

# Review of Medical Physiology

---

**William F. Ganong, MD**

*Jack and DeLoris Lange Professor of Physiology  
Chairman, Department of Physiology  
University of California  
San Francisco, California*

---

*Twelfth Edition*



**LANGE Medical Publications/Los Altos, California**

APPLETON-CENTURY-CROFTS/East Norwalk, Connecticut



# Section V. Gastrointestinal Function

## 25 | Digestion & Absorption

The gastrointestinal system is the portal through which nutritive substances, vitamins, minerals, and fluids enter the body. Proteins, fats, and complex carbohydrates are broken down into absorbable units (**digested**), principally in the small intestine. The products of digestion and the vitamins, minerals, and water cross the mucosa and enter the lymph or the blood (**absorption**). The digestive and absorptive pro-

cesses are the subject of this chapter. The details of the function of the various parts of the gastrointestinal system are considered in Chapter 26.

Digestion of the major foodstuffs is an orderly process involving the action of a large number of **digestive enzymes** (Table 25-1). Some of these enzymes are found in the secretions of the salivary glands, the stomach, and the exocrine portion of the

**Table 25-1.** Principal digestive enzymes.  
The corresponding proenzymes are shown in parentheses.

Source	Enzyme	Activator	Substrate	Catalytic Function or Products
Salivary glands	Salivary $\alpha$ -amylase	$\text{Cl}^-$	Starch	Hydrolyzes 1,4a linkages, producing $\alpha$ -limit dextrins, maltotriose, and maltose
Stomach	Pepsins (pepsinogens)	HCl	Proteins and polypeptides	Cleave peptide bonds adjacent to aromatic amino acids
Exocrine pancreas	Trypsin (trypsinogen)	Enteropeptidase	Proteins and polypeptides	Cleaves peptide bonds adjacent to arginine or lysine
	Chymotrypsins (chymotrypsinogens)	Trypsin	Proteins and polypeptides	Cleave peptide bonds adjacent to aromatic amino acids
	Elastase (proelastase)	Trypsin	Elastin, some other proteins	Cleaves bonds adjacent to aliphatic amino acids
	Carboxypeptidase A (procarboxypeptidase A)	Trypsin	Proteins and polypeptides	Cleaves carboxy terminal amino acids that have aromatic or branched aliphatic side chains
	Carboxypeptidase B (procarboxypeptidase B)	Trypsin	Proteins and polypeptides	Cleaves carboxy terminal amino acids that have basic side chains
	Pancreatic lipase	...	Triglycerides	Monoglycerides and fatty acids
	Pancreatic esterase	...	Cholesteryl esters	Cholesterol
	Pancreatic $\alpha$ -amylase	$\text{Cl}^-$	Starch	Same as salivary $\alpha$ -amylase
	Ribonuclease	...	RNA	Nucleotides
	Deoxyribonuclease	...	DNA	Nucleotides
Phospholipase A (prophospholipase A)	Trypsin	Lecithin	Lysolecithin	
Intestinal mucosa	Enteropeptidase	...	Trypsinogen	Trypsin
	Aminopeptidases	...	Polypeptides	Cleave N-terminal amino acid from peptide
	Dipeptidases	...	Dipeptides	Two amino acids
	Maltase	...	Maltose, maltotriose	Glucose
	Lactase	...	Lactose	Galactose and glucose
	Sucrase*	...	Sucrose	Fructose and glucose
	$\alpha$ -Limit dextrinase*	...	$\alpha$ -Limit dextrins	Glucose
Cytoplasm of mucosal cells	Nuclease and related enzymes	...	Nucleic acids	Pentoses and purine and pyrimidine bases
	Various peptidases	...	Di-, tri-, and tetrapeptides	Amino acids

\*Sucrase and  $\alpha$ -limit dextrinase are separate polypeptide chains that are parts of a single hybrid molecule.

pancreas. Other enzymes are found in the luminal membranes and the cytoplasm of the cells that line the small intestine. The action of the enzymes is aided by the hydrochloric acid secreted by the stomach and the bile secreted by the liver.

The mucosal cells in the small intestine have a **brush border** made up of numerous microvilli lining their apical surface (Fig 26–23). This border is rich in enzymes. It is lined on its luminal side by a layer that is rich in neutral and amino sugars, the **glycocalyx**. The membranes of the mucosal cells contain glycoprotein enzymes that hydrolyze carbohydrates and peptides, and the glycocalyx is made up in part of the carbohydrate portions of these glycoproteins that extend into the intestinal lumen. Next to the brush border and glycocalyx is a 100- to 400- $\mu\text{m}$  **unstirred water layer (UWL)** similar to the UWL adjacent to other biologic membranes (see Chapter 1). Solutes must diffuse across the UWL to reach the mucosal cells. The mucous coat overlying the cells also constitutes a significant barrier to diffusion.

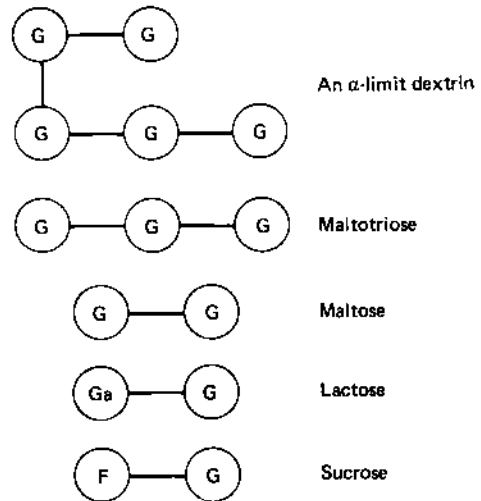
Substances pass from the lumen of the gastrointestinal tract to the extracellular fluid and thence to the lymph and blood by diffusion, facilitated diffusion, solvent drag, active transport, secondary active transport (coupled transport), and endocytosis. Most substances must pass from the intestinal lumen into the mucosal cells and then out of the mucosal cells to the extracellular fluid, and the processes responsible for movement across the luminal cell membrane are often quite different from those responsible for movement across the basal and lateral cell membranes to the extracellular fluid. The dynamics of transport in all parts of the body are considered in Chapter 1.

