and may miss focal changes in the duodenum, like diverticula.

**Abdominal Computed Tomography**

Abdominal computed tomography is useful for detecting focal intestinal lesions like thickening of the small bowel wall in Crohn’s disease or small intestinal lymphoma, intestinal fistula, and dilated bowel loops. Computed tomography is a sensitive test to detect enlarged abdominal lymph nodes, which are commonly present in disorders like Whipple’s disease, small bowel lymphoma, or small intestinal inflammatory diseases such as Crohn’s disease. Evidences for pancreatic disease that may be detected on computed tomography are calcifications of the pancreas, dilatation of the pancreatic duct, and an atrophic pancreas. Furthermore, tumors obstructing the pancreatic duct or hormone-secreting neuroendocrine tumors can be located by computed tomography.

**Other Radiographic Studies**

A plain film of the abdomen may be helpful to detect pancreatic calcifications if exocrine pancreatic insufficiency is suspected. It should be noted, however, that morphologic signs of chronic pancreatitis alone do not prove a pancreatic cause of malabsorption, because the function of the exocrine pancreas must be severely impaired before malabsorption becomes evident. A plain film of the abdomen may also document stagnant loops of intestine, predisposing to small bowel bacterial overgrowth or suggesting the presence of an obstruction.

Endoscopic retrograde pancreatography may be helpful in establishing the cause of pancreatic insufficiency (see Chapter 49). It can help to distinguish between chronic pancreatitis and pancreatic tumor or document pancreatic duct stones. Endoscopic retrograde cholangiography is the method of choice for documenting various causes of biliary obstruction. Noninvasive magnetic resonance cholangiography is increasingly used to replace diagnostic endoscopic retrograde cholangiography (see Chapter 61). Magnetic resonance imaging of the abdomen is also useful to demonstrate complications of Crohn’s disease, like fistulas.

If malabsorption is suspected to be caused by a neuroendocrine tumor (e.g., gastrinoma, somatostatinoma), an indium-111 octreotide scintigraphic scan or an endoscopic ultrasound examination of the pancreas may be helpful in establishing the diagnosis or demonstrating the extent of the disease (see Chapter 51).

Transabdominal ultrasound examinations are very popular in some countries, although they are very operator dependent. They have the advantage of having no radiation exposure and therefore can also be used in pregnant patients. Ultrasonography is frequently used to investigate the pancreas, although the sensitivity for the detection of tumors is lower compared with endoscopic retrograde cholangiopancreatography or computed tomography. Nevertheless, obstruction of the biliary tract, pancreatic calcifications, dilatation of the pancreatic duct, or stones within the pancreatic duct may be demonstrated. Ultrasound may also be used to document thickening of the bowel wall, abscesses, and fistula in Crohn’s disease.

**NONINVASIVE EVALUATION OF GASTROINTESTINAL ABSORPTIVE AND DIGESTIVE FUNCTION**

Some conditions causing malabsorption can be diagnosed by the use of noninvasive tests, although, as pointed out in Table 89–11, diagnostic accuracy may be limited, and further tests may be necessary to identify underlying diseases or to differentiate between primary and secondary causes. Apart from providing a diagnosis, tests evaluating gastrointestinal absorptive and digestive function may be helpful in the evaluation of complex disease presentations. For most or all of the following tests, the potential benefits with regard to the costs of workup or to patient acceptability have not been established. Because test procedures and analytical

<table>
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<td>Lactose malabsorption</td>
<td>Lactose hydrogen breath test</td>
<td>Tests do not differentiate among primary and secondary lactose malabsorption. Questionable clinical relevance</td>
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<td>Fructose malabsorption</td>
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<td>Vitamin B12 malabsorption</td>
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<td>Appropriate interventions needed to differentiate among gastric, intestinal, or pancreatic causes; diagnostic for pernicious anemia; further tests are needed if small bowel bacterial overgrowth, terminal ileal disease, and pancreatic disease are suspected</td>
</tr>
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*See text for diagnostic accuracy of the different tests mentioned.

†See chapter 46.

