06 - 336 Disorders of Absorption

336 Disorders of Absorption

and weight loss are signs and symptoms in patients with MD. Occult GI bleeding may occur, but overt bleeding is unusual and, when present, is due to superficial mucosal erosions. In fact, bleeding is more often seen in one of the common mimics of MD, gastric polyposis. Twenty to 100% of patients (depending on time of presentation) develop a pro tein-losing gastropathy due to hypersecretion of gastric mucus accom panied by hypoalbuminemia and edema. Gastric acid secretion is usually reduced or absent because of the decreased parietal cells. Large gastric folds are readily detectable by either radiographic (barium meal) or endoscopic methods. Endoscopy with deep mucosal biopsy, preferably full thickness with a snare technique, is required to establish the diagnosis and exclude other entities that may present similarly. A nondiagnostic biopsy may lead to a surgically obtained full-thickness biopsy to exclude malignancy. Although MD is considered premalig nant by some, the risk of neoplastic progression is not defined. Com plete blood count, serum gastrin, serum albumin, CMV and H. pylori serology, and pH testing of gastric aspirate during endoscopy should be included as part of the initial evaluation of patients with large gastric folds. A retrospective case-control study suggested an increased risk of developing gastric adenocarcinoma and decreased 5- and 10-year sur vival compared to a control cohort. Additional studies will be required to confirm these initial findings, but this may be difficult to achieve in light of the rarity of this unusual diagnosis.

TREATMENT Ménétrier’s Disease Medical therapy with anticholinergic agents, prostaglandins, PPIs, prednisone, somatostatin analogues (octreotide), and H2 receptor antagonists yields varying results. Ulcers should be treated with a standard approach. The discovery that MD is associated with overstimulation of the EGFR pathway has led to the successful use of the EGF inhibitory antibody, cetuximab, in these patients. Specifically, four of seven patients who completed a 1-month trial with this agent demonstrated near-complete histologic remission and improvement in symptoms. Cetuximab is now considered the first-line treatment for MD, leaving partial or total gastrectomy for severe disease with persistent and substantial protein loss despite therapy with this agent. PART 10 Disorders of the Gastrointestinal System ■ ■FURTHER READING Abrignani MG et al: Proton pump inhibitors and gastroprotection in patients treated with antithrombotic drugs: A cardiologic point of view. World J Cardiology 15:8, 2023. Bindu S et al: Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol 180:114147, 2020. Bjarnason I et al: Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. Gastroenterology 154:500, 2018. Brandi ML et al: Multiple endocrine neoplasia type 1: Latest insights. Endocr Rev 42:133, 2021. Chey WD et al: ACG clinical

guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol 112:212, 2017. Engevik A et al: The physiology of the gastric parietal cell. Physiol Rev 100:2, 2020. Jensen RT, Ito T: Gastrinoma, in Endotext [Internet]. Feingold KR, Anawalt B, Blackman MR, et al (eds). South Dartmouth (MA) 2000-. Updated Sept. 2023. Available from MDText.com https://www.ncbi.nlm.nih.gov/books/NBK279075/. Kavitt RT et al: Diagnosis and treatment of peptic ulcer disease. Am J Med 132:447, 2019. Luo Q et al: A review on the research progress on non-pharmaco logical therapy of Helicobacter pylori. Front Microbiol 14:1134254,

)23.
Malfertheiner P et al: Management of Helicobacter pylori infection: The Maastricht V/Florence Consensus Report. Gut 71:9, 2022.

Malfertheiner P et al: Helicobacter pylori infection. Nat Rev 9:19, 2023. Pennelli G et al: Gastritis: Update on etiological features and histo logical practice approach. Pathologica 112:153, 2020. Rao S et al: Survival times of patients with Menetrier's disease and risk of gastric cancer. Clin Gastroenterol Hepatol 19:10, 2021. Savarino V et al: Proton pump inhibitors: Use and misuse in the clini cal setting. Expert Rev Clin Pharmacol 11:1123, 2018. Shah SC et al: AGA Clinical Practice Update on the management of refractory Helicobacter pylori infection: Expert review. Gastroenterol ogy 160:5, 2021. Yao X, Smolka AJ: Gastric parietal cell physiology and Helicobacter pylori-induced disease. Gastroenterology 156:2158, 2019. Deborah C. Rubin

Disorders of Absorption A wide range of diseases affect gastrointestinal (GI) absorptive func tion and may result in malabsorption syndromes. These disorders affect one or more of the three phases of enteral nutrient processing. Luminal digestion is initiated by lingual and gastric lipase and gastric pepsin and continues in the small bowel by the actions of pancreatic enzymes and bile salts. Small-intestinal mucosal digestion and absorp tion are mediated by enterocyte brush border enzymes including disaccharidases, enterokinases, and peptidases, which digest nutri ents upon contact, and by mixed micelles containing lipids and bile salts. Protein and carbohydrate digestive products are transported into the enterocyte by carriers and transporters, and lipids enter by diffusion mediated by micelles. Once in the enterocyte, nutrients may be reprocessed for postmucosal absorption and entry into lymphatics (long-chain triglycerides as part of chylomicrons) or are transported into the bloodstream. Malabsorptive diseases or syndromes can be classified by their effects on one or more of these three phases of absorption (Table 336-1). Disorders of absorption also have diverse clinical presentations. For example, the deficiency of a single brush border membrane protein such as lactase causes symptoms of diarrhea by affecting the absorption of one nutrient, lactose. Celiac sprue may be localized to the duodenum and present with isolated iron deficiency or may cause diffuse intestinal mucosal disease, affecting the absorption of multiple nutrients and causing a constellation of symptoms and clini cal presentations. Definition of Diarrhea Diarrhea is the most common symptom associated with disorders of absorption. For most patients, diarrhea as a symptom is defined as an increase in stool number or frequency or a change in consistency. Because normal bowel patterns may vary from as many as two to four bowel movements per day to one stool per week, it is critical to use an objective measure of diarrhea to help direct evalu ation. In health, stool volume or weight is <200 mL or <200 g, respec tively, in 24 h. Collection of stool for weight/volume determination is one of the most useful tools for an evaluation of diarrhea. In particular, a 72-h collection for weight/volume and fecal fat determination is the gold standard for documenting the presence of steatorrhea, or fatty stool.

Steatorrhea, defined as increased stool fat excretion to >7% of dietary fat, is a common manifestation of malabsorption. Steatorrhea often results in large, bulky, and malodorous stools. Malabsorption of single nutrients like lactose may result in an osmotic diarrhea, in which the osmotically active unabsorbed nutrient causes fluid to be drawn into the GI tract lumen. Malabsorptive diarrhea frequently is precipitated by eating and resolves or significantly decreases at night,

TABLE 336-1 Classification of Malabsorption Syndromes Inadequate digestion Postgastrectomya Deficiency or inactivation of pancreatic lipase Exocrine pancreatic insufficiency Chronic pancreatitis Pancreatic carcinoma Cystic fibrosis Pancreatic insufficiency—congenital or acquired Gastrinoma—acid inactivation of lipase Drugs—orlistat Reduced intraduodenal bile-acid concentration/impaired micelle formation Liver disease Parenchymal liver disease Cholestatic liver disease Bacterial overgrowth in small intestine: Anatomic stasis Functional stasis Afferent loop Diabetesa Stasis/blind Sclerodermaa Loop/strictures/fistulae Intestinal pseudo-obstruction Interrupted enterohepatic circulation of bile salts Ileal resection Crohn’s disease Drugs (binding or precipitating bile salts)—neomycin, cholestyramine, calcium carbonate Impaired mucosal absorption/mucosal loss or defect Intestinal resection or bypassa Inflammation, infiltration, or infection: Crohn’s diseasea Celiac disease Amyloidosis Collagenous sprue Sclerodermaa Whipple’s diseasea Lymphomaa Radiation enteritisa Eosinophilic enteritis Folate and vitamin B12 deficiency Mastocytosis Infections—giardiasis Tropical sprue Graft versus host disease Genetic disorders Disaccharidase deficiency Agammaglobulinemia Abetalipoproteinemia Hartnup’s disease Cystinuria Impaired nutrient delivery to and/or from intestine: Lymphatic obstruction Circulatory disorders Lymphomaa Congestive heart failure Lymphangiectasia Constrictive pericarditis Mesenteric artery atherosclerosis Vasculitis Endocrine and metabolic disorders Diabetesa Hypoparathyroidism Adrenal insufficiency Hyperthyroidism Carcinoid syndrome aMalabsorption caused by more than one mechanism. with fasting, and thus can frequently be distinguished from secre tory diarrheas, for example from infectious causes such as bacterial enterotoxigenic Escherichia coli. In this circumstance, intestinal fluid and electrolyte secretion is stimulated by enterotoxin and will continue even during fasting.