## CARBOHYDRATES

### Digestion

The principal dietary carbohydrates are polysaccharides, disaccharides, and monosaccharides. Starches (glucose polymers) and their derivatives are the only polysaccharides that are digested to any degree in the human gastrointestinal tract. In glycogen, the glucose molecules are mostly in long chains (glucose molecules in 1,4 $\alpha$  linkage), but there is some chain branching (produced by 1,6 $\alpha$  linkages; see Fig 17–13). Amylopectin, which constitutes 80–90% of dietary starch, is similar but less branched, whereas amylose is a straight chain with only 1,4 $\alpha$  linkages. Glycogen is found in animals, whereas amylose and amylopectin are of plant origin. The disaccharides **lactose** (milk sugar) and **sucrose** (table sugar) are also ingested, along with the monosaccharides fructose and glucose.

Starch is attacked by ptyalin, the  $\alpha$ -amylase in the saliva. However, the optimal pH for this enzyme is 6.7, and its action is inhibited by the acid gastric juice when food enters the stomach. In the small intestine, the potent pancreatic  $\alpha$ -amylase also acts on the ingested polysaccharides. Both the salivary and the pan-



**Figure 25–1.** Principal end products of carbohydrate digestion in the intestinal lumen. Each circle represents a hexose molecule. G, glucose; F, fructose; Ga, galactose.

creatic  $\alpha$ -amylases hydrolyze 1,4 $\alpha$  linkages but spare 1,6 $\alpha$  linkages, terminal 1,4 $\alpha$  linkages, and the 1,4 $\alpha$  linkages next to branching points. Consequently, the end products of  $\alpha$ -amylase digestion are oligosaccharides: the disaccharide **maltose**, the trisaccharide **maltotriose**, some slightly larger polymers with glucose in 1,4 $\alpha$  linkage, and  **$\alpha$ -limit dextrins**, branched polymers containing an average of about 8 glucose molecules (Fig 25–1).

The oligosaccharidases responsible for the further digestion of the starch derivatives are located in the outer portion of the membrane of the microvilli, principally in the ileum.  $\alpha$ -Limit dextrinase hydrolyzes the  $\alpha$ -limit dextrins, and maltase splits glucose from maltose, maltotriose, and other polymers of glucose in 1,4 $\alpha$  linkage. Most of the glucose molecules that are formed enter the mucosal cells, although some reenter the intestinal lumen and are absorbed farther along. Ingested disaccharides are hydrolyzed by lactase or sucrose on the luminal surface of mucosal cells (Fig 25–2). Deficiency of one or more of these disaccharidases leads to diarrhea, bloating, and flatulence after ingestion of sugar. The diarrhea is due to the increased number of osmotically active oligosaccharide molecules that remain in the intestinal lumen, causing the volume of the intestinal contents to increase. The bloating and flatulence are due to the production of gas ( $\text{CO}_2$  and  $\text{H}_2$ ) from disaccharide residues in the lower small intestine and colon. The problem of milk intolerance can be relieved by administration of commercial lactase preparations, but this is expensive. Yogurt is better tolerated than milk in intolerant individuals because it contains its own bacterial lactase.

Lactase is of interest because, in most mammals and in many races of humans, intestinal lactase activity is high at birth, declines to low levels during childhood, and remains low in adulthood. The low lactase

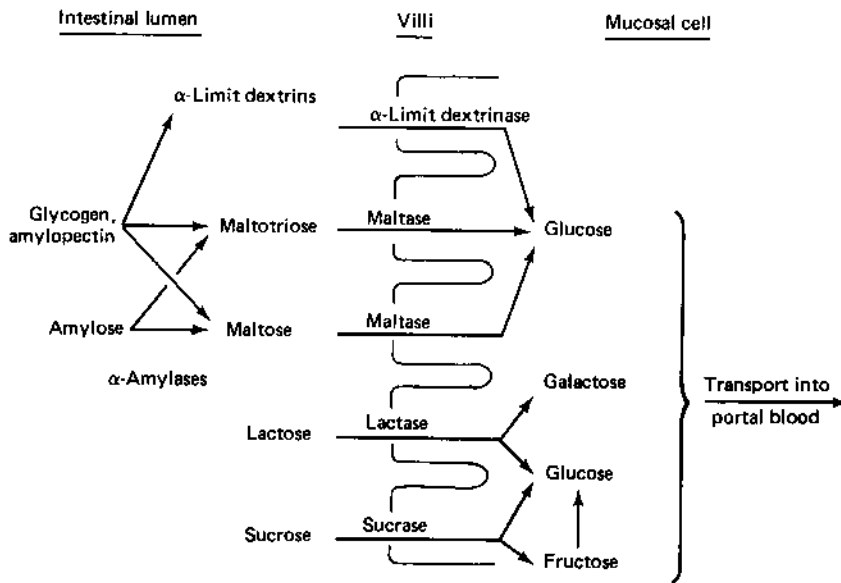


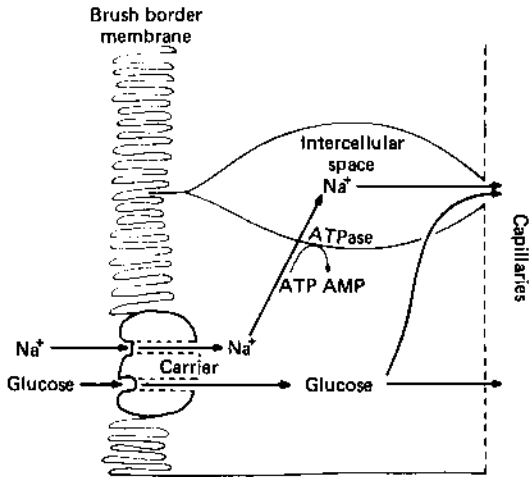
Figure 25-2. Outline of carbohydrate digestion and absorption. Some of the monosaccharides are also released into the intestinal lumen. (Modified from Gray GM: Carbohydrate digestion and absorption. *N Engl J Med* 1975;292:1225.)