‡14C TCA test; 14C-labeled taurocholic acid test; SeHCAT, selenium-75 labeled homotaurocholic acid test.
Tests for Fat Malabsorption

Quantitative Fecal Fat Analysis

The van de Kamer method, which is the titrimetric measurement of fatty acid equivalents and the expression of results as fecal fat output in grams per 24 hours, is considered to be the gold standard. Modifications in which the extracted fats are weighed rather than titrated have an excellent correlation with the results of the titrimetric method. Near-infrared reflectance analysis may be a less cumbersome method to quantify fecal fat output in quantitative stool collections, because it requires less handling of stool by the laboratory personnel, but it still requires a 48- to 72-hour stool collection to exclude the influence of day to day variability and mixing of the stool before a sample is obtained for analysis. In our own unpublished experience, the accuracy of the near-infrared reflectance analysis technology is influenced by stool consistency—in watery stools the accuracy of the method decreases.

Fecal fat excretion of less than 7 g/day on a 100-g/day fat diet is usually considered to be normal. It is, however, important to note that the volume effect of diarrhea by itself increases fecal fat output to levels of up to 14 g/day (secondary fat malabsorption); this latter normal value could be used in patients with diarrhea.

Quantitative fecal fat analysis is routinely available only in a few centers. Reasons for the limited clinical use of quantitative fecal fat measurements are as follows. First, if the main symptom of malabsorption is chronic diarrhea, measurement of fecal fat may not influence the subsequent workup because the diagnostic tests performed to establish the etiology of diarrhea are similar to the tests for the workup of steatorrhea. Second, an elevated fecal fat level cannot be used to differentiate between biliary, pancreatic, and enteric causes of malabsorption. Third, on clinical grounds, in many patients with severe steatorrhea, the porridge-like appearance of the stools is characteristic, and quantitative studies are not necessary to establish fat malabsorption. Fourth, fat absorption may be normal despite malabsorption of other nutrients. Therefore, a normal fat balance does not imply normal absorptive function of the gastrointestinal tract. Finally, accuracy depends on quantitative stool collections for 48 to 72 hours, adherence to an 80- to 100-g fat diet, and a diet diary to determine fat intake.

Keeping the limitations of quantitative fecal fat analysis in mind, it is nevertheless still useful in several clinical circumstances: to establish malabsorption when there are no overt features of intestinal or pancreatic disorders, like in cases of osteoporosis, osteomalacia, anemia, or weight loss; to monitor treatment in patients with established malabsorptive disorders, like exocrine pancreatic insufficiency or short bowel syndrome; to estimate fecal calorie loss in patients with severe malabsorption syndromes; and to quantitate fecal fat excretion in patients with diarrhea and ileal resections to help distinguish patients with steatorrhea due to bile acid deficiency from patients with secretory diarrhea caused by bile acid loss, because treatments for these conditions differ. Falsey elevated fecal fat values (pseudo-steatorrhea) can be observed in patients consuming a diet rich in the fat substitute olestra.

Semiquantitative Fat Analysis

For the acid steatocrit test, a sample of stool is diluted to a 1:3 concentration with distilled water in a test tube. The diluted stool is homogenized, and a 500-µL aliquot is pipetted into a tube. Then 100 µL of 5 M HClO4 is added. An aliquot of the diluted stool–HClO4 mixture is put into a nonheparinized microcapillary tube and sealed on one end. After centrifugation at 13,000 rpm for 15 minutes, the fatty layer (FL) and the solid layer (SL) are measured and the acid steatocrit (AS) is determined according to the following equation: AS (%) = [FL/(FL + SL)] × 100. An acid steatocrit of less than 31% is considered to be normal. In a small study, the acid steatocrit performed on random spot stool samples had a high sensitivity and specificity to detect steatorrhea, as compared with the van de Kamer method, which was performed on a 72-hour stool collection. There was also a linear correlation between results obtained with the acid steatocrit and results of the van de Kamer method, although there were quite divergent results in some patients. Considering the fact that quantitative fecal fat measurements are usually based on 48- to 72-hour stool collections to minimize the effect of day to day variability in fecal fat excretion, it cannot be expected that the acid steatocrit can replace quantitative measurement of fat output in borderline cases or in cases in which exact measurements of fecal fat loss are required.

