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AGA Technical Review on the Evaluation and Management of Chronic Diarrhea

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Chronic diarrhea is a common complaint of patients presenting to family practitioners, internists, and gastroenterologists. The differential diagnosis is complex, and the variety of tests applicable to these patients can be bewildering. Accurate diagnosis may be elusive, and treatment can be frustrating. The purpose of this review is to summarize the medical literature pertinent to the clinical evaluation and treatment of patients with chronic diarrhea to provide a sound basis for dealing with these patients and to identify issues that could benefit from further research.

The computerized MEDLINE database for 1966–1997 was queried using the keywords "chronic," "diarrhea," and "diarrhea, diagnostic evaluation," and articles in English were selected for review. Pertinent papers that appeared in peer-reviewed journals were read and were used. In this literature search, several points became obvious: (1) properly designed epidemiological and outcome studies are scarce; (2) there is a lack of large, controlled studies of diagnostic techniques and empirical treatment; (3) most recommendations for evaluation and treatment are based on expert opinion, not evidence-based reasoning; and (4) experts vary in their opinions (probably because of referral bias and the absence of convincing data), and relatively little consensus about evaluation and treatment exists at present. This situation is unlikely to change until more definitive information is provided by appropriate studies.

This technical review first focuses on problems with the definition of "diarrhea" and "chronic." The limited information available about prevalence, final diagnoses, and economic impact is then reviewed, and the clinical utility of various diagnostic tests is analyzed. An approach to the complaint of chronic diarrhea is presented, and empirical therapy is reviewed briefly. Finally, directions for future research are outlined.

Definition of Chronic Diarrhea

Diarrhea is defined in the dictionary as "an intestinal disorder characterized by an abnormal frequency and liquidity of fecal evacuations."[1] Although increased frequency of stools (>3/day) is considered part of the definition of diarrhea,[1–3] patients generally do not consider increased frequency of defecation alone as diarrhea.[4] On the other hand, increased liquidity holds up as a criterion used by patients.[5] Although stool weight has been cited frequently as a scientific definition of diarrhea, diarrhea should not be defined solely in terms of fecal weight (e.g., above the upper limit of normal fecal weight, 200 g/day). Some individuals have increased fecal weight (sometimes as high as 300 g/day) but have normal stool consistency and do not complain of diarrhea. Others have normal fecal weight and complain of diarrhea because their stools are loose or watery.[5]

A recent study has shed some light on objective determinants of decreased fecal consistency.[5] Considering a variety of potential factors, it was reported that the presence of water-insoluble fecal solids (such as those that might be derived from some forms of dietary fiber or bacterial cell walls) and their ability to hold or bind water in terms of the total amount of water present in the stool correlated best with fecal consistency as measured objectively. If there was too little water-holding capacity to bind all of the water present, stool consistency was loose, eventually to the point of having the pouring properties of water. On the other hand, when fecal solids had enough water-holding capacity and there was only a scant amount of nonbound ("free") water, stools remained thick or formed. (This is similar to runny pancake batter that thickens progressively as more flour is added.) The fact that fecal consistency best relates to this ratio (i.e., water-holding capacity of insoluble solids/total water) rather than the amount of water present per se further supports the concept that stool weight should not be considered in the definition of diarrhea.

Having defined diarrhea as a decrease in fecal consistency, we must consider the duration of symptoms necessary to define chronic diarrhea. Unfortunately, there has been and still is no consensus definition of chronic diarrhea.[6] The optimal definition will depend on the purpose for which it is proposed, i.e., whether it is for a review such as this, for a clinical study, or for a particular

patient being evaluated in clinical practice. Whatever the setting, the definition should include a period long enough to allow most cases of acute diarrhea to run their courses. This is because the causes of acute diarrhea (mostly self-limited infections) and chronic diarrhea (mostly noninfectious etiologies) differ. Four weeks probably is the shortest duration of diarrhea that could be considered chronic by this criterion, and 6–8 weeks would provide even more of a distinction. We use 4 weeks as our cutoff for clinical purposes.

Differentiation of Chronic Diarrhea From Irritable Bowel Syndrome and Fecal Incontinence

The irritable bowel syndrome (IBS) is currently defined by consensus as the combination of abdominal pain and abnormal bowel habits (constipation, diarrhea, or variable bowel movements) in the absence of other defined illnesses.[7] For many years, painless chronic diarrhea was included as a variation of IBS, but this is no longer tenable, given the emphasis on abdominal pain in the current definition of IBS. Patients with painless diarrhea may have a functional process (i.e., without a known organic cause) but should not be characterized as having IBS. "Functional diarrhea" should not be considered a final diagnosis; many of these patients have a specific, definable problem that can be discovered by appropriate testing and can be treated effectively.

