Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

JANSSEN-ORTHO

A.B.R. Thomson and E.A. Shaffer, editors

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The Small Intestine

H.J. Freeman and A.B.R. Thomson

1. GROSS ANATOMY AND HISTOLOGY OF THE SMALL INTESTINE

The small intestine is a specialized abdominal tubular structure with an adult length of about 6 m; the length may vary from 4 to 7 m depending on the method of measurement. The proximal portion, or *duodenum* (a Latin derivation from the Greek, *dodekadaktulon*, or 12 fingers breadth) consists of four parts: bulbar, descending, transverse and ascending portions. Most of the duodenum is retroperitoneal, located near the head of the pancreas; as a result, inflammatory or neoplastic masses in the pancreas sometimes compress the duodenum. From the ligament of Treitz, the more distal small intestine, or jejunoileum, is suspended on a mesentery crossing from left upper to right lower quadrants; then, the small intestine enters the large intestine, i.e., at the ileocecal "valve." The latter is not a true valvular structure but a physiological sphincter that acts to reduce luminal reflux into the small intestine. The proximal and distal parts of the jejunoileum are arbitrarily labeled jejunum and ileum, respectively, but their respective lengths are not precisely demarcated. More numerous and thicker folds, or plicae circulares, are evident in proximal jejunum compared to distal ileum. The narrower ileal lumen is more prone to obstruction. Lymphoid follicles, or Peyer's patches, can be visualized along the length of small intestine, particularly in distal ileum.

The blood supply to the small intestine derives mainly from the superior mesenteric artery, although the proximal duodenum derives some arterial supply from the celiac axis and its branches. Veins generally follow the arterial supply with the superior mesenteric vein flowing into the portal vein while lymphatic drainage also follows these vascular structures flowing into lymph nodes and eventually the cisterna chyli, thoracic duct and left subclavian vein.

Extrinsic innervation derives from the vagal nerve that supplies parasympathetic innervation while upper thoracic sympathetic fibers also supply the small intestine. Gut neurons project from the intestine to innervate the prevertebral sympathetic ganglia.

The intestinal wall is composed of four layers including serosa, muscularis propria, submucosa and mucosa. The serosa is a layer of mesothelial cells extending from the peritoneum while the muscularis propria includes outer longitudinal and inner circular layers separated by ganglion cells of the myenteric plexus (Auerbach's plexus). The submucosa consists of a connective tissue framework with numerous cell types. These include lymphocytes, plasma cells, mast cells, eosinophils, macrophages and fibroblasts. In addition, there are numerous ganglion cells and nerve fibers (Meissner's plexus) as well as vascular and lymphatic structures. The mucosa consists of a heterogeneous epithelial cell layer and the lamina propria with similar heterogeneous cell types and structures as described for the submucosa. The mucosa is separated from submucosa by a layer of muscle cells, the muscularis mucosae. The epithelial layer may be divided into villus and crypt regions. Villi are finger-like projections extending into the small intestinal lumen. They are longer in the jejunum compared to the ileum. Villi are covered with epithelial cells highly specialized for digestion and absorption along with goblet cells and intraepithelial lymphocytes. Cells from several adjacent crypts migrate into each villus and differentiate during their migration and eventual extrusion from the villus with a turnover of four to six days. The crypt epithelium consists of stem cells and less well-differentiated epithelial cells along with Paneth cells and enteroendocrine cells.

There is also a complex vascular and lymphatic network extending through the villus core that is involved in signal and nutrient trafficking to and from the epithelial cell layer. The enteric nervous system is even more complex, not only forming a myenteric and submucosal plexus, but containing intrinsic sensory neurons, interneurons for reflex activities and motor neurons that mediate actions of the enteric smooth muscle, glands and blood vessels. A distinct group of specialized cells, interstitial cells of Cajal (ICC), are responsible for pacemaker activity in the smooth muscle with development of slow waves that electrically couple to smooth muscle cells and lead to small bowel propulsive activity that promotes luminal movement of material from the proximal into the distal intestine.

Numerous cell types are found in the intestinal epithelium. Stem cells are located in the base of crypts and are pluripotential cells that do not migrate from the crypt bases. Undifferentiated crypt cells are the most common crypt cells that may proliferate rapidly but have poorly developed structure, including intracellular organelles and microvilli. Paneth cells are characterized by

eosinophilic granules that remain in the crypt bases and contain growth factors, digestive enzymes and antimicrobial peptides. Goblet cells are epithelial cells that contain visible mucins that may be discharged into the intestinal lumen and play a role in immune defense. Enteroendocrine cells contain secretory granules located in the cell base that may influence epithelial function through enterocyte basolateral membrane receptors. Enterocytes are polarized epithelial cells containing apical and basolateral membrane domains that are connected by a junctional complex. The apical or microvillus membrane faces the lumen, contains a complement of digestive enzymes, transporters and ion channels, different from those on the basolateral membrane. This polarized distribution of membrane proteins permits vectorial transport that differs in various regions of the small intestine. On the basolateral membrane, there are also receptors for growth factors, hormones and neurotransmitters. Other specialized cells involved in intestinal immune system function include M-cells and intraepithelial lymphocytes (IELs). M-cells are epithelial cells overlying lymphoid follicles that bind, process and deliver pathogens directly to lymphocytes, macrophages or other components of the immune system. IELs are specialized memory T-cells that migrate from the peripheral circulation to intercalate between basolateral membranes of epithelial cells.

2. SMALL INTESTINAL MOTILITY

The main function of the small intestine is digestion and absorption of nutrients. In this process, the role of small bowel motility is to mix food products with the digestive enzymes, to promote contact of chyme with the absorptive cells over a sufficient length of bowel and finally to propel remnants into the colon. Well-organized motility patterns occur in the small intestine to accomplish these goals in the fed as well as the fasting state. During fasting, a migrating motor complex (MMC) exists. This complex is characterized by a front of intense spiking activity (phase III activity) that migrates down the entire small intestine; as the front reaches the terminal ileum, another front develops in the gastroduodenal area and progresses down the intestine. The purpose of this phase III myoelectric and contractile activity is to sweep remnants of the previous meal into the colon and prevent stagnation and bacterial overgrowth. The MMC often starts in the lower esophagus. Sweeping through the stomach, it removes debris and residual material not emptied with the last meal. Absence of phase III activity is associated with bacterial overgrowth and diarrhea. Thus, the small bowel is active even during fasting.

During meals, this cycle is interrupted and the motility pattern in the small bowel becomes an irregular spiking activity called the fed pattern. This fed pattern of motility does not seem to move intestinal contents

forward to any great extent but does mix these contents with digestive juices, spreading them again and again over the absorptive surface of the brush border. Diarrhea can thus occur when this normal fed pattern is replaced by aggressive propulsive contractions.

3. PRINCIPLES OF ABSORPTION

Understanding the pathophysiology of diarrhea and malabsorption is based on understanding the normal steps in the digestion and absorption of food. The normal gastrointestinal tract is a finely integrated system geared to carry out the assimilation of ingested foodstuffs. Assimilation (the process by which ingested foods reach body fluids and cells) consists of two stages: (1) digestion (the breakdown of large molecules in the lumen of the intestine into their component small molecules) and (2) absorption (the transport across the intestinal mucosa to systemic body fluids).

Many disease processes directly or indirectly alter gastrointestinal physiology in such a manner that normal absorptive mechanisms are compromised, resulting in maldigestion or malabsorption of one or more dietary constituents. Too simplistic an approach to these diseases may be confusing because of the large number of illnesses involved and because of the plethora of diagnostic tests. This chapter will (1) present a classification of malabsorption and (2) outline the usefulness and potential pitfalls of common tests of intestinal function.

4. ABSORPTION OF VITAMINS AND MINERALS

4.1 Folic Acid (Pteroylglutamic Acid, $PteGlu_1$)

4.1.1 FOOD SOURCES

Dietary folates (folacins) are synthesized by bacteria and plants. They occur mostly as polyglutamates, which are not absorbed intact. All folacins, or polypteroylglutamates ($PteGlu_n$), are hydrolyzed to folic acid, or pteroylglutamic acid ($PteGlu_1$), during absorption. Pteroylglutamic acid ($PteGlu_1$) is absorbed at a faster rate than larger polymers ($PteGlu_n$). Only 25–50% of dietary folacin is nutritionally available; boiling destroys much of folate activity. Therefore, uncooked foods with a large portion of the monoglutamate form ($PteGlu_1$) – e.g., bananas, lima beans, liver and yeast – contain the highest availability of folacin. Average Canadian diets contain about 240 μg of folate a day. The daily requirement for folate is approximately 100 μg, although the recommended dietary allowance is 400 μg. Tissue stores of folate are only about 3 mg; therefore, malabsorption can deplete the body of folate within one month.

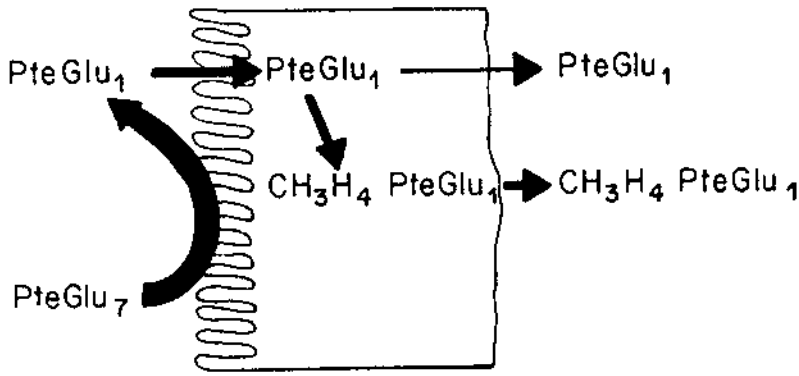

FIGURE 1. Proposed scheme of the digestion and absorption of dietary pteroylglutamates. Hydrolysis of polypteroylglutamates (shown here as $PteGlu_7$) probably occurs outside the intestinal epithelial cell. The overall rate of absorption into the mesenteric circulation is governed by the rate of transport of the monoglutamyl product ($PteGlu_1$). At physiologic doses, a substantial amount of $PteGlu_1$ is reduced and then methylated to $CH_3H_4PteGlu_1$ in the intestinal cell before release to the circulation.
SOURCE: Rosenberg IH. Folate absorption and malabsorption. N Engl J Med 1975; 293:1303.

4.1.2 HYDROLYSIS AND ABSORPTION OF POLYGLUTAMATE FOLATES

Polyglutamate forms of folate ($PteGlu_n$) hydrolyze sequentially down to the monoglutamate form ($PteGlu_1$). This hydrolysis takes place at the brush border by the enzyme folate conjugase (Figure 1). Folic acid ($PteGlu_1$) is absorbed from the intestinal lumen by a sodium-dependent carrier, which has been cloned. Once in the intestinal epithelial cell, folic acid is methylated and reduced to the tetrahydro form ($CH_3H_4PteGlu_1$).

Interference with folic acid absorption at the brush-border carrier site occurs with drugs such as phenytoin and sulfasalazine. In addition, folic acid deficiency itself can impair folic acid absorption by producing "megaloblastic" changes in columnar epithelial cells of the gut – an abnormal epithelium. Ethanol may inhibit hydrolysis but not uptake, a possible contributing factor to folate deficiency in alcoholics.

4.2 Cobalamin (Vitamin B_{12})

4.2.1 FOOD SOURCES

Cobalamin refers to cobalt-containing compounds with a corrin ring: these have biological activity for humans. Vitamin B_{12} is the generic term for all of these compounds with bioactivity in any species. Cobalamin is therefore the preferred term to distinguish those compounds that are active in humans from the many analogues produced by bacteria. Cobalamin enters animal tissues when the animal ingests bacteria-containing foods or from production in the animal's rumen. Microorganisms in the human colon synthesize cobalamin, but it is not absorbed. Thus, strict vegetarians who do not eat cobalamin-containing foods will develop cobalamin deficiency. The average Western diet contains 10–20 μg per day. The daily requirement for cobalamin is 1 μg. The human liver is the repository of approximately 5 mg of cobalamin. These large hepatic stores account for the delay of several years in the clinical appearance of deficiency after cobalamin malabsorption begins.

4.2.2 ROLE OF THE STOMACH, PANCREAS AND ILEUM

Once cobalamin is liberated from food, it is bound at acid pH to R proteins (so called because of their rapid movement during electrophoresis). R proteins are glycoproteins present in many body secretions, including serum, bile, saliva and gastric and pancreatic juices. Most of the gastric R protein is from swallowed saliva. The R proteins cannot mediate the absorption of cobalamin alone, and their physiologic function is incompletely understood. Rare cases of complete R-protein deficiency have occurred without obvious clinical effect on the patient.

The cobalamin/R protein complex leaves the stomach along with free intrinsic factor (IF) (Figure 2). In the duodenum, pancreatic proteases in the presence of bicarbonate (i.e., neutral pH) hydrolyze the R protein, thereby liberating free cobalamin. The cobalamin now combines with gastric intrinsic factor. A conformational change takes place, allowing the cobalamin/intrinsic-factor complex to be resistant to proteolytic digestion. This resistance allows the complex to safely traverse the small intestine and reach the ileum, its site of active absorption.

Since transfer of cobalamin from R protein to intrinsic factor depends upon pH, pancreatic insufficiency (with deficient bicarbonate production) or the Zollinger-Ellison syndrome (with excess hydrogen ion production) interferes with this process and may result in cobalamin deficiency.

In the ileum, the cobalamin/intrinsic-factor complex binds to a specific receptor located on the brush border. Free cobalamin does not bind to the ileal receptor. In the enterocyte the cobalamin is released from the instrinsic factor.

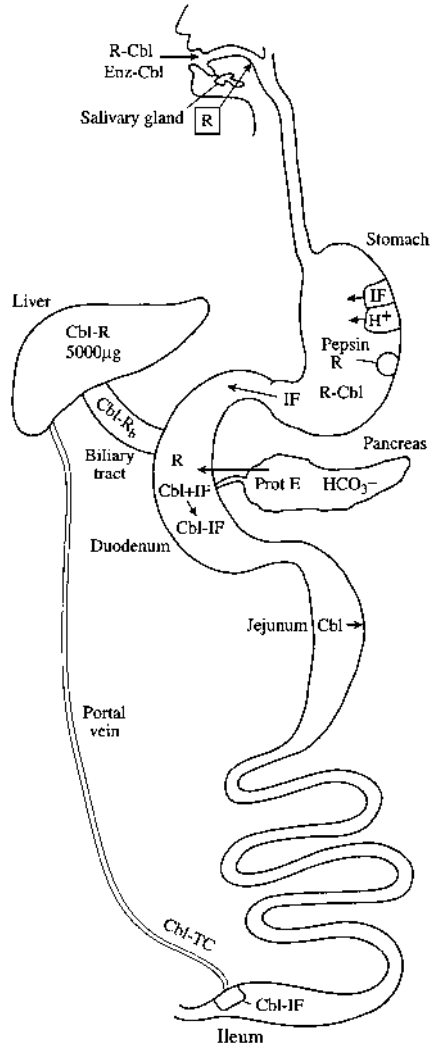

FIGURE 2. Absorption of cobalamin (Cbl) requires proteolysis and intrinsic factor (IF). The intrinsic factor secreted is far in excess of that needed for binding the available cobalamin. R protein derived from saliva is also present in great abundance. Note that Cbl binds initially to R protein in the stomach at acid pH. Only after R protein is degraded by protease does Cbl bind to IF. After Cbl is absorbed in the ileum, it is bound to transcobalamin II.
SOURCE: Kalser MH. Absorption of cobalamin (vitamin B_{12}), folate, and other water-soluble vitamins. In: Berk JE (ed.), Bockus gastroenterology, vol. 3. 4th ed. Philadelphia: WB Saunders, 1985:1556.

TABLE 1. Abnormalities of cobalamin absorption that produce deficiency

Physiologic step	*Disorder*
Decreased IF secretion	Pernicious anemia, gastrectomy, achlorhydria
Impaired transfer to IF (acidic pH)	Pancreatic insufficiency
Competition for uptake	Bacterial overgrowth
Impaired attachment to ileal receptor	Ileal disease or resection
Impaired passage through the ileal cell wall	Familial cobalamin malabsorption
Impaired uptake into blood	Transcobalamin II deficiency

After passage across the enterocytes, cobalamin is transported in blood bound to circulating proteins known as transcobalamins.

Understanding the normal absorptive processes allows an appreciation of a suggested classification of cobalamin malabsorption and deficiency (Table 1).

4.3 Iron

4.3.1 FOOD SOURCES

Iron is available for absorption from vegetables (nonheme iron) and from meats (heme iron). Heme iron is better absorbed (10–20%) and is unaffected by intraluminal factors or its dietary composition. Nonheme iron is poorly absorbed, with an efficiency of 1–6%, and absorption is largely controlled by luminal events. The average dietary intake of iron is 10–20 mg/day. Men absorb 1–2 mg/day, while menstruating women and iron-deficient patients absorb 3–4 mg/day. In acute blood loss, increased absorption of iron does not occur until three days later. Nonheme iron (in the ferric, Fe^{3+} state), when ingested into a stomach unable to produce acid, forms insoluble iron complexes, which are not available for absorption (Figure 3). In the presence of gastric acid and reducing agents such as ascorbic acid, however, ferrous iron (Fe^{2+}) forms. The ferrous iron complexes bind to a mucopolysaccharide of about 200,000 MW_r and are transported as an insoluble complex into the duodenum and proximal jejunum. Here, with the assistance of ascorbic acid, glucose and cysteine, the iron is absorbed. Dietary factors such as phosphate, phytate and phosphoproteins can render the iron insoluble and so inhibit nonheme iron absorption.

Heme iron (ferrous, Fe^{2+}) is ingested as myoglobin and hemoglobin. In the presence of gastric acid, the globin molecule is split off, and ferrous iron is liberated and transported with its phosphorin ring from the stomach into the duodenum and jejunum for absorption.

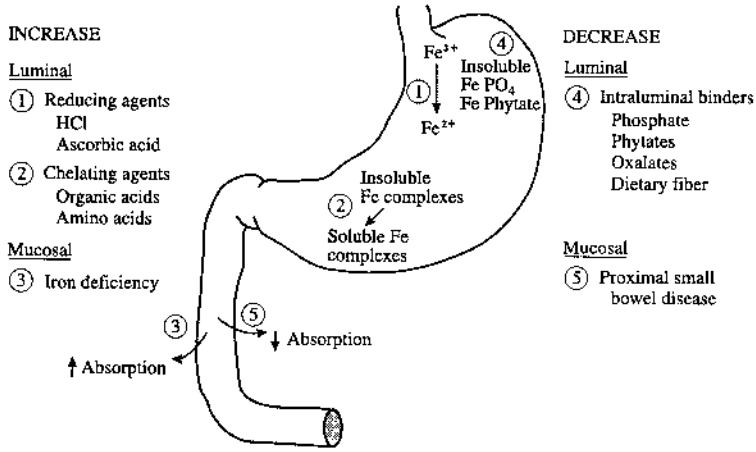

FIGURE 3. Factors that affect iron absorption. Nonheme iron absorption is affected both by intraluminal factors (1, 2 and 4) and by the total iron body content (3) as well as by small bowel disease (5). Heme iron absorption is altered only by those factors that affect the mucosa itself (3 and 5).
SOURCE: Alpers DH. Absorption of water-soluble vitamins, folate, minerals, and vitamin D. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:835.

Both heme and nonheme iron are absorbed most rapidly in the duodenum. Some of the iron taken up is deposited as ferritin within the enterocyte, and the remainder is transferred to the plasma-bound transferrin. When the enterocyte defoliates, iron deposited as ferritin is lost into the intestinal lumen. This mechanism for loss is probably overwhelmed by the large amounts of iron ingested. The amount of iron entering the body depends largely upon two factors: (1) total body iron content and (2) the rate of erythropoiesis. The mechanism of intestinal iron absorption is shown in Figure 4.

5. ABSORPTION OF WATER AND ELECTROLYTES

5.1 Passive Permeability to Ions and Water

The epithelium of the small intestine exhibits a high passive permeability to salt and water that is a consequence of the leakiness of the junctions between epithelial cells. Some water absorption may occur as the result of carrier-mediated transport of solutes. Osmotic equilibration between plasma and lumen is fairly rapid; therefore, large differences in ion concentration do not develop. These

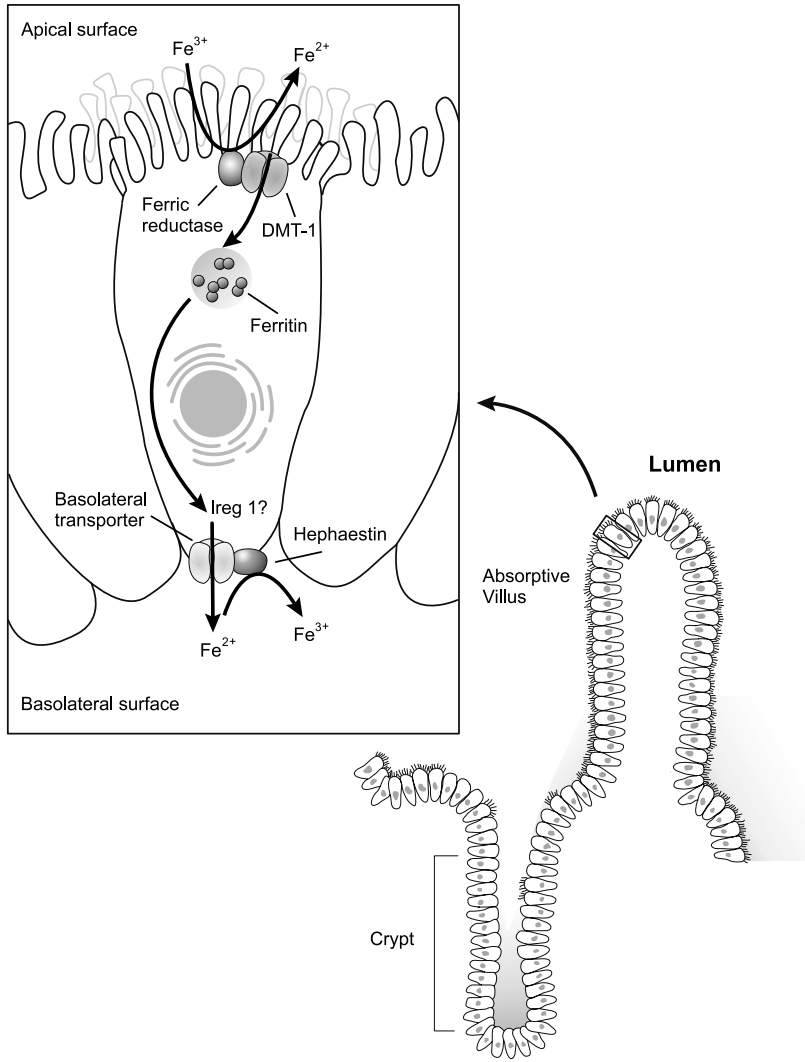

FIGURE 4. Intestinal absorption of iron. Iron is being transported across the brush-border membrane (BBM) by DMT (duodenal metal-transporter), and across the basolateral membrane possibly by Ireg 1, in conjunction with hephaestin, a ceruloplasmin-like molecule. Ferrureductase already in the BBM reduces Fe^{3+} to Fe^{2+} for transport by DMT. Absorption of iron is regulated by the amount of iron in the diet, by body iron stores and by the activity of the bone marrow erythropoiesis.

intercellular junctions are more permeable to cations than anions, so that lumen-to-blood concentration differences for Na^+ and K^+ are generally smaller than those for Cl^- and HCO^-_3. The colonic epithelium displays lower passive permeability to salt and water. This ionic permeability diminishes from cecum to rectum. It also decreases from duodenum to ileum. One consequence of this lower passive ionic permeability (higher electrical resistance) is that electric potential differences across the colonic epithelium are an order of magnitude greater than those in the small intestine (remember Ohm's law, E = IR, where E is electrical potential, I is electrical current, and R is electrical resistance). Active Na^+ absorption, which is the main transport activity of the distal colon, generates a serosa-positive charge or potential difference (PD). Under the influence of aldosterone (i.e., salt depletion), this PD can be 60 mV or even higher. A 60 mV PD will thus sustain a 10-fold concentration difference for a monovalent ion such as K^+. Most of the high K^+ concentration in the rectum is accounted for, therefore, by the PD. Despite the high fecal K^+ level, little K^+ is lost in the stool, since stool volume (about 200–300 mL per day) is normally so low. In contrast, during high-volume (several liters per day) diarrhea of small bowel origin, the stool K^+ concentration is considerably lower (10–30 mmol) but stool K^+ loss is nonetheless great because of the large volumes involved. In such states, the stool K^+ concentration is low (and the Na^+ concentration relatively high) because diarrheal fluid passes through the colon too rapidly to equilibrate across the colonic epithelium.