Table 25-2. Transport of substances by the intestine and location of maximum absorption or secretion.\*

	Location of Absorptive Capacity			
	Small Intestine			Colon
	Upper†	Mid	Lower	
<b>Absorption</b>				
Sugars (glucose, galactose, etc)	++	+++	++	0
Neutral amino acids	++	+++	++	0
Basic amino acids	++	++	++	?
Water-soluble vitamins	+++	++	0	0
Betaine, dimethylglycine, sarcosine	+	++	++	?
Gamma globulin (newborn animals)	+	++	+++	?
Pyrimidines (thymine and uracil)	+	+	?	?
Fatty acid absorption and conversion to triglyceride	+++	++	+	0
Bile salts	0	+	+++	
Vitamin B <sub>12</sub>	0	+	+++	0
Na <sup>+</sup>	+++	++	+++	+++
H <sup>+</sup> (and/or HCO <sub>3</sub> <sup>-</sup> secretion)	0	+	++	++
Ca <sup>2+</sup>	+++	++	+	?
Fe <sup>2+</sup>	+++	++	+	?
Cl <sup>-</sup>	+++	++	+	0
SO <sub>4</sub> <sup>2-</sup>	++	+	0	?
<b>Secretion</b>				
K <sup>+</sup>	0	0	+	++
H <sup>+</sup> (and/or HCO <sub>3</sub> <sup>-</sup> absorption)	++	+	0	0
Sr <sup>2+</sup>	0	0	+	?
Cl <sup>-</sup> (under special conditions)	+	?	?	?
I <sup>-</sup>	0	+	0	0

\*Modified from Wilson TH: *Intestinal Absorption*. Saunders, 1962. Amount of absorption or secretion is graded + to +++.

†Upper small intestine refers primarily to jejunum, although the duodenum is similar in most cases studied (with the notable exception that the duodenum secretes HCO<sub>3</sub><sup>-</sup> and shows little net absorption or secretion of NaCl).



**Figure 25-3.** Probable mechanism for glucose transport across intestinal epithelium. Glucose transport into the intestinal cell is coupled to Na<sup>+</sup> transport, utilizing a common carrier. Na<sup>+</sup> is then actively transported out of the cell. (Reproduced, with permission, from Gray GM: Carbohydrate digestion and absorption. *N Engl J Med* 1975;292:1225.)

levels are associated with intolerance to milk (lactose intolerance). However, most Western Europeans and their American descendants retain their intestinal lactase activity in adulthood. Lactose tolerance is also found in a few African tribes, but most blacks are intolerant. In the USA, 70% of the black population and only 20% of the white population are intolerant to lactose.

### Absorption

Hexoses and pentoses are rapidly absorbed across the wall of the small intestine (Table 25-2). Essentially all of the hexoses are removed before the remains of a meal reach the terminal part of the ileum. The sugar molecules pass from the mucosal cells to the blood in the capillaries draining into the portal vein.

The transport of some sugars is uniquely affected by the amount of Na<sup>+</sup> in the intestinal lumen; a high concentration of Na<sup>+</sup> on the mucosal surface of the cells facilitates and a low concentration inhibits sugar influx into the epithelial cells. It now appears that glucose and Na<sup>+</sup> share the same carrier molecule (symport). Intracellular Na<sup>+</sup> is low, and Na<sup>+</sup> moves into the cell along its concentration gradient. **Glucose moves with the Na<sup>+</sup> and is released in the cell (Fig 25-3).** The Na<sup>+</sup> is transported into the lateral intercellular spaces, and the glucose diffuses into the interstitium and thence to the capillaries. Thus, glucose transport is an example of secondary active transport (see Chapter 1); **the energy for glucose transport is provided indirectly, by the active transport of Na<sup>+</sup> out of the cell.** This maintains the concentration gradient across the luminal border of the cell, so that more Na<sup>+</sup> and consequently more glucose enter. **The glucose mechanism also transports galactose. Fructose apparently utilizes a different carrier, and its absorption is**

independent of Na<sup>+</sup> or the transport of glucose and galactose; it is transported instead by facilitated diffusion. Some fructose is converted to glucose in the mucosal cells. Pentoses are absorbed by simple diffusion.

Insulin has little effect on intestinal transport of sugars. In this respect, intestinal absorption resembles glucose reabsorption in the proximal convoluted tubules of the kidneys (see Chapter 38); neither process requires phosphorylation, and both are essentially normal in diabetes but depressed by the drug phlorrhizin. The maximal rate of glucose absorption from the intestine is about 120 g/h.

## PROTEINS & NUCLEIC ACIDS

### Protein Digestion

Protein digestion begins in the stomach, where pepsins cleave some of the peptide linkages. Like many of the other enzymes concerned with protein digestion, pepsins are secreted in the form of inactive precursors (**proenzymes**) and activated in the intestinal tract. The pepsin precursors are called pepsinogens and are activated by gastric hydrochloric acid. Human gastric mucosa contains 3 chromatographically distinct pepsinogens, which produce 3 pepsins with slightly different properties (pepsins I, II, and III). Pepsins hydrolyze the bonds between aromatic amino acids such as phenylalanine or tyrosine and a second amino acid, so the products of peptic digestion are polypeptides of very diverse sizes. A **gelatinase** that liquefies gelatin is also found in the stomach. **Chymosin**, a milk-clotting gastric enzyme also known as **rennin**, is found in the stomachs of young animals but is probably absent in humans.

Because pepsins have a pH optimum of 1.6-3.2, their action is terminated when the gastric contents are mixed with the alkaline pancreatic juice in the duodenum and jejunum. The pH of the intestinal contents in the duodenal cap is 2.0-4.0, but in the rest of the duodenum, it is about 6.5.