Fecal incontinence poses another problem.[8] Many patients will not volunteer this symptom and instead explain it to the physician as diarrhea. Although many of these patients have loose stools, their major problem is with the mechanisms of continence and not with intestinal fluid and electrolyte absorption. Tests designed to evaluate the symptom of diarrhea may not help patients with disorders of continence. All patients with diarrhea should be queried about the presence of fecal incontinence; if incontinence is present frequently, especially with low-volume stools, these patients should be evaluated for incontinence and not for diarrhea.

Prevalence of Chronic Diarrhea and Its Causes

The precise prevalence of chronic diarrhea is unknown. According to the World Health Organization, the prevalence of chronic diarrhea in children worldwide ranges from 3% to 20%.[9] Reliable international data for adults are lacking. Surveys of Americans have yielded varying prevalence rates. For example, a recent survey of 144 randomly selected individuals from a large metropolitan area indicated that 4% had loose or watery stools at least 3 days a week for 6 continuous months.[10] When chronic diarrhea was less stringently defined as passage of more than three bowel movements per day and/or loose stools at least 25% of the time, the prevalence increased to 14%–18%.[3,11] Many of these people had abdominal pain compatible with the IBS. When only patients without abdominal pain are considered, the number with more than three bowel movements daily was 3%.[12] Diarrhea persisted 12–20 months in 94% of these individuals. Although population differences may in part be responsible for the wide range of reported prevalence rates, the major factor is probably differing definitions of chronic diarrhea.[6] Based on excessive stool frequency (the most widely used criterion), the prevalence of chronic diarrhea in the United States seems to be approximately 5%.[10–12]

The main causes of chronic diarrhea seem to depend on the socioeconomic status of the population surveyed. In developed countries, the most frequent diagnoses made in patients with chronic diarrhea are IBS, idiopathic inflammatory bowel disease, malabsorption syndrome, chronic infections, and idiopathic secretory diarrhea (which also may be a chronic, but eventually self-limited, infection).[13–18] In less developed countries, chronic bacterial, mycobacterial, and parasitic infections are the most common causes of chronic diarrhea; functional disorders, inflammatory bowel disease, and malabsorption (from a variety of unspecified causes) are also common in this setting.[19–24]

Within a given population or country, the prevalence of different causes of chronic diarrhea is influenced by the level of subspecialization and the referral base of the particular institution reporting its findings. For example, surreptitious laxative abuse is common in tertiary care referral centers with a focused interest in diarrheal disorders but may be uncommon in primary care settings.[13,25] The frequency of various diagnoses in patients with undiagnosed or refractory diarrhea seen at our institution illustrates this sort of referral bias (Table 1).[17]

Economic Impact of Chronic Diarrhea

Observation of patients with chronic diarrhea suggests that chronic diarrhea can be a disabling problem. Many patients cannot maintain employment because of the need for or threat of frequent trips to the toilet. In the absence of credible incidence or prevalence data for diarrhea per se, it is difficult to estimate the economic impact of disability due to chronic diarrhea. For example, the National Health Interview Survey, 1983–1987, reported a prevalence of "enteritis" of just

Table 1. Diagnostic Categories of 193 Patients With Undiagnosed or Difficult to Manage Chronic Diarrhea Seen at Baylor University Medical Center, Dallas, 1985–1990

Diagnostic category	n	%
Low volume syndromes[a]	41	21.2
Idiopathic secretory diarrhea	39	20.2
After surgery[b]	39	20.2
Microscopic/collagenous colitis	29	15.0
Small bowel dysfunction[c]	21	10.8
Exocrine pancreatic insufficiency	10	5.2
Inflammatory bowel disease	5	2.6
Radiation enteritis	5	2.6
Laxative abuse	4	2.1

[a]Includes IBS, hyperdefecation syndromes, and fecal incontinence.
[b]Includes postvagotomy, postgastrectomy, postcholecystectomy, and post–intestinal resection diarrhea.
[c]Includes small bowel bacterial overgrowth, carbohydrate malabsorption, diabetes mellitus, motility disorders, *Strongyloides* infestation, sprue, and spruelike illnesses.
Reprinted with permission.[17]

under 1% of the population.[26] Six percent of these individuals (0.06% of the population) had some limitation of activity as a result of this illness, amounting to 20,319,000 restricted days per year, including 3,114,000 work loss days. At current median incomes, the work loss alone accounts for an economic loss of more than $350,000,000 annually. The costs of medical care, disability payments, and lost productivity are in addition to this. It is not clear from available data how many of these patients with "enteritis" had chronic diarrhea as the main symptom, and it is unknown how many patients with chronic diarrhea were not included in this diagnosis. Thus it is impossible to calculate the societal cost of chronic diarrhea accurately with currently available information.