5.2 Active Electrolyte Absorption Along the Intestine

The small intestine has the largest capacity for secreting water and electrolytes of any organ system in the body. In both the small bowel and the colon, secretion appears to arise predominantly, if not exclusively, in crypts; the more superficial villous tip epithelium is absorptive. Disease processes that result in damage to the villus or to superficial portions of the intestinal epithelium (e.g., viral enteritis) inevitably shift the overall balance between absorption and secretion toward secretion. This is especially important in patients with celiac disease, where there is villous atrophy as well as hypertrophy of the crypts of Lieberkühn.

In the small intestine, active electrolyte and fluid absorption can be conceived of as either *nutrient-dependent* or *nutrient-independent*.

5.2.1 NUTRIENT-DEPENDENT TRANSPORT

The absorptive processes for the nutrients glucose and neutral amino acids are Na^+-dependent – i.e., one Na^+ molecule is translocated across the brush border with each glucose or amino acid molecule (Figure 5). The sodium pump (Na^+/K^+-ATPase), which is located exclusively in the basolateral membrane of the enterocyte, extrudes Na^+ that has entered the enterocyte from the

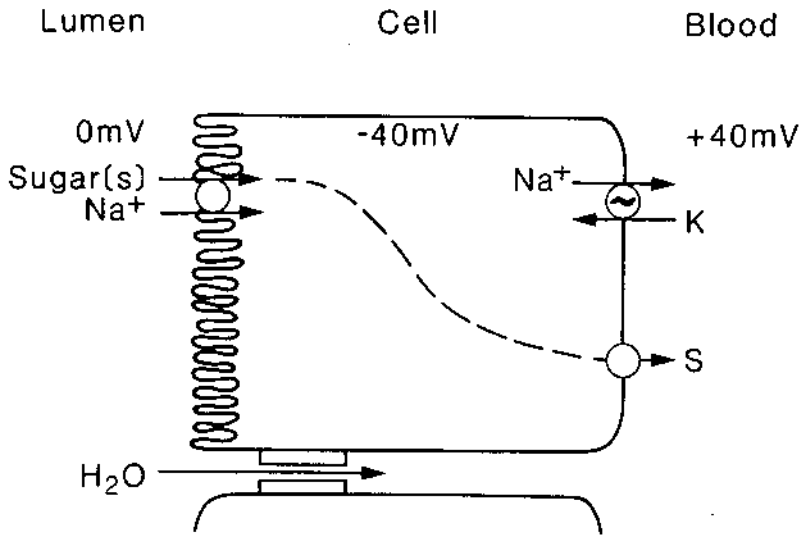

FIGURE 5. Na^+-coupled sugar absorption in the small intestine. This model presents the mechanism for sodium-coupled absorption of sugar. In addition to sugar, many amino acids, certain B vitamins and bile salts are absorbed through this mechanism. Sodium is taken up across the apical membrane in association with glucose (SGLT1) and exits by means of the basolateral sodium/potassium-ATPase. Glucose exits through a facilitated diffusion pathway in the basolateral membrane (GLUT2). Details of the model are described in the text.

lumen, thereby maintaining a low intracellular Na^+, a high intracellular K^+ and a negative intracellular electric potential. This Na^+/K^+ pump provides the potential energy for uphill sugar and amino acid absorption. Glucose is cotransported with sodium. Patients in intestinal secretory states such as cholera can absorb glucose normally. Na^+ (and thus water) are also absorbed, accompanying the transport of glucose. As a consequence, the fluid losses incurred by these patients can be replaced by oral glucose-electrolyte solutions[1] and do not require intravenous fluids unless the patient is comatose or too nauseated to drink the necessary large volumes of fluid to correct the dehydration. Application of this knowledge has had a major impact on world health, and especially on that of children, since the parts of the world where cholera-like diarrheas are prevalent generally have very limited hospital facilities and insufficient supplies of sterile electrolyte solutions.

[1] The WHO oral rehydration solution contains in mmol/L: glucose, 111; Na^+, 90; K^+, 20; Cl^-, 80; HCO_3^-, 30.

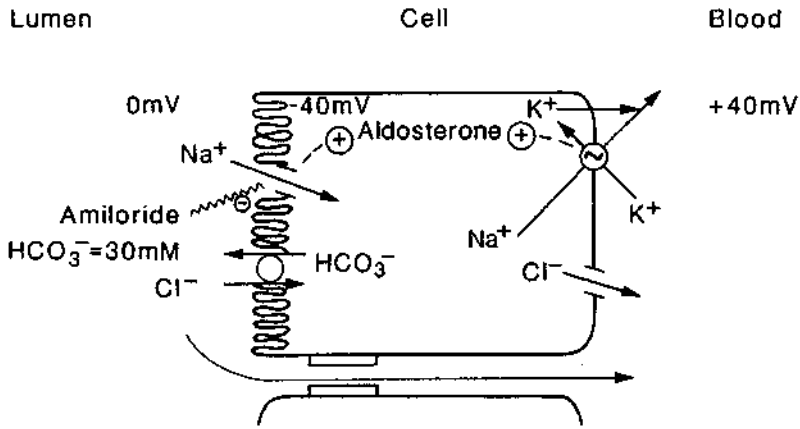

FIGURE 6. Electrogenic Na^+ absorption in the distal colon. Sodium enters the cell at the apical membrane through sodium channels and leaves the cell at the basolateral membrane through the sodium/potassium-ATPase. Details of the model are described in the text.

5.2.2 NUTRIENT-INDEPENDENT TRANSPORT

Nutrient-independent active absorption of electrolytes and water by intestinal epithelial cells occurs through several specific mechanisms, located at different levels of the mammalian intestinal tract. All of these mechanisms have in common the Na^+/K^+-ATPase pump, located on the basolateral membrane, and also a requirement for luminal Na^+.

In the distal colon (Figure 6), the luminal membrane contains Na^+ channels, which can be blocked by low concentrations of the pyrazine diuretic amiloride. The Na^+ entering through these channels in the luminal membrane is then extruded across the basolateral membrane by the Na^+/K^+-ATPase pump. Aldosterone increases the number of these channels and also, more slowly, increases the number of Na^+/K^+-ATPase pumps. Aldosterone therefore enhances active Na^+ absorption in the distal colon. To a more limited extent, aldosterone also causes the appearance of Na^+ channels more proximally in the colon and even in the distal ileum. Cl^- is absorbed along with Na^+ and traverses the epithelium by both cellular and paracellular routes. Its transcellular route involves a Cl^-/HCO_3^- exchanger in the luminal membrane and Cl^- channels in the basolateral membrane. Intracellular mediators such as cyclic AMP (cAMP) do not appear to affect these Na^+ channels. Thus, patients with secretory diarrheas, especially those who are salt-depleted and therefore have elevated blood levels of aldosterone, are able to reabsorb some of the secreted

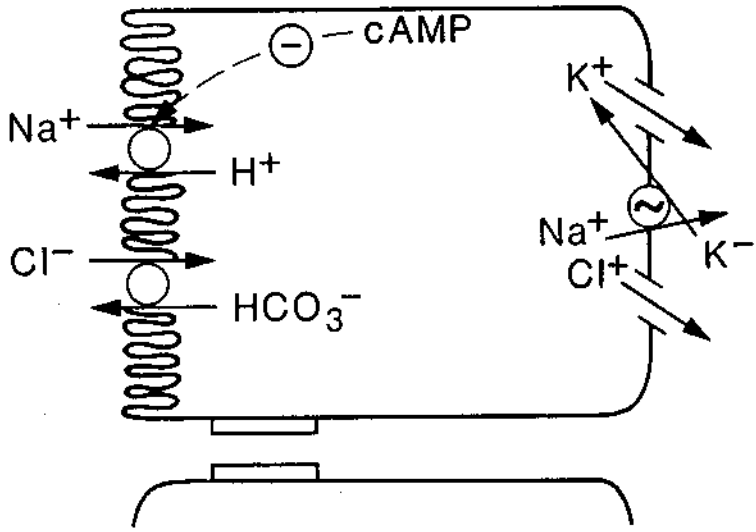

FIGURE 7. Electroneutral sodium chloride absorption in the small intestine and colon. Apical sodium chloride entry through sodium/hydrogen and chloride/bicarbonate permits sodium and chloride to enter the cell in an electroneutral fashion. Sodium exits the cell through the basolateral sodium/potassium-ATPase. The route of chloride efflux remains relatively speculative, but likely occurs through some basolateral channel. Details of the model are described in the text.

fluid in their distal colon. Spironolactone, which inhibits the action of aldosterone, can increase the severity of diarrhea in such patients.

In the more proximal colon and in the ileum, the luminal membrane contains Na^+/H^+ exchangers that permit net Na^+ entry (Figure 7). A family of Na^+/H^+ exchangers has been identified and cloned. The colon and the ileum (but not the jejunum) also have Cl^-/HCO_3^- exchangers in their luminal borders. Cell pH adjusts the relative rates of these two exchangers. Thus, H^+ extrusion by Na^+/H^+ exchange can cause cell alkalinization, which then stimulates Cl^- entry and HCO_3^- extrusion by this Cl^-/HCO_3^- exchange. The latter exchanger increases cell H^+, thereby sustaining Na^+/H^+ exchange. Increases in cell concentrations of cAMP and free Ca^{2+} inhibit the Na^+/H^+ exchange. Cyclic AMP and its agonists thereby cause cell acidification – which, in turn, inhibits Cl^-/HCO_3^- exchange. Therefore, electrolyte absorption in small and large intestinal segments (except the distal colon) can be downregulated by hormones, neurotransmitters and certain luminal substances (bacterial enterotoxins, bile salts, hydroxylated fatty acids) that increase cell

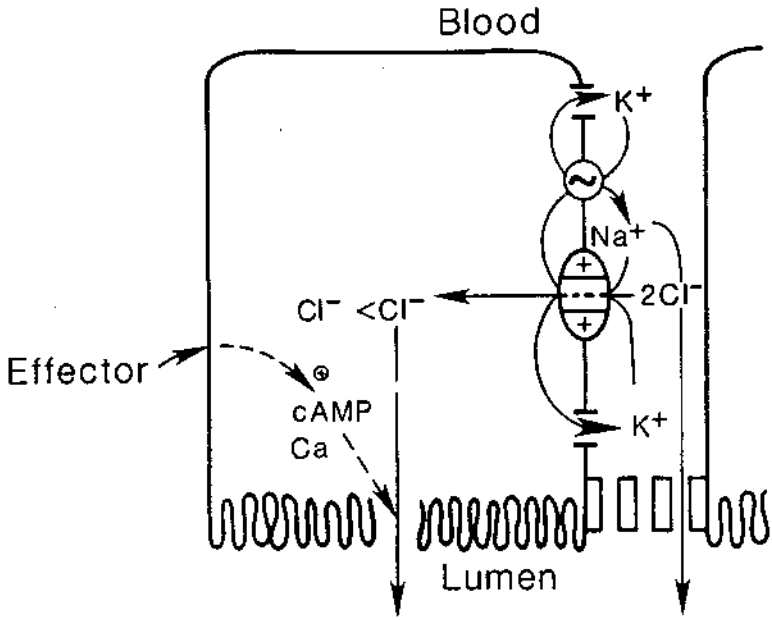

FIGURE 8. Electrogenic chloride secretion in both small and large intestine. A cyclic AMP–activated channel in the apical membrane permits hormone-stimulated chloride secretion. The chloride channel is coded by a gene (cystic fibrosis transmembrane conductance regulator [CFTR]) that is responsible for cystic fibrosis. Chloride enters the cell through a sodium/potassium transport along the basolateral surface. Details of this model are discussed in the text.

concentrations of cAMP or free Ca^{2+}. For this reason, body fluid secreted in response to these stimuli cannot be effectively reabsorbed in the absence of amino acids and sugars, except in the distal colon. In the jejunum, where Cl^-/HCO_3^- exchange does not appear to be present, Na^+/H^+ exchange can be well sustained by anaerobic glycolysis, which generates H^+ as well as some ATP.

There is also some evidence for a direct cotransport of Na^+ and Cl^-, although this is difficult to separate experimentally from dual exchangers. This entry mechanism may exist in the ileum and proximal colon.

5.3 Active Electrolyte Secretion Along the Intestine

In the secretory cell, the entry of Cl^- from the contraluminal bathing medium (blood or serosal side of the enterocyte) is coupled to that of Na^+ and probably also K^+ by a triple cotransporter with a stoichiometry of 1 Na^+, 1 K^+ and 2 Cl^-.

TABLE 2. Hormones and neurotransmitters that stimulate intestinal secretion

	Intracellular mediator	
cAMP	*Ca^{2+}*	*Unknown*
Vasoactive intestinal peptide	Bradykinin	Bombesin
Prostaglandins	Acetylcholine	Lipoxygenase products
Bradykinin	Substance P	Thyrocalcitonin
	Neurotensin	Histamine
	Serotonin	Vasopressin

Only agents found effective in vitro have been listed. Several other hormones have been found to stimulate secretion in vivo, but it is unclear whether they act directly on the intestinal mucosa. The latter include glucagon and pentagastrin.

Na^+ entering in this fashion is then recycled to the contraluminal solution by the Na^+/K^+ exchange pump (Figure 8). K^+, entering via the pump and also the triple cotransporter, diffuses back to the contraluminal side through K^+ channels. Owing to the Na^+ gradient, Cl^- accumulates above electrochemical equilibrium and can either (1) recycle back to the contraluminal solution through the $Na^+/K^+/2$ Cl^- cotransporter or through basolateral membrane Cl^- channels, or (2) be secreted into the lumen through luminal membrane Cl^- channels. When Cl^- is secreted into the lumen it generates a serosa-positive electric potential difference, which provides the driving force for Na^+ secretion through the paracellular pathway between cells. In the resting secretory cell, the luminal Cl^- channels are closed. When secretion is stimulated by a hormone or neurotransmitter, these channels open. Secretion is initiated, therefore, by opening the Cl^- "gate" in the luminal membrane of the secretory cell.

The known intracellular mediators of secretion are cAMP, cGMP and Ca^{2+} (Table 2). These can arise from the blood; nerve endings; endocrine cells in the epithelium (APUD cells); mesenchymal elements such as lymphocytes, plasma cells and mast cells; or the enterocytes themselves. Except for the cAMP agonists, lipoxygenase products and calcitonin, the actions of the other agonists are short-lived; desensitization rapidly develops. They operate to fine-tune electrolyte transport rather than invoke persistent secretion.

Predictably, since there are hormones and neurotransmitters that stimulate active electrolyte secretion in the gut, there are also agonists that inhibit secretion and/or stimulate absorption. These include adrenocorticosteroids, norepinephrine, somatostatin, enkephalins and dopamine. Glucocorticoids enhance electrolyte absorption throughout the intestinal tract, but the mechanisms involved are less well understood than for aldosterone. They may act in part by

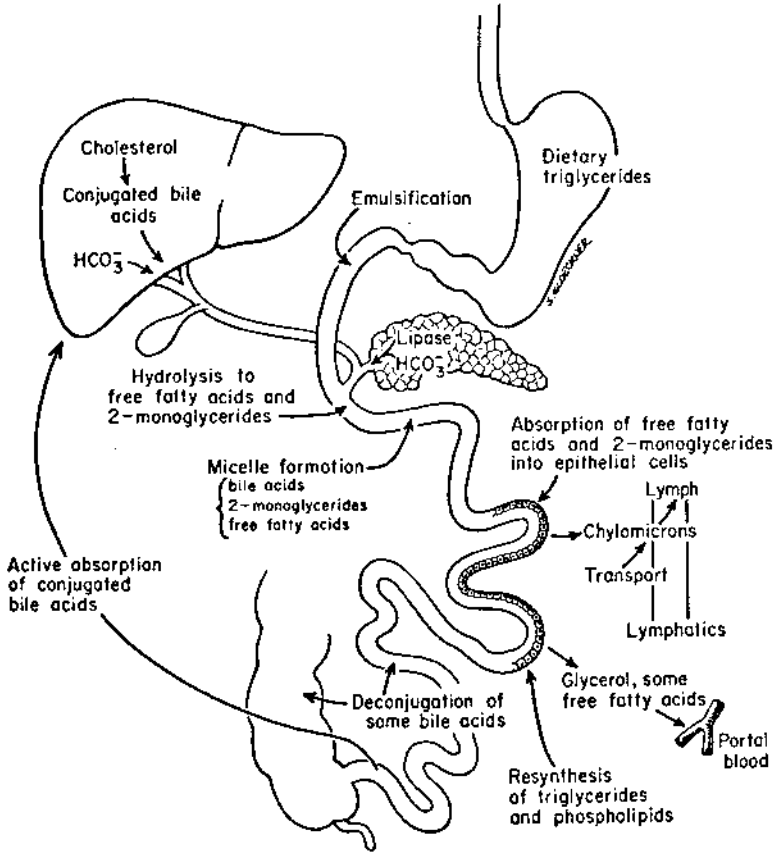

FIGURE 9. Diagram of the major steps in the digestion and absorption of dietary fat. These include (1) the lipolysis of dietary triglyceride (TG) by pancreatic enzymes; (2) micellar solubilization of the resulting long-chain fatty acids (FA) and β-monoglycerides (βMG; shown in figure as 2-monoglycerides) by bile acids secreted into the intestinal lumen by the liver; (3) absorption of the fatty acids and β-monoglycerides into the mucosal cell with subsequent re-esterification and formation of chylomicrons; and, finally, (4) movement of the chylomicrons from the mucosal cell into the intestinal lymphatic system. During the process of chylomicron formation, small amounts of cholesterol (C), cholesterol ester (CE), and phospholipid (PL) as well as triglyceride are incorporated into this specific lipoprotein fraction.
SOURCE: Wilson FA, Dietschy JM. Differential diagnostic approach to clinical problems of malabsorption. Gastroenterology 1971; 61:912.

inhibiting phospholipase A_2 and therefore the arachidonic acid cascade. The adrenergic receptors on enterocytes are almost exclusively α_2 in type. The sympathetic nervous system in the intestinal mucosa releases norepinephrine (an α_2 antagonist) and so inhibits electrolyte secretion and stimulates absorption. Sympathectomy, whether chemical or surgical, leads to diarrhea, at least transiently. Chronic diabetics with autonomic neuropathy sometimes develop persistent diarrhea that is associated with degeneration of adrenergic nerve fibers to the gut. Somatostatin and endogenous enkephalins are also antisecretory.

6. ABSORPTION OF FAT

The overall process of fat digestion and absorption consists of four distinct phases, related to the respective functions of the pancreas, liver, intestinal mucosa and lymphatics (Figure 9). Physiologically, these involve (1) lipolysis of dietary triglyceride (TG) to fatty acid (FA) and β-monoglyceride (MG); (2) micellar solubilization with bile acid; (3) uptake into the mucosal cell, with re-esterification of the MG with FA to form TG, and chylomicron formation in the presence of cholesterol, cholesterol esters, phospholipids and protein; and (4) delivery of chylomicrons in lymphatics to the body for utilization of fat.

The average North American diet contains 60–100 g of fat each day, mostly in the form of neutral fat or triglycerides. In the proximal intestine, TG comes under hydrolytic attack by lipases, producing glycerol, FA and MG. These products of lipolysis first form an emulsion and later a micellar solution.

Following the entry of food and particularly fat into the duodenum, cholecystokinin (CCK) is released from mucosal cells, causing gallbladder contraction. Bile acids, along with other biliary constituents, are released into the proximal small intestine. Bile acids chemically resemble detergent molecules, in that a portion of the molecule is polar and water-soluble, while another portion of the molecule is nonpolar and fat-soluble. When the bile acids are present in sufficient amounts, known as the critical micellar concentration (CMC), they form negatively charged spheres, called simple micelles. Incorporation of FA and MG forms a larger, polymolecular aggregate, a mixed micelle. All this is necessary to solubilize fat and disperse it in small packets more effectively, setting the stage for further luminal digestion by pancreatic lipase. This enzyme acts only at oil-water interfaces and requires a large surface area. Pancreatic lipase is secreted into the duodenal lumen where it acts on ingested food. Although lipase hydrolyzes luminal triglyceride, pancreatic colipase is required to permit close contact of lipase with the triglyceride molecule. Colipase is secreted as pro-colipase from the pancreas followed by trypsin activation.

Adequate concentrations of bile acid must be present within the jejunal lumen for effective micellar solubilization and lipolysis by pancreatic lipase,

a preliminary to esterification and uptake. Such adequate concentrations of bile acids are maintained by the constant reutilization of a relatively small pool of bile acid. In the liver, about 0.6 g of new bile acid is produced daily from cholesterol. This is added to the total bile acid pool of 3.0 g, which cycles 6 to 10 times daily from passive absorption in the jejunum and active absorption in the ileum. Approximately 96% of the bile acid is absorbed through these mechanisms with each cycle; the remainder is lost in the stool. The bile acid transporter has been cloned. A deficiency of this transporter may lead to bile salt malabsorption and diarrhea. Bile acids return to the liver via the portal vein and are excreted once more. This recirculation of bile acid between the intestine and the liver is called the enterohepatic circulation.

The principal role of the bile salt micelle is to facilitate lipid absorption by maintaining the lipid in a water-soluble form, overcoming the resistance of the unstirred water layer and maintaining a high concentration of a local source of fatty acid and cholesterol, which leave the micelle and enter the mucosal cell. Lipid uptake across the brush-border membrane is passive, but a number of lipid-binding proteins have been isolated; their role in lipid absorption remains to be determined.

Two important events occur within the mucosal cell: re-esterification and chylomicron formation. The fatty acids are first reattached to the monoglycerides through re-esterification, and the resultant triglyceride is then combined with small amounts of cholesterol and coated with phospholipids and apolipoproteins to form a specific class of lipoproteins known as chylomicrons. The intestine produces four apolipoproteins, apo A-I, A-IV, B and C. The chylomicrons are then released from the basal portion of the columnar epithelial cell and find their way into the central lacteal of the intestinal villus. From there, chylomicrons travel in lymph up the thoracic duct and eventually reach the general circulation. Chylomicrons are then transported in the blood to the sites of disposal and utilization in the periphery (e.g., liver, muscle and adipose tissue). A small amount of lipid may be absorbed into the portal circulation, bypassing the lacteals.

From these physiological considerations, malabsorption of fat due to impaired lipolysis or micellar solubilization would be expected to occur in the following circumstances: (1) rapid gastric emptying and improper mixing – e.g., following vagotomy or postgastrectomy; (2) altered duodenal pH – e.g., the Zollinger-Ellison syndrome, where excessive duodenal acidification inhibits the action of lipase; (3) pancreatic insufficiency; (4) cholestasis – e.g., biliary obstruction, liver disease; and (5) an interrupted enterohepatic circulation – e.g., ileal disease or loss, and bile salt deconjugation due to the bacterial overgrowth syndrome.

Fat malabsorption due to impaired mucosal uptake, assembly or delivery would be expected to occur following (1) generalized impaired enterocyte function – e.g., celiac disease, Whipple's disease; (2) failure of the packaging process

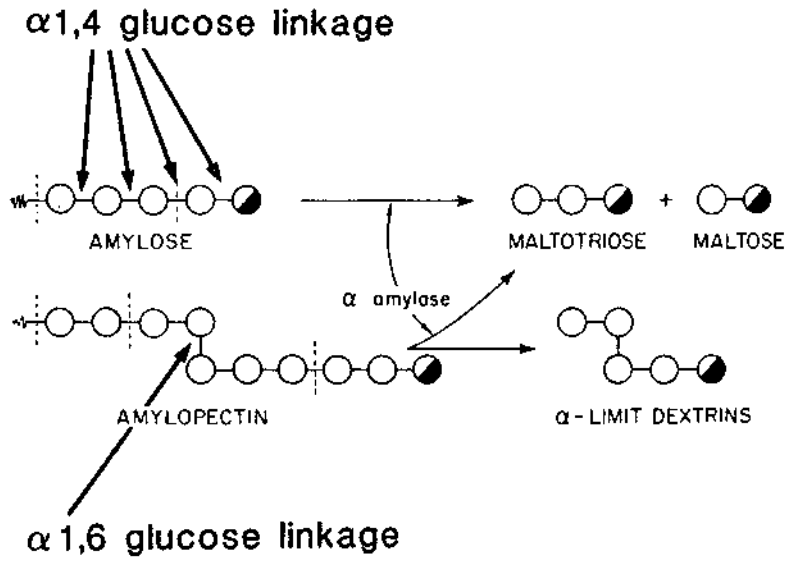

FIGURE 10. The action of pancreatic α-amylase on linear (amylose) and branched (amylopectin) starch. Circles indicate glucose residues and the reducing glucose unit.
SOURCE: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:851.