OVERVIEW: NUTRIENT DIGESTION

AND ABSORPTION Luminal digestive processes begin in the mouth and proceed through out the GI tract, mediated by salivary amylase, lingual and gastric lipases, gastric acid, pancreatic enzymes, and bile salts. As nutrients are digested in the lumen of the proximal GI tract, they are further pro cessed by enterocyte brush border enzymes including disaccharidases such as lactase and sucrase-isomaltase, which produce monosaccha rides, and peptidases, which hydrolyze polypeptides into tripeptides and dipeptides and amino acids. Lipids in mixed micelles are then absorbed into enterocytes.

The surface area of the small bowel, which is normally 600 cm long, is further enhanced by circular folds, villi, and microvilli. Fol lowing uptake into enterocytes, nutrients are further processed and transported into the lymphatics or into the portal circulation for use by other cells throughout the body. The intestine is also presented with 7–9 L of fluid daily, a volume comprising dietary fluid intake (1–2 L/day) and salivary, gastric, pancreatic, biliary, and intestinal fluid (6–7 L/day). In health, almost all of this fluid is reabsorbed by the small bowel and colon, resulting in a normal

stool volume of <200 mL or stool weight of <200 g. ■ ■SPECIFIC NUTRIENTS Lipids Lipid absorption is a complex process that requires hydroly sis by pancreatic enzymes and bile salts for physiochemical dispersion of fats, followed by absorption of processed lipid nutrients dispersed in bile salt–mixed micelles across the intestinal epithelium. Bile acids are synthesized in the liver, secreted into the intestinal lumen, and constantly recirculated by absorption in the ileum. The ileum expresses fibroblast growth factor 19 (FGF19), which is a physiologic bile acid sensor. FGF19 is secreted from the ileum into the bloodstream in response to bile acid flux and negatively regulates hepatic bile acid synthesis by affecting the transcription of hepatic CYP7A1. CHAPTER 336 Disorders of Absorption Thus, assimilation of dietary lipid requires three integrated pro cesses: an intraluminal or digestive phase, a mucosal or absorptive phase, and a delivery or postabsorptive phase (Table 336-2). Gastric lipases begin the lipolytic process. Following entry into the small bowel, long-chain triglycerides, with carbon lengths >12 and that are the major component of dietary lipid, are hydrolyzed by pancreatic lipases into fatty acids and monoglyceride during a process called lipolysis (Fig. 336-1). Long-chain free fatty acids are dispersed by bile salts into mixed micelles, which contact the brush border and permit fatty acid absorption into enterocytes across this specialized apical membrane. The other two types of fatty acids that compose fats, medium-chain and short-chain fatty acids, are soluble in the unstirred water layer. Medium-chain triglycerides with carbon chain lengths of 8–12 are found in coconut oil. Long-chain fatty acids are re-esterified to triglycerides in enterocytes, packaged into chylomicrons that con tain apolipoproteins on the surface, which are subsequently secreted into the extracellular space, and because of their size, are excluded TABLE 336-2 Defects in Lipid Digestion and Absorption in Steatorrhea PATHOPHYSIOLOGIC DEFECT DISEASE EXAMPLE PHASE, PROCESS Digestive Lipolysis formation Decreased lipase secretion Chronic pancreatitis Micelle formation Decreased intraduodenal bile acids Absorptive Mucosal uptake and re-esterification Mucosal dysfunction Celiac disease Postabsorptive Chylomicron formation Absent β-lipoproteins Abetalipoproteinemia Delivery from intestine Abnormal lymphatics Intestinal lymphangiectasia

Pancreas Liver Jejunal Mucosa Lipolysis Micellar Solubilization with Bile Acid Absorption (1) Esterification Fatty acids Fatty acids To tissues for utilization of fat Cholesterol Phospholipid β–Lipoprotein Triglycerides Triglycerides β-Monoglyceride β-Monoglyceride (2) Chylomicron formation FIGURE 336-1 Schematic representation of lipid digestion and absorption. Dietary lipid is in the form of long-chain triglycerides. The overall process can be divided into (1) a digestive phase that includes both lipolysis and micelle formation requiring pancreatic lipase and conjugated bile acids, respectively, in the duodenum; (2) an absorptive phase for mucosal uptake and re-esterification; and (3) a postabsorptive phase that includes chylomicron formation and exit from the intestinal epithelial cell via lymphatics. (Courtesy of John M. Dietschy, MD; with permission.) from capillaries and enter the lymphatics. Medium-chain triglycerides do not require micelle formation or pancreatic lipolysis as they are directly absorbed intact from the small bowel into the bloodstream, and short-chain fatty acids (carbon length <8) are produced by and absorbed in the colon. Carbohydrates Dietary carbohydrate consists of starch, sucrose, lactose, maltose, and monosaccharides such as glucose and fructose. Starch is digested by salivary α-amylase in the mouth, followed by pancreatic amylase. The main products include maltotriose, maltose, and α-dextrins. These are further digested on the brush border mem brane by disaccharidases such as glucoamylase and sucrase-isomaltase. Dietary lactose is digested by brush border lactase, sucrose by sucrase, and trehalose by trehalase. The final digested products are glucose, fructose, and galactose, which are transported into the enterocyte by transporters such as SLCA5 (formerly

SGLT-1), which transports glu cose or galactose in a sodium-dependent manner, and GLUT-5, which transports fructose by facilitated diffusion. Glucose, galactose, and fructose exit the cell via GLUT-2. PART 10 Disorders of the Gastrointestinal System Proteins Dietary protein digestion begins in the stomach by pepsin. Pancreatic proteases including endopeptidases, exopeptidases, and trypsin are activated in the small-bowel lumen. Trypsinogen is acti vated by brush border enterokinase to generate active trypsin. Trypsin in turn activates chymotrypsinogen to chymotrypsin, proelastase to elastase, and procarboxypeptidases to carboxypeptidases A and B. These enzymes digest protein into dipeptides, tripeptides, larger poly peptides, or free amino acids. At the brush border, peptidases digest larger peptides into dipeptides and tripeptides or free amino acids, which enter the enterocyte via specialized carriers. Most dipeptides and tripeptides are further metabolized intracellularly by cytoplasmic peptidase into amino acids, which directly enter the bloodstream via carriers in the basolateral membrane. Small amounts of dipeptides and tripeptides may also enter the bloodstream. ■ ■LUMINAL PHASE OF DIGESTION The luminal phase of digestion begins in the mouth, starting with mastication and lipase secretion by the tongue and salivary glands. The stomach continues the luminal digestive process, via gastric acid, gastric lipase, and pepsin secretion as well as mechanical trituration of contents. In the small-bowel lumen, pancreatic enzymes (amylase, lipases, carboxypeptidase, trypsin, and other endopeptidases) contrib ute to carbohydrate, lipid, and protein digestion, respectively. Bile salts produced by the liver are secreted into the intestinal lumen (and reab sorbed in the ileum via the enterohepatic circulation) and are required for efficient lipid absorption. Disorders That Affect the Luminal Phase of Digestion The luminal phase may be disrupted by disorders of gastric and intestinal

motility including the sequelae of gastric surgery, systemic diseases such as scleroderma, or endo crine disorders such as diabetes mellitus; pancreatic diseases leading to pancreatic insufficiency with reduced pancreatic enzyme secretion; or luminal bile salt deficiency caused by hepatobiliary disease, ileal disease, or small-bowel bacterial overgrowth. Lymphatics Delivery Gastric Resection Surgical procedures that remove or bypass part of the stomach and duo denal bulb such as Roux-en-Y gastric bypass for weight loss, or resection of the gastric antrum and duodenal bulb with creation of a Billroth II anastomosis for treatment of peptic ulcer disease, result in rapid gastric emptying into the jejunum, which leads to diarrhea and weight loss due to inadequate mixing of luminal nutrients with bile and pancreatic secretions. Disordered Intestinal Motility Hyperthy roidism may cause diarrhea and malabsorption due to increased intestinal motility with rapid transit, also resulting in inadequate nutrient mixing with pancre aticobiliary secretions. Long-standing diabetes mellitus may result in damage to the enteric nervous system resulting in increased motility and diarrhea, or reduced motility and constipation. Disorders that affect the intestinal smooth muscle such as connective tissue disorders including scleroderma may have profound effects on GI motility. Pancreatic Disorders Chronic pancreatitis (see Chap. 359) may result in a marked reduction in pancreatic enzyme secretion and pancre atic insufficiency, with subsequent fat, protein, and carbohydrate malab sorption. Patients with chronic pancreatitis present with steatorrhea, or fatty stools, which are often voluminous, bulky, and malodorous. Patients with steatorrhea also develop deficiency of fat-soluble vitamins including vitamins A, E, and most commonly, vitamins D and K, which depend on the same lipid absorption mechanisms and thus are malabsorbed along with dietary fat. Weight loss is common. For a discussion of causes of acute and chronic pancreatitis, please see Chap. 359. Disorders That Result in Luminal Bile Salt Deficiency Bile acid synthesis and the enterohepatic circulation are shown in Fig. 336-2. NORMAL Cholesterol Bile acids 0.5 g synthesized per day [Bile acids]