Qualitative Fecal Fat Analysis

Fat analysis by microscopic examination of random stool samples may provide a clue to the presence of steatorrhea, although it cannot be used to exclude steatorrhea. Its advantage is that it is easy to perform. A sample of stool is placed on a glass slide to which several drops of glacial acetic acid and Sudan III stain are added. Acidification of stool samples improves fat extraction and separation of the lipid layer. The acidified mixture is heated to boiling and examined while still warm for presence of orange fat globules. Up to 100 globules with a diameter less than 4 µm per high-power field are considered to be normal. Results of the Sudan stain and of quantitative fat analysis do not correlate very well. In a small study, Sudan staining of spot stool samples had a sensitivity of 78% and a specificity of 70% for the detection of steatorrhea. Recently, a new quantitative microscopic method of counting and measuring fat globules has been shown to correlate with chemically measured fecal fat output.

Breath Tests for Fat Malabsorption

The test principle of the 14C-triolein breath test is to measure 14CO2 in breath after ingestion of a triglyceride that has been radiolabeled with 14C. Fat malabsorption results in decreased pulmonary excretion of 14CO2. Because of erroneous results in a variety of metabolic and pulmonary dis-
Serum Tests for Fat Malabsorption

Experience with the measurement of the serum concentration of \( \beta \)-carotene for the qualitative assessment of fat malabsorption is limited. It has been suggested to be a useful screening test for steatorrhea, with values below 100 µg/100 mL suggestive of the presence of steatorrhea and values of less than 47 µg/100 mL strongly indicative of steatorrhea. \( \beta \)-Carotene can be measured photometrically at 456 nm. Concentrations in excess of 100 µg/100 mL do not exclude mild steatorrhea, although they make steatorrhea in excess of 16 g fat loss per day very unlikely. Normal values have also been established in the pediatric population. \( \beta \)-Carotene can be falsely low in liver diseases or in alcoholics who eat a \( \beta \)-carotene deficient diet. Disorders in lipoproteins or intake of carotene-containing food additives can also influence the results.

Tests for Carbohydrate Malabsorption

The hydrogen breath test is a noninvasive test that takes advantage of the fact that in most people bacterial carbohydrate metabolism results in accumulation of hydrogen, which then is absorbed by the intestinal mucosa and excreted in breath. Using different carbohydrates, like lactose or fructose, the hydrogen breath test can be used to detect whether malabsorption of these carbohydrates is present. Measurement of hydrogen excretion in breath after ingestion of lactulose has been used to assess oroecocal transit time, and glucose has been used as a substrate to detect small bowel bacterial overgrowth, although sensitivity and specificity are poor. Unfortunately, up to 18% of persons are hydrogen nonexcretors. In these persons hydrogen breath tests may be falsely negative because hydrogen is metabolized by bacteria to methane.

The diagnosis of lactose malabsorption is established if there is an increase in breath hydrogen concentration of more than 20 parts per million over baseline after ingestion of 50 g of lactose. An increase within the first 30 minutes after ingestion of lactose has to be disregarded, because it may be due to bacterial degradation of lactose in the oral cavity. It may take up to 4 hours until the increase in breath hydrogen concentration occurs. Breath hydrogen measurements obtained before and at 30, 60, 90, 180, and 240 minutes after ingestion of 50 g of lactose provide the best diagnostic yield at the least possible number of measurements.

Lactose hydrogen breath test is still considered to be the gold standard for the diagnosis of lactose malabsorption by many researchers, but this test may miss the disorder in hydrogen nonexcretors. In these patients a lactose tolerance test, that is, measurements of blood glucose before and 30 minutes after ingestion of 50 g of lactose, can be used. An increase in glucose concentration of less than 20 mg/dL over baseline within 30 minutes of ingestion of 50 g of lactose is indicative of lactose malabsorption. The lactose tolerance test has a lower sensitivity as compared with lactose hydrogen breath test.

In patients with diarrhea, a stool test to detect a fecal pH lower than 5.5 can serve as a qualitative indicator of carbohydrate malabsorption. In the research setting, fecal carbohydrates can be measured by the anthrone method, which measures carbohydrates on a weight basis. In contrast, the reducing sugar method gives results on a molar basis. Therefore, in contrast to the anthrone method, the reducing sugar method provides information about the osmotic activity of malabsorbed carbohydrates. Total short-chain fatty acids and lactic acid, which are the products of bacterial carbohydrate metabolism, can be measured in stool by titration. Individual short-chain fatty acids can be determined by gas chromatography.

Tests for Protein Malabsorption

The classic test to quantify protein malabsorption, measurement of fecal nitrogen content in a quantitatively collected stool specimen, is rarely used today. For research purposes, a combined \( \Delta ^{14} \)C octanoic acid/\( \Delta ^{13} \)C egg white breath test accompanied by measurement of the urinary output of phenol and p-cresol, which are specific metabolites of tyrosine, has been used to assess the effect of gastric acid on protein digestion.