– e.g., abetalipoproteinemia, which represents a genetic defect of lipoprotein B synthesis with consequent impairment of chylomicron formation; (3) disorders of lymphatics – e.g., intestinal lymphangiectasia, retroperitoneal fibrosis or lymphoma; and (4) loss of mucosal surface area – e.g., the short bowel syndrome.

7. ABSORPTION OF CARBOHYDRATES

Starch, sucrose and lactose constitute the main carbohydrates in the human diet. All are inexpensive sources of food. Together they constitute the major source of calories when considered worldwide. People in the Western world consume about 400 g of carbohydrates daily: 60% as starch, 30% as sucrose and 10% as lactose (milk contains 48 g of lactose per liter). Glycogen is a major storage form of polysaccharide but the amount found in the diet is small.

Starch present in wheat, rice and corn is a polysaccharide whose molecular weight ranges from 100,000 to greater than 1,000,000. The straight chain of glucose molecules in starch is bridged by an oxygen molecule between

the first carbon (C_1) of one glucose unit and the fourth carbon (C_4) of its neighbor (α1,4 glucose link). This type of starch is called amylose. Similar in structure to glycogen, it makes up as much as 20% of the starch in the diet. The glucose-to-glucose bridge is of the alpha type – in contrast to the beta type, which connects glucose units in cellulose, an indigestible saccharide. These non-starch polysaccharides provide most of the "unavailable carbohydrate" in the diet, mainly as dietary fibers,(e.g., cellulose and hemicelluloses). Colonic bacteria, however, may ferment some dietary fibers to short-chain fatty acids that may be later absorbed by colonic epithelial cells. Other dietary fibers include pectins, gums and alginates that may be partially hydrolyzed in the colon, while lignins are completely indigestible. Dietary fibers are active molecules that play an important role in altering the luminal content and mass, transit time and absorption of some nutrients. The remaining 80% of the starch that humans ingest has a branch point every 25 molecules along the straight α1,4 glucose chain. This starch is called amylopectin. These branches occur via an oxygen bridge between C_6 of the glucose on the straight chain and C_1 in the branched chain (α1,6 branch points), which then continues as another α1,4 glucose-linked straight chain (Figure 10).

Salivary and pancreatic α-amylases act on interior α1,4 glucose–glucose links of starch but cannot attack α1,4 linkages close to a 1,6 branch point. Amylase proteins are encoded by a gene family on human chromosome 1 (i.e., AMY1 in the parotid gland, AMY2 in the pancreas). Salivary amylase acts in the mouth and slow chewing improves its action while gastric acid leads to rapid inactivation. Pancreatic amylase is the major enzyme of starch digestion and acts mainly within the intestinal lumen. The products of amylase digestion are therefore maltose and maltotriose. Since α- amylase cannot hydrolyze the 1,6 branching links and has relatively little specificity for 1,4 links adjacent to these branch points, large oligosaccharides containing five to nine glucose units and consisting of one or more 1,6 branching links are also produced by α-amylase action. These are called α-limit dextrins, and represent about 30% of amylopectin breakdown. The end products of amylase hydrolysis are not single glucose molecules.

The responsibility for digesting the oligosaccharides, including α-limit dextrins, and the amylose and amylopectin rests with the hydrolytic enzymes on intestinal epithelial cells (Figures 11 and 12). These hydrolytic enzymes are called disaccharidases, but most are in fact oligosaccharidases: they hydrolyze sugars containing two or more hexose units. They are present in highest concentration at the villous tips in the jejunum and persist throughout most of the ileum, but not in the colon. Lactase breaks down lactose into glucose and galactose. Glucoamylase (maltase) differs from pancreatic α-amylase since it sequentially removes a single glucose from the nonreducing

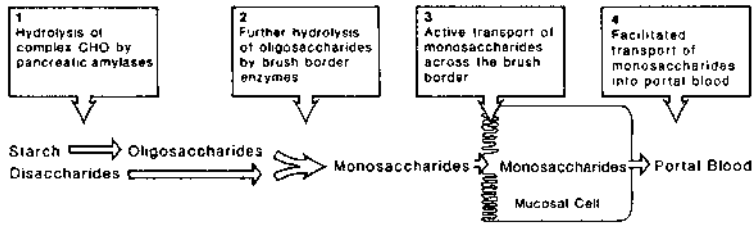

FIGURE 11. Major steps in the digestion and absorption of dietary carbohydrate.

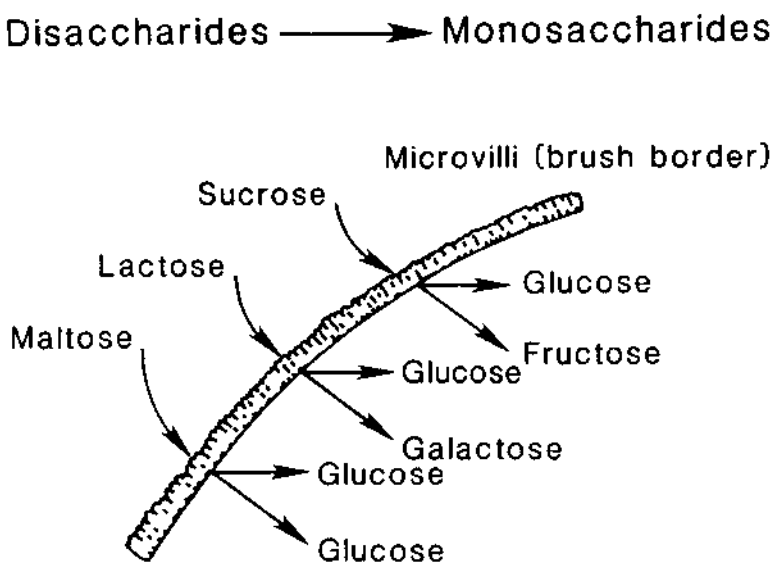

FIGURE 12. Disaccharides are split into monosaccharides at the brush border.

end of a linear α1,4 glucose chain, breaking down maltose into glucose. Sucrase is a hybrid molecule consisting of two enzymes – one hydrolyzing sucrose and the other, the α1,6 branch points of the α-limit dextrins. This enzyme is commonly called sucrase-isomaltase, because the isomaltase moiety hydro-lyzes isomaltose, the α1,6 glucosyl disaccharide. However, the only

products containing α1,6 linkages after amylase action on starch are the α-limit dextrins. Thus no free isomaltose is presented to the intestinal surface and the term "isomaltase" is a misnomer. The sucrase moiety thus breaks down sucrose into glucose and fructose.

Humans normally are born with a full complement of brush-border-membrane disaccharidases. Intake of large amounts of sucrose results in an increase in sucrase activity, probably as the substrate stabilizes the enzyme and reduces its rate of breakdown. In contrast, there is no evidence that dietary manipulation can regulate the activities of human lactase or maltase. Disaccharidase enzymes are glycoproteins that are synthesized in the endoplasmic reticulum and Golgi complex of the intestinal epithelial cell, and are eventually inserted in the brush border or microvillus membrane, projecting into the intestinal lumen as part of the glycocalyx. In normal adult small intestine, these enzymes appear to be expressed in more well-differentiated villous cells compared to crypt cells and their activities are greater in the proximal compared to distal small intestine. Sucrase-isomaltase is encoded by a single gene located on chromosome 3 at locus 3q-25-26 while the lactase gene is located on the long arm of chromosome 2.

Once the disaccharides are broken down, how are the monosaccharides absorbed? Sodium facilitates glucose uptake by binding to the brush-border membrane carrier (SGLT1) along with glucose. The gene for this carrier protein appears to be located on chromosome 22. A single missense mutation in amino acid 28 from aspartate to asparaginase is believed to be responsible for familial glucose-galactose malabsorption. Since intracellular Na^+ concentration is low, the Na^+ ion moves down its concentration gradient into the cell, to be pumped out subsequently at the basolateral membrane by Na^+/K^+-ATPase, an active process that utilizes energy derived from the hydrolysis of ATP. The electrochemical gradient thus developed by Na^+ provides the driving force for glucose entry. Glucose accompanies Na^+ on the brush-border carrier and is released inside the cell, where its concentrations may exceed those in the intestinal lumen. Small amounts of glucose (and other sugars) may be metabolized in the epithelial cell. Glucose then exits from the basolateral membrane of the cell into the portal system by a non–Na^+-dependent carrier (GLUT2).

Fructose, released from the hydrolysis of sucrose, is transported by facilitated diffusion, a carrier-mediated process in the brush-border membrane (GLUT5) that is independent both of Na^+ and of the glucose transport mechanism. The glucose and fructose are transported out of the enterocyte by GLUT2, a sodium-independent carrier in the basolateral membrane.

Some carbohydrate may escape digestion in the small intestine to be metabolized in the colon by bacteria. Short-chain fatty acids that are derived from

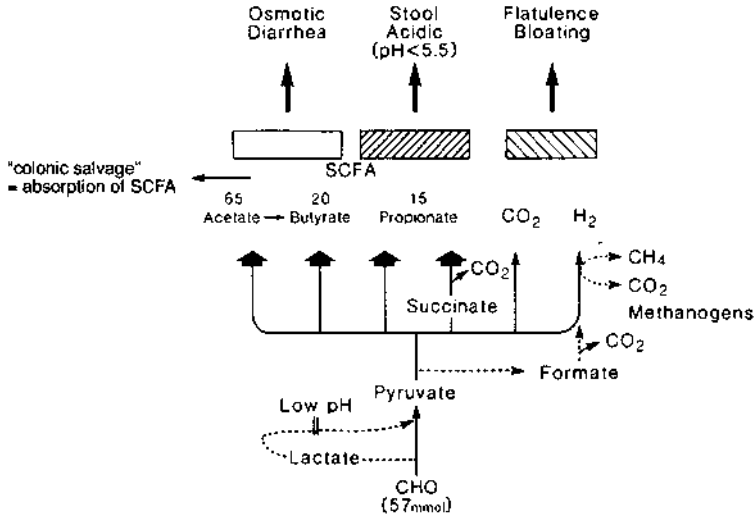

FIGURE 13. Intermediate and end products of anaerobic bacterial fermentation of carbohydrates. Minor pathways are depicted by dashed lines.
SOURCE: Soergel KH. The role of the colon in case of inhibition of carbohydrate absorption. In: Creutzfeldt W, Fölsch UR (eds.), Delaying absorption as a therapeutic principle in metabolic diseases. Stuttgart and New York: Thieme Verlag, 1983:854.

this bacterial metabolism can be absorbed while hydrogen and methane gas may be produced.

From these physiological considerations, carbohydrate malabsorption can occur in the following circumstances: (1) severe pancreatic insufficiency; (2) selective deficiencies of brush-border disaccharidases – e.g., lactase deficiency; (3) generalized impairment of brush-border and enterocyte function – e.g., celiac disease, tropical sprue, gastroenteritis; and (4) loss of mucosal surface area – e.g., the short bowel syndrome.

Although infants often have a deficiency of amylase, starch is not usually fed for the first few months of life. In the adult, there is a great excess of pancreatic amylase secreted into the intestinal lumen, so that even in patients with severe fat malabsorption due to pancreatic exocrine insufficiency, residual salivary and pancreatic amylase output appears to be sufficient to completely hydrolyze starch to the final oligosaccharides by the time a meal reaches the mid-jejunum. Hence, severe maldigestion of starch rarely occurs in humans.

Secondary deficiency of disaccharidases results from anatomic injury of the small intestine, as in celiac disease, tropical sprue and gastroenteritis. When

disaccharidase levels are sufficiently low, the particular oligosaccharide or disaccharide remains unhydrolyzed within the intestinal lumen and augments intraluminal fluid accumulation by virtue of its osmotic effect. Bacterial fermentation of disaccharides that reach the colon produces fatty acids (butyric, formic, acetic and propionic acids), alcohols and gases (H_2 and CO_2) (Figure 13). The benefits of this bacterial fermentation to the host are twofold. First, the bulk of the caloric value present in carbohydrates remains in the fermentative products. Reabsorption of fatty acids and alcohols in the colon "salvages" calories from malabsorbed carbohydrates. Second, this colonic "salvage" reduces the number of osmoles in the lumen and hence lessens the water lost in feces. During the fermentation of carbohydrates to organic acids, colonic bacteria liberate H_2 and CO_2 gas. In general, the passage of large quantities of rectal gas suggests that excessive carbohydrates are reaching the colon.

Other primary (congenital) deficiencies of disaccharidases are unusual. Such entities can be differentiated from a secondary defect, since general tests of absorption and mucosal histology are normal; however, assay of an intestinal biopsy reveals the absence of hydrolytic activity for a single disaccharide. Primary lactase deficiency is very common in certain ethnic groups, such as persons from South East Asia, and may limit the intake of milk in some adults.

8. ABSORPTION OF PROTEIN

An average adult consumes about 70 g of protein daily. However, about half of the protein in the intestine is derived from endogenous sources, including salivary, gastric and pancreatobiliary secretions, desquamated mucosal cells and plasma proteins. Protein digestion is initiated in the stomach. Pepsins are derived from precursor pepsinogens by autoactivation in an acid pH with loss of a small basic peptide. Pepsinogen release from chief cells may be stimulated by gastrin, histamine and acetylcholine. Pepsin hydrolysis results in a peptide mixture with a small amount of amino acids.

While pancreatic amylase is secreted in an active form, pancreatic proteases are secreted as proenzymes that require luminal activation. Enterokinase released from the brush border membrane converts trypsinogen to trypsin. Trypsin, in turn, activates the other proteases and autocatalyzes its own activation from trypsinogen. Proteases have been classified into endopeptidases (trypsin, chymotrypsin, elastase), to split internal peptide bonds, or exopeptidases (carboxypeptidases A and B), to remove single amino acids from the carboxyl-terminal end of peptides (Figure 14). The final products of luminal digestion consist of neutral and basic amino acids (about 30%) as well as oligopeptides of 2 to 6 amino acids (about 70%).

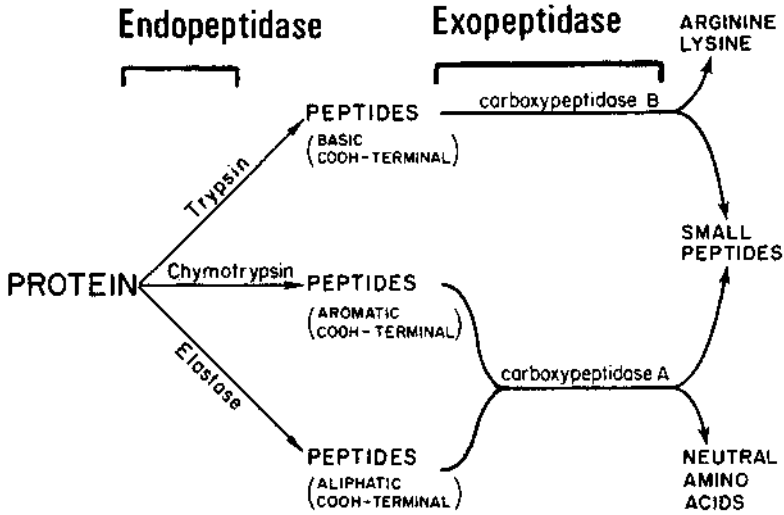

FIGURE 14. Sequence of events leading to hydrolysis of dietary protein by intraluminal proteases. SOURCE: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:854.

Both amino acids and some smaller peptides can be absorbed intact into the epithelial cell, and amino acids are more efficiently transported as peptides than single amino acids. The limiting size is probably a tripeptide although some studies suggested that tetrapeptides may also be absorbed intact. Because of this "alternate pathway," patients with inherited basic or neutral aminoacidurias (e.g., cystinuria, Hartnup's disease) are able to absorb sufficient amino acids through intact peptide transport so that protein deficiency states do not develop. Peptidase activities are present in the brush border and cytoplasm. Most oligopeptides are hydrolyzed by brush border peptidases but dipeptides and tripeptides can be either hydrolyzed on the brush border or absorbed intact and then hydrolyzed by cytoplasmic peptidases. A variety of peptidase activities are present. Most are aminopeptidases that remove an amino acid residue from the peptide amino terminus. Proline-containing oligopeptides, such as collagen, casein and gluten, are poorly hydrolyzed by most of the proteases but proline-specific carboxypeptidases have been identified in the brush border along with a cytoplasmic proline-specific enzyme. Another, dipeptidylaminopeptidase IV (DAP IV), releases dipeptides from

TABLE 3. Classification of malassimilation syndromes

Defective intraluminal digestion	*Defective intramural absorption*
Mixing disorders	Inadequate absorptive surface
Postgastrectomy	Intestinal resection or bypass
Pancreatic insufficiency	Mesenteric vascular disease with massive intestinal resection
Primary	Regional enteritis with multiple bowel resections
Cystic fibrosis	Jejunoileal bypass
Secondary	Mucosal absorptive defects
Chronic pancreatitis	Biochemical or genetic abnormalities
Pancreatic carcinoma	Celiac disease
Pancreatic resection	Disaccharidase deficiency
Reduced intestinal bile salt concentration	Hypogammaglobulinemia
Liver disease	Abetalipoproteinemia
Hepatocellular disease	Hartnup disease
Cholestasis (intrahepatic or extrahepatic)	Cystinuria
Abnormal bacterial proliferation in the small bowel	Monosaccharide malabsorption
Afferent loop stasis	Inflammatory or infiltrative disorders
Strictures	Regional enteritis
Fistulas	Amyloidosis
Blind loops	Scleroderma
Multiple diverticula of the small bowel	Lymphoma
Hypomotility states (diabetes, scleroderma, intestinal pseudo-obstruction)	Radiation enteritis
Interrupted enterohepatic circulation of bile salts	Eosinophilic enteritis
Ileal resection	Tropical sprue
Ileal inflammatory disease (regional ileitis)	Infectious enteritis (e.g., salmonellosis)
Drugs (by sequestration or precipitation of bile salts)	Collagenous sprue
Neomycin	Nonspecific ulcerative jejunitis
Calcium carbonate	Mastocytosis
Cholestyramine	Dermatologic disorders (e.g., dermatitis herpetiformis)
	Lymphatic obstruction
	Intestinal lymphangiectasia
	Whipple's disease
	Lymphoma

oligopeptides. Like brush border disaccharidases, most of the brush border peptidases are synthesized in endoplasmic reticulum and Golgi complex and inserted in the microvillus membrane as completed glycoproteins. Single amino acids and short peptides (dipeptides and tripeptides) are absorbed intact from the lumen by separate transporters. A gene for a peptide transport protein has been located on chromosome 13. Although sodium is involved, this peptide transport process may use an electrochemical hydrogen ion gradient

rather than a sodium gradient as the driving force. An acid pH in the lumen creates a brush border membrane hydrogen gradient. A single hydrogen ion is transported with peptide by a hydrogen-peptide cotransporter (hPepT 1). This is maintained by a brush border sodium-hydrogen exchanger and the Na^+/K^+ ATPase in the basolateral membrane. Amino acids appear to be absorbed by a variety of mechanisms — primarily, but not exclusively, by active carrier-mediated processes in the microvillus membrane. Transport of both amino acids and, rarely, some peptides, then occurs across the basolateral membrane into the portal circulation.

9. MALDIGESTION OR MALABSORPTION

Normal digestion and absorption of foods is essential for life and well-being. Given the length of the gastrointestinal tract, the number of organs involved in digestion, and the large number of nutrients that must be taken into our bodies, it is not surprising to find a large number of disease states that impair the processes of food digestion and absorption. Clinical malassimilation occurs in only one of two ways: (1) through intraluminal disorders (maldigestion of food) and (2) through intramural disorders (malabsorption of food).

9.1 Clinical Signs and Symptoms

Malassimilation may occur in two ways: first, through intraluminal disorders causing maldigestion, and second, through intramural, particularly, intestinal mucosal disorders causing malabsorption. Although several disorders may be appreciated that can cause malassimilation (Table 3), most often, impaired pancreatic function or a small intestinal cause are responsible (especially if significant liver disease or history of abdominal surgery can be historically excluded). A myriad of "classical" clinical signs and symptoms may be detected (Tables 4 and 5) that reflect the underlying disorder as well as the resultant nutrient deficiencies.

9.2 Manifestations of Carbohydrate Malassimilation

Carbohydrate malassimilation will result in both specific and generalized symptoms. Specific to the maldigestion and malabsorption of carbohydrates are diarrhea and excess flatus. Unfortunately, everyone has flatus, and a definition or measure of excessive "wind" is lacking. Malabsorbed carbohydrates that enter the colon are fermented by colonic bacteria to gases (CO_2, H_2 and CH_4) and organic acids (Figure 13). These organic acids produce diarrhea by acting directly on colonic epithelium to stimulate fluid secretion and by their osmotic effect, which further draws water into the lumen. The presence of organic acids in the stool reduces the pH below 6 and suggests carbohydrate

TABLE 4. Clinical signs and symptoms of malassimilation

	Clinical sign or symptom	*Deficient nutrient*
General	Weight loss	Calorie
	Loss of appetite, amenorrhea, decreased libido	Protein energy
Skin	Psoriasiform rash, eczematous scaling	Zinc
	Pallor	Folate, iron, vitamin B_{12}
	Follicular hyperkeratosis	Vitamin A
	Perifollicular petechiae	Vitamin C
	Flaking dermatitis	Protein energy, niacin, riboflavin, zinc
	Bruising	Vitamin K
	Pigmentation changes	Niacin, protein energy
	Scrotal dermatosis	Riboflavin
	Thickening and dryness of skin	Linoleic acid
Head	Temporal muscle wasting	Protein energy
Hair	Sparse and thin, dyspigmentation	Protein
	Easy to pull out	
Eyes	History of night blindness	Vitamin A
	Photophobia, blurring, conjunctival inflammation	Riboflavin, vitamin A
	Corneal vascularization	Riboflavin
	Xerosis, Bitot's spots, keratomalacia	Vitamin A
Mouth	Glossitis	Riboflavin, niacin, folic acid
	Bleeding gums	Vitamin C, riboflavin
	Cheilosis	Riboflavin
	Angular stomatitis	Riboflavin, iron
	Hypogeusia	Zinc
	Tongue fissuring	Niacin
	Tongue atrophy	Riboflavin, niacin, iron
	Scarlet and raw tongue	Niacin
	Nasolabial seborrhea	Pyridoxine
Neck	Goiter	Iodine
	Parotid enlargement	Protein
Thorax	Thoracic "rosary"	Vitamin D

(cont'd)

TABLE 4. Clinical signs and symptoms of malassimilation (cont'd)

	Clinical sign or symptom	*Deficient nutrient*
Abdomen	Diarrhea	Niacin, folate, vitamin B_{12}
	Distention	Protein energy
	Hepatomegaly	Protein energy
Extremities	Edema	Protein, thiamine
	Softening of bone	Vitamin D, calcium, phosphorus
	Bone tenderness	Vitamin D
	Bone ache, joint pain	Vitamin C
	Muscle wasting and weakness	Protein, calories
	Muscle tenderness, muscle pain	Thiamine
	Hyporeflexia	Thiamine
Nails	Flattening, brittleness, luster loss, spooning	Iron
	Transverse lines	Protein
Neurologic	Tetany	Calcium, magnesium
	Paresthesias	Thiamine, vitamin B_{12}
	Loss of reflexes, wrist drop, foot drop	Thiamine
	Loss of vibratory and position sense, ataxia	Vitamin B_{12}
	Dementia, disorientation	Niacin
Blood	Anemia	Iron, vitamin B_{12}, folate
	Hemolysis	Phosphorus

malassimilation. The gas produces flatulence, with associated borborygmi and abdominal distention. The presence of intraluminal H_2 gas, eventually absorbed into the circulation and exhaled, forms the basis of the hydrogen breath test to detect carbohydrate malabsorption. Physical examination often reveals a distended tympanitic abdomen with hyperactive bowel sounds. Stools float on the water because of their increased gas content (not because of their fat content).

