism is considerably less intense and of shorter duration, usually lasting for only 20 to 40 minutes, than is the inhibition caused by gastrointestinal filling.

2. Intermediate and long-term regulation of food intake

An animal that has been starved for a long time and is then presented with unlimited food eats a far greater quantity than does an animal that has been on a regular diet. Conversely, an animal that has been forcefed for several weeks eats very little when allowed to eat according to its own desires. Thus, the feeding control mechanism of the body is geared to the nutritional status of the body.

Effect of blood concentrations of glucose, amino acids, and lipids on hunger and feeding.

It has long been known that a decrease in blood glucose concentration causes hunger, which has led to the so-called glucostatic theory of hunger and feeding regulation. Similar studies have demonstrated the same effect for blood amino acid concentration and blood concentration of breakdown products of lipids such as the keto acids and some fatty acids, leading to the aminostatic and lipostatic theories of regulation. That is, when the availability of any of the three major types of food decreases, the desire for feeding is increased, eventually returning the blood metabolite concentrations back toward normal. Neurophysiologic studies of function in specific areas of the brain also support the glucostatic, aminostatic, and lipostatic theories, by the following observations:

- (1) A rise in blood glucose level increases the rate of firing of glucoreceptor neurons in the satiety center in the ventromedial and paraventricular nuclei of the hypothalamus.
- (2) The same increase in blood glucose level simultaneously decreases the firing of glucosensitive neurons in the hunger center of the lateral hypothalamus. In addition, some amino acids and lipid substances affect the rates of firing of these same neurons or other closely associated neurons.

Temperature regulation and food intake. When an animal is exposed to cold, it tends to increase feeding; when it is exposed to heat, it tends to decrease its caloric intake. This is caused by interaction within the hypothalamus between the temperature-regulating system and the food intake-regulating system. This is important, because increased food intake in a cold animal (1) increases its metabolic rate and (2) provides increased fat for insulation, both of which tend to correct the cold state.

Feedback signals from adipose tissue regulate food intake.

Most of the stored energy in the body consists of fat, the amount of which can vary considerably in different individuals. Recent studies suggest that the hypothalamus senses energy storage through the actions of leptin, a peptide hormone released from adipocytes. When the amount of adipose tissue increases (signaling excess energy storage), the adipocytes produce increased amounts of leptin, which is released into the blood. Leptin then circulates to the brain, where it moves across the blood-brain barrier by facilitated diffusion and occupies leptin receptors at multiple sites in the hypothalamus, especially the POMC neurons of the arcuate nuclei and neurons of the paraventricular nuclei. Stimulation of leptin receptors in these hypothalamic nuclei initiates multiple actions that decrease fat storage, including (1) decreased production in the hypothalamus of appetite stimulators, such as NPY and AGRP; (2) activation of POMC neurons, causing release of α -MSH and activation of melanocortin receptors; (3) increased production in the hypothalamus of substances, such as corticotropin-releasing hormone, that decrease food intake; (4) increased sympathetic nerve activity (through neural projections from the hypothalamus to the vasomotor centers), which increases metabolic rate and energy expenditure; and (5) decreased insulin secretion by the pancreatic beta cells, which decreases energy storage. Leptin may be an important means by which the adipose tissue signals the brain that enough energy has been stored and that intake of food is no longer necessary.

In mice or humans with mutations that render their fat cells unable to produce leptin or mutations that cause defective leptin receptors in the hypothalamus, marked hyperphagia and morbid obesity occur. In most obese humans, however, there does not appear to be a

deficiency of leptin production, because plasma leptin levels increase in proportion with increasing adiposity. Therefore, some physiologists believe that obesity may be associated with leptin resistance; that is, leptin receptors or post-receptor signaling pathways normally activated by leptin may be defective in obese people, who continue to eat despite very high levels of leptin. Another explanation for the failure of leptin to prevent increasing adiposity in obese individuals is that there are many redundant systems that control feeding behavior, as well as social and cultural factors that can cause continued excess food intake even in the presence of high levels of leptin.

The long-term regulatory system for feeding, which includes all the nutritional energy feedback mechanisms, helps maintain constant stores of nutrients in the tissues, preventing them from becoming too low or too high. The short-term regulatory stimuli serve two other purposes. First, they tend to make the person eat smaller quantities at each eating session, thus allowing food to pass through the gastrointestinal tract at a steadier pace, so that its digestive and absorptive mechanisms can work at optimal rates rather than becoming periodically overburdened. Second, they help prevent the person from eating amounts at each meal that would be too much for the metabolic storage systems once all the food has been absorbed.