> 4 mM Bile acid pool size 4.0 g Jejunum Ileum Na COLON 0.5 g Bile acids excreted per day FIGURE 336-2 Schematic representation of the enterohepatic circulation of bile acids. Bile-acid synthesis is cholesterol catabolism and occurs in the liver. Bile acids are secreted in bile and are stored in the gallbladder between meals and at night. Food in the duodenum induces the release of cholecystokinin, a potent stimulus for gallbladder contraction resulting in bile-acid entry into the duodenum. Bile acids are primarily absorbed via an Na-dependent transport process that is located only in the ileum. A relatively small quantity of bile acids (~500 mg) is not absorbed in a 24-h period and is lost in stool. Fecal bile acid losses are matched by bile-acid synthesis. The bile acid pool (the total amount of bile acids in the body) is ~4 g and is circulated twice during each meal or six to eight times in a 24-h period.

TABLE 336-3 Defects in Enterohepatic Circulation of Bile Acids PATHOPHYSIOLOGIC DEFECT DISEASE EXAMPLE PROCESS Synthesis Decreased hepatic function Cirrhosis Biliary secretion Altered canalicular function Primary biliary cholangitis Maintenance of conjugated bile acids Bacterial overgrowth Jejunal diverticulosis Reabsorption Abnormal ileal function Crohn’s disease Bile acids are synthesized from cholesterol in the liver. The two pri mary bile acids are cholic acid and chenodeoxycholic acid. These are conjugated in the liver to taurine and glycine and are secreted into bile ducts, stored in the gallbladder, and then delivered to the intestinal lumen. Conjugation prevents bile acids from passive diffusion in the small-bowel lumen, retaining bile acid concentrations required for lipid absorption. Bile acids emulsify fats and fat-soluble vitamins to facilitate their absorption. Bile acids are efficiently reabsorbed in the ileum into the portal circulation and are extracted by the liver in a process called enterohepatic circulation (Fig. 336-2). Small amounts are deconjugated in the ileum by bacteria or pass into the colon and are deconjugated and metabolized by colonic bacteria to become second ary bile acids. The two major secondary bile acids are lithocholic acid and deoxycholic acid. Processes that affect any of the above pathways may result in luminal bile salt deficiency and malabsorption. Thus, hepatobiliary diseases, intestinal ileal resection, extensive disease such as Crohn’s disease, and small-bowel bacterial overgrowth may result in luminal bile salt defi ciency and malabsorption (Table 336-3). Hepatobiliary Disease Hepatic disorders that result in decreased bile acid synthesis due to hepatocyte dysfunction or reduced secretion of bile into the gut lumen caused by diseases of the bile ducts such as primary sclerosing cholangitis or primary biliary cholangitis may result in luminal bile salt deficiency and fat malabsorption. These are discussed in Chap. 357. Ileal Resection or Ileal Disease Diseases that involve the ileal mucosa or that result in ileal resection may lead to reduced recycling of bile acids by the enterohepatic circulation and increased entry into and concentration of bile acids in the colon, which produces a secre tory diarrhea, or may result in malabsorption due to inadequate bile acid concentrations in the small-bowel lumen. In general, resection or disease involving <100 cm of ileum results in bile acid spillage into the colon; resections of >100 cm result in loss of bile acids that exceed liver synthetic capacity, and malabsorption becomes the dominant patho physiologic mechanism for diarrhea, due to bile acid deficiency (Table 336-4). The most common disorder of the GI tract that targets the ileum is Crohn’s disease (Chap. 337), which is a chronic inflammatory disorder that may involve the entire GI tract, but most commonly the TABLE 336-4 Comparison of Bile Acid and Fatty Acid Diarrhea BILE-ACID DIARRHEA FATTY ACID DIARRHEA

Extent of ileal disease Limited Extensive Ileal bile acid absorption Reduced Reduced Fecal bile acid excretion Increased Increased Fecal bile acid loss compensated by hepatic synthesis Yes No Bile acid pool size Normal Reduced Intraduodenal (bile acid) Normal Reduced Steatorrhea None or mild

> “ 20 g Response to cholestyramine Yes No Response to low fat diet No Yes

ileum and colon. If severe or refractory to treatment, Crohn’s disease may lead to chronic inflammation, marked epithelial dysfunction, and stricturing and fibrosis, and surgical resection may be required to treat small-bowel obstruction or refractory disease.

Primary Bile Acid Diarrhea A subset of patients with functional diarrhea or irritable bowel syndrome with diarrhea have been shown to have bile acid malabsorption. Although the mechanisms are still being elucidated, reduced FGF19 secretion by ileal enterocytes has been observed. FGF19 regulates serum 7-alpha-hydroxy-4-cholesten-3-one (C4) levels; reductions in circulating FGF19 lead to increased hepatic bile acid synthesis via increased C4 expression. Chronic diarrhea results from increased bile acid spillage into the colon, which induces a secretory diarrhea and exerts prokinetic effects via TGR5. Treatment Bile acid sequestrants are effective in reducing diarrhea by binding bile acids to prevent spillage into the colon. Hepatic synthe sis of bile acids is sufficient to maintain intraluminal concentrations that are adequate for fat absorption. Small-Intestinal Bacterial Overgrowth The intestine contains a rich microbiome. Bacterial titers increase along the horizontal axis of the gut from duodenum to ileum. However, intestinal disorders affecting motility or causing stasis of bowel contents may lead to smallintestinal bacterial overgrowth. These include scleroderma bowel, chronic intestinal pseudo-obstruction, the creation of blind surgi cal loops such as Roux-en-Y gastric bypass, Billroth II anastomosis, small-bowel strictures, or fibrosis from inflammatory disorders such as Crohn’s disease and diffuse diverticulosis (Fig. 336-3). Surgical resection of the ileocecal valve increases ileal bacterial counts from the colon. Hypochlorhydria from chronic proton pump inhibitor use also increases the risk of small-intestinal bacterial overgrowth. Bacterial overgrowth causes deconjugation of bile acids, which facilitates their absorption in the proximal bowel and results in luminal bile acid defi ciency, which in turn causes malabsorptive diarrhea with steatorrhea. Bacterial overgrowth may also damage the brush border and result in carbohydrate maldigestion and short-chain fatty acid production in the colon, with diarrhea and gas. These patients are also at risk for B12 deficiency due to bacterial metabolism of B12 resulting in macrocytic anemia and peripheral neuropathy. In contrast, elevated serum folate levels may also be observed, derived from bacterial synthesis of folate. CHAPTER 336 Disorders of Absorption Small-intestinal bacterial overgrowth has also been observed in patients with diarrhea-predominant irritable bowel syndrome. The underlying mechanisms are unclear, but treatment of bacterial over growth leads to resolution of symptoms in a subset of irritable bowel syndrome patients. Diagnosis Duodenal aspirate for bacterial titers is the gold standard but is not generally available to most practitioners. Breath hydrogen testing with administration of lactulose, a nondigestible disaccharide, or glucose is widely available but must be interpreted carefully to avoid false-positive results. Many clinicians choose to treat empirically with antibiotics (see “Treatment”) and observe for resolution of symptoms. Treatment When possible, surgical correction of blind loops, endoscopic or surgical treatment of strictures, and removal of large diverticula can be pursued for definitive therapy, in addition to treat ment of underlying disorders such as Crohn’s

disease to avoid recurrent stricture formation or fibrosis. Other disorders such as scleroderma or other diffuse motility disorders may not be easily treated. In these cir cumstances, treatment with the nonabsorbable antibiotic, rifaximin, or with other antibiotics such as metronidazole, doxycycline, amoxicillinclavulanic acid, or cephalosporins for several weeks is often pursued. Patients may require retreatment or even chronic therapy with rotating antibiotics depending on the severity of symptoms. ■ ■MUCOSAL PHASE OF DIGESTION

AND ABSORPTION The intestinal epithelium (also known as the mucosa) plays a critical role in continued digestion of nutrients and absorption from the intes tinal lumen into the bloodstream and lymphatics.