Tests for Cobalamin (Vitamin B\(_{12}\)) Malabsorption

Schilling Test

The Schilling test is used clinically to distinguish between gastric and ileal causes of vitamin B\(_{12}\) deficiency and to evaluate the function of the ileum in patients with diarrhea or malabsorption. The results of the test are not influenced by vitamin B\(_{12}\) replacement therapy. The Schilling test does not have an important clinical role for the assessment of pancreatic insufficiency or bacterial overgrowth, because more direct approaches to diagnose these disorders are available. Because in humans both intrinsic factor and hydrochloric acid are produced by parietal cells, alternative approaches to diagnosing pernicious anemia are to document atrophic gastritis by endoscopy and biopsy, to confirm achlorhydria by acid secretion analysis to detect increased gastrin levels, or to look for antibodies directed against parietal cells or intrinsic factor in the serum.

The Schilling test is performed by administering a small oral dose of radiolabeled vitamin B\(_{12}\) and, simultaneously or within 1 to 2 hours, a large intramuscular “flushing dose” of nonradiolabeled vitamin B\(_{12}\). The latter saturates vitamin B\(_{12}\) carriers; thus, radioactive vitamin B\(_{12}\) absorbed by the intestine is excreted in the urine. If less than 7% to 10% of the administered dose is recovered in urine within 24 hours, vitamin B\(_{12}\) malabsorption is confirmed. To specify the site of vitamin B\(_{12}\) malabsorption, a second phase of the Schilling test has to be performed subsequently with oral administration of intrinsic factor. In patients with pernicious anemia, the results of the Schilling test normalize after oral administration of intrinsic factor.
Patients with pancreatic exocrine insufficiency may have abnormal results of the Schilling test, with or without added intrinsic factor, but they normalize with the addition of pancreatic enzymes (see Chapters 38 and 46). In ileal disease or resection, abnormal results of the Schilling test persist despite use of intrinsic factor. The Schilling test is normal in patients with dietary vitamin B₁₂ deficiency, protein-bound (food-bound) vitamin B₁₂ malabsorption, and sometimes in congenital transcobalamin II deficiency. In patients with food-bound cobalamin malabsorption, a modified Schilling test using cobalamin bound to eggs, chicken serum, or various meats can be used to detect cobalamin malabsorption.

False-positive results of the Schilling test may be due to renal dysfunction or inadequate urine collections. The value of this test is diminished by the need for accurately timed urine collections. Results in the 5% to 10% excretion range are often difficult to interpret. A variation of the standard Schilling test is the dual-isotope or “single-stage” Schilling test, using two different cobalamin isotopes simultaneously, one of them bound to intrinsic factor. This makes it possible to perform the first two phases of the Schilling test in one day. However, the results of this test are not as accurate as the standard protocol.

Serum Test for Vitamin B₁₂ and Folate Deficiency

Measurements of serum cobalamin and folate concentrations are commonly used to detect deficiency states of these vitamins. The sensitivity and specificity of these tests are unknown, because there is no established gold standard and because serum levels do not always correlate with body stores. Some authors suggest that the disappearance of symptoms after cobalamin or folate replacement is probably the most sensitive marker for deficiency of these vitamins. Several causes of misleading serum cobalamin levels have been established. Serum vitamin B₁₂ levels can be normal although body stores are depleted in small intestinal bacterial overgrowth (due to production of inactive cobalamin analogs by the bacteria), in liver disease, in myeloproliferative disorders, and in congenital transcobalamin II deficiency. In contrast, use of oral contraceptives, pregnancy, and folate deficiency can cause low serum cobalamin levels despite normal body stores. Serum folate concentrations decrease within a few days of dietary folate restriction even if tissue stores are normal. Feeding also influences serum folate levels, and therefore determination of folate in the fasting state is recommended. Measurement of red blood cell folate has been considered a better estimate of folate tissue stores by some authors.