Obesity

Obesity can be defined as an excess of body fat. A surrogate marker for body fat content is the body mass index (BMI), which is calculated as:

$$\text{BMI} = \text{Weight in kg} / \text{Height m}^2$$

In clinical terms, a BMI between 25 and 29.9 kg/m² is called overweight, and a BMI greater than 30 kg/m² is called obese. BMI is not a direct estimate of adiposity and does not take into account the fact that some individuals have a high BMI due to a large muscle mass. A better way to define obesity is to actually measure the percentage of total body fat. Obesity is usually defined as 25 percent or greater total body fat in men and 35 percent or greater in women. Although percentage of body fat can be estimated with various methods, such as measuring skin-fold thickness, bioelectrical impedance, or underwater weighing, these methods are rarely used in clinical practice, where BMI is commonly used to assess obesity.

The prevalence of obesity in children and adults in the United States and in many other industrialized countries is rapidly increasing, rising by more than 30 per cent over the past decade. Approximately 64 percent of adults in the United States are overweight and nearly 33 per cent of adults are obese.

When greater quantities of energy (in the form of food) enter the body than are expended, the body weight increases, and most of the excess energy is stored as fat. Therefore, excessive adiposity (obesity) is caused by energy intake in excess of energy output. For each 9.3 Calories of excess energy that enter the body, approximately 1 gram of fat is stored. Fat is stored mainly in adipocytes in subcutaneous tissue and in the intraperitoneal cavity, although the liver and other tissues of the body often accumulate significant amounts of lipids in obese persons.

It was previously believed that the number of adipocytes could increase substantially only during infancy and childhood and that excess energy intake in children led to hyperplastic obesity, associated with increased numbers of adipocytes and only small increases in adipocyte size. In contrast, obesity developing in adults was thought to increase only adipocyte size, resulting in hypertrophic obesity. Recent studies, however, have shown that new adipocytes can differentiate from fibroblast-like preadipocytes at any period of life and that the development of obesity in adults is accompanied by increased numbers, as well as increased size, of adipocytes. An extremely obese person may have as many as four times as

many adipocytes, each containing twice as much lipid, as a lean person. Once a person has become obese and a stable weight is obtained, energy intake once again equals energy output. For a person to lose weight, energy intake must be *less* than energy expenditure.

The causes of obesity are complex. Although genes play an important role in determining food intake and energy metabolism, lifestyle and environmental factors may play the dominant role in many obese people. The rapid increase in the prevalence of obesity in the past 20 to 30 years emphasizes the important role of lifestyle and environmental factors, because genetic changes could not have occurred so rapidly.

Regular physical activity and physical training are known to increase muscle mass and decrease body fat mass, whereas inadequate physical activity is typically associated with decreased muscle mass and increased adiposity. For example, studies have shown a close association between sedentary behaviors, such as prolonged television watching and obesity. About 25 to 30 per cent of the energy used each day by the average person goes into muscular activity, and in a laborer, as much as 60 to 70 per cent is used in this way. In obese people, increased physical activity usually increases energy expenditure more than food intake, resulting in significant weight loss. Even a single episode of strenuous exercise may increase basal energy expenditure or several hours after the physical activity is stopped. Because muscular activity is by far the most important means by which energy is expended in the body, increased physical activity is often an effective means of reducing fat stores.

Although powerful physiologic mechanisms regulate food intake, there are also important environmental and psychological factors that can cause abnormal feeding behavior, excessive energy intake, and obesity. The importance of environmental factors is evident from the rapid increase in the prevalence of obesity in most industrialized countries, which has coincided with an abundance of high-energy foods (especially fatty foods) and sedentary lifestyles. Psychological factors may contribute to obesity in some people. For example, people often gain large amounts of weight during or after stressful situations, such as the death of a parent, a severe illness, or even mental depression. It seems that eating can be a means of releasing tension.

One factor that may contribute to obesity is the prevalent idea that healthy eating habits require three meals a day and that each meal must be filling. Many young children are forced into this habit by overly solicitous parents, and the children continue to practice it throughout life. The rate of formation of new fat cells is especially rapid in the first few years of life, and the greater the rate of fat storage, the greater the number of fat cells. The number of fat cells in obese children is often as much as three times that in normal children. Therefore, it has been suggested that overnutrition of children—especially in infancy and, to a lesser extent, during the later years of childhood—can lead to a lifetime of obesity.

People with hypophysial tumors that encroach on the hypothalamus often develop progressive obesity, demonstrating that obesity in human beings, too, can result from damage to the hypothalamus. Although hypothalamic damage is almost never found in obese people, it is possible that the functional organization of the hypothalamic or other neurogenic feeding centers in obese individuals is different from that in nonobese persons. Also, there may be abnormalities of neurotransmitters or receptor mechanisms in the neural pathways of the hypothalamus that control feeding. In support of this theory, an obese person who has reduced to normal weight by strict dietary measures usually develops intense hunger that is demonstrably far greater than that of a normal person. This indicates that the “set-point” of an obese person’s feeding control system is at a much higher level of nutrient storage than that of a nonobese person. Studies in experimental animals also indicate that when food intake is restricted in obese animals, there are marked neurotransmitter changes in the hypothalamus that greatly increase hunger and oppose weight loss. Some of these changes include increased

formation of orexigenic neurotransmitters such as NPY and decreased formation of anorexic substances such as leptin and α -MSH.