In the small intestine, the polypeptides formed by digestion in the stomach are further digested by the powerful proteolytic enzymes of the pancreas and intestinal mucosa. Trypsin, the chymotrypsins, and elastase act at interior peptide bonds in the peptide molecules and are called **endopeptidases**. The formation of the active endopeptidases from their inactive precursors is discussed in Chapter 26. The carboxypeptidases of the pancreas and the aminopeptidases of the brush border are **exopeptidases** that hydrolyze the amino acids at the carboxy and amino ends of the polypeptides. Some free amino acids are liberated in the intestinal lumen, but others are liberated at the cell surface by the aminopeptidases and dipeptidases in the brush border of the mucosal cells. Some di- and tripeptides are actively transported into the intestinal cells and hydrolyzed by intracellular peptidases, with the amino acids entering the bloodstream. Thus, the final digestion to amino acids occurs in 3

locations: the intestinal lumen, the brush border, and the cytoplasm of the mucosal cells.

### Absorption

After ingestion of a protein meal, there is a sharp transient rise in the amino nitrogen content of the portal blood. L Amino acids are absorbed more rapidly than the corresponding D isomers. The D amino acids are apparently absorbed solely by passive diffusion, whereas most L amino acids are actively transported out of the intestinal lumen. There are 4 separate transport systems: one that transports neutral amino acids; one that transports basic amino acids; one that transports proline, hydroxyproline, and glycine; and one that transports the dicarboxylic amino acids glutamic acid and aspartic acid. A separate system transports di- and tripeptides into the mucosal cells. Absorption of amino acids is coupled to  $\text{Na}^+$  transport and, like glucose transport, is facilitated by a high  $\text{Na}^+$  concentration on the mucosal side of the intestinal epithelial cells. The transported amino acids and those produced by intracellular hydrolysis of di- and tripeptides accumulate in the mucosal cells, and from these cells they apparently diffuse passively into the blood. The only small peptides known to enter portal blood are those from gelatin that contain proline and hydroxyproline and those from certain meats that contain carnosine and anserine.

Absorption of amino acids is rapid in the duodenum and jejunum but slow in the ileum. Approximately 50% of the digested protein comes from ingested food, 25% from proteins in digestive juices, and 25% from desquamated mucosal cells. Only 2–5% of the protein in the small intestine escapes digestion and absorption. Some of the ingested protein enters the colon and is eventually digested by bacterial action. The protein in the stools is not of dietary origin but comes from bacteria and cellular debris. There is evidence that the peptidase activities of the brush border and the mucosal cell cytoplasm are increased by resection of part of the ileum and that they are independently altered in starvation. Thus, these enzymes appear to be subject to homeostatic regulation. In humans, a congenital defect in the mechanism that transports neutral amino acids in the intestine and renal tubules causes **Hartnup disease**. A congenital defect in the transport of basic amino acids causes **cystinuria**.

In infants, moderate amounts of undigested proteins are also absorbed. The protein antibodies in maternal colostrum that contribute to passive immunity against infections enter the circulation from the intestine, although this transfer is relatively minor in humans. Absorption is probably by endocytosis and subsequent exocytosis. Protein absorption declines with age, but adults still absorb small quantities. Foreign proteins that enter the circulation provoke the formation of antibodies, and the antigen-antibody reaction occurring upon subsequent entry of more of the same protein may cause allergic symptoms. Thus, absorption of proteins from the intestine may explain the occurrence of allergic symptoms after eating certain

foods. However, true food allergies are probably rare, and the diagnosis is difficult to establish.

Absorption of protein antigens, particularly bacterial and viral proteins, takes place in large **microfold cells**, or **M cells**, specialized intestinal epithelial cells that overlie aggregates of lymphoid tissue (Peyer's patches). These cells pass the antigens to the lymphoid cells, and lymphoblasts are activated. The activated lymphoblasts enter the circulation, but they later return to the intestinal mucosa and other epithelia, where they secrete IgA in response to subsequent exposures to the same antigen. This **secretory immunity** is an important defense mechanism; it is discussed in more detail in Chapter 27.

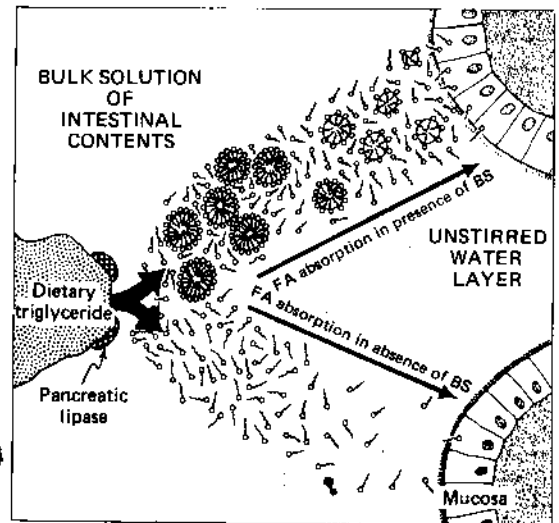
### Nucleic Acids

Nucleic acids are split into nucleotides in the intestine by the pancreatic nucleases, and the nucleotides are split into the nucleosides and phosphoric acid by enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugars and purine and pyrimidine bases. The bases are absorbed by active transport.