Effect of Chronic Diarrhea on Quality of Life

Chronic diarrhea can reduce a patient's quality of life. This has been best demonstrated in patients with the human immunodeficiency virus (HIV) surveyed in Northern California and in New England.[27,28] Although diarrhea can be a marker of more profound immunosuppression in these patients, it seemed to be an independent predictor of quality of life scores: patients with chronic diarrhea had significantly worse quality of life scores than similar patients without diarrhea. This information is not available for other clinical situations.

Evaluation of Diagnostic Tests

Some degree of diagnostic testing is usually indicated in patients with chronic diarrhea. The following sections discuss the specifics of some tests applied commonly in patients with chronic diarrhea.

Medical History

Although the facets of an appropriate medical history for patients with chronic diarrhea are numerous (see below), a few features separate certain general disorders from others, specifically functional from organic causes. Indicators of a functional etiology are long duration of symptoms ($\geq$1 year), lack of significant weight loss ($<$5 kg), absence of nocturnal diarrhea, and straining with defecation.[15,16] These indicators are only about 70% specific for functional problems.[16]

Spot Stool Analysis

Randomly collected diarrheal stool specimens can be tested for blood, pus, fat, microbes, pH, electrolyte and mineral concentrations, and laxatives. These tests can provide clues to the cause of diarrhea.

Occult blood. The utility of guaiac card testing in the evaluation of chronic diarrhea has not been published as such. A study from our institution showed that laxative-induced diarrhea, pancreatic maldigestion, idiopathic secretory diarrhea, and microscopic colitis were associated with fecal occult blood positivity rates equal to those of normally formed stools.[29] In contrast, approximately 50% of patients with celiac sprue and 70% of patients with refractory sprue had guaiac-positive stools.[29] The sensitivity and specificity of the guaiac card test for the detection of inflammatory or neoplastic conditions causing diarrhea has not been determined.

White blood cells. The standard method of detecting white blood cells (WBCs) in stool is with Wright's staining and microscopy.[30,31] The accuracy of the test results depends primarily on the experience and skill of the observer. Both false-positives and false-negatives can occur, and the significance of a result specifying "few WBCs seen" is unknown and frustrating.

A recently developed latex agglutination test for the neutrophil product lactoferrin is highly sensitive and specific for the detection of neutrophils in stool in acute infectious diarrhea and in pseudomembranous colitis caused by *Clostridium difficile*.[32–34] The usefulness of this test in the setting of chronic diarrhea has not been reported.

Sudan stain for fat. Data on the utility of Sudan staining for qualitative assessment of the amount and chemical structure of stool fat (triglycerides vs. free fatty acids) were presented in one study published in the early 1960s.[35] In that report, fat loss (expressed as a percent of intake) correlated with the number and size of Sudan-

stained fat droplets viewed microscopically. The test was 86% specific for a fat output of ≤5% of intake and 87%–100% sensitive for fat outputs of 6%–15% of intake.[35] However, the use of percent of intake as the unit of fat excretion (as opposed to the current standard, grams excreted per day) and qualitative expression of the results (as normal, slight increase, and definite increase) have led to confusion in interpretation of the significance of a positive qualitative fat test result. Furthermore, a high level of observer skill and experience is critical to the accuracy of the microscopic interpretation. In a more recent study, the number of stained fat droplets counted in a hematocytometer correlated well with fat output measured chemically.[36] However, this method was evaluated in only 41 patients and has not been applied widely elsewhere. The origin and types of fats that yield positive results on Sudan staining have been explored in another publication.[37] An alternative, semiquantitative measure of stool fat content, the steatocrit, has been used mainly in children and correlates well with quantitative fat output as measured using the van de Kamer method.[38–40]

Fecal cultures. Because bacterial infections are rarely the cause of chronic diarrhea in immunocompetent patients, routine fecal cultures usually are not obtained in most individuals with chronic diarrhea. However, at least one fecal culture should be performed at some point in the evaluation of these patients.[41,42] Cultures on special media and under specific environmental conditions are required to look for *Aeromonas* or *Pleisiomonas* species.[43–48] The epidemiological clues raising suspicion for the presence of these organisms include consumption of untreated well water and swimming in fresh water ponds and streams.[44]

In immunocompromised patients, but only rarely in normal hosts, common infectious causes of acute diarrhea, such as *Campylobacter* or *Salmonella*, can cause persistent diarrhea.[49,50] In this population, bacterial cultures ought to be part of the initial diagnostic evaluation.

Infections with yeast and fungi, mainly *Candida albicans*, have been reported as causes of both nosocomial and community-acquired chronic diarrhea, even in immunocompetent individuals.[51–54] Increasing use of broad-spectrum antibiotics with greater "killing power" may be selecting for overgrowth of what had previously been viewed as part of the normal flora. The yield of gram stains of stool and fungal cultures and the appropriateness of their use in patients with chronic diarrhea of unknown origin have not been studied.