Obesity definitely runs in families. Yet it has been difficult to determine the precise role of genetics in contributing to obesity, because family members generally share many of the same eating habits and physical activity patterns. Current evidence, however, suggests that 20 to 25 per cent of cases of obesity may be caused by genetic factors. Genes can contribute to obesity by causing abnormalities of (1) one or more of the pathways that regulate the feeding centers and (2) energy expenditure and fat storage. Three of the monogenic (single-gene) causes of obesity are (1) mutations of MCR-4, the most common monogenic form of obesity discovered thus far; (2) congenital leptin deficiency caused by mutations of the leptin gene, which are very rare; and (3) mutations of the leptin receptor, also very rare. All these monogenic forms of obesity account for only a very small percentage of obesity. It is likely that many gene variations interact with environmental factors to influence the amount and distribution of body fat.

Treatment of obesity depends on decreasing energy input below energy expenditure and creating a sustained negative energy balance until the desired weight loss is achieved. In other words, this means either reducing energy intake or increasing energy expenditure. The current National Institutes of Health (NIH) guidelines recommend a decrease in caloric intake of 500 kilocalories per day for overweight and moderately obese persons (BMI greater than 25 but less than 35 kg/m²) to achieve a weight loss of approximately 1 pound each week. A more aggressive energy deficit of 500 to 1000 kilocalories per day is recommended for persons with BMIs greater than 35 kg/m². Typically, such an energy deficit, if it can be achieved and sustained, will cause a weight loss of about 1 to 2 pounds per week, or about a 10 per cent weight loss after 6 months. For most people attempting to lose weight, increasing physical activity is also an important component of successful long-term weight loss.

To decrease energy intake, most reducing diets are designed to contain large quantities of "bulk," which is generally made up of non-nutritive cellulose substances. This bulk distends the stomach and thereby partially appeases hunger. In most lower animals, such a procedure simply makes the animal increase its food intake even more, but human beings can often fool themselves because their food intake is sometimes controlled as much by habit as by hunger. As pointed out later in connection with starvation, it is important to prevent vitamin deficiencies during the dieting period.

Various drugs for decreasing the degree of hunger have been used in the treatment of obesity. The most widely used drugs are amphetamines (or amphetamine derivatives), which directly inhibit the feeding centers in the brain. One drug for treating obesity is sibutramine, a sympathomimetic that reduces food intake and increases energy expenditure. The danger in using these drugs is that they simultaneously overexcite the central nervous system, making the person nervous and elevating the blood pressure. Also, a person soon adapts to the drug, so that weight reduction is usually no greater than 5 to 10 per cent. Another group of drugs works by altering lipid metabolism. For example, orlistat, a lipase inhibitor, reduces the intestinal digestion of fat. This causes a portion of the ingested fat to be lost in the feces and therefore reduces energy absorption. However, fecal fat loss may cause unpleasant gastrointestinal side effects, as well as loss of fat-soluble vitamins in the feces.

Significant weight loss can be achieved in many obese persons with increased physical activity. The more exercise one gets, the greater the daily energy expenditure and the more rapidly the obesity disappears. Therefore, forced exercise is often an essential part of treatment. The current clinical guidelines for the treatment of obesity recommend that the first step be lifestyle modifications that include increased physical activity combined with a reduction in caloric intake. For morbidly obese patients with BMIs greater than 40, or for patients with BMIs greater than 35 and conditions such as hypertension or type II diabetes

that predispose them to other serious diseases, various surgical procedures can be used to decrease the fat mass of the body or to decrease the amount of food that can be eaten at each meal.

Two of the most common surgical procedures used in the United States to treat morbid obesity are gastric bypass surgery and gastric banding surgery. Gastric bypass surgery involves construction of a small pouch in the proximal part of the stomach that is then connected to the jejunum with a section of small bowel of varying lengths; the pouch is separated from the remaining part of the stomach with staples. Gastric banding surgery involves placing an adjustable band around the stomach near its upper end; this also creates a small stomach pouch that restricts the amount of food that can be eaten at each meal. Although these surgical procedures generally produce substantial weight loss in obese patients, they are major operations, and their longterm effects on overall health and mortality are still uncertain.