## LIPIDS

### Fat Digestion

Significant fat digestion begins in the duodenum,



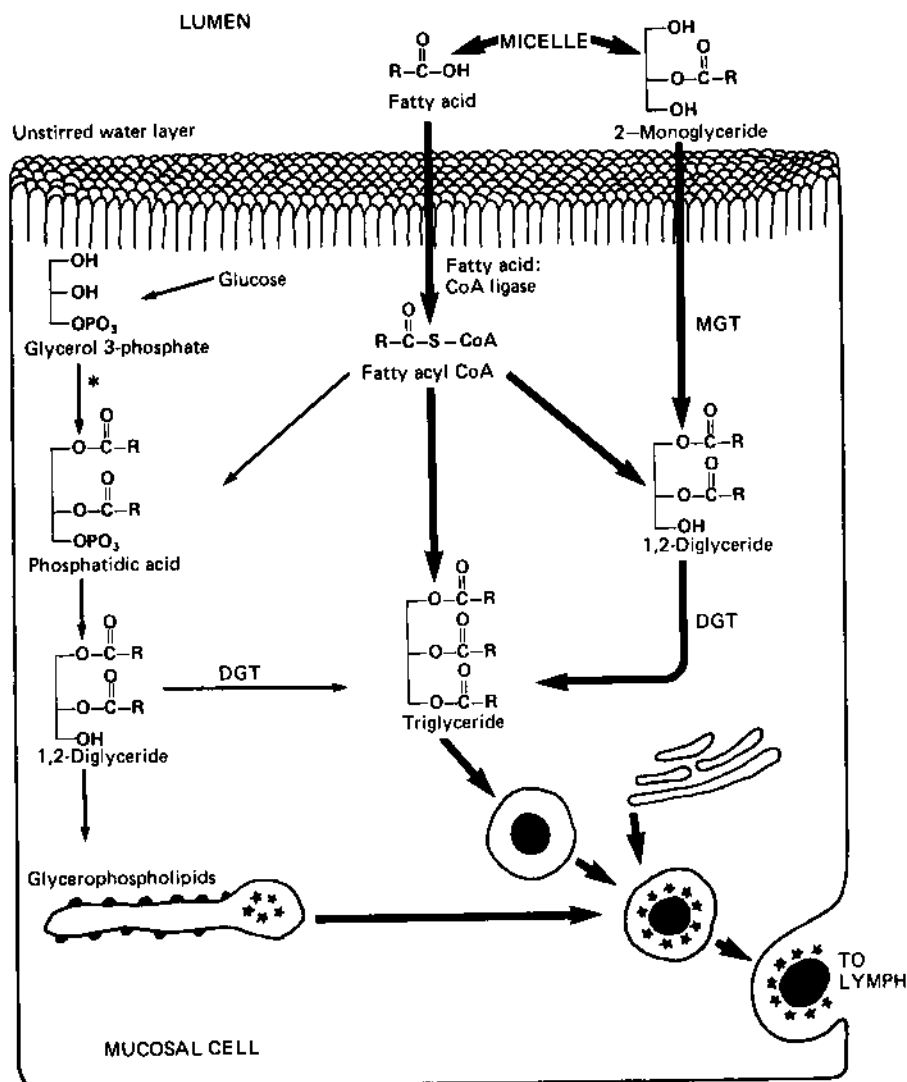
**Figure 25-4.** Lipid digestion and passage to intestinal mucosa. Fatty acids (FA) are liberated by the action of pancreatic lipase on dietary triglycerides and, in the presence of bile salts (BS), form micelles (the circular structures), which diffuse through the unstirred water layer to the mucosal surface. (Reproduced, with permission, from Thomson ABR: Intestinal absorption of lipids: Influence of the unstirred water layer and bile acid micelle. In: *Disturbances in Lipid and Lipoprotein Metabolism*. Dietschy JM, Gotto AM Jr, Ontko JA [editors]. American Physiological Society, 1978.)

pancreatic lipase being the most important enzyme involved. This enzyme hydrolyzes the 1- and 3- bonds of the triglycerides with relative ease but acts on the 2-bonds at a very slow rate, so the principal products of its action are free fatty acids and 2-monoglycerides. It acts on fats that have been emulsified. However, it cannot penetrate fat droplets covered by emulsifying agents without **colipase**, a protein with a molecular weight of about 11,000 that is also secreted by the exocrine portion of the pancreas. Colipase binds to the surface of the fat droplets, displacing the emulsifying agents and anchoring lipase to the droplet. There is a lipase in the gastric juice, but its action is physiologically of little importance. Most of the dietary chole-

sterol is in the form of cholesteryl esters, and pancreatic esterase hydrolyzes these esters in the intestinal lumen.

Fats are finely emulsified in the small intestine by the detergent action of bile salts, lecithin, and monoglycerides; bile salts alone are relatively poor emulsifying agents, but in the presence of phospholipids and monoglycerides, particles 200–5000 nm in diameter are formed. The structure of the bile salts is discussed in Chapter 26.

When the concentration of bile salts in the intestine is high, as it is after contraction of the gallbladder, lipids and bile salts interact spontaneously to form **micelles** (Fig 25-4). These spherical aggregates are



**Figure 25-5.** Lipid absorption. Triglycerides are formed in the mucosal cells from monoglycerides and fatty acids. Some of the glycerides also come from glucose via phosphatidic acid. The triglycerides are then converted to chylomicrons and released by exocytosis. From the extracellular space, they enter the lymph. \*, reaction inhibited by monoglyceride; MGT, monoacylglycerol acyltransferase; DGT, diacylglycerol acyltransferase. (Modified and reproduced, with permission, from Johnston JM: Esterification reactions in the intestinal mucosa and lipid absorption. In: *Disturbances in Lipid and Lipoprotein Metabolism*. Dietschy JM, Gotto AM Jr, Ontko JA [editors]. American Physiological Society, 1978.)

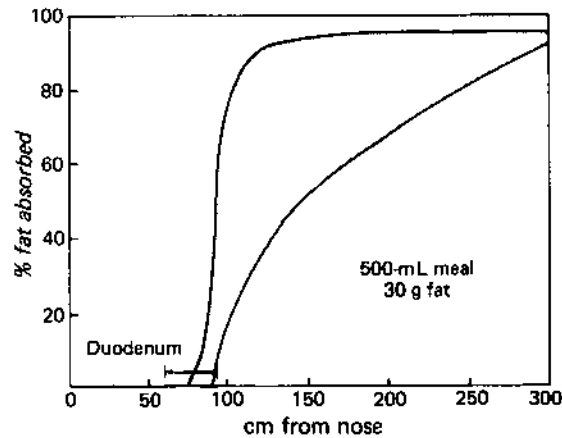
3–10 nm in diameter, with the polar hydroxy, peptide bond, and carbonyl or sulfate portions of the bile salts facing outward and the nonpolar steroid nuclear portions forming a hydrophobic center. Although their lipid concentration varies, they generally contain fatty acids, monoglycerides, and cholesterol. Micellar formation further solubilizes the lipids and provides a mechanism for their transport to the mucosal cells. Thus, the micelles move down their concentration gradient through the UWL to the brush border of the mucosal cells. The lipids diffuse out of the micelles, and a saturated aqueous solution of the lipids is maintained in contact with the brush border of the mucosal cells (Fig 25–4). The lipids enter the cells by passive diffusion and are rapidly esterified inside the cells, maintaining a favorable concentration gradient from the lumen into the cells. Unlike the ileal mucosa, the rate of uptake of bile salts by the jejunal mucosa is low, and the bile salts diffuse back into the intestinal lumen, where they are available for the formation of new micelles. Thus, the bile salt micelles solubilize lipids, transport them across the UWL, and keep a saturated solution of lipids in contact with the mucosal cells.