A B PART 10 Disorders of the Gastrointestinal System C D FIGURE 336-3 Barium contrast small-intestinal radiologic examinations. A. Normal individual. B. Celiac disease. C. Jejunal diverticulosis. D. Crohn's disease. (Courtesy of Morton Burrell, MD, Yale University; with permission.) The small-bowel epithelial or mucosal digestive and absorptive phase is mediated by enterocytic brush border enzymes, including peptidases and hydrolases. Brush border enterokinase is required for the conversion of pancreatic trypsinogen to trypsin, which further activates trypsinogen and other pancreatic protease proenzymes. The brush border membrane of the small-bowel epithelium expresses a wide variety of disaccharidases, peptidases, and other hydrolases that continue the digestive process for carbohydrates and proteins, with enzymatic digestion of disaccharides to monosaccharides and dipepti dases to amino acids, which are then absorbed by specific transporters. Long-chain fatty acids are re-esterified to triglycerides in enterocytes, packaged into chylomicrons with apolipoproteins on the surface, which are subsequently secreted into the extracellular space, and because of their size, are excluded from capillaries and enter the lymphatics. INTESTINAL MUCOSAL DISORDERS ■ ■DISORDERS OF ENTEROCYTE CARBOHYDRATE TRANSPORTERS AND ENZYME DEFICIENCIES Lactose Intolerance Due to Lactase Deficiency This is the most common brush border disaccharidase deficiency and is a frequent cause of diarrhea, abdominal pain, gassiness, and bloating. Lactose is present in many dairy products but is also a "hidden" component of a vast number of processed foods. Lactose malabsorption can result from lactase deficiency, which is regulated by primary genetic mechanisms (adult-type hypolactasia) or secondary due to damage to the epithelial (mucosal) lining of the gut, from infections (viral, bacterial, or parasitic) or from intestinal muco sal diseases. Congenital lactase deficiency is very rare and is an auto somal recessive disorder. Hypolactasia in adulthood is very common throughout the world and is considered to be the genetic wild-type;

lactase persistence results from a C to T mutation (LACTASE LCT13910CT and LCT-13910TT), and adults with hypolactasia have absence of this "persistence" allele. Lactose is metabolized by lactase into glucose and galactose, which are both absorbed by transporters at the enterocyte surface. Patients who are lactase deficient have elevated luminal lactose levels upon ingestion of lactose. The mechanism for diarrhea in lactase deficiency is complex. Undigested lactose acts as an osmotic substance to draw fluid into the small-bowel lumen. In addi tion, when unabsorbed lactose enters the colon, luminal bacteria fer ment lactose, producing intestinal gas (hydrogen, carbon dioxide, and methane), bloating, and abdominal pain. Luminal lactose is metabo lized by bacteria into short-chain fatty acids that can be absorbed by the colon, but watery diarrhea may occur when a large lactose load exceeds the colon's absorptive capacity. Diagnosis When lactose intolerance is suspected, a common initial approach is to institute a lactose-exclusion diet and

assess for resolu tion of symptoms. This is a rapid and generally effective diagnostic and therapeutic method. Patients are provided with a list of lactose-containing foods and lactose-free alternatives. Patients are also counseled on alternative calcium sources, because dairy-containing foods are a major source of dietary calcium, which is important for osteoporosis prevention. Should the results of dietary exclusion be ambiguous, a lactosetolerance test or breath hydrogen test may prove useful. For the lactosetolerance test, patients ingest a standardized liquid lactose solution (usually 50 g of lactose) followed by timed measurements of serum glucose for 90 min. If lactose digestion is normal, glucose levels should rise by >20 mg/L. Serum glucose rise <20 mg/L plus the presence of symptoms of lactose intolerance (abdominal discomfort, gassiness, and diarrhea) is considered a positive test. A breath hydrogen test is performed by measuring breath hydrogen levels following ingestion

of a standardized lactose load. Breath hydrogen levels should not exceed >20 ppm above the fasting baseline. Generally, the peak occurs between 2 and 4 h. Both methods may be inaccurate if the patient has abnormal gastric emptying or abnormal intestinal transit. Breath hydrogen measurements may be abnormal in the setting of bacterial overgrowth, which may cause very similar symptoms. Treatment Patients may elect to completely eliminate lactose from their diets. It is very important to consider calcium and vitamin D supplementation because elimination of milk and soft cheeses removes important dietary sources. They also may need to consult a dietitian for guidance about hidden lactose in prepared or other foods. An alterna tive is to consider using lactase supplementation, which is available over the counter but which may need to be titrated to avoid symptoms. Glucose-Galactose Malabsorption This rare congenital disor der is an autosomal recessive disease in which mutations occur in the SLC5A1 gene (also known as SGLT1). SLC5A1 is a brush border pro tein and member of the sodium-dependent glucose transporter family; mutations in this gene result in malabsorption of glucose and galactose. Gene sequencing has shown that most patients have loss-of-function single-nucleotide variations. SLC5A1 actively transports glucose or galactose coupled to sodium cotransport; patients who are homozy gous for these loss-of-function variants have severe congenital diarrhea and death if unrecognized. Treatment focuses on eliminating glucose- and galactose-containing foods and substituting fructose-containing foods. Fructose is absorbed by the brush border transporter GLUT5 by facilitated diffusion and is not dependent on SLC5A1. Sucrase-Isomaltase Deficiency This is another rare congenital autosomal recessive disorder, caused by mutations in the sucraseisomaltase gene. Infants present with diarrhea that begins with ingestion of sucrose coincident with the introduction of table foods. Sucrase-isomaltase gene variants have been identified that cause symp toms later in life and may be associated with increased risk of irritable bowel syndrome. Abetalipoproteinemia Abetalipoproteinemia is a rare disorder of lipid metabolism associated with abnormal erythrocytes (acan thocytes), neurologic symptoms, and steatorrhea (see Chap. 419). Lipolysis, micelle formation, and lipid uptake are all normal in patients with abetalipoproteinemia, but the re-esterified triglyceride cannot exit the epithelial cell because of the failure to produce chylomicrons. This disorder results from mutation of microsomal triglyceride transfer pro tein (MTP), which catalyzes the transfer of triglyceride onto nascent apolipoprotein B–containing particles. Mutations in MTP decrease this transfer and decrease formation of chylomicrons. Small-intestinal biopsy samples obtained from these rare patients in the postprandial state reveal lipid-laden small-intestinal epithelial cells that become normal in appearance after a 72- to 96-h fast. INTESTINAL MUCOSAL DISORDERS THAT RESULT IN MALABSORPTION OF MULTIPLE NUTRIENTS ■ ■CELIAC DISEASE Celiac disease, also known as celiac sprue or gluten-sensitive enter opathy, is a small-

intestinal enteropathy that results from an immune response to gluten ingestion and is characterized by autoantibodies to tissue transglutaminase. Gluten is found in foods produced from wheat, rye, barley, and some varieties of oats, and it is a common addi tive to prepared foods and pharmaceuticals. Tissue transglutaminase is involved in the pathogenesis of this disorder, as it deamidates gluta mine residues of gluten-derived peptides, facilitating their presentation by antigen-presenting cells. Epidemiology and Genetics The incidence and prevalence of celiac disease have been increasing worldwide. Increased awareness among clinicians and patients has led to increases in detection, but there is evidence that the true incidence appears to be increasing as well. Global prevalence has been measured at 1.4%. In the United States, data from the National Health and Nutrition Examination survey

showed seroprevalence of 0.2% in non-Hispanic black populations, 0.3% in Hispanic individuals, and 1.0% in white populations.

