

release of cytokines and other inflammatory mediators. The unifying feature on stool analysis is the presence of leukocytes or leukocyte-derived proteins such as calprotectin. With severe inflammation, exudative protein loss can lead to anasarca (generalized edema). Any middle-aged or older person with chronic inflammatory-type diarrhea, especially with blood, should be carefully evaluated to exclude a colorectal tumor.

**IDIOPATHIC INFLAMMATORY BOWEL DISEASE** The illnesses in this category, which include *Crohn's disease* and *chronic ulcerative colitis*, are among the most common organic causes of chronic diarrhea in adults and range in severity from mild to fulminant and life-threatening. They may be associated with uveitis, polyarthralgias, cholestatic liver disease (primary sclerosing cholangitis), and skin lesions (erythema nodosum, pyoderma gangrenosum). *Microscopic colitis*, including both lymphocytic and *collagenous colitis*, is an increasingly recognized cause of chronic watery diarrhea, especially in middle-aged women and those on NSAIDs, statins, proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs); biopsy of a normal-appearing colon is required for histologic diagnosis. It may coexist with symptoms suggesting IBS or with celiac sprue or drug-induced enteropathy. It typically responds well to anti-inflammatory drugs (e.g., bismuth), to the opioid agonist loperamide, or to budesonide.

**PRIMARY OR SECONDARY FORMS OF IMMUNODEFICIENCY** Immunodeficiency may lead to prolonged infectious diarrhea. With selective IgA deficiency or common variable *hypogammaglobulinemia*, diarrhea is particularly prevalent and often the result of giardiasis, bacterial overgrowth, or sprue.

**EOSINOPHILIC GASTROENTERITIS** Eosinophil infiltration of the mucosa, muscularis, or serosa at any level of the GI tract may cause diarrhea, pain, vomiting, or ascites. Affected patients often have an atopic history, Charcot-Leyden crystals due to extruded eosinophil contents may be seen on microscopic inspection of stool, and peripheral eosinophilia is present in 50–75% of patients. While hypersensitivity to certain foods occurs in adults, true food allergy causing chronic diarrhea is rare.

**OTHER CAUSES** Chronic inflammatory diarrhea may be caused by *radiation enterocolitis*, *chronic graft-versus-host disease*, *Behçet's syndrome*, and *Cronkhite-Canada syndrome*, among others.

**Dysmotility Causes** Rapid transit may accompany many diarrheas as a secondary or contributing phenomenon, but primary dysmotility is an unusual etiology of true diarrhea. Stool features often suggest a secretory diarrhea, but mild steatorrhea of up to 14 g of fat per day can be produced by maldigestion from rapid transit alone. *Hyperthyroidism*, *carcinoid syndrome*, and certain drugs (e.g., prostaglandins, prokinetic agents) may produce hypermotility with resultant diarrhea. Primary visceral neuromyopathies or idiopathic acquired intestinal pseudoobstruction may lead to stasis with secondary bacterial overgrowth causing diarrhea. *Diabetic diarrhea*, often accompanied by peripheral and generalized autonomic neuropathies, may occur in part because of intestinal dysmotility.

The exceedingly common IBS (10% point prevalence, 1–2% per year incidence) is characterized by disturbed intestinal and colonic motor and sensory responses to various stimuli. Symptoms of stool frequency typically cease at night, alternate with periods of constipation, are accompanied by abdominal pain relieved with defecation, and rarely result in weight loss.

**Factitial Causes** Factitial diarrhea accounts for up to 15% of unexplained diarrheas referred to tertiary care centers. Either as a form of *Munchausen syndrome* (deception or self-injury for secondary gain) or *eating disorders*, some patients covertly self-administer laxatives alone or in combination with other medications (e.g., diuretics) or surreptitiously add water or urine to stool sent for analysis. Such patients are typically women, often with histories of psychiatric illness, and disproportionately from careers in health care. Hypotension and hypokalemia are common co-presenting features. The evaluation of such patients may be difficult: contamination of the stool with water or urine is suggested by very low or high stool osmolality, respectively.

Such patients often deny this possibility when confronted, but they do benefit from psychiatric counseling when they acknowledge their behavior.

## APPROACH TO THE PATIENT: Chronic Diarrhea

The laboratory tools available to evaluate the very common problem of chronic diarrhea are extensive, and many are costly and invasive. As such, the diagnostic evaluation must be rationally directed by a careful history, including medications, and physical examination (Fig. 55-3A). When this strategy is unrevealing, simple triage tests are often warranted to direct the choice of more complex investigations (Fig. 55-3B). The history, physical examination (Table 55-4), and routine blood studies should attempt to characterize the mechanism of diarrhea, identify diagnostically helpful associations, and assess the patient's fluid/electrolyte and nutritional status. Patients should be questioned about the onset, duration, pattern, aggravating (especially diet) and relieving factors, and stool characteristics of their diarrhea. The presence or absence of fecal incontinence, fever, weight loss, pain, certain exposures (travel, medications, contacts with diarrhea), and common extraintestinal manifestations (skin changes, arthralgias, oral aphthous ulcers) should be noted. A family history of IBD or sprue may indicate those possibilities. Physical findings may offer clues such as a thyroid mass, wheezing, heart murmurs, edema, hepatomegaly, abdominal masses, lymphadenopathy, mucocutaneous abnormalities, perianal fistulas, or anal sphincter laxity. Peripheral blood leukocytosis, elevated sedimentation rate, or C-reactive protein suggests inflammation; anemia reflects blood loss or nutritional deficiencies; or eosinophilia may occur with parasitoses, neoplasia, collagen-vascular disease, allergy, or eosinophilic gastroenteritis. Blood chemistries may demonstrate electrolyte, hepatic, or other metabolic disturbances. Measuring IgA tissue transglutaminase antibodies may help detect celiac disease. Bile acid diarrhea is confirmed by a scintigraphic radiolabeled bile acid retention test; however, this is not available in many countries. Alternative approaches are a screening blood test (serum C4 or FGF-19), measurement of fecal bile acids, or a therapeutic trial with a bile acid sequestrant (e.g., cholestyramine or colestevlam).

A therapeutic trial is often appropriate, definitive, and highly cost-effective when a specific diagnosis is suggested on the initial physician encounter. For example, chronic watery diarrhea, which ceases with fasting in an otherwise healthy young adult, may justify a trial of a lactose-restricted diet; bloating and diarrhea persisting since a mountain backpacking trip may warrant a trial of metronidazole for likely giardiasis; and postprandial diarrhea persisting following resection of terminal ileum might be due to bile acid malabsorption and be treated with cholestyramine or colestevlam before further evaluation. Persistent symptoms require additional investigation.

Certain diagnoses may be suggested on the initial encounter (e.g., idiopathic IBD); however, additional focused evaluations may be necessary to confirm the diagnosis and characterize the severity or extent of disease so that treatment can be best guided. Patients suspected of having IBS should be initially evaluated with flexible sigmoidoscopy with colorectal biopsies to exclude IBD, or particularly microscopic colitis, which is clinically indistinguishable from IBS with diarrhea; those with normal findings might be reassured and, as indicated, treated empirically with antispasmodics, antidiarrheals, or antidepressants (e.g., tricyclic agents). Any patient who presents with chronic diarrhea and hematochezia should be evaluated with stool microbiologic studies and colonoscopy.

In an estimated two-thirds of cases, the cause for chronic diarrhea remains unclear after the initial encounter, and further testing is required. Quantitative stool collection and analyses can yield