Inanition, anorexia and cachexia

Inanition is the opposite of obesity and is characterized by extreme weight loss. It can be caused by inadequate availability of food or by pathophysiologic conditions that greatly decrease the desire for food, including psychogenic disturbances, hypothalamic abnormalities, and factors released from peripheral tissues. In many instances, especially in those with serious diseases such as cancer, the reduced desire for food may be associated with increased energy expenditure, causing serious weight loss.

Anorexia can be defined as a reduction in food intake caused primarily by diminished appetite, as opposed to the literal definition of “not eating.” This definition emphasizes the important role of central neural mechanisms in the pathophysiology of anorexia in diseases such as cancer, when other common problems, such as pain and nausea, may also cause a person to consume less food. Anorexia nervosa is an abnormal psychic state in which a person loses all desire for food and even becomes nauseated by food; as a result, severe inanition occurs.

Cachexia is a metabolic disorder of increased energy expenditure leading to weight loss greater than that caused by reduced food intake alone. Anorexia and cachexia often occur together in many types of cancer or in the “wasting syndrome” observed in patients with acquired immunodeficiency syndrome (AIDS) and chronic inflammatory disorders. Almost all types of cancer cause both anorexia and cachexia, and more than half of cancer patients develop anorexia-cachexia syndrome during the course of their disease.

Central neural and peripheral factors are believed to contribute to cancer-induced anorexia and cachexia. Several inflammatory cytokines, including tumor necrosis factor- α , interleukin-6, interleukin-1 β , and a proteolysis-inducing factor, have been shown to cause anorexia and cachexia. Most of these inflammatory cytokines appear to mediate anorexia by activation of the melanocortin system in the hypothalamus. The precise mechanisms by which cytokines or tumor products interact with the melanocortin pathway to decrease food intake are still unclear, but blockade of the hypothalamic melanocortin receptors appears to almost completely prevent their anorexic and cachectic effects in experimental animals. Additional research, however, is needed to better understand the pathophysiologic mechanisms of anorexia and cachexia in cancer patients and to develop therapeutic agents to improve their nutritional status and survival.

Depletion of food stores in the body tissues during starvation

Even though the tissues preferentially use carbohydrate for energy over both fat and protein, the quantity of carbohydrate normally stored in the entire body is only a few hundred grams (mainly glycogen in the liver and muscles), and it can supply the energy required for body

functions for perhaps half a day. Therefore, except for the first few hours of starvation, the major effects are progressive depletion of tissue fat and protein. Because fat is the prime source of energy (100 times as much fat energy is stored in the normal person as carbohydrate energy), the rate of fat depletion continues unabated, until most of the fat stores in the body are gone.

Protein undergoes three phases of depletion: rapid depletion at first, then greatly slowed depletion, and, finally, rapid depletion again shortly before death. The initial rapid depletion is caused by the use of easily mobilized protein for direct metabolism or for conversion to glucose and then metabolism of glucose mainly by the brain. After the readily mobilized protein stores have been depleted during the early phase of starvation, the remaining protein is not so easily removed. At this time, the rate of gluconeogenesis decreases to one third to one fifth its previous rate, and the rate of depletion of protein becomes greatly decreased.

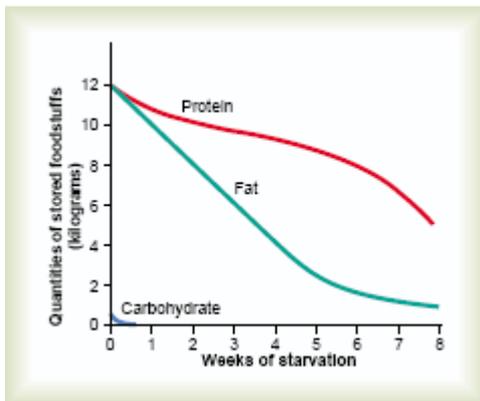


Figure 12 Effect of starvation on the food of the body

The lessened availability of glucose then initiates a series of events that leads to excessive fat utilization and conversion of some of the fat breakdown products to ketone bodies, producing the state of ketosis. The ketone bodies, like glucose, can cross the blood-brain barrier and can be used by the brain cells for energy. Therefore, about two thirds of the brain's energy is now derived from these ketone bodies, principally from beta-hydroxybutyrate. This sequence of events leads to at least partial preservation of the protein stores of the body. There finally comes a time when the fat stores are almost depleted, and the only remaining source of energy is protein. At that time, the protein stores once again enter a stage of rapid depletion. Because proteins are also essential for the maintenance of cellular function, death ordinarily ensues when the proteins of the body have been depleted to about half their normal level.

The stores of some of the vitamins, especially the water-soluble vitamins—the vitamin B group and vitamin C—do not last long during starvation. Consequently, after a week or more of starvation, mild vitamin deficiencies usually begin to appear, and after several weeks, severe vitamin deficiencies can occur. These deficiencies can add to the debility that leads to death.