The prevalence of celiac disease is 10–15% in first-degree rela tives. Host genetic factors include histocompatibility locus antigens HLADQ2 and DQ8; the presence of one of the two haplotypes is necessary but not sufficient for developing celiac disease. HLADQ2 and DQ8 are found in 25–35% of the general population; because most carriers never develop celiac disease, detection of these alleles is not useful for diagnosis. However, a negative test is very useful for ruling out celiac disease, with a negative predictive value of >99%. This is particularly helpful in patients who self-discontinued gluten ingestion prior to serologic or endoscopic testing. Presentation Patients with celiac disease have a wide variety of disease manifestations, ranging from being asymptomatic, to having isolated iron-deficiency anemia due to duodenal disease, to severe diarrhea, weight loss, and malabsorption of multiple nutrients with more diffuse disease. Celiac disease primarily affects the proximal small intestine; it may involve the duodenum only or may cause wide spread jejunal disease resulting in severe symptoms. Diarrhea, weight loss, and growth failure in children are common presenting complaints, but additional signs and symptoms have become increasingly recognized to be associated with celiac disease, including bloating and irregular bowel habits, migraine headaches, and ataxia. In addition, patients may be identified after presenting with osteoporosis, iron-deficiency anemia, or detection of abnormal liver enzymes. Mechanism of Diarrhea Patients with celiac disease have villus atrophy in the proximal small intestine and thus develop steatorrhea from mucosal malabsorption and may have lactase deficiency. How ever, they also develop a secretory component due to crypt hyperplasia and fluid hypersecretion from the crypt epithelium. CHAPTER 336 Associated Diseases Patients with celiac disease have a higher incidence of other autoimmune disorders such as type 1 diabetes mel litus and autoimmune thyroid disease. Dermatitis herpetiformis is a skin disorder that is highly associated with celiac disease, characterized by a vesicular rash mediated by IgA deposits in the skin. Down syndrome and Turner syndrome patients also have an increased risk of celiac disease. Disorders of Absorption Diagnosis Patients are screened for celiac disease first by testing for serum antibodies, including the screening test of choice, which is tissue transglutaminase IgA (TTG-IgA). Serum IgA levels should also be measured to detect false-negative results from IgA deficiency. If a patient is IgA deficient, IgG-based testing including TTG-IgG or anti- deamidated gliadin peptide (DGP-IgG) antibody testing can be performed. The diagnosis in adults with positive antibody levels is con firmed by endoscopy with small-intestinal biopsy; biopsy is required in most patients to confirm the diagnosis. Biopsies typically show characteristic villus blunting, crypt hyperplasia, and inflammation, including increased intraepithelial lymphocytes. The Marsh classifica tion categorizes

different types of celiac disease–related lesions and is currently used to quantify severity of disease involvement. Family members of patients with celiac disease are screened if symp tomatic; recommendations regarding screening asymptomatic family members are still controversial. Complications Complications of celiac disease include refractory celiac disease, enteropathy-associated T-cell lymphoma, hyposplenism, and small-bowel adenocarcinoma. Refractory Celiac Disease This complication is most common in patients with ongoing active celiac disease, found in about 10% of patients with persistent active disease. Patients have ongoing diarrhea and weight loss with persistent villus atrophy on biopsy after 1 year of following a strict gluten-free diet. These patients also have negative celiac serology, confirming their adherence to the gluten-free diet. Type 1 refractory celiac disease has a normal intraepithelial lympho cyte population, whereas type 2 disease has clonal expansion of CD3+ intraepithelial lymphocytes that also contain a monoclonal rearrange ment of the gamma chain of the T-cell receptor. Type 2 refractory

celiac disease has a worse prognosis due to its association with T-cell lymphoma, which occurs in 33–50% of cases after 5 years. The therapy for celiac disease–related lymphoma is intense and includes high-dose chemotherapy and sometimes stem cell transplantation.

Small-bowel adenocarcinoma is a very rare cancer in the general population but is increased in celiac disease patients. Therapy and Follow-Up The mainstay of celiac disease treatment is institution of a strict gluten-free diet. This is challenging for patients because of the widespread presence of gluten in both raw and prepared foods, inaccurate food labeling, and cross-contamination during food preparation. Patients must receive rigorous dietary instruction from a dietitian and adhere lifelong to a gluten-free diet. For patients whose symptoms resolve, serologic follow-up is gener ally recommended to confirm compliance with a gluten-free diet. A follow-up biopsy to document complete healing of villus atrophy is also generally recommended. However, subsequent biopsies are not recom mended unless symptoms recur. For patients without symptom resolu tion, a biopsy is required to determine the degree of disease activity and to rule out other causes of persistent diarrhea and complications such as refractory celiac disease or T-cell lymphoma. The most common cause of residual disease activity is dietary nonadherence or inadver tent gluten exposure. These patients pursue repeat consultation with a dietitian and efforts to reduce restaurant or other out-of-the-home exposure or cross-contamination at home. If biopsies are negative but symptoms persist, other causes of abdominal pain and diarrhea that are associated with celiac disease are considered, including irritable bowel syndrome, microscopic colitis, small-bowel bacterial overgrowth, and lactose or fructose intolerance. Nonceliac Gluten Sensitivity These patients have symptoms consistent with celiac disease but have negative serology and nega tive biopsies and no evidence for wheat allergy. Upon discontinuation of gluten, they have relief of abdominal pain, diarrhea, headaches/ migraines, and other celiac disease–type symptoms. The etiology of this disorder remains unknown. PART 10 Disorders of the Gastrointestinal System ■ ■WHIPPLE’S DISEASE Whipple’s disease is a chronic, multiorgan disease caused by Troph eryma whipplei, a gram-positive non-acid-fast, periodic acid–Schiff (PAS)–positive rod, which is ubiquitous in the environment. Whipple’s disease most commonly occurs in middle-aged men. Classic Whipple’s disease is defined by the presence of arthralgias, weight loss, diarrhea, and abdominal pain. Other manifestations including central nervous system (CNS) and cardiac involvement are common and occur later in the disease. T. whipplei can be detected by polymerase chain reaction on involved tissue and is difficult to detect in the bloodstream. The intestinal lesion is also characterized by PAS-positive macrophages. Clinical Presentation

Arthralgias and arthritis are present for an average of 6 years before the GI symptoms begin, consistent with a per sistent and substantial lag in diagnosis, which is still a problem today. Joint disease is present in >80% of patients. GI manifestations include diarrhea, abdominal pain, and weight loss from malabsorption. CNS involvement is common and may include symptoms such as psychi atric manifestations or memory problems. Dementia and encephalitis may occur in later stages. Cardiac involvement may include endocar ditis, pericarditis, and myocarditis. Diagnosis For patients with GI manifestations, endoscopy with biopsies is performed and tissue is tested for T. whipplei by polymerase chain reaction. Tissue is also stained for PAS-positive macrophages, and immunohistochemistry may also be performed to detect T. whipplei. Treatment Prolonged antibiotics are recommended, although the optimal regimen is still uncertain. Relapses are common and often associated with the first manifestations of CNS involvement. ■ ■TROPICAL SPRUE Tropical sprue is a poorly understood syndrome that is manifested by chronic diarrhea, steatorrhea, weight loss, and nutritional deficiencies, including both folate and vitamin B12. Malabsorption of two unrelated

substances is required for diagnosis. This disease occurs in 8–20% of people who have had an attack of infectious gastroenteritis in India and is considered by some to be a postinfectious complication. It is prevalent in some but not all tropical areas, including southern India, Pakistan, the Philippines, Puerto Rico, Haiti, and Cuba. It occurs in residents of as well as visitors to these areas. Chronic diarrhea in a tropical environment is most often caused by infectious agents, including Giardia lamblia, Yersinia enterocolitica, Entamoeba histolytica, Clostridioides difficile, Cryptosporidium parvum, Isospora belli, Strongyloides stercoralis, and Cyclospora cayetanensis. Tropical sprue should not be entertained as a possible diagnosis until the presence of cysts and trophozoites has been excluded in three stool samples. Infections of the GI tract and diarrhea are discussed in Chaps. 49, 138, 139, 169–173, and 230. Etiology Because tropical sprue responds to antibiotics, the con sensus is that it may be caused by one or more infectious agents. None theless, the etiology and pathogenesis of tropical sprue are uncertain. Its occurrence is not evenly distributed in all tropical areas; it is rarely observed in Africa, Jamaica, or Southeast Asia. The incidence of tropi cal sprue appears to have decreased substantially during the past two or three decades, perhaps in relation to improved sanitation in many tropical countries during this time. Some have speculated that the reduced occurrence is attributable to the wider use of antibiotics in acute diarrhea, especially in travelers to tropical areas from temper ate countries. Folic acid is absorbed exclusively in the duodenum and proximal jejunum, and most patients with tropical sprue have evidence of folate malabsorption and depletion. The clinical pattern of tropical sprue varies in different areas of the world (e.g., India vs Puerto Rico). Not infrequently, individuals in southern India initially report the occurrence of acute enteritis before the development of steatorrhea and malabsorption. In contrast, in Puerto Rico, a more insidious onset of symptoms and a more dramatic response to antibiotics are seen compared with some other locations. Tropical sprue in different areas of the world may not be the same dis ease, and similar clinical entities may have different etiologies. Diagnosis The diagnosis of tropical sprue is based on an abnormal small-intestinal mucosal biopsy in an individual with chronic diarrhea and evidence of malabsorption who is either residing or has recently lived in a tropical country. The small-intestinal biopsy in tropical sprue does not reveal pathognomonic features but resembles, and can often be indistinguishable from, that seen in celiac disease (Fig. 336-4). The biopsy sample in tropical sprue has less villous architectural alteration and more mononuclear cell infiltrate in the lamina propria. In contrast to those of celiac disease, the histologic features of tropical sprue mani fest with a similar degree of