In cobalamin deficiency, serum concentrations of methymalonic acid and total homocysteine are elevated. Folate deficiency results only in an increase in serum homocysteine concentration. In cases of patients with slightly low or borderline serum cobalamin levels, determination of methymalonic acid and homocysteine may therefore be helpful in establishing the diagnosis of a deficiency state. These metabolites tend to normalize within 1 to 2 weeks after replacement therapy, and some authors have suggested that the measurement of these metabolites can be used to distinguish between cobalamin and folate deficiency states. The distinction is important because in cobalamin-deficient patients supplemental replacement of folate may correct hematologic changes, despite progression of neurologic disease.

Tests for Bacterial Overgrowth

Tests for the diagnosis of bacterial overgrowth are covered in more detail in Chapter 90. Briefly, tests used to diagnose bacterial overgrowth are the quantitative culture of a small intestinal aspirate (which is considered to be the gold standard) and several breath tests, including the ¹⁴C-glycocholate breath test, the ¹⁴C-D-xylose breath test, the lactulose-H₂ breath test, and the glucose-H₂ breath test. The rationale for the breath tests is the production of volatile metabolites, that is, ¹⁴CO₂ or H₂, from the administered substances by intraluminal bacteria, which can be measured in the exhaled air. Details about the sensitivity and specificity of the various tests are provided in Chapter 89.

Tests for Exocrine Pancreatic Function

Pancreatic function tests are discussed in detail in Chapter 46. Invasive pancreatic function tests require duodenal intubation and measurement of pancreatic enzyme, volume, or bicarbonate output after pancreatic stimulation by a liquid test meal (Lundh test) or by injection of cholecystokinin and/or secretin. Noninvasive tests include measurement of fecal chymotrypsin or elastase concentration, the fluorescein dilaurate test, and the N-benzoyl-L-tyrosyl para-aminobenzoic acid (NBT-PABA) test. In many clinical settings the measurement of fecal concentration of chymotrypsin or elastase may be sufficient for the diagnosis or exclusion of exocrine pancreatic insufficiency. Elastase may have a higher sensitivity for the detection of exocrine pancreatic insufficiency as compared with chymotrypsin.

Tests for Bile Salt Malabsorption

In patients with steatorrhea due to ileal disease or resection, bile salt malabsorption is usually present, but measurement of bile acid malabsorption is of limited clinical value in these patients. In some patients with diarrhea without steatorrhea, bile salt malabsorption may be present in the absence of overt ileal disease, and in these cases measurement of bile salt absorption may be helpful.

Measurement of Fecal Bile Acid Output

Elevated fecal bile acid concentrations and/or output can indicate intestinal bile acid malabsorption. Under steady-state conditions, the increased fecal bile acid output reflects increased hepatic synthesis of bile acids. However, in severe bile acid malabsorption, fecal bile acid output theoretically can be reduced if hepatic synthesis of bile acids is impaired. The measurement can be performed by either enzymatic methods or by gas chromatography. This test requires a
quantitative stool collection, and the analytic techniques are time consuming and require considerable expertise.

**14C-Taurocholate Bile Acid Absorption Test**

This test requires a 72-hour stool collection after ingestion of a radioactively labeled bile acid. The rate of intestinal bile acid absorption is calculated from the fecal recovery of 14C-labeled taurocholic acid (14C-TCA). Normal values for this test have been established in normal subjects with laxative-induced diarrhea, because diarrhea by itself can increase fecal losses of bile acids. Clinical limitations of this test are that it requires substantial analytical work, access to a gamma camera, and a time-consuming stool collection.

**Therapeutic Trial of Bile Acid Binding Resins (Cholestyramine)**

A therapeutic trial of cholestyramine or other bile acid binding resins can be used to diagnose bile acid malabsorption as a cause of diarrhea. It is, however, controversial to what extent a clinical response to cholestyramine correlates with the presence of bile acid malabsorption, because cholestyramine may have a nonspecific effect in patients with diarrhea from other causes. Failure to improve diarrhea significantly in patients with established bile acid malabsorption results in steatorrhea, cholestyramine may even aggravate fat malabsorption and diarrhea. In patients with established bile acid malabsorption in whom there is no improvement on bile acid binding resins, it is very unlikely that bile acid malabsorption is the cause of diarrhea. In these patients, bile acid malabsorption is considered to be a secondary phenomenon due to the “washout effect.” It should be noted that in patients with severe bile acid malabsorption resulting in steatorrhea, cholestyramine may even aggravate fat malabsorption and diarrhea. Therefore, without further testing for bile acid malabsorption, neither a positive nor a negative result of a therapeutic trial are a proof for the presence or absence of bile acid malabsorption.