Pancreatectomized animals and patients with diseases that destroy the exocrine portion of the pancreas have fatty, bulky, clay-colored stools (**steatorrhea**) because of the impaired digestion and absorption of fat. The steatorrhea is due in part to the lipase deficiency, but micelle formation is also depressed in pancreatic insufficiency because, in the absence of the bicarbonate that is secreted from the pancreas, the relatively acid milieu in the duodenum inhibits the incorporation of fatty acids in the micelles. Acid also inhibits pancreatic lipase and precipitates some bile salts. This is why patients with excess secretion of gastric acid due to a gastrin-secreting tumor (gastrinoma; see Chapter 26) and a consequent low duodenal pH may develop steatorrhea. Another cause of steatorrhea is defective reabsorption of bile salts in the distal ileum (see Chapter 26).

### Fat Absorption

Monoglycerides, cholesterol, and fatty acids from the micelles enter the mucosal cells by passive diffusion. The subsequent fate of the fatty acids depends on their size. Fatty acids containing less than 10–12 carbon atoms pass from the mucosal cells directly into the portal blood, where they are transported as free (unesterified) fatty acids. The fatty acids containing more than 10–12 carbon atoms are reesterified to triglycerides in the mucosal cells. In addition, some of the absorbed cholesterol is esterified. The triglycerides and cholesteryl esters are then coated with a layer of protein, cholesterol, and phospholipid to form chylomicrons, which leave the cell and enter the lymphatics (Fig 25–5).

In mucosal cells, most of the triglyceride is formed by the acylation of the absorbed 2-monoglycerides, primarily in the smooth endoplasmic reticulum. However, some of the triglyceride is formed from glycerophosphate, which in turn is a product of glu-



**Figure 25–6.** Fat absorption, based on measurement after a fat meal in humans. (Redrawn and reproduced, with permission, from Davenport HW: *Physiology of the Digestive Tract*, 2nd ed. Year Book, 1966.)

cose catabolism. Glycerophosphate is also converted into glycerophospholipids that participate in chylomicron formation. The acylation of glycerophosphate and the formation of lipoproteins occur in the rough endoplasmic reticulum. Carbohydrate moieties are added to the proteins in the Golgi apparatus, and the finished chylomicrons are extruded by exocytosis from the basal or lateral aspects of the cell.

Fat absorption is greatest in the upper parts of the small intestine, but appreciable amounts are also absorbed in the ileum (Fig 25–6). On a moderate fat intake, 95% or more of the ingested fat is absorbed. The stools contain 5% fat, but much of the fecal fat is probably derived from cellular debris and microorganisms rather than from the diet. The processes involved in fat absorption are not fully mature at birth, and infants fail to absorb 10–15% of ingested fat. Thus, they are more susceptible to the ill effects of disease processes that reduce fat absorption.

### Absorption of Cholesterol & Other Sterols

Cholesterol is readily absorbed from the intestine if bile, fatty acids, and pancreatic juice are present. Closely related sterols of plant origin are poorly absorbed. Absorption of cholesterol is said to be limited to the distal portions of the small intestine. Almost all the absorbed cholesterol is incorporated into chylomicrons that enter the circulation via the lymphatics, as noted above. Nonabsorbable plant sterols such as those found in soybeans reduce the absorption of cholesterol, probably by competing with cholesterol for esterification with fatty acids.

## ABSORPTION OF WATER & ELECTROLYTES

### Water, Sodium, & Potassium

Overall water balance in the gastrointestinal tract

Table 25–3

<b>Ingested</b>
Endogenous secretions
Salivary glands
Stomach
Bile
Pancreas
Intestine
<b>Total input</b>
<b>Reabsorbed</b>
Jejunum
Ileum
Colon

### Balance in stool

\*Data from Moore & Malpica: *Electrolyte Absorption*

is summarized and presented each day plus 700 mL of the gastrointestinal fluid. Ninety-eight percent of the daily fluid load

It should be noted that reabsorption of water and electrolytes amounts of water and electrolytes moves through the small intestine and the large intestine. In addition, Na<sup>+</sup> and K<sup>+</sup> are located on the ileum and the blood is fact

In the small intestine, an important in the absorption of amino acids and electrolytes, the small intestine facilitates physiologic loss in diarrhea containing 10% fat. It has even been reported that cholera, a disease that causes diarrhea, stays in the small intestine that activates an increase in the secretion of water and electrolytes. The function of the small intestine is absorption of water and electrolytes. In diarrhea, the carrier for

Table 25-3. Daily net water turnover (mL) in the gastrointestinal tract.\*

Ingested		2000
Endogenous secretions		7000
Salivary glands	1500	
Stomach	2500	
Bile	500	
Pancreas	1500	
Intestine	1000	
		7000
Total input		9000
Reabsorbed		8800
Jejunum	5500	
Ileum	2000	
Colon	1300	
		8800
Balance in stool		200

\*Data from Moore EW: *Physiology of Intestinal Water and Electrolyte Absorption*, American Gastroenterological Society, 1976.

is summarized in Table 25-3. The intestines are presented each day with about 2000 mL of ingested fluid plus 7000 mL of secretions from the mucosa of the gastrointestinal tract and associated glands. Ninety-eight percent of this fluid is reabsorbed, with a daily fluid loss of only 200 mL in the stools.