severity throughout the small intestine, and a gluten-free diet does not result in either clinical or histologic improvement in tropical sprue. Treatment Broad-spectrum antibiotics and folic acid are most often curative, especially if the patient leaves the tropical area and does not return. Tetracycline should be used for up to 6 months and may be associated with improvement within 1–2 weeks. Folic acid alone induces hematologic remission as well as improvement in appetite, weight gain, and some morphologic changes in small-intestinal biopsy. Because of marked folate deficiency, folic acid is most often given together with antibiotics. ■ ■ENVIRONMENTAL ENTERIC DYSFUNCTION Environmental enteric dysfunction (EED; formerly known as tropical enteropathy) occurs in low- and middle-income countries and is char acterized by altered crypt villus morphology with crypt atrophy and mucosal inflammation and barrier dysfunction, resulting in chronic low-grade malabsorption. It is associated with childhood stunting, a major worldwide health problem. Gut microbiota and adverse envi ronmental and economic conditions contribute to its pathogenesis. Although the gold standard for diagnosis is small-bowel biopsy, this is often limited by lack of resources. Therapies for EED are the subject of intense investigation.

A B C D E F G FIGURE 336-4 Small-intestinal mucosal biopsies. A. Normal individual. B. Untreated celiac disease. C. Treated celiac disease. D. Intestinal lymphangiectasia. E. Whipple’s disease. F. Lymphoma. G. Giardiasis. (Courtesy of Marie Robert, MD, Yale University; with permission.) ■ ■SHORT-BOWEL SYNDROME ■ ■OVERVIEW Short-bowel syndrome results from intestinal resection to treat a mul titude of disorders including Crohn’s disease, vascular diseases such as mesenteric arterial or venous thrombosis resulting in intestinal ischemia, volvulus, trauma, internal herniation, radiation enteritis, and diffuse carcinoma, among others. In children, the most common causes of short-bowel syndrome are necrotizing enterocolitis, intestinal atresias, volvulus, and malrotation. Short-bowel syndrome is defined as extensive removal of small intestine resulting in <200 cm of remain ing small bowel. Intestinal failure is functionally defined as persistent parenteral nutrition dependence, generally found in patients who have <100 cm of remaining small bowel and no residual colon in continuity. Clinical Features Loss of small-bowel surface area in short-bowel syndrome results in severe diarrhea, weight loss, and malabsorption of multiple nutrients, including fat, protein, and carbohydrate. The severity of symptoms and ultimate dependence on parenteral nutrition are generally related to the extent of resection, presence or absence of

 residual colon in continuity, retention of the ileocecal valve, and sever ity of the underlying disease. The intestine has a remarkable capacity to adapt to loss of small-bowel surface area, but this adaptive process is variable from patient to patient. Following resection, the adapting residual intestine exhibits an increase in crypt cell proliferation result ing in epithelial hyperplasia. The adaptive process generally continues for up to 2 years after resection, but improvements in nutrient, fluid, and electrolyte absorptive capacity have been reported even as late as 3–5 years after surgery. Massive diarrhea generally occurs in the first three postoperative months, associated with increased gastric acid secretion and malabsorption. Gradually, patients show enhanced func tional capacity and reduced diarrhea. Specific nutrient deficiencies are dependent upon which segment of gut has been removed. For example, resection of the ileum results in loss of B12 absorptive and bile salt reabsorptive capacity. Malabsorbed bile salts reach the colon and cause a secretory diarrhea. In addition, resection of >100 cm of ileum results in such severe bile salt malabsorption that the liver cannot compen sate by increased synthesis, thus precipitating fat malabsorption due to bile salt insufficiency/deficiency. Substantial

resection of the colon

also results in fluid and electrolyte loss and imbalance. The colon also plays a role in nutrient absorption because it metabolizes malabsorbed carbohydrate into short-chain fatty acids that can be absorbed by the colon and can contribute several hundred additional calories per day.

Long-Term Complications Because massive resection often leads to severe fat malabsorption, fat-soluble vitamin deficiency is common, and vitamin D deficiency can be very difficult to treat even with highdose oral vitamin D supplementation, resulting in an increased risk of osteoporosis. Patients with a history of multiple surgeries often have extensive adhesive disease, and the residual intestine may have mark edly abnormal motility or areas of stricturing and narrowing, resulting in recurrent bacterial overgrowth. The frequency of renal calcium oxalate stones increases in patients with a shortened small bowel with an intact colon in continuity; calcium is saponified in the intestinal luminal contents that contain fatty acids, freeing oxalate to be absorbed in the colon resulting in hyperoxaluria. Treatment The major focus of treatment for short-bowel syndrome is to control diarrhea and normalize nutrient, fluid, and electrolyte absorption so that patients can maintain their weight and have a healthy nutritional status without the support of parenteral nutrition. Medications include opiates and derivatives including loperamide and diphenoxylate-atropine, which slow intestinal motility to allow for more contact time between luminal nutrients and the small-bowel mucosal surface. In the first year following resection, acid-blocking medications are used to treat gastric hypersecretion, including proton pump inhibitors or histamine 2 antagonists. Small-bowel bacterial overgrowth is common and is treated with antibiotics if suspected. The only medication that is specific for short-bowel syndrome but limited for use in parenteral nutrition or intravenous fluid–dependent patients is teduglutide, a glucagon-like peptide 2 (GLP-2) analogue that enhances crypt cell proliferation and villus hyperplasia and increases nutrient and fluid and electrolyte absorption. Patients treated with teduglutide have an average reduction of 20% of their parenteral nutri tion requirements. Greater efficacy has been noted for patients without a residual colon, likely due to lower circulating endogenous GLP-2 levels compared to those with a colon in continuity. Dietary Therapy Patients with short-bowel syndrome must con sume three to four times their normal caloric intake to maintain their weight. The presence of luminal nutrients is required for the adaptive process to occur, so early feeding is recommended, even if parenteral nutrition is also required. These effects are most likely mediated by direct contact with the mucosa as well as stimulation of secretion of gut hormones such as GLP-2. PART 10 Disorders of the Gastrointestinal System If the patient has all or part of their colon remaining in continuity, a low-fat diet is instituted to reduce the concentration of malabsorbed fatty acids that induce a secretory diarrhea. High complex carbohy drates are encouraged because when malabsorbed and present in the colon, they are converted to short-chain fatty acids and are absorbed, contributing several hundred additional kilocalories per day. All patients are asked to take a high-potency multivitamin on a daily basis. Patients in whom oral nutrition fails are fed with parenteral nutrition. Monitoring Patients with short-bowel syndrome are at high risk for osteoporosis due to dietary calcium and vitamin D malabsorption, so they are periodically monitored for vitamin D deficiency and calcium levels and with dual x-ray absorptiometry (DEXA) studies to assess bone density. Malabsorption of vitamins and minerals is common; therefore, fat-soluble vitamins, vitamin B12, folic acid, iron, magnesium, and zinc are monitored periodically. More unusual deficiencies include copper, selenium, and chromium, but these are usually seen in paren teral nutrition–dependent patients and can be corrected by adjusting daily intravenous

dosages. Signs and symptoms of vitamin and mineral deficiency are also carefully monitored (e.g., hair loss, skin and nail changes, neurologic symptoms such as peripheral neuropathy). ■ ■DISORDERS OF POSTMUCOSAL ABSORPTION Following uptake into enterocytes, nutrients are further processed and transported into the lymphatics or into the portal circulation for use