Generally, lack of carbohydrate as an energy source will result in decreased plasma insulin levels, increased plasma glucagon and cortisol levels and decreased peripheral T_4-to-T_3 conversion. Given sufficient time, the body will enter a state of oxidative metabolism: fat and muscle will be catabolized. Physical examination may reveal signs of weight loss from both fat stores and lean body mass. The patient will be weak and will easily develop fatigue. Fat loss will generally be noted as sunken cheeks and flat buttocks, with wrinkled

TABLE 5. Specific vitamin and mineral deficiencies

Vitamin/mineral		*Clinical manifestation*
Vitamin A	Eyes	Night blindness Xerosis (dry bulbar conjunctiva) Bitot's spots (conjunctiva plaques) Keratomalacia (corneal ulceration)
	Skin	Hyperkeratosis
Vitamin B_{12}	Hematologic, neurologic systems	Anemia Nonreversible loss of vibratory and position sense Paresthesia
	Gastrointestinal	Diarrhea
Vitamin C	Skin	Perifollicular papules (brittle hair) Perifollicular hemorrhages Gum bleeding Skin purpura, ecchymosis
Vitamin D	Bone	Bone pain and softening Joint pain Rickets Proximal myopathy
Vitamin K		Bruising Bleeding
Vitamin B_6 (Pyridoxine)	Skin	Seborrheic dermatitis Cheilosis Glossitis
Niacin		Dermatitis Diarrhea Dementia
Thiamine	CVS CNS	Congestive heart failure Wernicke's encephalopathy Wernicke-Korsakoff syndrome
Zinc	Skin	Acrodermatitis enteropathica Alopecia
	Taste	Hypogeusia
Folate	Hematologic, neurologic systems	Anemia Reversible loss of position and vibratory sense

CVS = cardiovascular system; CNS = central nervous system

or loose skin indicative of loss of subcutaneous fat stores. The loss of muscle mass is easily noted as thenar mass reduction and sunken soft tissues between the extensor tendons on the dorsum of the hands. There may be direct evidence of a reduced metabolic rate secondary to decreased T_3 conversion. The patient will often be mentally slowed.

9.3 Manifestations of Fat Malassimilation

Failure to digest or absorb fats results in a variety of clinical symptoms and laboratory abnormalities. These manifestations are the result of both fat malassimilation per se and a deficiency of the fat-soluble vitamins. In general, loss of fat in the stool deprives the body of calories and contributes to weight loss and malnutrition. More specific is the action of unabsorbed long-chain fatty acids, which act on the colonic mucosa to cause diarrhea by an irritant effect on the colon. In addition, fatty acids bind calcium, which would normally be available to bind oxalate. In fat malabsorption, oxalate is not bound to calcium and remains free (undissociated) within the colonic lumen, where it is readily absorbed. This results in oxaluria and calcium oxalate kidney stones. This occurs in Crohn's disease more readily than in other cases of fat malabsorption (steatorrhea).

Failure to absorb the fat-soluble vitamins A, D, E and K also results in a variety of symptoms. Vitamin K deficiency presents as subcutaneous, urinary, nasal, vaginal and gastrointestinal bleeding. Deficiencies in factors II, VII, IX and X produce defective coagulation. Vitamin A deficiency results in follicular hyperkeratosis. Vitamin E deficiency leads to a progressive demyelination of the central nervous system. Malabsorption of vitamin D causes rickets and osteopenia, as discussed later.

9.4 Manifestations of Protein Malassimilation

Severe loss of body protein may occur before the development of laboratory abnormalities. Impaired protein synthesis from liver diseases and excessive protein loss in renal diseases can further aggravate protein deficiencies. Clinically, protein deficiency results in edema and diminished muscle mass. Since the immune system is dependent upon adequate proteins, protein deficiency can manifest as recurrent infections. Protein deficiency in children results in growth retardation, mental apathy and irritability, weakness and muscle atrophy, edema, hair loss, deformity of skeletal bone, anorexia, vomiting and diarrhea. Protein-calorie malnutrition is known as marasmus, whereas protein malnutrition by itself is known as kwashiorkor.

9.5 Manifestations of Iron Deficiency

Hypochromic microcytic anemia characterizes iron deficiency. Since malassimilation may result in folate or B_{12} deficiency (producing megaloblastic red

cells), the microcytosis of iron deficiency may be obscured with automated cell counters; a dimorphic picture is present. Rarely accompanying the development of anemia may be symptoms of pica and dysphagia. Pica originally referred to the eating of clay or soil; however, the commonest "pica" in North America is the eating of ice. Dysphagia may be due to the Plummer-Vinson (Paterson-Kelly) syndrome (with atrophic papillae of the tongue and post-cricoid esophageal webs), and/or cheilosis (reddened lips with angular fissures, also known as cheilitis or angular stomatitis). Weakness, fatigue, dyspnea and edema also can occur. Physical examination often reveals pallor, an atrophic tongue and koilonychia (brittle, flat or spoon-shaped fingernails).

The clinical picture of vitamin B_{12} and folic acid deficiency includes the nonspecific manifestations of megaloblastic anemia and its sequelae – i.e., anemia, glossitis, megaloblastosis, and elevated serum lactate dehydrogenase (LDH). In addition, deficiency of B_{12} may induce neurologic abnormalities consisting of symmetrical paresthesias in the feet and fingers, with associated disturbances of vibration sense and proprioception, progressing to ataxia with subacute combined degeneration of the spinal cord. This subacute combined spinal cord degeneration includes cortisospinal as well as dorsal column damage. Neurologic manifestations are not part of folic acid deficiency alone.

9.6 Manifestations of Calcium, Vitamin D and Magnesium Malabsorption

Impaired absorption of calcium, magnesium and vitamin D may lead to bone pain, fractures, paresthesias and tetany. In latent tetany, the neuromuscular instability can be brought out by provocative tests. Chvostek's sign and Trousseau's sign are provocative tests of clinical manifestations of hypocalcemia that are caused by neuromuscular instability. Osteomalacia resulting from vitamin D deficiency principally affects the spine, rib cage and long bones with or without fractures (Milkman's fractures), and may cause extreme pain, particularly in the spine, pelvis and leg bones. A child with calcium or vitamin D malabsorption will present with classical rickets. Hypomagnesemia may cause seizures and symptoms identical to those of hypocalcemia. In addition, hypomagnesemia may reduce the responsiveness of the parathyroids to calcium and impair parathyroid regulation of calcium homeostasis.

9.7 Diagnostic Approach to Malassimilation

A detailed history and physical examination may, in some instances, provide an immediate clue to the cause and further focus the clinical evaluation, for example the detection of dermatitis herpetiformis might suggest the closely linked disorder, celiac disease. Or, a history of repeated bouts of severe abdominal pain and weight loss in a chronic alcohol abuser might suggest chronic pancreatic insufficiency after repeated bouts of alcohol-induced pancreatitis.

TABLE 6. Therapy for malassimilation syndromes

Site of defect	*Therapy*
Pancreas	Enzyme supplements; insulin; dietary counseling; surgery for pancreatic duct obstruction or cancer
Hepatobiliary	Endoscopic therapy or surgery for obstruction of biliary tree
Mucosa	Diet, such as gluten withdrawal or milk-free diet; nutrient supplements; 5-ASA compounds or steroids for Crohn's disease; antibiotics for bacterial overgrowth or Whipple's disease
Lymphatics	Low-fat diet; medium-chain triglycerides (MCTs)

A complete blood count may show a macrocytic or microcytic anemia. A peripheral blood smear may demonstrate microcytic cells (i.e., iron deficiency), changes suggestive of megaloblastosis with hypersegmented polymorphs (i.e., folate or vitamin B_{12} deficiency) or splenic hypofunction (i.e., Howell-Joly bodies in celiac disease). Serum calcium, phosphorus and alkaline phosphatase (from bone origin) may suggest osteomalacia. Serum albumin may provide an index of the nutritional state and protein stores. Serum carotene, prothrombin time (vitamin K) or International Normalized Ratio (INR) may indirectly assess fat assimilation and clotting status (before a small intestinal biopsy). Body iron stores may be assessed from the measurement of serum iron, total iron binding capacity (TIBC) and ferritin. If depleted, iron malabsorption or loss, possibly from blood loss may be present. Dual Energy X-ray Absorptiometry (DEXA) bone scanning may be useful to detect osteopenic bone disease. Serum vitamin B_{12}, an index of body stores of vitamin B_{12}, may be depleted owing to reduced intake, deficient production of intrinsic factor, abnormal luminal pH, pancreatic insufficiency, bacterial overgrowth or impaired ileal absorption. Fecal studies to exclude an infectious or parasitic cause should be done. In the past, extensive algorithms listing numerous tests for investigation of suspected maldigestion or malabsorption appeared in many texts of medicine. These were usually logical and function-oriented, but costly, time-consuming and difficult to perform. Moreover, their development often preceded an evolving appreciation for the value of modern imaging methods (e.g., CT scanning of pancreas). Often many of these tests are now circumvented by proceeding directly to small intestinal mucosal biopsy although some may become necessary for complete evaluation including barium radiographs of the small intestine. Other imaging modalities, including colonoscopy to view the distal ileum and, possibly, videocapsule imaging devices (e.g, the "camera pill" or the mouth-to-anus (M2A) capsule) may be increasingly used and supplant barium imaging. Traditionally, definition of

steatorrhea was considered very useful to confirm the presence of generalized malassimilation. Quantitative fecal fat determinations were often done, but these have become largely historical and most laboratories, even in sophisticated teaching hospitals, no longer perform the test. In the normal individual, the amount of fat appearing in the stool appeared relatively constant despite small changes in the quantity of dietary fat. Even with a daily fat intake of zero, the fecal fat output has been estimated to be about 2.9 g/day, possibly derived from endogenous sources, including sloughed mucosal cells, excreted bile lipids (cholesterol, bile acids) and bacterial lipids. With increasing amounts of dietary fat intake, the fecal fat increases to about 5 to 6 g/day. Unfortunately, accurate fecal collections are difficult, even with well-controlled conditions. Limited food intake, interruptions in intake associated with the need for fasting for many hospital tests, constipation and incomplete fecal collections are notorious causes of spuriously low values. Finally, definition of steatorrhea does not define the cause of impaired fat assimilation and an elevated fecal fat level, if accurate, may be due to intraluminal maldigestion or mucosal malabsorption.

Although "classical" features of impaired assimilation may focus investigations, the modern clinical presentation of some disorders, such as celiac disease may be very subtle, often without diarrhea or other intestinal symptoms. Instead, weight loss or anemia due to impaired absorption of iron might be the presenting features that should lead to consideration of a small intestinal cause, such as celiac disease. "Celiac blood tests" have also been developed for population screening and case finding (e.g., endomysial antibodies or tissue transglutaminase). If positive, a small intestinal biopsy should be done to confirm the serological suspicion of celiac disease before treatment.

The therapy for some specific maldigestion or malabsorption syndromes are detailed in Table 6 and representative doses of some nutritional therapies are noted in Table 7.

10. ACUTE DIARRHEA

With a complaint of "diarrhea," the physician must establish if this represents a change in the patient's bowel habit and if the complaint arises from a perception of increased frequency of stool, increased volume or both. To the patient, the term *diarrhea* usually means a change in the frequency or fluid-nature of the stools.

If the diarrhea is acute (i.e., lasting less than two weeks), the malabsorption of fluid and electrolytes probably has an infectious or toxic cause (Table 8). When diarrhea lasts for a longer period of time, other explanations need to be considered. In the absence of prior gastric surgery, the four most common causes of chronic diarrhea are (1) the irritable bowel syndrome;

TABLE 7. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes

Minerals		
Calcium	PO:	requires at least 1,000 mg elemental calcium daily as: (a) Calcium gluconate (93 mg Ca^{2+}/500 mg tablet) (b) Calcium carbonate (200 mg Ca^{2+}/500 mg tablet)
	IV:	Calcium gluconate, 10 mL (9.3 mg Ca^{2+}/mL) of 10% soln over 5 min
Magnesium	PO:	Magnesium gluconate (29 mg Mg^{2+}/500 mg tablet), 2–6 g/day
	IV:	Magnesium sulfate (50% soln, 1 mL contains 2.03 mmol Mg^{2+})
Iron	PO:	Ferrous fumarate (65 mg elemental Fe/200 mg tablet), 200 mg tid Ferrous gluconate (35 mg elemental Fe/300 mg tablet), 600 mg tid Ferrous sulfate (60 mg elemental Fe/300 mg tablet), 300 mg tid
	IM:	Iron dextran 1 mL once daily (calculated from existing Hb)*
	IV:	Iron dextran approx. 30 mL (calculated from existing Hb)* in 500 cc 5% D/W over 4 hrs, beginning with slow observed infusion
	*NOTE: IM/IV Fe for deficit replacement only	
Zinc	PO:	Zinc sulfate (89 mg elemental zinc/220 mg capsule), 220 mg tid
Vitamins		
Vitamin A	Water-miscible vitamin A (25,000 IU/capsule), 25,000 IU daily	
Vitamin B_{12}	100 µg/IM monthly	
Vitamin D_2	(Ergocalciferol) (50,000 IU/capsule), 50,000 IU 3 times per week	
Vitamin E	Water-miscible vitamin E (100 IU/capsule), 400 IU daily	
Vitamin K_1	(Phytonadione) has caused fatal reactions, thus should be avoided	
Vitamin K_3	(Menadione) water-soluble PO: 5–10 mg/day IV: 5–10 mg/day	
Folic acid	PO:	1 mg/day
Other water-soluble	Multiple vitamin 1/day	

(cont'd)

TABLE 7. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes (cont'd)

Pancreatic supplements

		Enzyme activity (IU/unit)			
Preparation	*Type*	*Lipase*	*Trypsin*	*Proteolytic*	*Amylase*
Ku-Zyme HP®	Capsule	2,330	3,082	6,090	594,048
Festal®	Enteric-coated	2,073	488	1,800	219,200
Cotazym®	Capsule	2,014	2,797	5,840	499,200
Viokase®	Tablet	1,636	1,828	440	277,333
Pancrease®	Micro-encapsulated	> 4,000	> 25,000		

Usually taken as 4–8 capsules with each meal and half that number with snacks. Some patients will need higher doses or will need acid-lowering therapy with an H_2-receptor antagonist or a proton pump inhibitor to alkalize the fluid in the duodenum and achieve greater activity of the pancreatic enzymes

Bile salt binding agents

Cholestyramine 4 g (1 scoop), 3–6 times daily, according to response
Psyllium and aluminum hydroxide gel may also be effective
Colestipol 1 g 3–6 times daily, according to response

(cont'd)

(2) inflammatory bowel disease; (3) malabsorption; and (4) carcinoma of the colon. The physician also must consider altered bowel function due to drug or alcohol abuse (see Section 11). Associated tenesmus, urgency or a sense of incomplete evacuation suggests involvement of the rectum or sigmoid colon. The passage of blood, pus and mucus suggests bowel inflammation, ischemic bowel disease or cancer. Malassimilation syndromes (discussed in the previous section) are suspect if there is passage of food and oil droplets, or if the patient develops symptoms suggestive of nutrient deficiency, particularly weight loss.

In Western societies, stool weight is approximately 200 g/day. Since stools are 70–90% water, regardless of their consistency, excess fecal water must accompany diarrheal diseases with elevated stool weight. This concept leads directly to consideration of the mechanisms responsible for the malabsorption or stimulated secretion of water.

Two caveats need to be remembered. First, fecal bulk varies with the diet, being influenced most notably by the content of indigestible carbohydrates (dietary fiber). Stools are smaller in developed countries than they are among societies whose members regularly ingest large amounts of dietary fiber. Second,

TABLE 7. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes (cont'd)

Caloric supplements

Medium-chain triglyceride oil: (8 cal/mL), 60 mL/day po, 480 cal/day

Portagen®: medium-chain triglyceride + other oils: (1 cal/mL), 1 L/day

Enteral supplements:

Product	*Kcal*/ 1,000 mL*	*Grams of protein/ 1,000 mL*	*Na mg/L*	*K mg/L*	*Osmolality mOsm/kg Water*
Ensure®	1,060	37	740	1,270	450
Isocal®	1,040	34	530	1,320	300
Osmolite®	1,060	37	540	1,060	300
Precision Isotonic Diet®	960	29	800	960	300
Precision LR Diet®	1,110	26	700	810	525
Travasorb STD® (unflavored)	1,000	45	920	1,170	450
Standard Vivonex® (unflavored)	1,000	21	470	1,170	550
High-Nitrogen Vivonex® (unflavored)	1,000	44	530	1,170	810
Meritene Powder® in milk	1,065	69	1,000	3,000	690
Compleat B®	1,000	40	1,200	1,300	390
Formula 2®	1,000	38	600	1,760	435–510

*When prepared in standard dilution

Parenteral supplements: Intralipid® 1 L/day IV (10 mL/kg/day)
Travasol® 2 L/day IV (mix as per patient's protein requirements)

disease of the distal colon or rectum can lead to the frequent, often painful passage of small stools (due to limited capacity as a reservoir), yet there may be little fecal water and no increase in stool weight. In fact, "constipation" may be common in patients with proctitis.

Acute diarrhea is thus defined as stool weight > 200 g/day for less than 14 days' duration. It always will represent a change in bowel habit for the individual and will often be associated with an increased frequency of bowel movements.

10.1 Bacterial Diarrhea

In immunocompetent individuals, enteric infections are usually self-limiting and resolve in less than two weeks. Acute bacterial diarrheas can be classified

TABLE 8. Common causes of acute diarrhea

Drugs	*Bacteria (toxin-mediated, cytotoxic)*
Laxatives	Clostridium difficile
Antacids	Staphylococcus aureus
Antibiotics	Shigella dysenteriae
Cholinergic drugs	Campylobacter jejuni
Lactose	Yersinia enterocolitica
Guanethidine	
Quinidine	*Bacteria (invasive)*
Digitalis	Salmonella
Colchicine	Enteroinvasive Escherichia coli
Potassium supplements	
Lactulose	*Bacteria (unknown mechanism)*
	Enteropathogenic Escherichia coli
	Enteroadherent Escherichia coli
	Viruses
Bacteria (toxin-mediated, cytotonic)	Parvovirus (Norwalk agent)
Enterotoxigenic Escherichia coli (both heat-labile and heat-stable toxins)	Reovirus (rotavirus)
	Protozoa
Vibrio cholerae	Cryptosporidia
Vibrio parahaemolyticus	Giardia lamblia
Clostridium perfringens	Entamoeba histolytica
Bacillus cereus	
	Parasites
	Strongyloides
	Trichuris

into *toxigenic types*, in which an enterotoxin is the major pathogenic mechanism, and *invasive types*, in which the organism penetrates the enterocyte as a primary event, although an enterotoxin may be produced as well. Enterotoxins are either *cytotonic* (producing intestinal fluid secretion by activation of intracellular enzymes, without damage to the epithelial surface) or *cytotoxic* (causing injury to the enterocyte as well as inducing fluid secretion). Three major clinical syndromes caused by bacterial infections are (1) food poisoning, (2) infectious gastroenteritis and (3) traveler's diarrhea.

10.1.1 FOOD POISONING

The food poisoning syndrome characteristically features the development of a brief but explosive diarrheal illness in subjects following exposure to a common food source contaminated with bacteria or bacterial toxins. Staphylococcus aureus, Salmonella, Clostridium perfringens and Bacillus cereus are responsible for 90% of these outbreaks.

Staphylococcus aureus produces a heat-stable, odorless and tasteless enterotoxin that is generated in poorly refrigerated desserts and seafoods. Ingestion of the preformed enterotoxin causes nausea, vomiting and profuse diarrhea within 4 to 8 hours. Spontaneous resolution occurs within 24 hours. No specific therapy is available or necessary.

Clostridium perfringens produces a preformed toxin from spores that germinate in contaminated meats cooked to less than 50°C. Symptoms are diarrhea and crampy abdominal pain without vomiting, beginning 8 to 24 hours after the meal. The illness lasts less than 24 hours. No specific therapy is indicated.

Bacillus cereus produces either a diarrheal syndrome or a vomiting syndrome, depending upon the enterotoxin. The vomiting syndrome is always associated with ingestion of rice and is caused by a preformed toxin that is elaborated when rice is left to cool unrefrigerated. Flash-frying later does not generate enough heat to destroy the toxin. The diarrheal syndrome occurs after ingestion of the organism itself. Both illnesses are short-lived and require no specific therapy.

The diagnosis of food poisoning is usually made by history. Except in special circumstances (e.g., botulism), isolation of the toxin is not cost-effective.

10.1.2 GASTROENTERITIS

The organisms responsible for bacterial gastroenteritis exert their predominant effects by invading and destroying the intestinal epithelium or by producing various enterotoxins.

10.1.2.1 Toxin-mediated, cytotoxic bacterial gastroenteritis

Vibrio cholerae is the prototypic cause of toxigenic diarrhea. The Vibrio cholerae organisms elaborate a toxin that attaches to the inner cell membrane and activates adenylate cyclase (formerly “adenyl cyclase”). The presence of adenylate cyclase then elevates cyclic AMP (cAMP) levels. Cyclic AMP then stimulates the enterocyte to secrete fluid and electrolytes while at the same time impairing their absorption. Stool output can exceed 1 L/hour. Treatment is based on restoring fluid and electrolyte balance and maintaining intravascular volume. Even though fluid and electrolyte transport is impaired, glucose transport is intact. Since glucose absorption carries Na^+ (and thus water with it), an oral rehydration solution containing glucose, sodium and water will enhance water absorption during the profound dehydration stage of cholera.

Several types of Escherichia coli (E. coli) are intestinal pathogens. Each exerts its effects through different mechanisms (Table 9). Invasive forms of E. coli may cause colitis that resembles colitis from other bacterial infections and also may resemble ischemia clinically, endoscopically and histologically.

TABLE 9. Types of Escherichia coli intestinal pathogens

Name	*Toxin*	*Mechanism*
Enteropathogenic (EPEC)	Shiga-like toxin	Adherence
Enterotoxigenic (ETEC)	Labile toxin (LT) Stable toxin (ST)	Activates adenylate cyclase Activates guanylate cyclase
Enteroinvasive (EIEC)	Shiga-like toxin	Penetrates epithelium
Enteroadherent (EAEC)	—	Adherence
Enterohemorrhagic (EHEC)	Shiga-like toxin (verotoxin)	Unknown

Enterotoxigenic E. coli (ETEC) colonizes the upper small intestine after passing through the acid barrier of the stomach. The organisms colonize the surface without penetrating the mucus layer. Like cholera, ETEC causes no mucosal damage and no bacteremia. Two types of enterotoxins are produced by ETEC: the heat-labile toxin (also called "labile toxin" or LT) and the heat-stable toxin (also called "stable toxin" or ST). ETEC can elaborate LT only, ST only, or both toxins. ST produces diarrhea by stimulating intestinal secretion through guanylate cyclase and subsequently cyclic GMP. LT produces diarrhea by a similar mechanism, except that it acts through adenylate cyclase and cyclic AMP. After a 24- to 48-hour incubation period, the disease begins with upper abdominal distress followed by watery diarrhea. The infection can be mild (with only a few loose movements) or severe (mimicking cholera). Treatment is symptomatic. Antibiotic therapy is ineffective and favors the emergence of resistant ETEC strains.

Vibrio parahaemolyticus causes acute diarrheal disease after consumption of seafood: raw fish or shellfish. The common factor in most outbreaks appears to be storage of the food for several hours without proper refrigeration. Explosive, watery diarrhea is the cardinal manifestation, along with abdominal cramps, nausea and vomiting. Fever and chills occur in 25% of cases. The duration of illness is short, with a median of three days. Treatment is symptomatic; there is no role for antimicrobial therapy.

After ingestion, Shigella dysenteriae organisms attack the colon, sparing the stomach and small bowel. Shigella organisms adhere to the mucosal surface, penetrate the mucosal surface, and then multiply within epithelial cells, moving laterally through the cytoplasm to adjacent cells by filopodium-like

protrusions. Shigella organisms rarely penetrate below the intestinal mucosa and almost never invade the bloodstream. Both attached and intracellular organisms elaborate toxic products.

Even a small inoculum of 200 organisms (as contrasted with Salmonella, which requires greater than 10^7 organisms) will lead to crampy abdominal pain, rectal burning and fever associated with multiple small-volume bloody mucoid bowel movements. Intestinal complications include perforation and severe protein loss. Extraintestinal complications include respiratory symptoms, meningismus, seizures, the hemolytic uremic syndrome, arthritis and rashes. Ampicillin 500 mg q.i.d. or co-trimoxazole 2 tablets b.i.d. for 5 days is the treatment of choice. Amoxicillin, interestingly, is not effective therapy for shigellosis.