It should be noted that the figures for intestinal reabsorption are net rather than gross. Only small amounts of water move across the gastric mucosa, but water moves in both directions across the mucosa of the small and large intestines in response to osmotic gradients. Some  $\text{Na}^+$  diffuses into or out of the small intestine depending on the concentration gradient. In addition,  $\text{Na}^+$  is actively transported out of the lumen in the small intestine and colon by pumps that appear to be located on the basal and lateral walls of the cells. In the ileum and jejunum,  $\text{Na}^+$  transport from intestine to blood is facilitated by aldosterone.

In the small intestine, active transport of  $\text{Na}^+$  is important in bringing about absorption of glucose, amino acids, and other substances (see above). Conversely, the presence of glucose in the intestinal lumen facilitates the reabsorption of  $\text{Na}^+$ . This is the physiologic basis for the treatment of  $\text{Na}^+$  and water loss in diarrhea by oral administration of solutions containing  $\text{NaCl}$  and glucose. This type of treatment has even proved to be beneficial in the treatment of cholera, a disease associated with very severe and, if untreated, frequently fatal diarrhea. The cholera vibrio stays in the intestinal lumen, but it produces a toxin that activates adenylate cyclase, causing a marked increase in intracellular cyclic AMP. Some strains of diarrhea-producing *Escherichia coli* produce a similar toxin. The accumulation of cyclic AMP increases  $\text{Cl}^-$  secretion from the intestinal glands and inhibits the function of the mucosal carrier for  $\text{Na}^+$ , reducing  $\text{NaCl}$  absorption. The resultant increase in electrolyte and water content of the intestinal contents causes the diarrhea. However, the  $\text{Na}^+$  pump and the common carrier for glucose and  $\text{Na}^+$  are unaffected, so coupled

reabsorption of glucose and  $\text{Na}^+$  bypasses the defect.

Water moves into or out of the intestine until the osmotic pressure of the intestinal contents equals that of the plasma. The osmolality of the duodenal contents may be hypertonic or hypotonic, depending on the meal ingested, but by the time the meal enters the jejunum, its osmolality is close to that of plasma. This osmolality is maintained throughout the rest of the small intestine; the osmotically active particles produced by digestion are removed by absorption, and water moves passively out of the gut along the osmotic gradient thus generated. In the colon,  $\text{Na}^+$  is pumped out and water moves passively with it, again along the osmotic gradient. Saline cathartics such as magnesium sulfate are poorly absorbed salts that retain their osmotic equivalent of water in the intestine, thus increasing intestinal volume and consequently exerting a laxative effect.

There is some secretion of  $\text{K}^+$  into the intestinal lumen, especially as a component of mucus, but for the most part, the movement of  $\text{K}^+$  across the gastrointestinal mucosa is due to diffusion. The net movement of  $\text{K}^+$  is proportionate to the potential difference between the blood and the intestinal lumen. In the jejunum, this potential difference is about 5 mV (lumen negative to blood), whereas in the ileum, it is about 25 mV and in the colon about 50 mV. Consequently, the concentration of  $\text{K}^+$  on the basis of diffusion alone would be about 6 meq/L in the jejunum, about 13 meq/L in the ileum, and about 30 meq/L in the colon. This is why the loss of ileal or colonic fluids in chronic diarrhea can lead to severe hypokalemia.

### Chloride & Bicarbonate

In the ileum and the colon, it appears that  $\text{Cl}^-$  is actively reabsorbed in a one-for-one exchange for  $\text{HCO}_3^-$ . This tends to make the intestinal contents more alkaline. However, the physiologic significance of this exchange is uncertain.

## ABSORPTION OF VITAMINS & MINERALS

### Vitamins

Absorption of water-soluble vitamins is rapid, but absorption of the fat-soluble vitamins A, D, E, and K is deficient if fat absorption is depressed because of lack of pancreatic enzymes or if bile is excluded from the intestine by obstruction of the bile duct. Most vitamins are absorbed in the upper small intestine, but vitamin  $\text{B}_{12}$  is absorbed in the ileum. This vitamin binds to intrinsic factor, a protein secreted by the stomach, and the complex is absorbed across the ileal mucosa (see Chapter 26).

### Calcium

Thirty to 80% of ingested calcium is absorbed. Active transport of  $\text{Ca}^{2+}$  out of the intestinal lumen occurs primarily in the upper small intestine, and there is also some absorption by passive diffusion. Active

transport is facilitated by 1,25-dihydroxycholecalciferol, the metabolite of vitamin D that is produced in the kidney. The metabolite induces the synthesis of a  $\text{Ca}^{2+}$ -binding protein in the mucosal cells (see Chapter 21). The rate of production of 1,25-dihydroxycholecalciferol is increased when the plasma calcium is decreased and reduced when the plasma calcium is elevated (see Chapter 21). Consequently,  $\text{Ca}^{2+}$  absorption is adjusted to body needs; absorption is increased in the presence of  $\text{Ca}^{2+}$  deficiency and decreased in the presence of  $\text{Ca}^{2+}$  excess.  $\text{Ca}^{2+}$  absorption is also facilitated by lactose and protein. It is inhibited by phosphates and oxalates because these anions form insoluble salts with  $\text{Ca}^{2+}$  in the intestine. Magnesium absorption is facilitated by protein.