Protozoa and parasites are endemic in third world countries but can also affect both immigrants to and natives of developed countries, including the United States. Poorly sensitive cytological and pathological tests for detection of *Giardia lamblia* are being replaced by more sensitive and specific methods of detection, such as fecal enzyme-linked immunosorbent assay (ELISA) for *Giardia*-specific antigen.[55] Although the old-fashioned stool examination for "O and P" remains popular, its positive and negative predictive value in developed countries is undefined. Observer skill is essential to the success of this stool examination.[56] Detection of some pathogens, such as *Strongyloides* larva, may be of clinical importance; however, cysts and ova of other organisms, including *Entamoeba histolytica*, may be innocent colonists rather than pathogens, especially in inhabitants of third world countries.[57] Special techniques are required to detect cryptosporidia and microsporidia in stool; these organisms may cause diarrhea in immunocompetent as well as immunocompromised people. Chronic viral infections (a diagnostic consideration practically limited to immunocompromised hosts) usually are diagnosed from gastrointestinal mucosal biopsy specimens rather than stool samples.

pH, electrolytes and minerals, and laxatives. The utility of these measurements on a spot stool specimen is the same as when they are measured in a quantitatively collected specimen, as discussed below.

Quantitative Stool Collection and Analysis

A 48- or 72-hour quantitative stool collection is useful in the work-up of chronic diarrhea. Although this test is not necessary in every case, it can be helpful in characterizing the volume of diarrhea and segregating likely diagnostic possibilities from less likely ones (e.g., by finding significant steatorrhea). However, the potential benefits of obtaining these measurements (e.g., less costly directed work-up or fewer patient complications from invasive procedures) have not been established. The necessary duration of the collection has not been defined scientifically for clinical purposes. In general, the higher the daily stool weight is, the more accurate and representative shorter collection periods can be. Practical considerations mandate a 48-hour collection for most inpatients and outpatients. In patients in whom 48-hour collection yields a small or unrepresentative sample, the collection can be extended.

General principles. Full analysis of the collection includes measurement of weight, fat content, osmolality, electrolyte concentrations, magnesium concentration and output, pH, occult blood, and when appropriate, fecal chymotrypsin or elastase activity (for assessment of pancreatic function) and screening for laxatives. If these analyses cannot be performed locally, many clinical

laboratories and referral hospital laboratories can analyze a representative aliquot of stool (approximately 200 g) taken from a homogenized collection after it is weighed. (The aliquot should be frozen immediately; if mailing is necessary, it should be mailed in a container packed with dry ice, along with a record of the total weight of the 48- or 72-hour collection.)

Quantitative stool collection can be done easily and successfully at home or in the hospital. Some simple equipment can facilitate collection, including a disposable collection unit that fits onto the commode and allows separation of stool and urine, several preweighed containers for the collected stool (e.g.,plastic or metal containers with airtight lids that hold at least 1 or 2 L each), and a receptacle to keep these collection containers cold during the collection period, such as a small, portable refrigerator (usually used for inpatients) or a picnic cooler containing refreezable "blue ice" packs (ideal for outpatients).

Several days before and during the collection period, the patient should eat a regular diet of moderately high fat content. It may be useful to prescribe a fixed diet for some patients to ensure that adequate amounts of fat and calories are consumed. We encourage patients to consume 80–100 g of fat during the collection, but fractional absorption can be calculated for any intake. During collection, the patient should keep a record of bowel activity and a diary of food and liquid intake (so that calorie, fat, carbohydrate, and fiber intake can be estimated from dietary tables). During the collection period, no diagnostic tests should be done that would disturb the normal eating pattern, aggravate diarrhea (e.g., lactose– or D-xylose–absorption tests or tests using enteral iodinated contrast media), diminish diarrhea (by requiring fasting or use of opiates), add foreign material to the gut (e.g., barium radiography studies), or risk an episode of incontinence. All but essential medications should be avoided, and any antidiarrheal medication begun before the collection period should be held.

Stool output may vary considerably from day to day and week to week. When evaluating the results of a quantitative stool analysis, the physician needs to know whether the submitted stool was collected during a time that the patient was having what he or she considered to be diarrhea. It is advantageous for the physician to look at the collected specimen and assess stool consistency visually because the definition of diarrhea depends on the fact that stools are abnormally loose or liquid.

Fecal weight. Knowledge of stool weight may help to clarify the nature of the patient's problem and to localize the region of the intestine most likely to be responsible for diarrhea (although the reliability of this is untested). In some instances, knowledge of stool weight is of direct help in diagnosis and management. For example, stool weights greater than 500 g/day are rarely if ever seen in patients with IBS,[58,59] and stool weights of less than 1000 g/day are evidence against pancreatic cholera syndrome. Also, very high stool weights alert the physician to the possible need for vigorous fluid replacement; patients with stool weights greater than 2000 g/day usually require supplemental intravenous fluids. Low stool weight in a patient complaining of "severe diarrhea" suggests that incontinence or pain may be the dominant problem.