Salmonella food poisoning has been attributed to an enterotoxin similar to that of Staphylococcus aureus, but none has been clearly identified. Within 12 to 36 hours after ingestion of contaminated foods (usually poultry products), there is a sudden onset of headaches, chills and abdominal pain, with nausea, vomiting and diarrhea. These symptoms may persist for one to four days before subsiding. Antibiotic therapy of nontyphoidal Salmonella gastroenteritis fails to alter the rate of clinical recovery. In fact, antibiotic therapy will increase the duration of intestinal carriage of the Salmonella and is thus contraindicated.

Campylobacter jejuni–induced diarrhea is more common than diarrhea from either Salmonella or Shigella. Infection is from consumption of improperly cooked or contaminated foodstuffs. Campylobacter attaches to the mucosa and releases an enterotoxin that destroys the surrounding epithelia. Clinically, there is often a prodrome of constitutional symptoms along with headache and generalized malaise. A prolonged diarrheal illness follows – often with a biphasic character, with initial bloody diarrhea, slight improvement, then increasing severity. The illness usually lasts less than one week, although symptoms can persist for a longer period, and relapses occur in as many as 25% of patients. Erythromycin 500 mg q.i.d. for 7 days is optimal therapy.

Yersinia enterocolitica is often transmitted to humans from pets or food sources. The organism invades epithelial cells and produces an enterotoxin. Clinically, the spectrum of illness ranges from simple gastroenteritis to invasive ileitis and colitis that needs to be distinguished from Crohn's disease or ulcerative colitis (Chapter 9). This organism causes diarrheal illness most frequently in children less than 5 years of age. Children over 5 years of age develop mesenteric adenitis and associated ileitis, which mimic acute appendicitis. Yersinia is less likely to cause disease in adults; if it does, the illness is an acute diarrheal episode that may be followed two to three weeks later by joint symptoms and a rash (erythema nodosum). Treatment is symptomatic. There is no evidence that antibiotics alter the course of the gastrointestinal infection. Clostridium difficile causes antibiotic-associated colitis (Section 10.4).

10.1.2.2 Invasive bacterial gastroenteritis

Certain strains of E. coli are invasive, producing an illness indistinguishable from shigellosis. Isolates of E. coli 0157:H7 have been identified in the stools of patients with a diarrheal illness clinically designated as "hemorrhagic colitis." Infection has been traced to contaminated hamburger meat obtained from a variety of sources, including large national restaurant chains. E. coli 0157:H7 infection may be complicated by thrombotic thrombocytopenic purpura, or by the hemolytic uremic syndrome, which sometimes leads to death.

Ingestion of this organism results in severe crampy abdominal pain and fever, followed within 24 hours by bloody diarrhea that lasts five to seven days. Since the organism is shed in the stool for only a short period of time, early stool collections are critical for the diagnosis. Treatment is symptomatic, as antibiotics do not appear to alter the disease course. In severe cases with possible toxic megacolon, systemic antibiotics may be in order.

Approximately 1,700 serotypes and variants of Salmonella are potential pathogens for humans. A dose of approximately 10^7–10^9 organisms is required to produce a clinical illness. Salmonella organisms invade the mucosa of the small intestine and (particularly) the colon. This form of gastroenteritis produces nausea and vomiting followed by abdominal cramps and diarrhea that lasts three to four days and then gradually subsides. In 10% of the cases bacteremia of the Salmonella organism occurs, and in approximately 5% there are disseminated infections to bones, joints and meninges. Certain conditions increase the risk of salmonellosis: hemolytic anemia, malignancy, immunosuppression, achlorhydria and ulcerative colitis. With uncomplicated Salmonella gastroenteritis, treatment is symptomatic. In fact, antibiotic therapy increases the duration of intestinal carriage of these organisms. Patients with complicated Salmonella gastroenteritis (e.g., those with predisposing conditions or sepsis, or who are very young or very old) should be treated with ampicillin or co-trimoxazole.

10.1.2.3 Bacterial gastroenteritis of unknown mechanism

Enterohemorrhagic E. coli–induced diarrhea tends to occur in neonates and young children. Only occasionally does it affect older children and adults. The pathogenic mechanism of this diarrhea is unclear; adherence of the organism to the intestinal epithelial cell seems to cause intestinal damage. There is no indication for specific treatment except for neonates in a nursery epidemic. In this case, oral nonabsorbable aminoglycosides should be used.

TABLE 10. Traveler's diarrhea: recommendations for treatment

General

Avoid ice cubes, raw vegetables and fruits, raw fish and shellfish, unrefrigerated food.
Drink canned pop and beer, boiled water.
Drink oral replacement solutions for acute attacks.
Avoid over-the-counter preparations sold locally for acute attacks.

Specific

To provide symptomatic relief of acute attack:
- Diphenoxylate 1 tab, 2.5 mg, after each bowel movement to max 8 tab/day
- Loperamide 1 cap, 2.0 mg, after each bowel movement to max 8 cap/day
- Pepto-Bismol® 30 mL q 30 min ˇ 8 doses

To decrease severity of acute attack:
- Co-trimoxazole 1 tab bid po ˇ 3 days
- Doxycycline 100 mg bid po ˇ 3 days

Prophylaxis:
Not recommended except for persons who are immunosuppressed or suffer chronic illness. If indicated, then:
- Co-trimoxazole 1 tab bid po ˇ 3 days
- Doxycycline 100 mg bid po ˇ 3 days
- Ciprofloxacin 500 mg bid po ˇ 7 days

10.1.3 TRAVELER'S DIARRHEA

Traveler's diarrhea is a syndrome characterized by an increase in frequency of unformed bowel movements, typically four to five loose stools per day. Associated symptoms include abdominal cramps, nausea, bloating, urgency, fever and malaise. Traveler's diarrhea usually begins abruptly, during travel or soon after returning home, and is generally self-limiting, lasting three to four days. Ten percent of cases persist longer than one week, approximately 2% longer than one month and very few beyond three months. Enterotoxigenic E. coli (ETEC) is the most common causative agent of traveler's diarrhea. These organisms adhere to the small intestine, where they multiply and produce an enterotoxin that causes fluid secretion and hence diarrhea. Salmonella gastroenteritis, Shigella dysentery, and viral enteric pathogens (rotavirus and Norwalk-like virus) are less common causes of traveler's diarrhea.

Since traveler's diarrhea is usually mild and self-limiting, with complete recovery even in the absence of therapy, therapy should be considered optional (Table 10). The value of prophylaxis for travelers is unclear. Bismuth preparations are helpful, but their use is limited by the large volumes necessary and by their taste. Antibiotic prophylaxis can reduce the likelihood of developing diarrhea, but carries its own risks.

10.2 Viral Gastroenteritis

At least two groups of viruses are capable of producing an acute diarrheal illness.

10.2.1 NORWALK VIRUS

The Norwalk virus causes a self-limiting syndrome that affects children and adults, mainly in winter. An incubation period of 24 to 48 hours is followed by a variable combination of fever, anorexia, nausea, vomiting, myalgia, abdominal pain and diarrhea. Spontaneous recovery occurs two to three days later. Immune electron microscopy of fecal filtrates demonstrates a characteristic 27 nm viral particle (the Norwalk agent). No specific treatment is available. The vomiting represents delayed gastric emptying; there are no morphologic features of gastritis.

10.2.2 ROTAVIRUSES

Rotaviruses are the most common causes of acute nonbacterial gastroenteritis in infancy and childhood. Rotaviruses invade mucosal epithelial cells. The resulting illness is more severe than that caused by the Norwalk virus. Rotavirus infection commonly requires hospital admission and intravenous fluids. Infection occurs mainly in children from 6 to 24 months old, and almost always in winter. Virus excretion is maximum three to four days after the onset of symptoms and disappears after a further three to four days. The stability of the virus and the large number of viral particles excreted make environmental contamination inevitable, with a high risk of secondary infection in susceptible contacts. For example, 20% of the rotavirus infections diagnosed in pediatric hospitals are acquired in the hospital. Most older children and adults have antibodies to rotaviruses, so any subsequent infection is generally mild.

10.3 Parasitic Enteritis

The parasites that infect the intestine may be divided into three broad groups. These include protozoa, roundworms and flatworms. The flatworms may be further divided into cestodes (tapeworms) and trematodes (flukes). This chapter will focus upon only a few protozoa seen in immunocompetent Canadian residents (infections seen in immunocompromised persons are discussed in Chapter 8).

10.3.1 GIARDIA LAMBLIA

Giardia lamblia is endemic in many areas of the world, including Canada. Some patients with giardiasis (“beaver fever”) present with an abrupt, self-limiting illness that develops one to three weeks after infection and lasts three to four days. Others may develop chronic and episodic diarrhea associated with bloating and, at times, steatorrhea and a malabsorption syndrome clinically like celiac disease. Diagnosis is made by recovery of the organism;

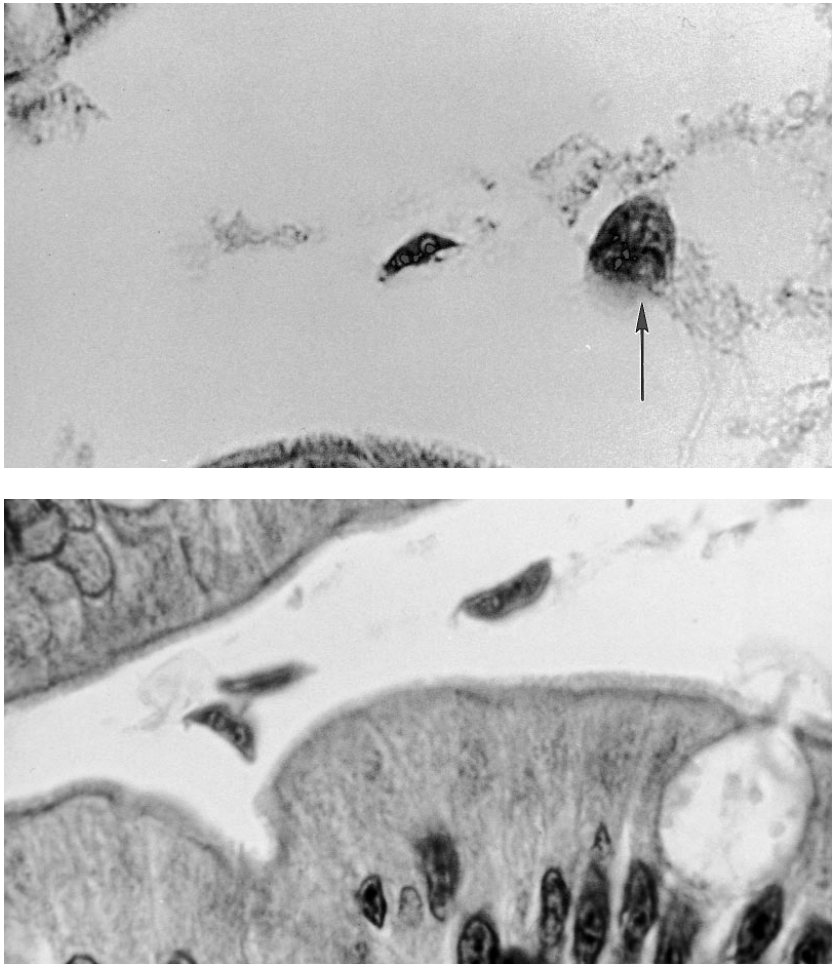

FIGURE 15A and B. Two high-power views of giardiasis show the typical appearance in cross-section. The crescentic shape and double nuclei are characteristic. One cut shows the organism in longitudinal section (arrow); the organism has the pear shape more familiar from smear preparations. Only one of the two nuclei is visible.

it is found in the stool of approximately 50% of patients and in 90% of histologically examined smear preparations obtained from small bowel biopsy specimens (Figure 15A, B). The treatment of choice in both asymptomatic and symptomatic patients is metronidazole 250 mg t.i.d. for 7 days. Repeat therapy will occasionally be needed to totally eradicate the organism. Quinacrine 100 mg t.i.d. for 7 days also is effective.

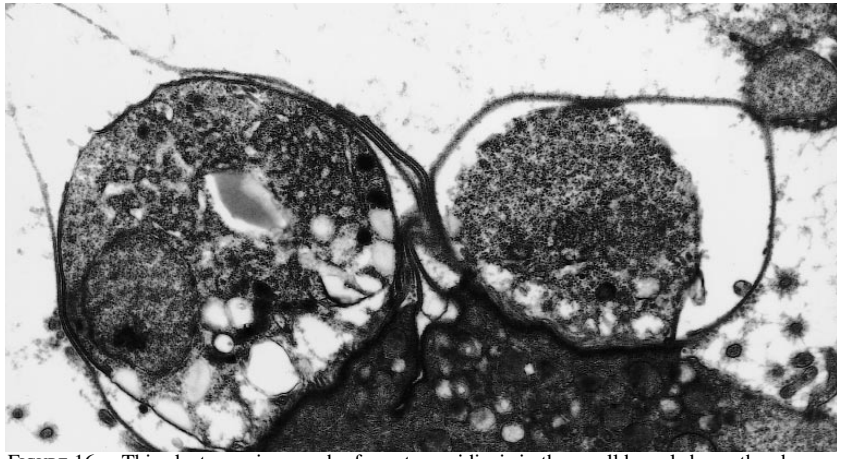

FIGURE 16. This electron micrograph of cryptosporidiosis in the small bowel shows the characteristic intracellular but extracytoplasmic location of the organisms.

10.3.2 AMEBIASIS

This is an acute and chronic disease caused by the organism Entamoeba histolytica. Although there are numerous species of ameba that inhabit the human intestinal tract, E. histolytica seems to be the only variety that is pathogenic for humans. Its manifestations vary from the asymptomatic carrier state to a severe fulminating illness with mucosal inflammation and ulceration. Asymptomatic patients harbor only cysts in their stools and have no evidence of tissue invasion. Since the cysts are resistant to the outside environment, the disease can be transmitted by individuals unaware of their infective potential. This is in contrast to patients with acute or chronic invasive disease, who harbor a trophozoite that cannot survive outside the host.

The acute illness is characterized by diarrhea with the passage of blood and mucus, and by variable degrees of abdominal pain. In its most severe form it may mimic fulminating ulcerative colitis and may progress to a toxic dilation (toxic megacolon) and perforation of the colon. During the acute illness, trophozoites may be recovered in the stool, from biopsies of shallow ulcers in the rectum, or from smears of rectal mucus.

Chronic infectious features may develop many years after the patient has left an endemic area. Patients present with nonspecific bowel complaints and may show radiologic changes in the distal small bowel and colon that mimic ulcerative colitis, cancer or tuberculosis. Diagnosis necessitates recovering trophozoites from the stool. As an adjunct, the indirect hemagglutination test can help detect patients with invasive disease.

Intestinal complications of amebiasis include massive intestinal hemorrhage, which is rare; ameboma formation in any part of the colon, which may lead to obstruction or intussusception; permanent stricture formation during the healing stage; and postdysenteric colitis, which usually resolves over several weeks or months without specific therapy.

Systemic dissemination of the ameba may involve other organs, such as the brain, lung, pericardium and liver. Liver abscess is the most common extraintestinal infection by the ameba.

Therapeutic agents used for the treatment of amebiasis act at selected sites: intraluminally, intramurally or systemically. Treatment must therefore be individualized to the location of the disease. Asymptomatic carriers are treated with iodoquinol 650 mg t.i.d. for 20 days; this agent acts against amebas located intraluminally. Acute or chronic intestinal disease is treated with metronidazole 750 mg t.i.d. for 10 days. However, because metronidazole is less effective against organisms within the bowel lumen, iodoquinol (650 mg t.i.d. for 20 days) must be added.

10.3.3 CRYPTOSPORIDIA

Cryptosporidia are a genus of protozoa classified within the subclass Coccidia. In immunocompetent persons cryptosporidia infection presents as a transient, self-limiting diarrheal state lasting from one to seven days. Adults are less commonly affected than young children. In most, the illness is mild and medical help is not sought. With immunological incompetence (e.g., AIDS, neoplasia, hypogammaglobulinemia or concurrent viral infection), a persistent chronic watery diarrhea may occur. Diagnosis is made by demonstrating Cryptosporidia oocysts in the stool or, better still, by mucosal biopsy and examination of the microvillus border for embedded Cryptosporidia oocysts (Figure 16).

A successful treatment for Cryptosporidia has not yet been found. Spiramycin and hyperimmune bovine colostrum remain experimental, as does thalidomide.

10.4 Drug-Related Diarrhea

Since almost every drug can cause diarrhea, the first question to ask a patient is “What medications, both prescribed and over-the-counter, are you currently taking?” Discontinuing the drug is often the only therapeutic move required. Although many drugs can cause diarrhea, little is understood about the ways in which they do so. The common causes of drug-induced diarrhea with pathogenic mechanisms follow.

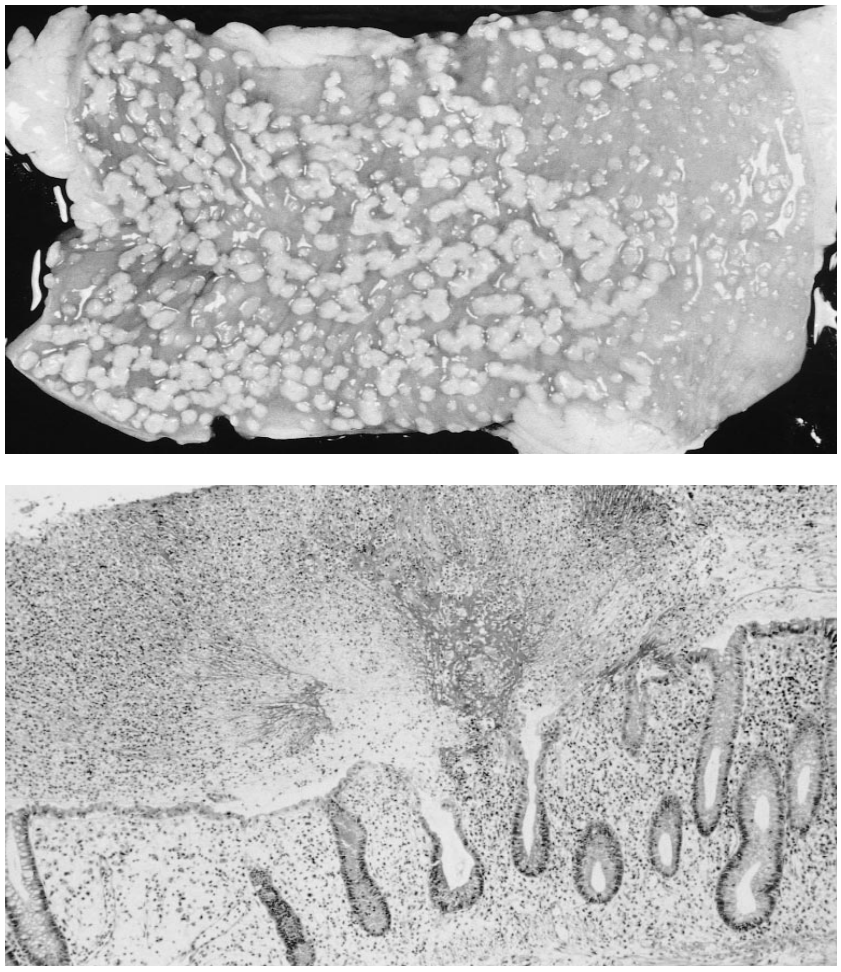

FIGURE 17A and B. The confluent white patches of pseudomembraneous colitis are typical. In Figure 17B the pseudomembrane is seen to arise like a volcano from a point of mucosal damage and is composed of an exudative fibrin and neutrophils.

10.4.1 ANTIBIOTIC-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS

Antibiotics are the most common cause of drug-induced diarrhea. In many cases, the condition is self-limiting. The development of pseudomembranous colitis (PMC) in association with antibiotics may be a serious and sometimes life-threatening condition.

PMC can follow virtually any antibiotic use. It may occur months after antibiotic exposure, and may rarely occur without a past history of antibiotic use. The frequency of diarrhea or colitis does not appear to be related to dose or route of administration of the antibiotic. Symptoms can occur while the patient is on the antibiotic or within six weeks following its discontinuation. Only increasing age is clearly identifiable as a risk factor. The diarrhea is usually loose with mucus. Frank bleeding is uncommon. The diarrhea can be devastating, with up to 30 bowel movements in a 24-hour period. The diarrhea may be associated with varying degrees of abdominal pain and low-grade fever. Depending on the severity of the diarrhea and the amount of fluid loss, hypotension, shock and even death have been reported. In many patients the problem is self-limiting and resolves spontaneously with discontinuation of the antibiotic. Further investigation is required in those patients who have severe diarrhea associated with systemic symptoms and those whose diarrhea persists despite discontinuing the implicated antibiotic.

An accurate history is usually sufficient to suggest the diagnosis of PMC, and a sigmoidoscopy may be all that is required for confirmation. The presence of copious amounts of mucus and typical raised white pseudomembrane plaques are characteristic features on sigmoidoscopy. Biopsies help confirm the diagnosis (Figure 17A and B). The distal colon is involved in most cases so that sigmoidoscopy is usually adequate. Sometimes the pseudomembrane lesions may be restricted to the right colon, necessitating colonoscopy to identify the PMC lesions.

Isolation of C. difficile toxin in the stools provides the diagnosis. If it is certain that there is no other likely cause for the diarrhea, treatment can be undertaken while awaiting assay results, although it is usually possible to quickly obtain a sigmoidoscopy to demonstrate the pseudomembranes. If symptoms are resolving with discontinuance of the antibiotic, no further therapy may be indicated. In mild cases, metronidazole 250 mg p.o. t.i.d. for 7–10 days is effective. In severe hospitalized cases the drug of choice is vancomycin 125 mg p.o. q.i.d. for 14 days. Vancomycin is poorly absorbed and central nervous system and renal toxic effects are uncommon. The high cost of this medication limits its use, even though the eradication rate is high. If oral therapy cannot be used, as with severe ileus or recent surgery, parenteral metronidazole is preferred. Some 20% of treated patients will have a recurrence of symptoms, PMC or C. difficile, usually within 4 to 21 days of stopping treatment. In this case, another course of metronidazole or vancomycin should be given. Cholestyramine (Questran®) binds the toxin and can provide symptomatic relief even though it will not eliminate the microorganism.

10.4.2 MAGNESIUM-CONTAINING ANTACIDS

Usually, the osmotic diarrhea produced by Mg^{2+} is mild; it may even be welcomed by previously constipated patients. A change to a magnesium-free, aluminum-containing antacid is all that is required to control the situation in some. The use of antacids is a common cause of diarrhea in dyspeptic patients. Magnesium can be used to induce diarrhea by the rare patient with the Münchausen syndrome seeking medical attention for self-induced problems.

10.4.3 ANTIARRHYTHMIC DRUGS

The antiarrhythmic drugs most commonly associated with diarrhea include quinidine, procainamide and disopyramide. The mechanism involved is unknown. Changing the antiarrhythmic drug may halt the diarrhea.

10.4.4 OTHER MEDICATIONS

Colchicine, often administered for acute gout, produces diarrhea as a common side effect. It resolves with discontinuance of the medication. The mechanism of the diarrhea is unknown, but may relate to an intestinal cytotoxic effect of colchicine. Antimetabolites (e.g., methotrexate) often cause diarrhea as a result of damage to the small or large bowel mucosa. This type of diarrhea can be devastating and difficult to control. Except for rehydration and stopping the drug, little can be done.

11. CHRONIC DIARRHEA

11.1 Pathogenesis

There are at least four basic mechanisms that cause chronic diarrhea, including osmotic, secretory and exudative factors, and abnormal intestinal transit (Table 11). If the diarrhea ceases when fasting, then an osmotic cause for the diarrhea is suspect. A significant osmotic gap in the stool water may be present but, under normal clinical circumstances, this is not measured. Examples include diarrhea after ingesting milk (a result of lactase deficiency) or drugs such as laxatives and antacids, or the excessive use of artificial sweeteners such as sorbitol and mannitol, which contain polycyclic alcohols.