**Selenium-75 Labeled Homotaurocholic Acid Test**

The radioactive taurocholic acid analog used for this test is resistant to bacterial deconjugation. After oral administration, the patient undergoes serial gamma scintigraphy to measure whole-body bile acid retention or, as suggested by some authors, bile acid retention in the gallbladder. The limitations of this test are that normal values for bile acid retention, which are used to compare between normal and abnormal bile acid absorption, were obtained only in healthy subjects without diarrhea. However, as mentioned above, “secondary” bile acid malabsorption can be induced by diarrhea itself and is proportional to the stool weight, as demonstrated with the 14C-TCA test. To be of clinical usefulness, adequate normal values need to be established for patients with diarrhea for this test. This test is very time consuming because bile acid retention needs to be measured, depending on the protocol, 4 or 7 days after the bile acid administration.

**D-Xylose Test**

The D-xylose test was introduced in the 1950s to distinguish small intestinal from pancreatic causes of malabsorption. Most verification studies have involved patients with celiac disease or inflammatory bowel disease. The test is of limited clinical value today and has mostly been replaced by a small bowel biopsy.

Absorption of D-xylose, a pentose, is facilitated by passive diffusion. About 50% of the absorbed D-xylose is metabolized, and the remainder is excreted in urine. After an overnight fast, a 25-g dose of D-xylose is swallowed and the patient is encouraged to drink to maintain good urine output. Urine is collected for the next 5 hours. As an alternative, 1 hour after ingestion of D-xylose a venous sample may be taken. Less than 4 g (16% excretion) of D-xylose in the urine collection or a serum xylose concentration below 20 mg/dL is indicative of abnormal intestinal absorption. In direct comparisons, the traditional urine test appears to be more reliable than the 1-hour blood test.

False-positive results occur if the duration of urine collection is too short or if the patient is dehydrated or has renal dysfunction. Falsely low absorption is seen in patients with bacterial overgrowth, and portal hypertension. D-Xylose absorption may be normal in patients with only mild impairment of mucosal function or with predominantly distal small bowel disease. Because D-xylose is susceptible to bacterial metabolism, absorption is diminished in patients with bacterial overgrowth, although the test has a poor sensitivity for detection of this condition.

**Intestinal Permeability Tests**

Intestinal permeability tests are mostly used in studies of the pathophysiology of intestinal disorders. They do not provide a specific diagnosis.

Most current permeability tests are based on the differential absorption of mono- and disaccharides. Mucosal damage results in an increased permeability for disaccharides and oligosaccharides due to epithelial damage and a decreased permeability of monosaccharides due to reduction of mucosal surface area. Absorption is measured by urinary excretion. The expression of results as the absorption ratio of the mono- and disaccharide minimizes the influence of gastric emptying, intestinal transit, renal and hepatic function, and variations in time of urine collections.

Increased intestinal permeability has been shown to predict the development of Crohn’s disease or relapse in patients with this disease. In celiac disease, permeability tests are a sensitive marker for advanced disease and have also been used to assess response to a gluten-free diet. Hypertransaminasemia in patients with celiac disease correlates with increased intestinal permeability. Disturbances of intestinal permeability have been documented in users of...
nonsteroidal anti-inflammatory drugs,\(^\text{122}\) in inflammatory joint disease,\(^\text{123}\) and in diabetic diarrhea.\(^\text{124}\)

\(^{13}\text{C} \) Breath Tests

The increasing availability of methods for analyzing stable isotopes has raised interest in replacing the radioactive \(^{14}\text{C}\) by nonradioactive \(^{13}\text{C}\).\(^\text{125–127}\) With regard to malabsorption, \(^{13}\text{C}\)-labeled substrates have been evaluated for the diagnosis of steatorrhea,\(^\text{128}\) evaluation of the digestibility of egg protein,\(^\text{102}\) and the diagnosis of small bowel bacterial overgrowth and exocrine pancreatic insufficiency.\(^\text{129}\) In general, because of concerns about diagnostic accuracy, costs of the substrates, and the equipment and limited availability, these tests have not gained widespread acceptance.