On rare occasions (e.g., when fecal volumes are extraordinarily high or there appears to be both a malabsorptive and a secretory component to the diarrhea), it is useful to determine the degree to which diarrhea persists during fasting. Continuation of diarrhea during a 48-hour fast is one criterion for classification of the diarrhea as a secretory (nonosmotic) process.[60] (Fecal weight may decrease some with fasting, even in secretory diarrhea, because fluid input to the intestine decreases; however, continued diarrhea on the second day of fasting is an indicator of a secretory process.) Alternatively, complete cessation of diarrhea during fasting is strong evidence that the mechanism of diarrhea involves something ingested (which could be a nonabsorbable substance or nutrient causing osmotic diarrhea, or unabsorbed fatty acids or laxatives causing secretory diarrhea). The response to fasting is more helpful for determination of pathophysiology, thereby limiting the spectrum of potential diagnoses, rather than for making a specific diagnosis.[61,62]

Electrolytes and calculation of an osmotic gap. Fecal electrolyte concentrations are measured in stool water after homogenization of the entire specimen (by manual stirring or in a mechanical blender) and centrifugation of an aliquot to obtain supernatant for analysis. Placement of dialysis bags in the stool is another reported but less commonly used method of obtaining stool water for analysis.[63] The osmotic gap of fecal fluid can be used to estimate the contribution of electrolytes and nonelectrolytes to retention of water in the intestinal lumen. In secretory diarrhea, unabsorbed electrolytes retain water in the lumen; in osmotic diarrhea, nonelectrolytes cause water retention. The osmotic gap is calculated from electrolyte concentrations in stool water by the following formula: $290 - 2([Na^+] + [K^+])$. The sum of the sodium and potassium concentrations is multiplied by a factor of 2 to account for associated anions. The osmolality of stool within the distal intestine (estimated as 290 mOsm/kg because it equilibrates with plasma osmolality) should be used for this calculation rather than the

osmolality measured in fecal fluid, because measured fecal osmolality begins to increase in the collection container almost immediately when carbohydrates are converted by bacterial fermentation to osmotically active organic acids. The advantages of using 290 mOsm/kg instead of measured fecal osmolality for calculation of the fecal osmotic gap have been substantiated in two studies.[64,65]

The osmotic gap should be large (>125 mOsm/kg) in pure osmotic diarrhea, in which nonelectrolytes account for most of the osmolality of stool water, and small (<50 mOsm/kg) in pure secretory diarrhea, in which electrolytes account for most of stool osmolality.[64] In mixed osmotic and secretory processes and in cases of modest carbohydrate malabsorption (in which most of the carbohydrate load is converted to organic anions that obligate the fecal excretion of cations including Na^+ and K^+), the osmotic gap may lie between 50 and 125.[64]

Measured osmolality. Although measured fecal fluid osmolality should not be used to calculate the osmotic gap, measurement of fecal fluid osmolality may be useful in patients with unexplained diarrhea. Low osmolalities (<290 mOsm/kg) indicate contamination of stool with water or dilute urine[66] or the presence of a gastrocolic fistula and ingestion of hypotonic fluid. As mentioned previously, osmolalities of >290 mOsm/kg are common because of bacterial metabolism of fecal carbohydrate during storage of the stool sample (up to 600 mOsm/kg). Even higher values for fecal osmolality can be observed with ingestion of large amounts of poorly absorbable carbohydrate or dietary fiber, with fecal contamination by concentrated urine, or with a gastrocolic fistula and ingestion of hypertonic fluids.

Fecal pH. A low fecal pH is characteristic of diarrhea caused solely by carbohydrate malabsorption. The results of measurement of fecal pH in experimentally induced diarrhea showed that a fecal pH of <5.3 indicates that carbohydrate malabsorption (such as that associated with lactulose or sorbitol ingestion) is a major cause of diarrhea, whereas a pH of >5.6 argues against carbohydrate malabsorption as the only cause of diarrhea.[64] In generalized malabsorption syndrome that involves fecal loss of amino acids and fatty acids in addition to carbohydrate, the fecal pH usually is higher (e.g., 6.0–7.5).[67]