If the patient's diarrhea persists when fasting (such as may occur at nighttime when the diarrhea awakens the person from sleep), a secretory diarrhea is likely. Secretory diarrhea usually arises from infection or inflammation associated with toxigenic and invasive bacteria. Secretory diarrhea may also result from the spillage of excess bile acids into the colon (choleretic enteropathy) or from the cathartic effect of hydroxy fatty acids arising from the colonic bacterial action on malabsorbed fat. Very rarely, secretory diarrhea

TABLE 11. Pathophysiologic mechanisms of chronic diarrhea

Major disturbance	*Probable mechanisms*	*Examples/Associated conditions*
Osmotic*	Ingestion	Antacids, laxatives
	Maldigestion	Pancreatic insufficiency, disaccharidase deficiency
	Malabsorption	Carbohydrate malabsorption, congenital chloridorrhea
Disorders of intestinal transit	*Slow* transit ("blind loop syndrome") – excessive contact time	Fistulas, strictures (such as in the patient with Crohn's disease), diabetic neuropathy
	Rapid transit – insufficient contact time	Intestinal resection, hyperthyroidism, irritable bowel
Secretory**	Bacterial enterotoxins	Vibrio cholerae, enterotoxigenic E. coli
	Secretagogues	Bile acids, fatty acids, ethanol, prostaglandins, phenolphthalein, dioctyl sodium sulfosuccinate, VIP, gastrin, calcitonin
Exudative	Increased passage of body fluids into lumen	Ulcerative colitis, Crohn's disease

*See Table 12. **See Table 13.

can arise from a tumor producing an intestinal secretagogue (e.g., pancreatic islet cell tumor producing vasoactive intestinal peptide or gastrin).

Exudative diarrhea results from mucosal damage to the small or large bowel, which interferes with absorption of salt and water, and may be associated with the exudation of serum proteins, blood, and mucus and sloughed cells. This mechanism is seen in infectious, inflammatory and neoplastic disorders.

Disorders of intestinal transit may give rise to diarrhea secondary to abnormal intestinal motility in hyperthyroidism or diabetic neuropathy. Scleroderma leads to bacterial overgrowth and steatorrhea (as can the rapid transit in hyperthyroidism). The mechanism of diarrhea in these conditions relates to a combination of bacterial overgrowth, bile salt wastage and disorders of motility (slow or rapid intestinal transit).

11.1.1 OSMOTIC DIARRHEA

Retention of solute molecules within the bowel lumen generates osmotic forces that retard the normal absorption of water (Table 12). Practical examples

TABLE 12. Causes of osmotic diarrhea

Carbohydrates
Specific disaccharidase deficiencies
Glucose–galactose malassimilation
Fructose malassimilation
Mannitol, sorbitol ingestion ("chewing gum diarrhea")
Lactulose therapy
Divalent ions
Magnesium sulfate (Epsom salts)
Sodium sulfate
Sodium phosphate
Sodium citrate
Magnesium-containing antacids

include poorly absorbed carbohydrates or a divalent ion. Poorly absorbed divalent ions (e.g., phosphate, sulfate and magnesium) are the laxative constituents of several common antacids and saline purges. Since the "pores" through which ions are absorbed are highly charged, these polyvalent ions tend to be absorbed slowly. Thus, they accumulate within the intestinal lumen, raise the osmolality, and so retard the normal absorption of water or even act to draw water from the circulation into the intestinal lumen.

Carbohydrates constitute the other major group of osmotic agents. Some are poorly absorbed by everybody; lactulose, for example, was developed to be a nonhydrolyzable, nonabsorbable disaccharide that would act as a cathartic. The action of lactulose mimics the effects of *primary lactase deficiency*. This condition normally develops after weaning in the majority of African-, Caribbean- or Asian-Canadians and occurs in 30% of persons with southern European ancestry. The unabsorbed lactose acts osmotically to retain water in the small intestine. In fact, any disease that interferes with carbohydrate absorption (e.g., impaired intraluminal digestion due to pancreatic disease, primary disaccharidase deficiencies, and secondary disaccharidase deficiencies due to small bowel disease) will lead to osmotic diarrhea. Since carbohydrates are not inert in the colon, their metabolism leads to further osmotic forces. Once carbohydrate reaches the fecal flora, anaerobic fermentation occurs (Figure 13). Intermediary products are ethanol and formic, succinic and lactic acids. These products are further consumed to varying degrees. CO_2 and H_2 are rapidly absorbed, and CO_2 rises in exhaled air. (Exhaled H_2 is the basis for the hydrogen breath test described earlier.) Excess gas production causes borborygmi and flatus rich

in H_2. Short-chain fatty acids (SCFAs) are also produced (acetic acid, propionic acid and butyric acid) and account for the acidic stool pH noted in diarrhea of carbohydrate malabsorption. The caloric loss due to carbohydrate malabsorption is diminished to the extent that short-chain fatty acids can be absorbed from the colon (where they may be used as nutrients by the colonocytes), thus "salvaging" some of the malabsorbed carbohydrates that enter the colon.

The consequences of malabsorption are as follows: With minor impairment of sugar absorption, colonic fermentation is complete and only small amounts of excess solute are present in stool water. Stool volume and stool pH do not change much initially, and up to three-quarters of the glucose energy is returned to the body in the form of short-chain fatty acids (colonic "salvage"). As the extent of carbohydrate malabsorption increases, more short-chain fatty acids are formed than can be reabsorbed. This results in diarrhea due to the presence of osmotically active short-chain fatty acids. The stool pH consequently begins to fall, which further decreases colonic salvage.

Clinically, osmotic diarrhea should stop when the patient stops ingesting the poorly absorbed solute. Stool analysis should not reveal fat, RBC or WBC. Although rarely measured, there may be a detectable positive osmotic gap – that is, stool osmolality minus stool Na^+ plus stool K^+ times 2 (multiplied by 2 to account for anions) is greater than 50, the size of the osmotic gap being approximately equivalent to the concentration of poorly absorbed solutes in fecal water.

11.1.2 INTESTINAL TRANSIT AND DIARRHEA

The basal electrical rhythm of the small intestine alters the excitability of the muscle cells. The motility patterns of the small intestine consist of three essential patterns: (1) migrating motor complex (MMC), periodic bursts of contractile activity lasting at least 5 minutes that are succeeded by periods of quiescence and appear to migrate down the small intestine at a slow rate of less than 5 cm/min; (2) minute rhythm, regular groups of between 3 and 10 contractions that occur at intervals of 1 to 2 minutes, separated by periods of quiescence, and appear to migrate down the small intestine at a rapid rate of 60–120 cm/min; (3) migrating action potential complex, a single ring contraction or single burst of spike potentials that migrates down the intestine at a rate exceeding 90 cm/min.

These forms of small intestinal motility control the rate at which material travels along the intestine and hence arrives at the anus. Gastrointestinal motor activity also determines the time and thus the degree of contact between gut contents, the digestive enzymes and the absorptive epithelium. Accelerated transit of material through the gut produces diarrhea by limiting digestion and absorption.

TABLE 13. Causes of secretory diarrhea

Pathophysiologic mechanisms
Enterotoxins
Circulating secretagogues (VIP, calcitonin, prostaglandins, serotonin)
Increased hydrostatic pressure and tissue pressure
Gastric hypersecretion (Zollinger-Ellison syndrome)
Pancreatic hypersecretion
Laxatives (ricinoleic acid, bisacodyl, phenolphthalein, oxyphenisatin, dioctyl sodium sulfosuccinate, aloe, senna, danthron)
Bile salts
Fatty acids
Clinical syndromes
Acute secretory diarrhea
Chronic secretory diarrhea
Surreptitious laxative ingestion
Pancreatic cholera syndrome (VIP)
Medullary carcinoma of the thyroid (calcitonin)
Ganglioneuroma, ganglioneuroblastoma, neurofibroma
Zollinger-Ellison syndrome (gastrin)
Malignant carcinoid syndrome (serotonin)
Idiopathic secretory diarrhea
Congenital chloridorrhea (some cases)
Secreting villous adenoma
Total villous atrophy of small bowel mucosa
Niacin deficiency
Intestinal lymphoma
Miscellaneous
Intestinal obstruction
Intestinal distention/ileus

Understanding of motility-associated diarrhea remains limited, and only rudimentary measures of intestinal myoelectrical activity exist for humans. The oral–anal transit times of radiolabeled markers, radiopaque tubing, or nonabsorbable carbohydrate markers provide the only clinical assessments. Even small intestinal motility, unlike esophageal motility, remains a research tool.

The ileocecal valve is important to gut function. The ileocecal sphincter extends over a 4 cm length of distal small intestine and produces a high-pressure zone of about 20 mmHg. Distention of the ileum results in a decrease in the ileocecal sphincter pressure, whereas distention of the colon results in an increased pressure in this area. The ileocecal valve slows down intestinal transit (ileal "break") and prevents backwash from the colon. By this mechanism the ileocecal valve is important in regulating intestinal transit. Removal of the

ileocecal valve during surgery will result in marked intestinal hurry as well as the potential for bacterial overgrowth from fecal "backwash." Disorders that impair peristalsis in the small gut allow bacterial overgrowth, resulting in diarrhea. Lastly, premature evacuation of the colon because of an abnormality of its contents or because of intrinsic colonic "irritability" or inflammation results in a reduced contact between luminal contents and colonic mucosa and, therefore, in more frequent, liquid stools.

11.1.3 SECRETORY DIARRHEA

The small intestine normally secretes as well as absorbs fluid and electrolytes; the secretion rate is lower than the absorption rate. Therefore, the net effect of small bowel transport is absorption of fluid. This is an important concept, because it means that a pathophysiologic event may reduce the net absorption rate in either of two ways: by stimulating secretion or inhibiting absorption. Either or both can result in what is clinically recognized as secretory diarrhea. It is not usually possible to ascertain which of the two events is predominant. For clinical purposes, it seems best to consider inhibition of ion absorption and stimulation of ion secretion together.

The prototype of secretory diarrhea is Vibrio cholerae; its clinical description first aroused interest in the secretory process as a mechanism for diarrhea (Table 13).

Bacterial secretagogues fall into two major classes. The first class comprises large (MW 84,000), heat-labile proteins, of which cholera enterotoxin is the prototype. These toxins appear to stimulate secretion by activating mucosal adenylate cyclase and thus increasing cyclic AMP levels in the mucosa. The intracellular "messenger" for secretion is less well defined; cyclic AMP is considered important, though there are additional steps that might also involve intracellular levels of Ca^{2+} and the calcium regulatory protein, calmodulin. A second class of secretagogues comprises smaller proteins that are heat-stable. The best studied is the ST (heat-stable toxin) of E. coli, which stimulates secretion by activating mucosal guanylate cyclase, leading to higher levels of cyclic GMP in the mucosa.

Bacterial toxins, however, are only part of the story. Secretion is also stimulated experimentally by hormones, peptides acting locally (paracrine hormones), luminal factors (e.g., dihydroxy bile acids and fatty acids), neurotransmitters, prostaglandins and physical factors (e.g., distention). Bile acids and fatty acids not absorbed in the small intestine evoke secretion of electrolytes and water by the colon. The exact mechanism(s) for this are uncertain. Both groups have multiple effects on the bowel, including stimulation of secretion, increased intestinal permeability and transient alterations in morphology.

One or more humoral stimuli can elicit a massive secretion of water and electrolytes from the small bowel. The colon is usually not involved directly, but it may be unable to adequately reabsorb the fluid load imposed on it. A key question, difficult to answer, is "What is the responsible hormone?" Putative secretagogues include vasoactive intestinal peptides in the pancreatic cholera syndrome, calcitonin in medullary carcinoma of the thyroid, gastrin in the Zollinger-Ellison syndrome, serotonin in the malignant carcinoid syndrome, and glucagon in glucagonomas. Prostaglandins are also potent stimulators of intestinal secretion. Diarrhea secondary to prostaglandin-stimulated intestinal secretion is a common side effect of orally administered prostaglandin analogues.

The intestinal distention that occurs with obstruction or ileus also produces a local secretory state proximal to the obstruction. The mechanism is not entirely clear and may be related to changes in permeability (as tight junctions are stretched and broken) as well as to direct, perhaps neural, stimulation of secretory mechanisms.

Secretory diarrhea is recognized clinically by four features: (1) the stools are large volume, watery and often >1 L/day; (2) if measured, there may be a stool osmolar gap of < 50 mOsm/L; and (3) there is a measured stool osmolar gap of < 50 mOsm/L; and (4) patients with secretory diarrhea do not have excessive fat, blood or pus in their stools, but often develop depletion in fluid, Na^+ and K^+.

Therapeutically, the offending agent must be removed. A variety of empirical therapies that influence the secretory process (e.g., somatostatin, prostaglandin inhibitors, phenothiazines, calcium channel blockers, α_2-adrenergic agonists and lithium) may be effective but should be reserved for use in a research center. Oral glucose-saline replacement therapy is useful for maintenance of hydration. For bile acid-induced diarrhea, cholestyramine works well unless there has been a greater than 100 cm resection of the terminal ileum. With more extensive resections (>100 cm) there will be both steatorrhea and bile salt wastage, and treatment must be focused on the steatorrhea.

11.1.4 EXUDATIVE DIARRHEA

Exudation is a far simpler concept. Structural disruption of the intestinal wall by diffuse ulceration, inflammation, infiltrations and tumors will add cellular debris, mucus, serum proteins and blood to the lumen. The effects on stool volume will be most pronounced when the lesions also involve the colon, since there will be little opportunity for normal mechanisms of colonic fluid and electrolyte absorption to compensate for the increased volume of chyme.

11.1.5 SELF-INDUCED DIARRHEA

The possibility that the diarrhea is self-induced must be considered when a

patient complains of chronic diarrhea and when the routine investigations are negative. In general, abusing laxatives, diuretics and sometimes thyroid hormones will induce diarrhea. Often the diarrhea is sufficiently severe to cause electrolyte disturbances, acid-based problems and dehydration. The diagnosis can be extremely difficult since the history is often misleading or not obtained. The usual investigations (including sigmoidoscopy and radiographs) will be negative, unless the patient is taking a drug that can cause melanosis coli (brown-black pigmentation of the colonic mucosa), such as the anthracene laxatives senna or aloe. Stool analysis for Mg^{2+}, sennas or phenolphthalein may reveal the culprit. Finding packages of laxatives and other drugs in room searches is often the only method that permits the diagnosis; this approach has been criticized because of ethical considerations, but may be the only way to uncover the problem. Ethical issues and respect for the patient's privacy must be carefully considered before embarking on a room or locker search.

11.2 Investigation of the Patient with Chronic Diarrhea

For a patient with chronic diarrhea, a careful history and physical examination can help define the site in the intestinal tract responsible (Table 14). Although there is considerable symptom overlap, it may be possible to differentiate a small intestinal cause from a colonic cause for diarrhea. Colorectal disease often is associated with small, frequent bloody motions accompanied by tenesmus and urgency. Small intestinal diseases (or pancreatic diseases) often produce loose pale and bulky stools that are uncommonly bloody or accompanied by urgency. Despite overlap, this "bedside" definition of the characteristics of the diarrhea may be helpful to avoid a less productive "shotgun" approach.

12. DISACCHARIDASE DEFICIENCIES

Disaccharide intolerance is a characteristic symptom complex resulting from the ingestion of ordinary dietary quantities of disaccharides, which produces a symptomatic diarrhea. The cause is a deficiency of one or more disaccharidases, but not all people with such a deficiency will experience symptoms.

Dietary carbohydrates are presented to the surface of the jejunal mucosa in the form of isomaltose, maltotriose and three major disaccharides – maltose, sucrose and lactose. Trehalose, a disaccharide contained in young mushrooms and in certain insects, is a minor component of modern Western diets. Deficiencies of disaccharidases may be *primary* (hereditary) or *secondary* (acquired) deficiencies. Characteristically in primary deficiencies, which are rare, only one enzyme is involved; the deficiency is present at birth (with the exception of the common adult-onset form of lactase deficiency), not associated with intestinal disease, and irreversible. Secondary deficiencies usually

TABLE 14. Anatomic approach to the causes of chronic diarrhea

Gastric
Excessive use of antacids*
Hypergastrinemia/Zollinger-Ellison syndrome
Postoperative unmasked celiac disease, lactase deficiency or pancreatic insufficiency
Postoperative dumping syndrome*
Small intestine
Crohn's disease*
Celiac disease*
Lymphoma
Whipple's disease
Bacterial, viral or parasitic infection*
Abnormal intestinal integrity: scleroderma, amyloidosis, diabetes
Large bowel
Colon neoplasia*
Irritable bowel syndrome*
Inflammatory bowel disease*: ulcerative colitis, Crohn's disease
Drugs
Antacids*
Antibiotics*
Alcohol*
Antimetabolites
Laxatives
Digitalis
Colchicine
Metabolic
Hyperthyroidism
Hypoparathyroidism
Addison's disease
Diabetes*
Carcinoid syndrome
VIPoma syndrome

*Common causes within the group

involve all the disaccharidases, may occur at any age, are associated with a disorder of the small intestinal mucosa, and may be reversed if the intestinal disorder (e.g., celiac disease, stasis syndromes or acute enteritis) heals. Because primary lactase deficiency is uncommon in Canadians with northern European ancestors, the appropriate tests need to be performed to exclude secondary causes such as celiac disease.

The clinical manifestations of enzyme deficiency result from the osmotic diarrhea following ingestion of the disaccharide. The affected individual develops crampy, abdominal distress and distention, relieved by the expulsion of liquid stool and flatus. The severity of the diarrhea varies with the disaccharide load, the degree of deficiency of enzyme activity and any associated/causal intestinal disease. The clinical diagnosis can be confirmed by direct enzyme assay of jejunal mucosal biopsies or by indirect methods for detecting disaccharide malabsorption (e.g., the breath hydrogen test). Treatment of hereditary deficiencies is usually by elimination diets. For children and adolescents (who have high nutritional requirements) and for adults who enjoy milk, low-lactose milk is available. It can also be prepared by adding yeast lactase (available in commercial form, Lactaid®) to milk and refrigerating it for 24 hours.

Delayed-onset (adult-onset) hereditary lactase deficiency is extremely common and probably "normal" for humans. Beginning as early as age 2 years in some racial groups, and as late as adolescence in others, the activities of lactase in the majority of the world's populations drop sharply. This is the result of the genetically controlled "switching off" of lactase synthesis by intestinal cells. Individuals of northern European ancestry maintain lactase activity throughout adulthood.

13. GLUTEN-INDUCED ENTEROPATHY (CELIAC DISEASE)

In celiac disease (gluten-induced or gluten-sensitive enteropathy) the mucosa of the small intestine is damaged by gluten-containing foods (i.e., those containing wheat, rye, barley and possibly oats). This causes a characteristic though nonspecific lesion and clinically significant malabsorption of some nutrients. The precise mechanism of gluten toxicity is unknown, but there is likely both a genetic and an immunological component. Fractionation of cereal proteins reveals that the component that is toxic to the intestinal mucosa is a portion of the gluten molecule called gliadin. Although gliadin can be inactivated in a test tube by enzymatic degradation, digestion to smaller peptides by pepsin and trypsin does not alter its toxicity in humans. In susceptible people, symptoms and pathologic changes occur within 12 hours of gluten intake. The immune system is also involved. The small intestine in patients with untreated celiac disease shows an increase in lamina propria lymphocytes, plasma cells and intraepithelial lymphocytes. Immunocytochemical studies indicate that cells producing IgA, IgG and particularly IgM are increased. Increased levels of serum IgA and decreased levels of serum IgM have also been reported and appear to revert toward normal with treatment.

TABLE 15. Intestinal and extraintestinal symptoms of celiac disease in adults

Manifestations	*Probable causes or deficiencies*
Common	
Anemia	Iron, folate, B_{12}, pyridoxine
Glossitis	Iron, folate
Weight loss/weakness	Malassimilation – Negative nitrogen balance
Diarrhea/flatulence	Fat and carbohydrate malassimilation
Abdominal pain	Increased intestinal gas production secondary to carbohydrate malassimilation
Occasional	
Follicular hyperkeratosis and dermatitis	Vitamin A, folate
Pigmentation	Associated adrenal insufficiency
Edema	Hypoproteinemia
Tetany	Vitamin D, calcium, magnesium
Osteomalacia	Vitamin D, calcium
Purpura	Hypoprothrombinemia (vitamin K)
Rare	
Spinal cord degeneration	B_{12}
Peripheral neuritis	B_{12}, vitamin E, thiamine, pyridoxine
Psychosis and other psychological disturbances	B_{12}; other causes likely
Malignancy (usually small bowel lymphoma)	Unknown

Genetic studies indicate that about 10% of the patient's first-order relatives have asymptomatic disease. HLA-B8 and HLA-DW3, generally associated through linkage disequilibrium, are present in 80% of patients (compared to 20% of the general population). In addition, a specific antigen is present on the surface of B lymphocytes in approximately 80% of celiac disease patients (compared to 10–15% of controls). It is found in all parents of affected individuals, which suggests that this antigen is inherited by an autosomal recessive method. Celiac disease is also present in about 2% of insulin-dependent diabetics.

13.1 Clinical Features

13.1.1 CHILDHOOD PRESENTATION

In children, onset of symptoms suggestive of celiac disease is gradual with failure to thrive after the introduction of cereals in the diet. The affected infant is irritable, anorexic, pale and wasted. Physical examination discloses generalized hypotonia and abdominal distention. The stools are soft, bulky, clay-

colored and offensive. In the slightly older child, abdominal pain may be the presenting complaint. The pain may be sufficiently severe to simulate an intestinal obstruction. Older children may also present with anemia, rickets and failure to grow normally. Quite often, adolescents have a clinical quiescence of the disease. Even if relatively asymptomatic in childhood, affected people often do not attain their normal growth potential, being shorter than their sibs.

13.1.2 ADULT PRESENTATION

Celiac disease can present at any age, even after 70 years, but in adults it usually occurs between 20 and 60 years. In adult and adolescent patients, presentations with classical features of diarrhea, weight loss and malnutrition, or bone pain (osteomalacia) have become much less common (Table 15). Mild and subclinical forms are frequent, occurring in more than 50% of patients. The sole presentation may be an otherwise unexplained hematologic abnormality (iron deficiency with or without anemia, folate deficiency, macrocytosis), constitutional symptoms or fatigue with minimal weight loss and no intestinal symptoms, or mild abdominal or digestive complaints. The entity is most common in those of Irish and Scottish background or those who have a family history.

Diarrhea is common but many patients experience normal bowel habits, alternating diarrhea and constipation, and even constipation. The diarrhea is usually mild, with fewer than three bowel movements per day in most. Floating stools, also common in healthy subjects excreting high amounts of stool gas, are often not reported. Indeed, stools suggesting steatorrhea (i.e., unformed, bulky and hard to flush, greasy, sticky, pale and foul-smelling) are quite uncommon. Flatulence, abdominal distention, abdominal cramps and borborygmi are common complaints. Fatigue is the most frequent symptom at presentation. Weight loss is usually moderate (averaging 10 kg) and may be absent in mild cases. Clinically overt metabolic (tetany) and bone (osteomalacia) diseases have become uncommon with our generous Western diets, but these situations are hallmarks of celiac disease. A clue to the diagnosis of celiac disease is the development of lactose intolerance in person whose heritage is northern European.

Patients with dermatitis herpetiformis have gluten enteropathy but often without clinical impact. Overall, mucosal involvement in celiac disease progresses from duodenum to jejunoileum and is most severe proximally; the length of bowel involved determines to a great extent the clinical picture of the disease.

13.2 Laboratory Findings

Laboratory findings, as clinical signs and symptoms, vary widely. The defini-

tive diagnosis of celiac disease requires the demonstration of small bowel mucosal histologic changes characterized by crypt hyperplasia and villous atrophy that improves after administration of a strict gluten-free diet. In practice, several tests can be used to strengthen the suspicion of celiac disease and/or evaluate the possible biochemical consequences. The tests that are most useful to point to a diagnosis of celiac disease are hematological, serological and stool examination. The definitive diagnostic test is a small bowel biopsy.

13.2.1 HEMATOLOGICAL TESTS

Anemia is present in less than 50% of adult patients and may be secondary to iron, folate or (very rarely) vitamin B_{12} deficiency. Since celiac disease involves the proximal small bowel (i.e., the duodenum, where iron absorption occurs) most severely, iron deficiency is the most common laboratory abnormality. Folate deficiency also commonly occurs. Decreased absorption of B_{12} and malabsorption of vitamin K (with prolonged prothrombin time) are uncommon.

13.2.2 SEROLOGICAL TESTS

The demonstration of antibodies in the serum to gliadin, reticulin or endomysium may occur with celiac disease. Anti-endomysial IgA antibody measurement has been used in screening studies, but is observer-dependent. An IgA-antibody to tissue transglutaminase may be useful for screening studies or case finding but false-positive tests occur (e.g, autoimmune liver disease), and as with endomysial antibody testing, may produce a false-negative result if immunoglobulin A deficiency is present (occasionally associated with celiac disease). If a screening blood test is positive, a small intestinal biopsy should be done to confirm that the biopsy changes are present before treatment is initiated. This is a significant diagnosis that requires life-long effort to ensure a strict gluten-free diet. In addition, a correct diagnosis of celiac disease has prognostic implications related to other associated (e.g., osteopenic bone disease) or complicating conditions (e.g., small intestinal lymphoma or carcinoma). Unfortunately, serological testing is not an accurate reflection of dietary compliance.