MALABSORPTION IN SPECIFIC DISEASE STATES

Lactose Malabsorption and Intolerance

Deficiency of the intestinal brush border enzyme lactase may lead to lactose malabsorption, which may result in lactose intolerance. Lactase deficiency in infants may have several causes. Unlike other intestinal disaccharidases, which develop early in fetal life, lactase levels remain low until the 34th week of gestation.\(^\text{130}\) Transient lactase deficiency in premature infants may lead to symptoms of lactose malabsorption, like diarrhea, until normal intestinal lactase activity develops. In rare cases, in which enzyme deficiency is manifest at the time of birth and is permanent, congenital lactase deficiency has to be considered. Reversible lactase deficiency may occur at every age as a result of transient small bowel injury associated with acute diarrhea illnesses.

Acquired primary lactase deficiency is the most common form of lactase deficiency worldwide. Most populations lose considerable lactase activity in adulthood.\(^\text{131}\) The decline in lactase activity is a multifactorial process that is regulated at the gene transcription level and leads to decreased biosynthesis or retardation of intracellular transport or maturation of the enzyme lactase-phlorizin hydrolase.\(^\text{133}\) This "normal" form of lactase deficiency usually manifests symptoms only in adulthood, although lactase levels in these persons start to decline during childhood.\(^\text{134}\)

Lactase activity persists in most adults of western European heritage (Table 89–12). Even in adults with preserved lactase activity, the activity of lactase is only about half the activity of sucrase and less than 20% the activity of maltase.\(^\text{134}\) This makes lactose digestion much more susceptible to a reduction of mucosal digestive function in acute or chronic gastrointestinal illnesses.

In lactose malabsorbers it may remain unclear whether lactose malabsorption is due to acquired primary lactase deficiency or is the consequence of another small bowel disorder. Therefore, in the individual lactose malabsorber, especially if he or she has an ethnic background with a low prevalence of acquired primary lactase deficiency, it may be necessary to exclude other malabsorptive small bowel disorders, like celiac disease.

The main symptoms of lactose intolerance are bloating, abdominal cramps, increased flatus, and diarrhea. The development of bloating and abdominal cramps is presumably associated with increased perception of luminal distension by gas.\(^\text{135}\) There is no clear relation between the amount of lactose ingestion and the severity of these symptoms.\(^\text{136}\) Ingestion of as little as 3 g of lactose to as high as 96 g of lactose may be required to induce symptoms in individuals with lactose malabsorption.\(^\text{137}\) Severity of gastrointestinal symptoms, including diarrhea, has been shown to be greater in adults with shorter small bowel transit time,\(^\text{138}\) but there is no such relation between intestinal transit and symptoms in children.\(^\text{139}\) Also, in pregnant women and in thyrotoxic patients with Graves’ disease, changes in intestinal motility play a role in the clinical manifestation of lactose malabsorption.\(^\text{140, 141}\)

Considering the poor correlation between lactose malabsorption and lactose intolerance, it is very important to monitor symptoms during a lactose hydrogen breath test and to confirm with the patient that symptoms during the test are representative of the patient’s symptoms.

 Patients in whom a clear association between symptoms and lactose malabsorption can be established should be educated about a lactose-reduced or lactose-free diet. Yogurts may be better tolerated by these patients,\(^\text{142}\) and they provide a good source of calcium. Consumption of whole milk or chocolate milk, rather than skim milk, and consuming milk with meals may reduce symptoms of lactose intolerance, presumably due to prolongation of gastric emptying. Alternatively, supplementation of dairy products with lactase of microbiologic origin may be suggested.\(^\text{143}\) Furthermore, because many carbohydrates other than lactose are incompletely absorbed by the normal small intestine and because dietary fibers also may be metabolized by colonic bacteria, persistence of some symptoms of “lactose intolerance” while the patient is on a lactose-free diet is not uncommon. It also has to be kept in mind that symptoms after ingestion of dairy products may also be due to milk protein allergy or to intolerance of fat.