Fecal fat concentration and output. The concentration of fat per 100 g of stool can be quantitated by either titration or gravimetric methods,[68–72] and the daily excretion rate is obtained by multiplying this concentration by the average daily weight of the 2- or 3- day stool specimen. In most clinical laboratories, the upper limit of normal for daily fecal fat output measured in normal subjects (without diarrhea) ingesting normal amounts of dietary fat is approximately 7 g/day (9% of dietary fat intake). By definition, values greater than this are abnormal and signify the presence of steatorrhea. However, in a study of normal subjects with induced diarrhea (stool weights up to 1400 g/day), 35% had fecal fat excretion measured above the upper limit of normal, with values as high as 13.6 g/day.[73] Thus, even when mechanisms of digesting and absorbing dietary fat are intact, diarrhea itself causes steatorrhea ("secondary steatorrhea"). Therefore, in patients with diarrhea, an abnormal fecal fat value between 7 and 14 g/day has low specificity for the diagnosis of primary defects of fat digestion or absorption. On the other hand, abnormal values of 14 g/day or higher are more specific for diseases that impair fat digestion or absorption (i.e., diseases of the exocrine pancreas, the small intestinal mucosa, or the enterohepatic circulation of bile salts).

Dietary fat intake during the stool collection should be estimated from a diet diary. Most patients with diarrhea, especially patients with malabsorption, curb their food intake (particularly of fatty foods) in an attempt to lessen their diarrhea. Nausea and anorexia may also limit dietary fat intake. If this is done during quantitative stool collection, patients with malabsorptive disorders may have fecal fat outputs lower than expected for their syndrome. Stool fat excretion normally should be <9% of dietary intake.

Although the reported fat concentration in stool (i.e., fat per 100 g of stool) frequently is ignored, fecal fat concentration may provide a clue to the cause of steatorrhea. In one study a fecal fat concentration of <9.5 g/100 g of stool was more likely to be seen in small intestinal malabsorptive syndromes because of the diluting effects of coexisting fluid malabsorption, whereas fecal fat concentrations of ≥9.5 g/100 g of stool were seen in pancreatic and biliary steatorrhea, in which fluid absorption in the small bowel is intact.[74] Although in this study the test was 100% sensitive, a second study found a sensitivity of only 42%.[75] However, specificity was high in both studies (80%–92%), meaning that, when present, a high fecal fat concentration should suggest the presence of pancreatic or biliary steatorrhea.

Tests for fecal carbohydrate. Although tests for carbohydrate content are not done routinely on collected stool, qualitative tests for carbohydrates can be used to identify malabsorbed carbohydrates. However, these tests, originally designed for measuring urinary carbohydrates, have not been standardized for stool analysis. Based on the reagents in these products, the following conclusions are likely: dipsticks based on glucose oxidase should give a positive reaction with glucose and should be negative with all other sugars; Clinitest tablets (Ames Division,

Miles Laboratories, Elkhart, IN) should give a positive reaction with glucose, galactose, fructose, maltose, and lactose (reducing sugars) but a negative result with sucrose, lactulose, sorbitol, and mannitol (nonreducing sugars or sugar alcohols). Anthrone reagent, used as a research tool to quantitate fecal carbohydrate,[76] is sensitive to the presence of starches, oligosaccharides, disaccharides, and all hexoses but does not detect sorbitol and mannitol (sugar alcohols).

Analysis for laxatives. Diagnosis of factitious diarrhea requires a high index of suspicion. Analysis for laxatives should be done early in the evaluation of diarrhea of unknown etiology.[23,77–79] Because patients may ingest laxatives intermittently, negative studies may have to be repeated.[77,80] The simplest test for a laxative is alkalinization of 3 mL of stool supernatant or urine with one drop of concentrated (1N) sodium hydroxide. This will result in a pink or red color with a maximal spectrophotometric absorption of 550–555 nm if phenolphthalein is present.[81] (Phenolphthalein has been withdrawn from the market in the United States because of fears of carcinogenicity but may be available elsewhere.) Stool water can be analyzed specifically for phenolphthalein, emetine (one component of ipecac syrup),[82] and bisacodyl and its metabolites,[83] using chromatographic or chemical tests. Urine can be analyzed for anthraquinone derivatives.[84,85]

In searching for surreptitious laxative ingestion, stool water should be analyzed for osmolality and electrolytes.[86] If findings suggest secretory diarrhea (osmotic gap <50), the patient may have ingested a laxative capable of causing secretory diarrhea. Diarrhea caused by sodium sulfate or sodium phosphate ingestion also appears to be a secretory diarrhea by electrolyte analysis, even though pathophysiologically it is an osmotic diarrhea. This occurs because the negative charges of unabsorbed sulfate or phosphate obligate sodium, potassium, and other cations remain in the colonic lumen.[64,87] The fecal concentration and daily output of sulfate and phosphate can be measured by chemical testing, but the upper limits of normal have not been established. A high fecal sodium concentration in the presence of a low fecal chloride concentration should also raise the suspicion of ingestion of sodium sulfate or sodium phosphate.[64]