13.2.3 STOOL EXAMINATION

Steatorrhea can be confirmed by a 72-hour fecal fat study. It is usually mild (10–20 g/24 hours) and may be absent in some patients. Its severity correlates with the extent of the intestinal lesion, so that patients whose disease is limited to the proximal small intestine often have normal stool fat excretion.

13.2.4 BLOOD CHEMISTRY TEST

Depletion of minerals (zinc, magnesium) and ions (potassium) occurs only with

severe disease. Plasma proteins are often within normal limits but this protein-losing enteropathy (leakage of serum protein into gut lumen) and possible malnutrition may result in decreased serum albumin. A low serum carotene (and sometimes cholesterol) level may be a clue to the presence of the disease.

13.2.5 CARBOHYDRATE TOLERANCE TEST

Approximately two-thirds of patients with celiac disease exhibit an abnormal D-xylose test. D-xylose is an aldopentose that is absorbed in the upper small intestine and is excreted in the urine almost completely within the first five hours after ingestion. Abnormal D-xylose absorption is best evaluated by the serum concentration after ingestion and points specifically to small bowel disease or luminal bacterial overgrowth. Similarly, the absorptive cell lesion also results in secondary lactase deficiency; thus, the H_2-lactose breath test may be abnormal in celiac disease. Because of the low sensitivity and specificity of the D-xylose test for celiac disease, it is not recommended.

13.2.6 RADIOGRAPHIC STUDIES

Barium studies of the small bowel may show dilation of the bowel and slight thickening of the mucosal folds. Intraluminal signs of malabsorption with flocculation, segmentation and clumping of the barium (features due to excess amount of fluid present within the lumen) are variable and not common. (The new barium suspensions now used have made this a rare finding.) Radiographic findings in celiac disease are not specific for this syndrome of malabsorption.

13.2.7 PERMEABILITY TESTS

The intestine of patients with celiac disease may be "leaky" and allow passage from the lumen into the blood and then into the urine of sugars such as mannitol or lactulose. The finding of increased amounts of these sugars in the urine after an oral dose suggests an abnormal intestinal permeability barrier. Such a finding of increased permeability may suggest the presence of celiac disease or other small intestinal disorders.

13.2.8 SMALL BOWEL BIOPSY

Small intestinal biopsies can be obtained endoscopically from the distal duodenum. Rarely, when diagnostic uncertainty persists, a larger mucosal specimen may be needed and obtained from the duodenojejunal area using the peroral Rubin tube or the Crosby capsule.

A flat mucosal biopsy from a white adult in the Western world is almost certain to indicate celiac disease, although other disorders can be associated

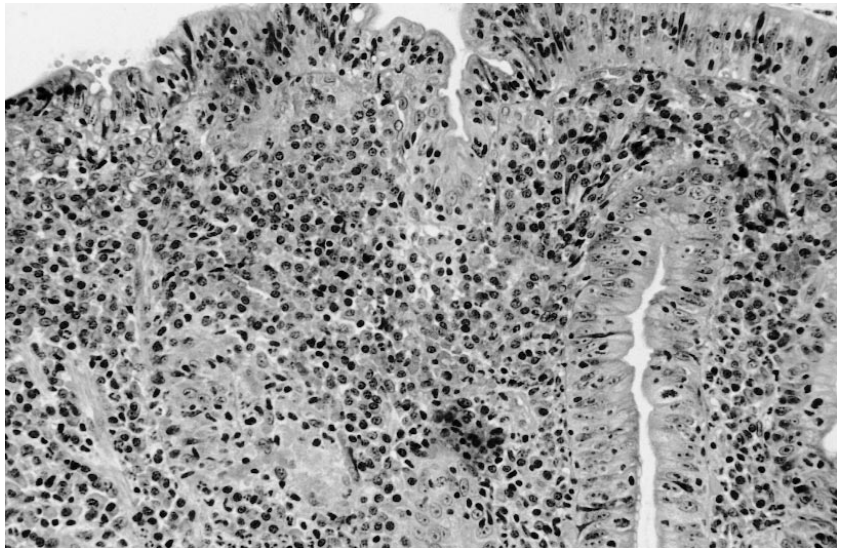

FIGURE 18. The high-power view of the small intestinal mucosa in gluten-induced enteropathy shows complete flattening of the mucosal surface, crypt expansion, increased numbers of intraepithelial lymphocytes, and lamina propria plasmacytosis.

with similar changes (e.g., tropical sprue, diffuse lymphoma of small bowel, immunoglobulin deficiency syndromes and the Zollinger-Ellison syndrome with gastric hypersecretion). In infants, soy protein intolerance, cow's milk protein intolerance and viral gastroenteritis produce a similar appearance. Therefore, to establish unequivocally the diagnosis of celiac disease, clinical improvement with a gluten-free diet is needed. Proving this improvement with a second biopsy is usually not necessary in adults. Mucosal small bowel atrophy improves similarly, although reversion of histology toward normal requires many months of gluten withdrawal and often is not complete.

Microscopically the characteristic "flat" lesion of celiac disease will demonstrate absence of villi, an abnormal cuboidal surface epithelium, markedly lengthened crypts and increased numbers of plasma cells and lymphocytes in the lamina propria. The lesion may be very subtle and include increased intraepithelial lymphocytes and a change in the normal position of the nuclei in the enterocyte (Figure 18). In a subtle lesion with shortened villi, proper orientation of the specimen is important in order to correctly estimate the height of the villi. The proximal small bowel is most severely involved, while

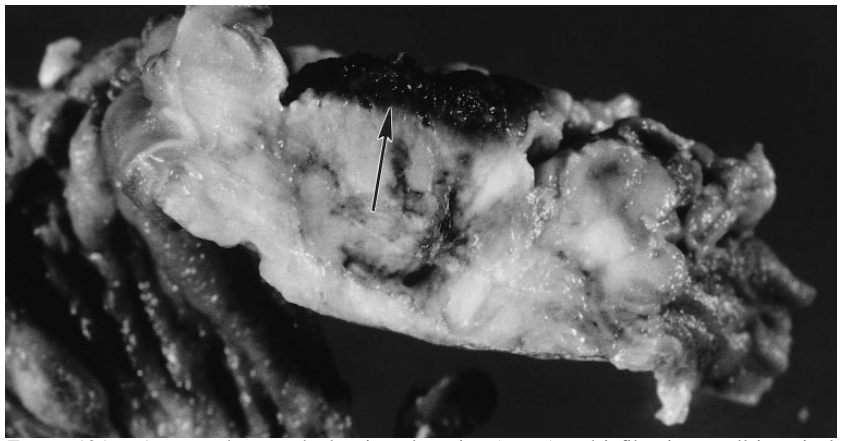

FIGURE 19A. A gross photograph showing ulcerating (arrow) and infiltrating small intestinal lymphoma.

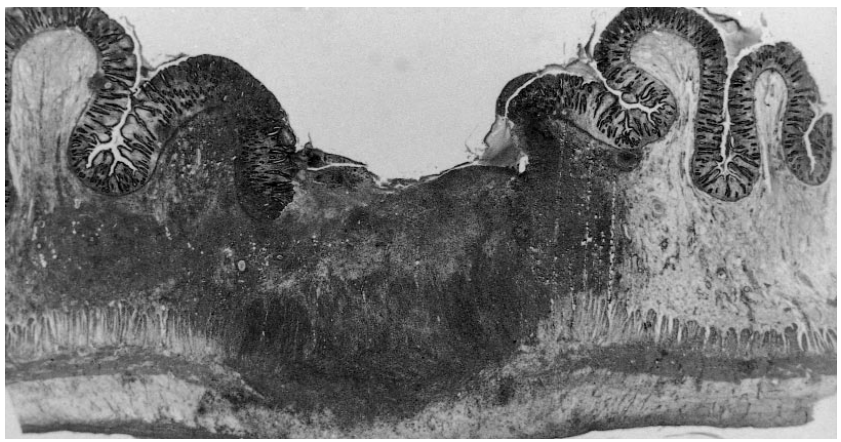

FIGURE 19B. A very low-power view showing the surface ulceration and infiltration of the lymphomatous tissue through virtually the full thickness of the bowel wall. Note the mucosal flattening adjacent to the neoplasm in this case of enteropathy-associated T-cell lymphoma.

the lesion decreases in severity toward the distal small intestine. The lesion may be patchy. Celiac disease will not spare the proximal small intestine while involving the distal small intestine, however. Sometimes the gross appearance of the mucosa observed at the time of an upper endoscopy may alert the physician to the possibility of celiac disease (scalloping or loss of folds) and direct her/him to obtain a duodenal biopsy.

13.3 Treatment

The mainstay of therapy for celiac disease is the gluten-free diet, which requires avoiding wheat, rye, barley and oats but allows widely diversified foods. Expert dietetic counseling is a major determinant of successful treatment. Supplements of iron and folic acid are often needed. If milk products cause diarrhea, commercially available lactase enzymes may be used for the first few months. Usually, clinical symptoms improve within weeks, but drastic changes may be seen in sicker patients after a few days.

13.4 Complications and Prognosis

A primary failure to respond to treatment is usually due to incomplete (often involuntary) exclusion of gluten from the diet. Revision of the diet is necessary. A dietary consultation may help to identify sources of unsuspected gluten such as medications, candies or toothpaste. Motivation for continuing with the gluten-free diet is provided by contacts with the physician and dietitian. Other causes of primary failure include diagnostic error (tropical sprue, lymphoma, etc.), dysgammaglobulinemia syndromes, "functional" associated pancreatic insufficiency and so-called refractory sprue. Deterioration after a period of clinical improvement suggests dietary indiscretions, malignancies (there is increased risk of lymphoma) or rare instances of refractory sprue, collagenous sprue and nongranulomatous ulcerative jejunoileitis (Figure 19A and B).

13.4.1 REFRACTORY SPRUE

Refractory sprue is a disease in which malabsorptive symptoms and mucosal biopsy changes recur after an initial response to a gluten-free diet. If symptoms and mucosal biopsy changes persist and do not respond to a gluten-free diet, then the small intestinal disease cannot be defined as celiac disease. Some have termed this disorder unclassified sprue or sprue-like intestinal disease. It may represent a heterogeneous group, but some eventually prove to have an occult lymphoma.

13.4.2 NONGRANULOMATOUS ULCERATIVE JEJUNOILEITIS

This very rare complication presents with abdominal pain, intestinal bleeding and diarrhea. Unfortunately, most have a difficult-to-diagnose ulcerating lymphoma. Ulcers may lead to small bowel perforations or strictures. Presentation with an acute abdomen in celiac disease due to a perforated small bowel ulcer should lead to a strong suspicion for underlying ulcerating lymphoma as the cause of the perforation. The mortality rate for this condition is very high.

13.4.3 COLLAGENOUS SPRUE

This rare disorder is generally associated with severe malabsorption. In addition

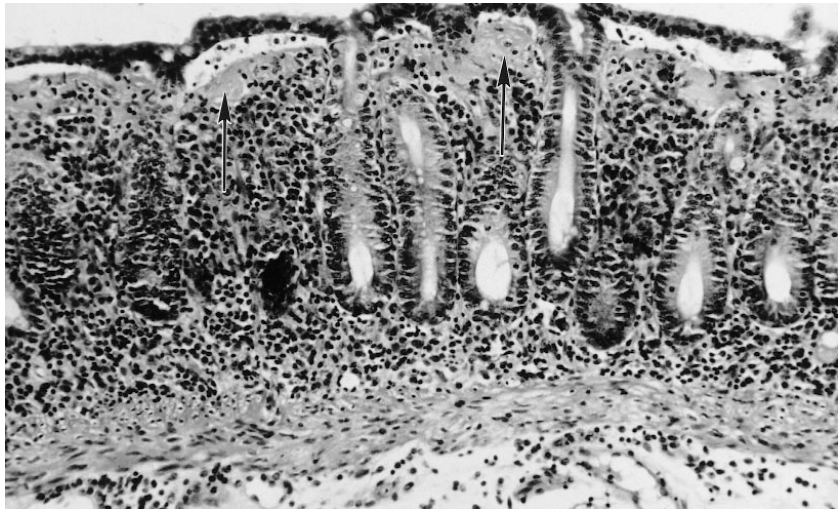

FIGURE 20. This case of collagenous sprue shows the characteristic thick subepithelial fibrous layer (arrows) as well as the characteristic flattening and surface epithelial damage of sprue.

to the characteristic small intestinal biopsy of untreated celiac disease, a striking trichrome-positive band of collagen is seen beneath the surface epithelium (Figure 20). Changes may be patchy, necessitating multiple biopsies from different sites to confirm the diagnosis. There is no effective therapy other than nutritional supportive care.

13.4.4 MALIGNANCIES

Incidence of malignancies is increased in patients with celiac disease. Most of these are small bowel lymphomas, particularly, but not exclusively, T-cell type. Lymphomas in celiac disease may also be located in extra-intestinal sites, and even extra-abdominal sites. A strict gluten-free diet may reduce this risk. Overall, the vast majority of patients with celiac disease have a normal life expectancy.

14. SHORT BOWEL SYNDROME

The severity of symptoms following resections of large segments of the small bowel relates to the extent of the resection, to the specific level of the resected small bowel and to the reason for which the resection was undertaken. The level of resection is important because absorption of nutrients is most effective

in the proximal small bowel (iron, folate and calcium). Resection of up to 40% of the intestine is usually tolerated provided the duodenum and proximal jejunum and distal half of the ileum and ileocecal valve are spared. In contrast, resection of the distal two-thirds of the ileum and ileocecal valve alone may induce severe diarrhea and significant malabsorption even though only 25% of the total small intestine has been resected. Resection of 50% of the small intestine results in significant malabsorption, and resection of 70% or more of the small intestine will result in severe malnutrition sufficient to cause death unless the patient's malnutrition is aggressively treated.

The most common cause of massive resection of the small bowel is small bowel ischemia due to thrombosis or embolism of the superior mesenteric artery, thrombosis of the superior mesenteric vein, or low flow in the splanchnic vessels. Less commonly, volvulus, strangulated hernias, Crohn's disease, neoplasm and trauma necessitate massive resection.

Two major types of diarrhea can develop after massive ileal resection. One is induced primarily by malabsorbed bile acids, and the other by malabsorbed fat. When the ileal resection is small (less than 100 cm), hepatic synthesis of bile acids is sufficient to compensate for increased fecal losses. The luminal concentrations of bile acids are maintained within the micellar range, and significant steatorrhea does not occur. However, with inadequate absorption in the terminal ileum, bile acids enter the colon, impairing electrolyte and water absorption. Thus the term "bile acid diarrhea" is applied to this circumstance.

When the ileal resection is extensive (greater than 100 cm), hepatic compensation for wastage of bile acids is incomplete and the concentration of bile acids in the lumen is too low for adequate micellar solubilization of fat. Steatorrhea results. Here the malabsorbed fat is primarily responsible for the diarrhea. With excessive amounts of fatty acids now in the colon, electrolyte and water absorption are further impaired.

Consistent with these proposed pathogenic mechanisms are the therapeutic observations that a reduction in the dietary intake of long-chain fats will reduce the severity of diarrhea in the second instance (extensive resection and steatorrhea), whereas a sequestrant of bile acids such as cholestyramine, colestipol or aluminum hydroxide is needed for effective therapy of bile acid diarrhea.

Additional metabolic complications arise from the short bowel syndrome. These include hyperoxaluria and subsequent nephrolithiasis. Normally dietary oxalate is excreted in the feces, bound to calcium as an insoluble complex. However, in a patient with steatorrhea, fatty acids in the intestine preferentially bind to calcium, leaving the oxalate soluble and available for absorption in the colon. The short bowel syndrome may also give rise to cholelithiasis. If bile acid malabsorption is extensive, a lithogenic bile will be produced, predisposing to gallstone formation.

15. POSTGASTRECTOMY MALDIGESTION AND MALABSORPTION

Postgastrectomy malabsorption frequently follows gastric surgery. The small size of the gastric remnant causes inadequate mixing of food with digestive juices, particularly after a gastroenterostomy. With the loss of the pylorus, there may be rapid gastric emptying ("dumping"), poor mixing of bile and pancreatic secretions, and rapid transit down the small intestine. Incoordinated secretion and poor mixing of bile and pancreatic juice leads to fat maldigestion. Bacterial contamination in a blind loop (with gastroenterostomy) results in maldigestion of fat, carbohydrate, protein, vitamins and minerals. Gastric surgery that allows food to enter into the upper small intestine without dilution and with minimal digestion may "unmask" clinically occult celiac disease, lactase deficiency or pancreatic insufficiency.

16. NORMAL SMALL INTESTINAL FLORA

The concentration and population of microorganisms that constitute the normal intestinal flora vary with the location along the intestine. Flora in the stomach, duodenum, jejunum and proximal ileum are sparse, usually less than 10^5/mL. The distal ileum represents a transitional zone between the sparse flora of the proximal small intestine and the luxuriant flora of the lower bowel, where microorganism concentrations reach 10^{11}/mL. The predominant species are strict anaerobes, including bacteroides, anaerobic streptococci, bifidobacteria and Clostridium. The commonest aerobic organisms are E. coli; however, their concentration (10^8/mL) is only 1/1,000 of the usual concentration of anaerobes in the colon.

Normally, bacterial flora are present in the intestinal lumen and in the mucus layer overlying the epithelium, and attached to the mucosal cells themselves. There is a specific tissue or cell type to which each microbial species attaches. For example, Streptococcus mutans, the oral organism that causes tooth decay, attaches only to the enamel surface of teeth; removal of the teeth leads to the disappearance of S. mutans from the oral microflora. This phenomenon of adherence may play an important role in the establishment and maintenance of a normal flora.

What are the mechanisms controlling normal small intestinal flora? First, in the stomach, acid suppresses the growth of most organisms that enter from the oropharynx. Bile added in the duodenum has additional antibacterial properties. Second, small intestinal motility mechanically sweeps bacteria downstream, helping to maintain a low concentration of organisms in the proximal small intestine. Third, the ileocecal valve plays an important role in preventing reflux of large amounts of colonic organisms. Additionally, mucus secreted by goblet cells and immunoglobulins has antibacterial properties.

TABLE 16. Etiology of the bacterial overgrowth syndrome

Breakdown of normal defense mechanisms
Achlorhydria
Stasis: Anatomic (Crohn's disease, multiple small bowel diverticula, lymphoma, strictures)
Functional (scleroderma, diabetic autonomic neuropathy, pseudo-obstruction)
Loss of ileocecal valve
Contamination
Postinfection
Enteroenteric fistulas, gastrocolic fistulas

Whereas the small intestine regulates the number of organisms present, in the colon the microorganisms themselves are responsible for maintaining their own population levels. Volatile fatty acids (e.g., acetic, butyric and propionic acid) are produced by anaerobes as well as by some coliforms. These short-chain fatty acids reduce the intraluminal pH and suppress the growth of certain organisms, thereby serving to control proliferation. In addition, some organisms produce other substances that inhibit bacterial growth, called bacteriocins.

Thus far we have considered what the microorganisms are, where they are located, and how their numbers are controlled. We next examine the concept that the normal flora exert a profound influence on intraluminal constituents, including food, urea, bilirubin, bile salts, drugs and potential toxins. Bacteria ferment dietary carbohydrates, yielding short-chain fatty acids, hydrogen and carbon dioxide. Fatty acids from carbohydrates and those from fat in the diet are hydroxylated by the intestinal flora. The hydroxy fatty acids formed stimulate fluid secretion and are thus cathartics.

Similarly, bacteria alter protein and amino acids. Tryptophan is converted to indole compounds, glycine to ammonia, and methionine to hydrogen sulfide. Urea is converted to ammonia, a reaction that may contribute to hepatic encephalopathy. Bilirubin is metabolized to urobilinogen; bile salts may be deconjugated (removing glycine and taurine) and dehydroxylated (cholic acid becomes deoxycholic acid, and chenodeoxycholic acid becomes lithocholic acid). This deconjugation and dehydroxylation renders bile acids more insoluble and less capable of forming micelles. Bacteria also can affect vitamin synthesis and metabolism. Vitamin B_{12} may be bound, thereby becoming unavailable for absorption (hence the abnormal Schilling test in bacterial overgrowth) and vitamin K and folic acid produced.

The normal flora also affect drugs and other ingested materials. Sulfasalazine, a drug used in ulcerative colitis, is unabsorbed in its native form. Intestinal bacteria, however, convert the substance into two moieties, a

TABLE 17. Diagnosis of the bacterial overgrowth syndrome

Jejunal culture
Tests of bile salt deconjugation
^{14}C-glycocholate breath tests
In vitro deconjugation assessment
Tests of malassimilation
Vitamin B_{12} (Schilling test)
D-xylose, glucose, lactulose
H_2 breath tests

therapeutically active aminosalicylic acid and an inactive sulfapyridine. The sulfa drug succinylsulfathiazole is itself inactive, but is converted by intestinal bacteria to sulfathiazole, which is an active antimicrobial agent. Another example is cyclamate, unabsorbed and inert in its native form. Intestinal bacteria produce cyclohexylamine, a potential carcinogenic agent. Thus, bacteria can activate pro-drugs and produce carcinogens.

17. BACTERIAL OVERGROWTH SYNDROME

The bacterial overgrowth syndrome (small bowel bacterial contamination syndrome) can result from any disease that interferes with the normal balance (ecosystem) of the small intestinal flora and brings about loss of gastric acidity; alteration in small bowel motility or lesions predisposing to luminal stasis; loss of the ileocecal valve; or overwhelming contamination of the intestinal lumen (Table 16).

The bacterial overgrowth syndrome gives rise to clinical abnormalities arising from the pathophysiological effects on the luminal contents and the mucosa. Bacteria can consume proteins and carbohydrates. In bacterial overgrowth there may be defective transport of sugars, possibly related to the toxic effect of deconjugated bile acids. Steatorrhea results from the deconjugation and dehydroxylation of bile acids; lithocholic acid is precipitated and free bile acids are reabsorbed passively, making them unavailable and incapable of performing micellar solubilization. There may also be mucosal damage. Fats, cholesterol and fat-soluble vitamins are malabsorbed. Vitamin B_{12} is also malabsorbed as a result of the binding and incorporation of this vitamin into the bacteria. Folate deficiency, however, is not a common occurrence in bacterial overgrowth; unlike vitamin B_{12}, folate synthesized by microorganisms in the

small bowel is available for host absorption. In patients with small bowel bacterial overgrowth, serum folate levels tend to be high rather than low. The enteric bacteria also produce vitamin K, and patients with bacterial overgrowth who are on the anticoagulant warfarin may have difficulty in maintaining the desired level of anticoagulation. In addition to steatorrhea, patients with bacterial overgrowth frequently complain of watery diarrhea. Important mechanisms in producing this diarrhea include (1) disturbances of the intraluminal environment with deconjugated bile acids, and hydroxylated fatty and organic acids; and (2) direct changes in gut motility.

In some patients, symptoms of the primary disease predominate, and evidence of bacterial overgrowth may be found only on investigation. In others, the primary condition is symptomless, and the patient presents with a typical malabsorption syndrome due to bacterial overgrowth. Once diagnosis of bacterial overgrowth is suspected a careful history should be performed to identify possible causes. Physical examination may be normal or may demonstrate signs related to specific nutrient deficiencies.

A small bowel biopsy is of value in excluding primary mucosal disease as the cause of the malabsorption. Histologic abnormalities of the jejunal mucosa are usually not seen in patients with bacterial overgrowth. The sine qua non for the diagnosis of bacterial overgrowth is a properly collected and appropriately cultured aspirate of the proximal small intestine (Table 17). Specimens should be obtained under anaerobic conditions and quantitative colony counts determined. Generally, bacteria concentrations of greater than 10^5 organisms per mL are highly suggestive of bacterial overgrowth. Such methods are difficult and usually undertaken only in a research setting. Alternatively, one can attempt to demonstrate a metabolic effect of the bacterial overgrowth, such as intraluminal bile acid deconjugation by the ^{14}C-glycocholate breath test. Cholylglycine-^{14}C (glycine-conjugated cholic acid with the radiolabeled ^{14}C on the glycine moiety) when ingested circulates normally in the enterohepatic circulation without deconjugation. Bacterial overgrowth within the small intestine splits the ^{14}C-labeled glycine moiety and subsequently oxidizes it to ^{14}C-labeled CO_2, which is absorbed in the intestine and exhaled. Excess $^{14}CO_2$ appears in the breath. The bile acid breath test cannot differentiate bacterial overgrowth from ileal damage or resection where excessive breath $^{14}CO_2$ production is due to bacterial deconjugation within the colon of unabsorbed ^{14}C-labeled glycocholate. This creates clinical difficulties, since bacterial overgrowth may be superimposed on ileal damage in such conditions as Crohn's disease.