by other cells throughout the body. Primary or secondary disorders of the lymphatics may result in significant diarrhea and malabsorption. Primary disorders of the intestinal lymphatics include intestinal lym phangiectasia, which may be congenital or acquired. Secondary causes of intestinal lymphatic damage or blockage include retroperitoneal fibrosis, fibrosing mesenteritis, and lymphoma. Circulatory causes of impaired delivery of nutrients from the intestine include Fontan physi ology, congestive heart failure, and constrictive pericarditis. The end result of damage to lymphatic channels is malabsorption and diarrhea with concomitant protein-losing enteropathy. ■ ■PROTEIN-LOSING ENTEROPATHY Protein-losing enteropathy refers to a large group of GI and non-GI disorders characterized by hypoproteinemia and edema in the absence of liver disease with reduced protein synthesis, or kidney disease with proteinuria. These diseases are characterized by excess protein loss in the GI tract. Diseases that may result in increased protein loss into the GI tract can be classified into three groups: (1) mucosal ulceration, such that the protein loss primarily represents exudation across dam aged mucosa (e.g., ulcerative colitis, GI carcinomas); (2) nonulcerated mucosa, but with evidence of mucosal damage so that the protein loss represents loss across epithelia with altered permeability (e.g., celiac disease and Ménétrier’s disease [hypertrophic gastropathy] in the small intestine and stomach, respectively); and (3) lymphatic dysfunction, representing either primary lymphatic disease or lymphatic disease secondary to partial lymphatic obstruction that may occur as a result of enlarged lymph nodes or cardiac disease. These result in increased lymphatic pressure, causing exudation of protein into the GI tract lumen. Diagnosis The diagnosis of protein-losing enteropathy is suggested by diarrhea, peripheral edema, and low serum albumin and globulin levels in the absence of renal and hepatic disease. An individual with protein-losing enteropathy rarely has selective loss of only albumin or only globulins. Therefore, marked reduction of serum albumin with normal serum globulins should suggest renal and/or hepatic disease. Likewise, reduced serum globulins with normal serum albumin lev els are more likely a result of reduced globulin synthesis rather than enhanced globulin loss into the intestine. Alpha-1 antitrypsin, a pro tein that accounts for ~4% of total serum proteins and is resistant to proteolysis, can be used to detect enhanced rates of serum protein loss into the intestinal tract but cannot be used to assess gastric protein loss because of its degradation in an acid milieu. Alpha-1 antitrypsin can be measured in a spot or 24-h stool collection and, if elevated, is diagnostic. A more accurate determination is alpha-1 antitrypsin clear ance, measured by determining stool volume as well as both stool and plasma alpha-1 antitrypsin concentrations. In addition to the loss of protein via abnormal and distended lymphatics, peripheral lympho cytes may be lost via lymphatics, with consequent relative lymphopenia and specifically loss of CD3+ T cells. Thus, lymphopenia in a patient with hypoproteinemia indicates increased loss of protein into the GI tract. Patients with increased protein loss into the GI tract from lymphatic obstruction often have steatorrhea and diarrhea. The steatorrhea is a result of altered lymphatic flow as lipid-containing chylomicrons exit from intestinal epithelial cells via intestinal lymphatics (Table 336-2; Fig. 336-4). In the absence of mechanical or anatomic lym phatic obstruction, intrinsic intestinal lymphatic dysfunction—with or without lymphatic dysfunction in the peripheral extremities—has been designated intestinal lymphangiectasia. Similarly, ~50% of indi viduals with intrinsic peripheral lymphatic disease (Milroy’s disease) also have intestinal lymphangiectasia and

hypoproteinemia. Other than steatorrhea and enhanced protein loss into the GI tract, all other aspects of intestinal absorptive function are normal in intestinal lymphangiectasia. Endoscopy and Imaging Endoscopy (including double-balloon enteroscopy) with biopsy and video capsule endoscopy may be per formed to rule out mucosal disease. Magnetic resonance enterography or computed axial tomography may provide additional insight into the

underlying cause and can detect specific lesions, and lymphangiogra phy can be used for diagnosis and potential therapeutic intervention. Other Causes Ménétrier's disease (also called hypertrophic gas tropathy) is an uncommon entity that involves the body and fundus of the stomach and is characterized by large gastric folds, reduced gastric acid secretion, and, at times, enhanced protein loss into the stomach. Patients who have idiopathic protein-losing enteropathy without evidence of GI disease should be examined for cardiac disease. As more patients with congenital heart disease reach adulthood, Fontan physiol ogy has become a more common cause of protein-losing enteropathy. Other cardiac causes include right-sided valvular disease and chronic pericarditis (Chaps. 277, 278, 279 and 281). Treatment As excess protein loss into the GI tract is most often sec ondary to a specific disease, treatment should be directed primarily to the underlying disease process and not to the hypoproteinemia. When enhanced protein loss is secondary to lymphatic obstruction, it is criti cal to establish the nature of this obstruction. Identification of mesen teric nodes or lymphoma may be possible by imaging studies. Similarly, it is important to exclude cardiac disease as a cause of protein-losing enteropathy. Patients with congenital heart disease may be examined by intranodal lymphangiography or noncontrast magnetic resonance lymphangiography and may undergo embolization of the site of lym phatic leakage or surgical lymphatic interventions to decompress the lymphatic system or target exclusion of abnormal lymphatic channels. The increased protein loss that occurs in intestinal lymphangiectasia is a result of distended lymphatics associated with lipid malabsorption. The hypoproteinemia is treated with a low-fat, high-protein diet and the administration of medium-chain triglycerides, which do not exit from the intestinal epithelial cells via lymphatics but are delivered to the body via the portal vein. Other medical therapies including octreo tide, a somatostatin analogue, intravenous heparin, budesonide and other glucocorticoids, and sirolimus have been studied but have gener ally been ineffective. Supportive care includes repletion of nutritional deficiencies and support stockings for leg edema control. APPROACH TO THE PATIENT Evaluation of the Patient with Suspected Malabsorption The evaluation of patients with malabsorption is often challenging due to the large number of underlying disorders and the wide array of available tests. Thus, an extensive history and careful physical examination are essential to develop a more limited differential diagnosis and thereby avoid extensive and unnecessary testing. HISTORY A careful history should include questions about symptoms includ ing abdominal pain, diarrhea, weight loss, bloating, symptoms or signs of selective nutrient deficiency including iron-deficiency ane mia, bone fracture, or osteoporosis suggesting vitamin D and/or cal cium deficiency, peripheral neuropathy resulting from vitamin B12 deficiency, hair loss that may result from generalized protein defi ciency, predisposing disorders such as chronic pancreatitis or liver disease particularly involving the bile ducts such as primary biliary cholangitis or primary sclerosing cholangitis, history of small-bowel resection (due to Crohn's disease, trauma, ischemic bowel disease, etc.), and travel history. A multitude of nonspecific symptoms such as fatigue and weakness may also be reported. The protean mani festations of malabsorption and the underlying pathophysiology of clinical manifestations are summarized in Table 336-5. PHYSICAL EXAMINATION A careful physical examination may provide clues to underlying nutrient deficiencies and help assess severity of the malabsorptive process. For

example, evidence of significant weight loss may be detected by bitemporal wasting and reduced arm circumference,

TABLE 336-5 Pathophysiology of Clinical Manifestations of Malabsorption Disorders SYMPTOM OR SIGN MECHANISM Weight loss/malnutrition Anorexia, malabsorption of nutrients Diarrhea Impaired absorption or secretion of water and electrolytes; colonic fluid secretion secondary to unabsorbed dihydroxy bile acids and fatty acids Flatus Bacterial fermentation of unabsorbed carbohydrate Glossitis, cheilosis, stomatitis Deficiency of iron, vitamin B12, folate, and