Fructose Malabsorption and Intolerance

Fructose is found in modern diets either as a constituent of the disaccharide sucrose or as the monosaccharide, which is
used as a sweetener in a variety of food items. Fructose as the constituent of sucrose is absorbed by a well-characterized absorptive system integrating enzymatic hydrolysis of the disaccharide by sucrase and transfer of the resulting two monosaccharides through the apical membrane of the epithelial cell. In contrast, the absorptive capacity for fructose, which is not accompanied by glucose, is relatively small.\(^1\)

Ingestion of food that contains fructose may result in symptoms like abdominal bloating or diarrhea\(^2\) and may also provoke symptoms in irritable bowel syndrome.\(^3\) Fructose malabsorption is usually identified by a positive breath hydrogen test after ingestion of 25 or 50 g of fructose. Because fructose content in and soft drinks is usually below 8 g/100 g of fruit or drink, the amounts of fructose used in the breath hydrogen test are unphysiologic, and there are no data on how many asymptomatic people would have a positive test result. Nevertheless, fructose contents of 30 to 40 g/100 g can be present in chocolate or hard nougat.\(^4\)

Most studies on fructose malabsorption are limited to patients who presented with symptoms of fructose intolerance, which in this context means development of gastrointestinal symptoms after ingestion of fructose-containing food. In a group of patients with isolated fructose malabsorption, no defect of the gene encoding for the luminal fructose transporter (GLUT5) could be detected.\(^5\) It is therefore currently unclear whether patients who present with symptoms of fructose malabsorption really have a defect of intestinal fructose absorption or belong to a subset of people in whom ingestion of foods rich in fructose provokes symptoms related to other disorders, like irritable bowel syndrome. Patients who develop symptoms after ingestion of fructose-rich food may also represent a subset of persons with special, and not necessarily abnormal, colonic bacterial activity.\(^6\)

In conclusion, testing for fructose malabsorption by the hydrogen breath test may be useful in identifying a subset of patients in whom dietary restriction of foods with excessive fructose content may be useful for the treatment of bloating and diarrhea. Symptoms most likely are the result of ingestion of unphysiologic amounts of fructose rather than the consequence of a defect in fructose absorption.

**Steatorrhea due to Ileal Bile Acid Malabsorption**

Bile acid malabsorption is usually present in patients with resections, bypass operations, or severe diseases of the ileum, where specific bile acid transport proteins are normally located. The clinical consequences of bile acid malabsorption depend on whether bile acid loss can or cannot be compensated by increased synthesis by the liver.\(^7\) Ileal resection of more than 100 cm usually results in severe bile acid malabsorption that cannot be compensated by increased hepatic synthesis and therefore causes steatorrhea by impaired micelle formation due to decreased luminal concentrations of conjugated bile acids.\(^8\) In ileal resections of less than 100 cm, bile acid malabsorption can usually be compensated by increased hepatic synthesis, and malabsorbed bile acids cause secretory diarrhea rather than steatorrhea.\(^9\)

**Amyloidosis**

Amyloidosis has been reported in AL-amyloid amyloidosis, and familial amyloidosis.\(^10\) Fat malabsorption occurs in less than 5% of patients with Al disease,\(^11\) whereas fat malabsorption was present in Swedish patients with familial amyloidosis.\(^12\) Feces can reach levels up to 60 g/day.\(^13\) Gastric absorption of D-xylene and vitamin B\(_12\) can be reduced and protein losing enteropathy may occur.\(^14\) Amyloids are found in the muscle layers, the stroma of the muscularis propia and the submucosa, the wall of mucosal and submucosal vessels of the gastrointestinal tract, and in extrinsic nerves.\(^15\), \(^16\)

In many amyloidosis patients with diarrhea and/or symptoms suggestive of autonomic neuropathy present.\(^17\) Diarrhea and malabsorption in an individual with amyloidosis are most likely multifactorial. Diarrhea and malabsorption may be mediated intestinal transit due to autonomic neuropathy and myopathy,\(^18\) decreased absorption due to a physical effect of amyloid deposits,\(^19\) or small intestinal overgrowth.\(^20\) Bile acid malabsorption, which is many amyloidosis patients with autonomic neuropathy be a contributing factor.\(^21\) Barium studies in amyloidosis patients are usually normal, but they may show folds, nodular lesions, filling defects, dilatation of intestinal segments, or altered transit of the gastrointestinal tract. The endoscopic appearance of the gastrointestinal tract can show a fine granular appearance, polyloid protrusions, ulcerations, atrophic changes, and mucosal atrophy, but in many affected patients there are no macroscopic changes.\(^22\) Histologic examination demonstrates deposits in 72% of esophageal, 75% to 95% of gastroduodenal, 75% to 95% of small intestinal, and 75% to 95% of c biopsies.\(^23\), \(^24\), \(^25\) Subcutaneous fat pad aspiration may more safely make the diagnosis without having to endoscopic biopsy and its risks (e.g., bleeding).