Breath hydrogen analysis allows a distinct separation of metabolic activity of intestinal flora of the host, since no hydrogen production is known to occur in mammalian tissue. Excessive and early breath hydrogen production has

been noted in patients with bacterial overgrowth following the oral administration of 10 g of lactulose, or a poorly absorbed sugar that is metabolized by the luminal bacteria to H_2.

Another hallmark of bacterial overgrowth is steatorrhea, detected by the 72-hour fecal fat collection.

The Schilling test may also be abnormal. ^{57}Co-B_{12} is given with intrinsic factor following a flushing dose of nonradioactive B_{12} given parenterally to prevent tissue storage of the labeled vitamin. In healthy subjects, ^{57}Co-B_{12} combines with intrinsic factor and is absorbed and > 8% excreted in the urine within 24 hours. In patients with bacterial overgrowth, the bacteria combine with or destroy intrinsic factor, the vitamin or both, causing decreased vitamin B_{12} absorption. Following treatment with antibiotics the B_{12} absorption returns to normal.

Treatment of bacterial overgrowth involves removing the cause, if possible. The addition of an antibiotic (tetracycline 250 mg q.i.d., or metronidazole 250 mg q.i.d., for 10 days) will often induce a remission for many months. If the cause cannot be eliminated and symptoms recur, good results can be achieved with intermittent use of antibiotics (e.g., once a day, one day a week, or one week out of every four).

18. PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy describes a wide range of gastrointestinal disorders that are associated with an excessive loss of plasma protein into the gut lumen. Normal daily enteric loss of plasma protein corresponds to less than 1–2% of the plasma pool. The route of plasma protein loss across the normal mucosa is not well defined. It is likely that rapid shedding of epithelial cells from the mucosal surface is accompanied by loss of plasma proteins from the lamina propria at the site of cell extrusion.

In virtually any small intestinal disease, excessive transmural loss of plasma proteins may result from several mechanisms: in mucosal disease without ulceration but with increased permeability; in mucosal disease with erosion or ulceration (loss of inflammatory exudate that contains protein occurs); and in lymphatic obstruction with direct leakage of intestinal lymph from obstructed lacteals. Protein-losing enteropathy may also occur as a result of colonic inflammation, ischemia or tumor. Adaptive changes in endogenous synthesis of individual plasma proteins may compensate partially for excessive enteric loss.

Clinically, albumin loss may be manifested by dependent edema. A depression of the levels of thyroid and cortisol binding proteins will lower the total plasma level of these hormones, although normal levels of free hormone will maintain normal hormone function. Excessive enteric loss of plasma proteins

other than albumin rarely leads to clinical problems; secondary hypogammaglobulinemia in these patients does not predispose them to infection, and the loss of blood clotting factors is rarely sufficient to impair hemostasis.

Patients with protein-losing enteropathy due to lymphatic obstruction, however, lose not only albumin and other plasma proteins but also intestinal lymph, with loss of long-chain triglycerides, fat-soluble vitamins and small lymphocytes.

Protein-losing enteropathy is considered in patients who exhibit hypoproteinemia and in whom other causes for hypoproteinemia (e.g., proteinuria, protein malnutrition and liver disease) are excluded. Fecal protein loss can then be quantitated using ^{51}Cr-labeled albumin or α_1-antitrypsin clearance into stool.

Management of protein-losing enteropathy involves the appropriate treatment of the disease(s) causing the protein loss. Enteral or parenteral feeding can be used to improve nutrition while the underlying disease is being treated. Enteric protein loss in patients with intestinal lymphangiectasia usually decreases with a low-fat diet. The normal absorption of long-chain triglycerides stimulates intestinal lymph flow; in their absence there is a decrease in the pressure within intestinal lymphatic vessels and hence a diminished loss of lymph into the lumen. Medium-chain triglycerides, which do not require intestinal lymphatic transport, can be substituted for the long-chain triglycerides and further decrease intestinal lymphatic pressure, with subsequent reduction in enteric lymph and protein loss.

19. MECKEL'S DIVERTICULUM

Meckel's diverticulum, an omphalomesenteric duct remnant, is a congenital outpouching usually located in the distal 100 cm of the ileum. Such diverticula are present in 1–3% of the general population. Of these, 30–40% are asymptomatic. Complications of Meckel's diverticulum include hemorrhage, intestinal obstruction, diverticulitis, umbilical discharge, perforation and peritonitis. Bleeding is the most common complication, resulting from ulceration of the ileal mucosa adjacent to ectopic gastric mucosa located within the diverticulum. (However, in the patients with a Meckel's diverticulum but without ectopic gastric mucosa, bleeding does not usually occur.) This bleeding is often painless and is usually encountered in children and young adults. Meckel's diverticulum accounts for nearly 50% of all lower gastrointestinal bleeding in children. Technetium-99m pertechnetate is normally taken by the ectopic gastric mucosa, providing the basis for the Meckel scan. Since only 60% of Meckel's diverticula contain ectopic gastric mucosa, false negative results occur. If the scan is positive, increased sensitivity can be achieved by

repeating the scan after a short course of a histamine$_2$-receptor antagonist (H_2-RA): the H_2-RA releases acid secretion by the ectopic parietal cells in the Meckel's diverticulum and may thereby convert a positive into a negative scan.

20. CARCINOID SYNDROME

Over 90% of carcinoid tumors originate in the gastrointestinal tract. The most frequent sites are the appendix, terminal ileum and rectum. In general, non-metastasized carcinoid tumors are asymptomatic. The carcinoid syndrome is associated only with carcinoid tumors that have metastasized extensively to the liver or are extraintestinal (e.g., lung tumors). Metastasis is infrequent in carcinoids of the appendix, but is common in extra-appendiceal carcinoids.

Although carcinoid tumors differ in their ability to produce and store 5-hydroxytryptamine (5-HT), the excessive production of this substance and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) remains their most characteristic chemical abnormality. Production of this hormone (as well as histamine, catecholamines, kinase and prostaglandins) causes the majority of symptoms. The symptom complex comprises diarrhea, flushing, wheezing, cluster headache, valvular heart disease (particularly pulmonary stenosis) and a pellagra-like skin rash. The carcinoid syndrome can be suspected clinically and confirmed biochemically by the demonstration of increased urinary 5-HIAA or platelet 5-HT.

Once the carcinoid syndrome is apparent, cure is usually impossible, since the tumor has metastasized by this time. Nevertheless, the intestinal origin of the tumor should be removed if it is causing obstruction. Serotonin antagonists (e.g., methysergide and cyproheptadine) can sometimes reduce symptoms. The somatostatin analogue octreotide may prove to be very effective in reducing the patient's symptoms; interferon may also prove to be useful. It is prudent to delay initiation of chemotherapy or radiation in the early metastatic stage of the disease, since the course is often indolent and patients survive many years with diffuse metastatic disease.

21. WHIPPLE'S DISEASE

Whipple's disease characteristically occurs in middle-aged men, who present with weight loss, fever, abdominal pain, arthralgias and intestinal symptoms of diarrhea and malabsorption. Small bowel biopsy characteristically demonstrates PAS-positive macrophages containing the bacillus Tropheryma whippelii plus an enteropathy with villous atrophy (Figure 21A and B). Treatment improves the fever and joint symptoms within a few days; the diarrhea and malabsorption disappear within two to four weeks. Because some patients with Whipple's disease may

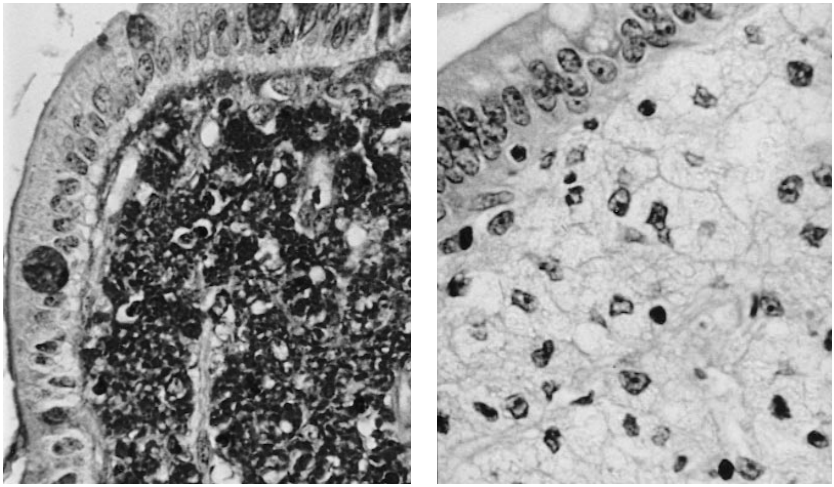

FIGURE 21A. The right-hand panel shows the H & E appearance of Whipple's disease with foamy histiocytes replacing normal lamina propria structures. The enterocytes are normal morphology. The left-hand panel shows the intense PAS positivity of the Whipple cells (as well as goblet cells and the brush border).

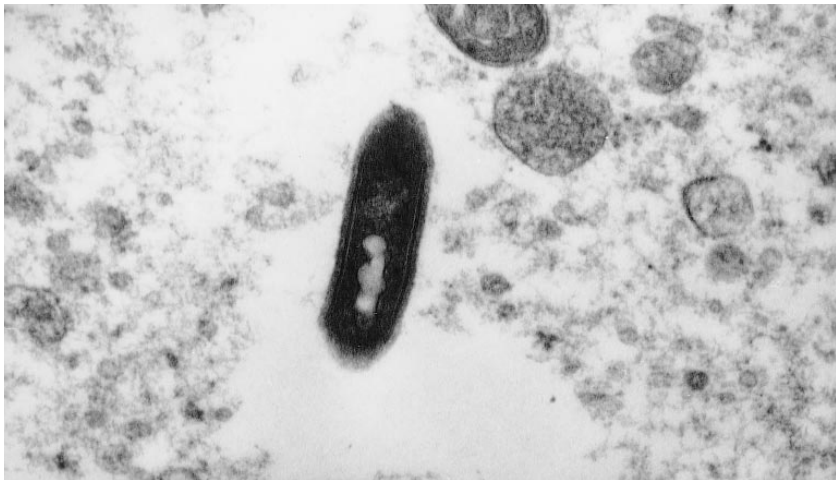

FIGURE 21B. Electron micrograph showing the characteristic fine structure of the Whipple bacillus.

develop CNS involvement with the recently identified organism, trimethoprim-sulfamethoxazole antibiotics are recommended; treatment is continued for one year. Relapses may occur up to one or two years later and require repeat therapy.

22. IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

Idiopathic intestinal pseudo-obstruction is a disease of the muscular layer or of the enteric nervous system of the intestine. The myogenic form of idiopathic intestinal pseudo-obstruction is an autosomal dominant disease characterized by thinning of the intestinal musculature due to degeneration, fibrosis, malaligned smooth fibers and abnormal contractile filaments. All parts of the intestinal tract may be involved, but usually the small intestine, esophagus and colon are the most severely affected.

The neurogenic form of this disease is characterized by abnormal neuronal and glial cells. The damage may be in the spinal cord or in the splanchnic ganglia. When the splanchnic ganglia are involved, intranuclear inclusion bodies can be identified. The condition is characterized by abnormal systemic neural function, with an inappropriate blood pressure response to phenylephrine, Valsalva's maneuver, or achieving the upright posture. There is a lack of sweating on warming of the skin, pupillary denervation hypersensitivity, and lack of intestinal spike activity after small intestinal distention.

Treatment of both the myogenic and neurogenic forms of idiopathic intestinal pseudo-obstruction is generally unsuccessful. Various promotility agents have been tried with only transient success. The somatostatin analogue octreotide may be useful in some patients. Associated bacterial overgrowth may worsen bloating and diarrhea, and should be treated with antibiotics. Surgery only aggravates the disorder and provides long intervals of severe ileus. Home parenteral nutrition may be the only alternative to maintain the patient's nutritional status, reduce the frequency and severity of the associated intestinal complaints, and improve the quality of the patient's life.

23. SMALL INTESTINAL VASCULAR DISORDERS

This topic is considered in detail in Chapter 7, and is only reviewed briefly here.

23.1 Acute Mesenteric Ischemia

The major causes of acute mesenteric ischemia are embolic obstruction thrombosis of the superior mesenteric artery (SMA), mesenteric venous thrombosis and nonocclusive ischemia. The congenital hypercoagulable states due to protein C or S antithrombin III deficiency can also cause thrombosis of the superior mesenteric vein. Embolic obstruction of the superior mesenteric artery is usually associated with cardiac arrhythmias, valvular disease, recent myocardial infarction or mycotic aneurysm. When an embolus lodges at the origin of the superior mesenteric artery, the entire small bowel and proximal colon are affected. Mesenteric venous thrombosis usually involves the superior mesenteric vein or

its branches and the portal vein. It can be "primary" or "secondary" to a variety of hypercoagulable states (e.g., polycythemia rubra vera, carcinomatosis, oral contraception); to intra-abdominal sepsis (e.g., cholangitis, diverticular abscess); or to a condition in which blood flow is impaired (e.g., cardiogenic shock).

Nonocclusive bowel ischemia is the most common and lethal form of intestinal vascular insufficiency, accounting for at least 50% of all cases, with a mortality rate approaching 100%. It is commonly associated with reduced cardiac output, intra-abdominal sepsis and advanced malignant neoplasms. Digitalis constricts the splanchnic circulation and may aggravate or even precipitate mesenteric ischemia.

The typical patient is over 50 years of age, with arteriosclerotic or valvular heart disease, poorly controlled long-standing congestive heart failure, hypotension, recent myocardial infarction or cardiac arrhythmias. Abdominal pain is characteristically periumbilical and crampy. In the early stages, physical signs are often minimal. The abdomen is soft, sometimes slightly distended, with mild tenderness on palpation. Abdominal pain of any degree of severity associated with minimal abdominal findings and a high WBC (often over 20,000/mm^2) is an important early clue to the correct diagnosis. Signs of advanced ischemia include nausea, vomiting, peritoneal irritation, leukocytosis and a progressive metabolic acidosis. In a minority, unexplained abdominal distention or gastrointestinal bleeding, or the rapid onset of confusion and acidosis in an elderly patient, may be the first manifestation of small bowel ischemia.

Initial resuscitation is directed at correcting the predisposing or precipitating cause(s). Restoration of cardiac output with IV fluid is paramount. Digitalis, diuretics and vasoconstrictors should be discontinued if possible. Plain radiographs, ultrasound or CT scans as appropriate should exclude other radiologically diagnosable causes of acute abdominal pain. After volume repletion, the key step in the management of acute mesenteric ischemia is abdominal angiography. Remember that angiography in a hypovolemic or hypotensive patient frequently shows mesenteric vasoconstriction; for such patients the technique loses its usefulness as a diagnostic tool. Also, angiography in a volume-depleted patient may precipitate renal failure. If the angiogram is normal, the patient should be carefully observed, and a diagnostic laparotomy performed only if peritoneal signs develop. If the angiogram shows a minor arterial occlusion and clinically there is no peritoneal irritation, papaverine can be infused into the superior mesenteric artery through the catheter used for angiography at a rate of 60 mg/hour. (The role of angioplasty or other angiographic techniques remains unproven.) If peritoneal signs occur at any time, a laparotomy with resection of the ischemic segment is indicated. If the angiogram shows a major obstruction at the origin of the superior mesenteric artery, laparotomy should be carried out immediately. An embolus can usually be easily removed, while

thrombotic obstruction requires a bypass graft from the aorta to an area of the artery distal to the site of obstruction. After revascularization, any nonviable bowel should be resected. It is advisable to save all bowel that may be viable and to re-explore the patient 24 hours later. The decision to perform a "second look" operation is made at the initial laparotomy and should not be changed on the basis of a favorable postoperative course. Since acute occlusion of the superior mesenteric artery is associated with prolonged vasospasm, the artery should be perfused with papaverine for 24 hours postoperatively.

If nonocclusive splanchnic vasoconstriction is present, intra-arterial papaverine infusion should be started. If, in spite of the infusion, abdominal pain persists and signs of peritoneal irritation appear, a laparotomy must be performed without delay.

Venous thrombosis is characterized on the angiogram by a prolonged arterial phase and a lack of opacity in the venous system. If a firm diagnosis of venous thrombosis has been made, anticoagulants are appropriate. However, if the patient develops peritoneal signs, immediate laparotomy and resection are indicated.

This systemic approach to the management of ischemia originating in the superior mesenteric artery results in earlier diagnosis and avoidance of surgery. The overall mortality rate has been reduced to about 50%; 90% of the patients who have no peritoneal signs at the time of angiography survive.

23.2 Chronic Mesenteric Ischemia

This uncommon condition occurs in elderly patients with partial occlusion of at least two of the three principal mesenteric vessels (the celiac axis and the superior and inferior mesenteric arteries). Epigastric or periumbilical abdominal pain beginning after a meal and lasting for one to three hours ("*intestinal angina*") is the most characteristic clinical feature, although it is not often elicited. The pain may lead to a reduction in food intake (sitophobia) and secondarily a significant loss of weight. Bloating, flatulence and diarrhea are common, and steatorrhea is present in 50% of patients. This is the case because chronic mesenteric ischemia can cause mucosal damage. The physical examination is usually not diagnostic. A systolic abdominal bruit is present in 50% of patients but is not pathognomonic. (Epigastric bruits are common in normal persons.) Patients in whom the syndrome is suspected, and who have no other demonstrable abnormality to explain their symptoms, should have abdominal angiography. If angiography shows greater than 90% occlusion of at least two vessels, either angioplasty or an aorto-SMA (superior mesenteric artery) graft is required. The mortality rate for this procedure is less than 10% and the majority of patients will be relieved of their postprandial intestinal angina. It is important to identify and to treat chronic mesenteric ischemia because of the high risk of thrombosis of the SMA.

24. SMALL BOWEL TUMORS

24.1 Benign Small Bowel Tumors

Both benign and malignant small bowel tumors are rare. Adenomas, leiomyomas and lipomas are the three most frequently discovered primary tumors of the small intestine. Hamartomas, fibromas, angiomas and neurogenic tumors are much less common. As a general rule, benign tumors are least common in the duodenum and increase in frequency toward the ileum. Benign tumors often remain asymptomatic and are usually found incidentally.

Symptomatic benign tumors present primarily with obstructive features, giving rise to intermittent colicky abdominal pain or complete bowel obstruction. Bleeding may occur, particularly from leiomyomas that ulcerate centrally. Intussusception occurs with polypoid distal lesions.

24.2 Malignant Neoplasms of the Small Intestine

Adenocarcinomas, lymphomas, leiomyosarcomas and carcinoids are the most common primary small bowel malignant tumors. Metastatic cancer to the small intestine occurs rarely in patients with melanoma, breast cancer and lung cancer. Primary adenocarcinomas occur in the duodenal and proximal jejunum as annular lesions, narrowing the lumen and presenting with the signs and symptoms of obstruction. Adenocarcinomas of the small bowel are more common in patients with Crohn's disease (distal small intestine) and celiac disease (proximal small intestine). Leiomyosarcomas are evenly distributed along the small bowel. Symptoms are similar to those of adenocarcinoma – i.e., crampy abdominal pain and bleeding. Lymphoma of the small bowel must be carefully evaluated to determine whether the tumor has originated in the small intestine (primary lymphoma) or whether the small bowel is involved by a diffuse systemic lymphoma. Lymphoma of the small bowel is more common in patients with celiac disease. Primary lymphoma of the small intestine is usually a B-cell type, although a specialized form of T-cell lymphoma or T-cell enteropathy may occur, sometimes associated with celiac disease. The lymphoma is most often proximal and presents with abdominal pain, weight loss, malabsorption, perforation and anemia. There is an increased incidence of primary lymphoma in patients with longstanding celiac disease or immunodeficiency states and in renal transplant patients receiving chronic immunosuppressive therapy.

A specific form of malignant lymphoma called immunoproliferative small intestinal disease occurs in people of Mediterranean descent. It is characterized by proliferation of mucosal B cells and has a high incidence of α-heavy chain paraproteinemia. It typically involves the duodenum and proximal jejunum, presenting with diarrhea and malabsorption. Recent evidence suggests that some of these may be caused by a bacterial infection that may respond to antibiotics.

SUGGESTED READING LIST

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Freeman HJ. Small intestinal mucosal biopsy for investigation of diarrhea and malabsorption in adults. Gastroenterol Clin North Am 2000; 10:739-753.
Thomson ABR, Drozdowski L, Iordache C, Thomson BKA, Vermeire S, Clandinin T, Wild G. Small Bowel Review: Normal physiology and diseases of the small intestine. Dig Dis Sci 2003; 48:1546-1599.

OBJECTIVES

1. Discuss the intestinal fluid and electrolyte transport mechanisms.
2. Explain the normal digestion and absorption processes of fat, protein and glucose.
3. Describe the normal pathway of vitamin B_{12}, folate and iron absorption.
4. Locate the absorption sites of Fe, folate and B_{12}.
5. Utilize a proper diagnostic approach to the patient with chronic diarrhea.
6. Discuss normal enterohepatic circulation of bile acids.
7. Discuss normal assimilation of fat-soluble vitamins (A, D, E and K).

Diarrhea

1. Define diarrhea.
2. Classify the causes of diarrhea.
3. Discuss the pathogenic mechanisms of diarrhea.
4. Review diarrhea as altered fluid and electrolyte transport.
5. Differentiate between large and small bowel diarrhea.
6. Discuss diagnostic plans in patients with chronic diarrhea.
7. List conditions that are associated with typical small bowel lesions on biopsy.
8. List the complications of celiac disease.
9. List extraintestinal manifestations of celiac disease.
10. Outline the diagnosis and dietary management of celiac disease.
11. Give the differential diagnosis of "unresponsive" sprue.
12. Discuss the immunologic basis of celiac disease.
13. Recognize the principal manifestation of the carcinoid syndrome.
14. Discuss pharmacologic agents used in the carcinoid syndrome.
15. List biochemical tests used in diagnosing the carcinoid syndrome.
16. Discuss the management of traveler's diarrhea.
17. List the common causes of traveler's diarrhea.
18. Discuss the mechanisms of E. coli-induced diarrhea.
19. List the infectious causes of diarrhea and their management.

20. Discuss the use and mechanisms of antidiarrheal agents.
21. Give the differential diagnosis of abnormal terminal ileum.
22. Describe the radiographic features of small bowel obstruction.
23. Outline the etiology of vitamin B_{12} deficiency with the bacterial overgrowth syndrome.
24. List the underlying conditions associated with bacterial overgrowth.
25. Discuss the mechanisms of steatorrhea associated with the bacterial overgrowth syndrome.
26. Recognize the clinical presentations of the bacterial overgrowth syndrome.
27. Outline the management of the bacterial overgrowth syndrome.
28. Utilize appropriate diagnostic tests for the bacterial overgrowth syndrome.
29. Recognize complications of the short bowel syndrome and their mechanisms.
30. Discuss the adaptive mechanisms of the small bowel following resection.
31. Discuss the management of the short bowel syndrome.
32. Give the indications for the use of medium-chain triglycerides.
33. Outline the diagnosis and treatment of giardiasis.
34. Recognize the clinical presentations and treatment of amebiasis.
35. Describe typical features of Whipple's disease.
36. List the causes of protein-losing enteropathy.
37. List the possible mechanisms of diarrhea in patients with diabetes mellitus.
38. List the possible mechanisms of diarrhea in the Zollinger-Ellison syndrome.
39. List mechanisms of diarrhea following gastric surgery.
40. Discuss diagnostic tests for lactase deficiency/lactose intolerance.
41. List conditions associated with protein-losing enteropathy.
42. Recognize the features of intestinal lymphangiectasia and outline its treatment.

Skills

1. Give the indications for gastroscopy, small bowel biopsy, sigmoidoscopy and colonoscopy.
2. Arrange the proper sequences of GI diagnostic procedures, including radiographic examination (ultrasound, CT scan), and the appropriate order of investigational tests.
3. Utilize proper tests – including malabsorption screen, ^{14}C breath test, H_2 breath test, Schilling test, 72-hour stool collection, x-ray, small bowel biopsy and jejunal aspiration – in the investigation of chronic diarrhea.