vitamin A Abdominal pain Bowel distention or inflammation, pancreatitis Bone pain Calcium, vitamin D malabsorption, protein deficiency, osteoporosis Tetany, paresthesia Calcium and magnesium malabsorption Weakness Anemia, electrolyte depletion (particularly K+) Azotemia, hypotension Fluid and electrolyte depletion Amenorrhea, decreased libido Protein depletion, decreased calories, secondary hypopituitarism Anemia Impaired absorption of iron, folate, vitamin B12 Bleeding Vitamin K malabsorption, hypoprothrombinemia Night blindness/ xerophthalmia Vitamin A malabsorption Peripheral neuropathy Vitamin B12.thiamine, vitamin E, pyridoxine, and niacin deficiency Dermatitis Deficiency of vitamin A, zinc, and essential fatty acid CHAPTER 336 iron deficiency may cause nail spooning, and vitamin B12 deficiency may result in significant peripheral neuropathy resulting in sensory reduction with tingling or numbness. Disorders of Absorption LABORATORY EXAMINATION Diseases that exclusively affect the proximal small intestine (e.g., celiac disease limited to the duodenum) may result in irondeficiency anemia. Resection or disease of the terminal ileum frequently results in B12 deficiency since B12 absorption occurs exclusively in the ileum, causing a macrocytic anemia. Disorders that cause steatorrhea are almost invariably associated with fatsoluble vitamin deficiency, specifically vitamin D (very common), vitamin E, vitamin A, and vitamin K. The functional result of vitamin K deficiency is an elevated prothrombin time/international normalized ratio (INR), so this blood test is frequently measured instead of vitamin K levels. Serum carotene levels can suggest fat malabsorption but may decrease simply due to poor dietary con sumption of leafy vegetables. To diagnose steatorrhea, a spot stool can be submitted for Sudan III staining, which is specific for fecal fat. This is a useful qualitative but not quantitative test. Stool for elastase is helpful for diagnosing pancreatic insufficiency. A 24-h assessment of stool volume/weight is useful to establish the presence of clinically significant absorp tive or secretory diarrhea versus diarrhea from other causes such as proctitis, which causes frequent, small, low-volume stools. The gold standard for documenting steatorrhea is the 72-h fecal fat col lection, which is performed in concert with the patient’s consump tion of a 100-g fat diet. This test is highly accurate but difficult to obtain due to patient reluctance to collect stool. Also patients with fat malabsorption may poorly tolerate a 100-g fat diet. A diet with strictly quantified albeit reduced fat calories may be substituted. Finally, the calculation of the stool osmotic gap is a very useful and easy way to diagnose an osmotic diarrhea. A spot stool sample is sent to the lab for quantitation of fecal sodium and potassium con centration. Although stool osmolality can also be measured in the lab, measurements are often inaccurate due to bacterial degradation of nonabsorbed carbohydrate as the stool sits prior to examination.

Because normal stool osmolality reflects serum osmolality at 290 mOsm/kg H_2O, the osmotic gap may be calculated as follows: 290 – 2 (stool [Na+] + stool [K+]). If >50–100, a stool osmotic gap is present indicating the presence of unmeasured osmoles (e.g., malabsorbed lactose), and osmotic

diarrhea can be diagnosed. If <50, one can presume a secretory component. Of note, malabsorbed fatty acids may also cause a secretory diarrhea by inducing secretion in the colon, so a malab sorptive diarrhea may have both an osmotic and secretory compo nent. Extensive celiac disease may cause both osmotic diarrhea due to malabsorbed carbohydrate and also secretory diarrhea due to crypt hyperplasia. Urinary D-xylose Test The urinary d-xylose test for carbohydrate absorption provides a measure of proximal small-bowel absorp tive function. d-Xylose, a pentose, is absorbed almost exclusively in the proximal small intestine and is excreted in the urine. The d-xylose test is usually performed by administering 25 g of d-xylose and collecting urine for 5 h. An abnormal test (excretion of <4.5 g) primarily reflects duodenal/jejunal mucosal disease. The ease of obtaining a mucosal biopsy of the small intestine by endoscopy and the false-negative rate of the d-xylose test have led to its diminished use. When small-intestinal mucosal disease is suspected, a smallintestinal mucosal biopsy should be performed. The d-xylose test can also be abnormal in patients with delayed gastric emptying, impaired renal function, and sequestration in patients with large collections of fluid in a third space (i.e., ascites, pleural fluid). PART 10 Disorders of the Gastrointestinal System Radiologic Examination A small-bowel follow-through barium examination may be very useful for detecting evidence of smallbowel diseases such as celiac disease, jejunal diverticulosis that predisposes to small-bowel bacterial overgrowth, or Crohn’s dis ease (Fig. 336-3). Magnetic resonance enterography and computed tomography enterography are commonly used for diagnosis and management of inflammatory, stricturing disorders such as Crohn’s disease and as an initial assessment of malabsorption, providing a means to visualize the entire luminal GI tract as well as the hepato biliary tree and pancreas. Endoscopic Evaluation and Small-Bowel Biopsies Endoscopy with small-bowel biopsy is essential in the evaluation of patients with documented steatorrhea or chronic diarrhea, as well as to evaluate abnormalities detected by radiologic imaging or by cap sule endoscopy. In patients with documented steatorrhea and no evidence of pancreatic or hepatobiliary disease, an upper endoscopy and possible small-bowel enteroscopy are required to examine the small-bowel mucosa and to take biopsies for analysis. An upper endoscopy will visualize the stomach and duodenum; the maxi mum reach of the typical upper endoscopy scope is the ligament of Treitz. Small-bowel enteroscopy using a longer scope such as a pediatric colonoscope can be used to visualize the jejunum. Single- and double-balloon enteroscopy provide a means for examining much more of the jejunum and, if successful, will reach the ileum. Capsule endoscopy provides another means for visualizing the entire small bowel. Colonoscopy can be used for a retrograde view and biopsy of the terminal ileum. Biopsy Analysis Small-bowel pathology may be divided into the three groups (Table 336-6) described below.

1. Diffuse histopathologic findings involving the entire or majority of the mucosa that are specific for a particular disease entity; these include agammaglobulinemia (e.g., combined variable immuno deficiency) and abetalipoproteinemia. Immune globulin deficiency is associated with a variety of histopathologic findings on smallintestinal mucosal biopsy. The characteristic feature is the absence of or substantial reduction in the number of plasma cells in the lamina propria; the mucosal architecture may be either perfectly normal or flat (i.e., villous atrophy). Abetalipoproteinemia is characterized by

TABLE 336-6 Diseases That Can Be Diagnosed by Small-Intestinal Mucosal Biopsies LESIONS PATHOLOGIC FINDINGS Diffuse, Specific Agammaglobulinemia No plasma cells; either normal or absent villi (“flat mucosa”) Abetalipoproteinemia Normal villi; epithelial cells vacuolated with fat postprandially Patchy, Specific Intestinal lymphoma Malignant cells in lamina propria and submucosa Intestinal lymphangiectasia Dilated lymphatics; clubbed villi Eosinophilic gastroenteritis

Eosinophil infiltration of lamina propria and mucosa Amyloidosis Amyloid deposits Crohn’s disease Noncaseating granulomas Infection by one or more microorganisms (see text) Specific organisms Mastocytosis Mast cell infiltration of lamina propria Whipple’s disease Lamina propria includes macrophages containing material positive on periodic acid–Schiff staining; can be diffuse or patchy. Diffuse, Nonspecific Celiac disease Short or absent villi; mononuclear infiltrate; epithelial cell damage; hypertrophy of crypts Tropical sprue Similar to celiac disease Bacterial overgrowth Patchy damage to villi; lymphocyte infiltration Folate deficiency Short villi; decreased mitosis in crypts; megalocytosis Vitamin B12 deficiency Similar to folate deficiency Radiation enteritis Similar to folate deficiency Zollinger-Ellison syndrome Mucosal ulceration and erosion from acid Protein-calorie malnutrition Villous atrophy; secondary bacterial overgrowth Drug-induced enteritis Variable histology a normal mucosal appearance except for the presence of mucosal absorptive cells that contain lipid postprandially and disappear after a prolonged period of either fat-free intake or fasting. 2. Patchy lesions that are specific for a disease entity include, for example, intestinal lymphoma or intestinal lymphangiectasia. Several diseases feature an abnormal small-intestinal mucosa with a patchy distri bution. As a result, biopsy samples obtained randomly or in the absence of endoscopically visualized abnormalities may not reveal diagnostic features. Intestinal lymphoma can at times be diagnosed on mucosal biopsy by the identification of malignant lymphoma cells in the lamina propria and submucosa (Chap. 113). Dilated lymphat ics in the submucosa and sometimes in the lamina propria indicate lymphangiectasia associated with hypoproteinemia secondary to protein loss into the intestine. Eosinophilic gastroenteritis comprises a heterogeneous group of disorders with a spectrum of presentations and symptoms, with an eosinophilic infiltrate of the lamina propria, and with or without peripheral eosinophilia. The patchy nature of the infiltrate and its presence in the submucosa often lead to an absence of histopathologic findings on mucosal biopsy. Amyloid deposition can be identified by Congo red staining in some patients with amyloidosis involving the duodenum (Chap. 117). Whipple’s disease exhibits PAS-positive macrophages, and immunohistochemi cal analysis can detect the pathogenic organism. Although in severe cases the lesions are diffuse, patchy disease may also occur, requiring enteroscopy and sampling of multiple mucosal sites. 3. Diffuse nonspecific lesions may be found in more than one disorder. For example, villus atrophy/absence may be found in celiac disease, tropical sprue, or bacterial overgrowth, among other disorders. Several microorganisms can be identified in small-intestinal biopsy samples, establishing a correct diagnosis. At times, the biopsy is

---

Revision #1
Created 2026-01-06 16:34:33 UTC by Omar Ayman
Updated 2026-01-06 16:34:33 UTC by Omar Ayman