### Iron

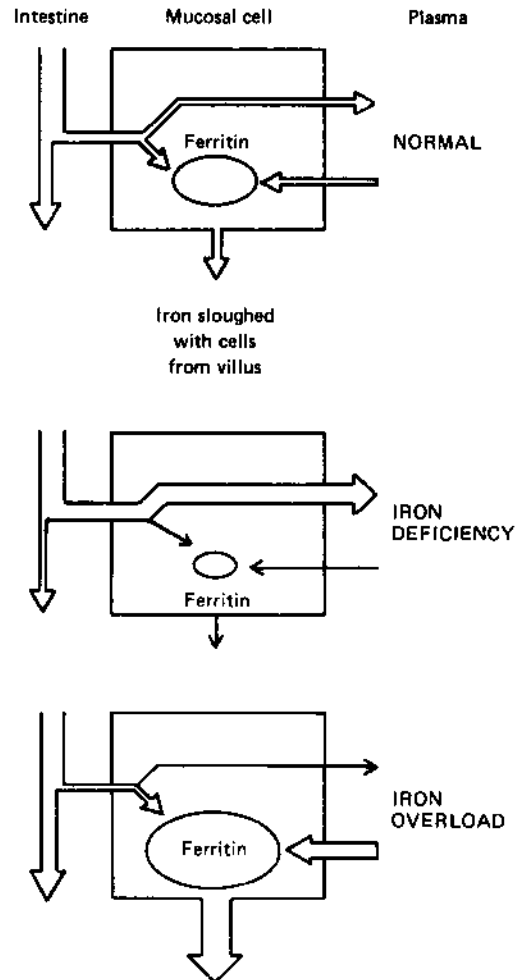
In adults, the amount of iron lost from the body is relatively small. Men lose about 0.6 mg/d, whereas women have a variable, larger loss averaging about twice this value because of the additional iron lost in the blood shed during menstruation. The average daily iron intake in the USA and Europe is about 20 mg, but the amount absorbed is equal only to the losses; if it were any greater, iron overload would develop. Thus, the amount of iron absorbed ranges normally from about 3 to 6% of the amount ingested.

Iron is more readily absorbed in the ferrous state ( $\text{Fe}^{2+}$ ), but most of the dietary iron is in the ferric form ( $\text{Fe}^{3+}$ ). No more than a trace of iron is absorbed in the stomach, but the gastric secretions dissolve the iron and provide a milieu favorable to its reduction to the  $\text{Fe}^{2+}$  form. The importance of this function in humans is indicated by the fact that iron deficiency anemia is a troublesome and relatively frequent complication of partial gastrectomy. Ascorbic acid and other reducing substances in the diet facilitate conversion of ferric to ferrous iron. Heme is also absorbed, and the  $\text{Fe}^{2+}$  that it contains is released in the mucosal cells. Other dietary factors affect the availability of iron for absorption; for example, the phytic acid found in cereals reacts with iron to form insoluble compounds in the intestine. So do phosphates and oxalates. Pancreatic juice inhibits iron absorption.

Iron absorption is an active process. Most of the absorption occurs in the upper part of the small intestine (Table 25-2). Other mucosal cells can transport iron, but the duodenum and adjacent jejunum contain most of the iron suitable for absorption. A protein, **mucosal transferrin**, binds iron in the lumen of the intestine and transports it across the mucosal brush border. The mucosal cells pass part of the iron directly into the bloodstream, but much of it is bound to **apoferritin**. This protein, which is also found in many other tissues, combines with iron to form **ferritin**. The iron bound to ferritin in intestinal cells is lost with the cells when they are shed into the intestinal lumen at the end of their life cycle and passed in the stool.

Apoferritin is a globular protein made up of 24 subunits. Iron forms a micelle of ferric hydroxyphosphate, and in ferritin, the subunits surround this

micelle. The ferritin molecule can contain as many as 4500 atoms of iron. Ferritin is readily visible under the electron microscope and has been used as a tracer in studies of phagocytosis and related phenomena. It is the principal storage form of iron in tissues. Ferritin molecules in lysosomal membranes may aggregate in deposits that contain as much as 50% iron. These deposits are called **hemosiderin**. Seventy percent of the iron in the body is in hemoglobin, 3% in myoglobin, and the remainder in ferritin. Ferritin iron is in equilibrium with plasma iron. Ferritin is also found in plasma, but most iron is transported bound to a polypeptide called **transferrin** or **siderophilin**. This



**Figure 25-7.** Diagrammatic representation of the control of iron absorption by the cells of the intestinal mucosa. The width of the arrows is proportionate to the amount of iron in each pathway. The size of the ovals indicates the size of the ferritin stores. Note that the ferritin stores are low in iron deficiency, and the amount of iron absorbed is large. Conversely, the amount of ferritin in the mucosal cells is large in iron overload, and the amount of iron absorbed is small. (Modified from Conrad ME: Factors affecting iron absorption. In: *Iron Deficiency*. Hallberg L, Harworth HG, Vanotti A [editors]. Academic Press, 1970.)

polypeptide has 2 iron-binding sites. Normally, transferrin is about 35% saturated with iron, and the normal plasma iron level is about 130  $\mu\text{g/dL}$  (23  $\mu\text{mol/L}$ ) in men and 110  $\mu\text{g/dL}$  (19  $\mu\text{mol/L}$ ) in women.

Iron absorption into the bloodstream is increased when body iron stores are depleted or when erythropoiesis is increased, and decreased in the opposite conditions. The amount of ferritin in the cells appears to determine the rate at which iron enters cells and the rate at which it leaves them to enter the plasma (Fig 25-7). In iron deficiency, the amount of ferritin is decreased and more iron enters the plasma. In iron overload, ferritin stores are large and absorption from the intestine is decreased. The term "mucosal block" has been used to refer to the ability of the mucosa to prevent excess ingested iron from being absorbed.

The normal operation of the factors that maintain iron balance is essential for health. Iron deficiency causes anemia. If more iron is absorbed than is ex-

creted, iron overload results. However, normal individuals can maintain a normal rate of absorption even when the ingested load is 5 or 10 times more than needed. Ferritin and hemosiderin accumulate in the tissues when the overload is prolonged. Large ferritin and hemosiderin deposits are associated with **hemochromatosis**, a syndrome characterized by pigmentation of the skin, pancreatic damage with diabetes ("bronze diabetes"), cirrhosis of the liver, a high incidence of hepatic carcinoma, and gonadal atrophy. Hemochromatosis can be produced by prolonged excessive iron intake and by a number of other conditions. Idiopathic hemochromatosis is a congenital disorder due to an autosomal recessive gene related to the HLA complex in which the mucosal regulatory mechanism behaves as if iron deficiency were present and absorbs iron at a high rate in the face of elevated rather than depleted body iron stores.