If stool electrolyte analysis suggests osmotic diarrhea (osmotic gap >125 mOsm/kg), magnesium (Mg^{2+}) laxatives may have been ingested. A soluble fecal Mg concentration greater than 45 mmol/L (90 mEq/L) or a daily fecal Mg output much above 15 mmol/day (30 mEq/day) strongly suggests Mg-induced diarrhea.[88] Factitious diarrhea may be caused by deliberate contamination of a stool collection with water urine. If fecal osmolality is significantly less than 290 mOsm/kg (the osmolality of plasma), water or hypotonic urine has been added to the stool.[66] If the osmolality is far above that of plasma, hypertonic urine may have been added to stool (although this finding also may be caused by the production of fermentation products in vitro). Urinary contamination can be confirmed by a finding of high monovalent cation concentration (e.g., $[Na^+] + [K^+] > 165$, physiologically impossible in stool water) and a high concentration of urea or creatinine in stool water.

Because many institutions lack analytical methods for all available laxatives, searching the patient's hospital room or home for hidden laxatives has been used to establish the diagnosis of factitious diarrhea. Discovery of caches of laxatives can also be helpful in convincing relatives that the diarrhea is caused by laxative ingestion. In one series, a room search had a higher diagnostic yield for factitious diarrhea than any other test.[89] However, some physicians think that it is unethical invasion of privacy to search a patient's belongings for laxatives and diuretics without permission. Others believe that a search should be viewed as a diagnostic study, requiring informed consent and including a discussion with the patient of the procedure, its risks and benefits, and alternatives.[90] On the other hand, failure to discover laxative abuse may lead to needless hazardous tests and treatment, such as insertion of central venous catheters, administration of total parenteral nutrition, and diagnostic and/or "therapeutic" operations, such as partial pancreatectomy and total colectomy. Even more importantly, laxative abuse may be fatal in children whose caregivers are poisoning them with laxatives.[87,91] Despite the potential of protecting the patient from self-induced harm, the legality of searching a patient's belongings without permission is questionable, and such searches are discouraged by most attorneys. Because laxative assays are readily available from reference laboratories, room searches should be done only under exceptional circumstances.

Tests for protein-losing enteropathy. A diagnosis of protein-losing enteropathy should be considered when a patient has hypoalbuminemia but does not have nephrotic syndrome or hepatic dysfunction. Confirmation of enteric protein loss can come from measurement of the fecal clearance of α_1-antitrypsin.[92] Clearance of this protein from plasma via the intestinal tract is based on the same concepts as renal inulin clearance and is calculated in similar fashion. Radioimmunoassay is used to measure α_1-antitrypsin concentrations in stool and plasma; total fecal output is calculated from concentration and volume and is divided by plasma concentration. Measurement of the concentration of α_1-antitrypsin in randomly passed stools has been tried as a simpler

method to measure intestinal protein loss in children but has had only moderate success.[93] Fecal excretion of radioiodinated albumin and immunoglobulin G administered parenterally has also been reported as a method of measuring enteric protein loss but is not available routinely.[94,95]

Blood and Urine Tests

Analysis of urine. Urine collections may be helpful for laxative identification and for measurement of excretion of 5-hydroxyindole acetic acid (for carcinoid syndrome), vanillylmandelic acid (VMA; for pheochromocytoma, metanephrine (for pheochromocytoma), and histamine (for mast cell disease and foregut carcinoids). If volume depletion or hypokalemia are present, analysis of urine electrolytes can determine whether renal conservation of sodium and potassium is appropriate. If the urinary concentration or output of sodium or potassium is inappropriately high, surreptitious diuretic use may be present and may suggest coexisting laxative abuse. Also, measurement of urine electrolytes and aldosterone may distinguish hypervolemia from volume depletion in the setting of hypernatremia caused by ingestion of sodium-containing laxatives.[88]

Vasoactive intestinal polypeptide and other peptide hormones. Pancreatic cholera syndrome is a rare cause of secretory diarrhea attributable to secretion of vasoactive intestinal polypeptide (VIP) by a neuroendocrine tumor. It should be suspected if diarrhea of unknown origin has lasted longer than 4 weeks, has the clinical features of secretory diarrhea, has a volume greater than 1 L/day, is associated with hypokalemia, and causes clinically significant volume depletion and if surreptitious laxative and diuretic abuse and organic disease of the gastrointestinal tract have been excluded. It is only in this rare subgroup of patients that serum assay for VIP is likely to be useful. Measurement of a few other specific peptides can be helpful in the diagnosis of other neuroendocrine tumors. These include measurement of calcitonin for the diagnosis of medullary carcinoma of the thyroid, gastrin for suspected Zollinger–Ellison syndrome, and glucagon for the rare patient with a glucagonoma.[17] Measurement of large panels of enteric peptides not specific for particular tumor syndromes, such as motilin, neurotensin, pancreatic polypeptide, substance P, and gastrin-releasing peptide, should not be done in patients with chronic diarrhea because of their poor specificity and extremely low positive predictive value,[17] which is attributable to the rarity of these tumors and the high frequency of false-positive assays.

Serological tests. Serological tests that occasionally may provide useful diagnostic information include tests for antinuclear antibodies[96]; antigliadin immunoglobulin (Ig) A and IgG antibodies and antiendomysial IgA antibodies[97–103]; perinuclear antineutrophil cytoplasmic antibodies[104–107]; HLA typing[108–110]; quantitation of serum immunoglobulin concentrations[111]; and antibodies to HIV and *Entamoeba histolytica* (Table 2).

Serological testing for celiac sprue is of special interest, not only for diagnosis but also for evaluation of patients after treatment. Antigliadin IgA antibodies are more specific, but less sensitive for a diagnosis of celiac sprue (specificity, 67%–100%; sensitivity, 69%–100%) than the IgG fraction (specificity, 47%–70%; sensitivity, 89%–100%). IgA antigliadin antibody also is more predictive of recent gliadin ingestion because after 1–3 months of a gluten-free diet, serum levels begin decreasing, and by 6–12 months they usually disappear if the patient's diet has been completely gluten-free. The IgG serum fraction, on the other hand lingers longer than IgA, and although some reduction can be seen over time,

Table 2. Serological Tests That May Be Useful in Patients With Chronic Diarrhea

Test	Disorders	Application
Antinuclear antibody	Vasculitis, scleroderma, celiac sprue, microscopic colitis, hypothyroidism, autoimmune enteropathy	Diagnosis
Antigliadin, antiendomysial antibodies	Celiac sprue	Diagnosis; follow-up of condition and compliance with treatment
Perinuclear antineutrophil cytoplasmic antibody	Ulcerative colitis	Diagnosis; distinguishing from Crohn's colitis
Quantitative immunoglobulins	Selective IgA deficiency, common variable immunodeficiency	Diagnosis; assessment of response to Ig infusions
HLA-DR, DQ typing	Celiac sprue, refractory or unclassified sprue, possibly Crohn's disease and ulcerative colitis	Confirmation of a diagnosis of celiac sprue (by finding DR3 or DQ2) when necessary; assessment of refractoriness in a patient with a sprue-like illness; in the future possibly for the diagnosis and/or distinction of Crohn's and ulcerative colitis
Erythrocyte sedimentation rate, C-reactive protein	Inflammatory bowel disease	Diagnosis; response to therapy; disease activity
Antibody titers to *E. histolytica*	Amebiasis of the colon and/or liver	Diagnosis
Antibodies to HIV	AIDS	Diagnosis

IgG antigliadin antibodies may never disappear completely.

Antiendomysial antibodies are the most specific of the serological tests for celiac sprue, with a specificity in villous atrophic disease of nearly 100%. However, their sensitivity has ranged from as low as 74% up to 100%. There is inadequate information regarding the sensitivity of antiendomysial antibodies in less severe forms of gluten sensitivity, but it may well be lower. Until now, the only test to detect endomysial antibodies has been indirect immunofluorescence in monkey esophagus or human umbilical cord tissue substrates. As with all immunofluorescent tests, correct interpretation of results is highly dependent on the skill and experience of a technician interpreting the fluorescence pattern in tissues, and quantitation of the amount of antibody present relies on repeat examinations after serial dilutions of serum. An ELISA test that can detect and quantitate serum endomysial antibody probably will be available soon for clinical use.

Endoscopic Examination and Mucosal Biopsy

Sigmoidoscopy and colonoscopy. Examination of the mucosa of the colon and rectum and mucosal biopsy may be useful in patients with chronic diarrhea, but it is unclear whether the initial procedure should involve a 60-cm flexible sigmoidoscopy or a full colonoscopy. The advantages of the former include its ease (i.e., simple preparation, no need for sedation, shorter procedure, and greater chance for successful completion), lower risk of perforation, and lower cost. Patient acceptance may be better or worse than with colonoscopy (because patients are usually sedated for colonoscopy). The main concern with sigmoidoscopy is that the causative disease may be present only in the proximal colon or terminal ileum and will be missed by a limited examination. Although this can occur in Crohn's disease and other rare idiopathic inflammatory conditions,[112] the pathological process occurs diffusely throughout the colon in most diseases that can be diagnosed by lower endoscopy. For example, microscopic and collagenous colitis are usually diffuse processes, but inflammatory changes or subepithelial collagen band thickening may occur only in the proximal colon in approximately 10% of patients.[113,114] Thus relatively few cases remain undiagnosed with limited examination. Therefore, in light of the advantages of flexible sigmoidoscopy over colonoscopy listed above, sigmoidoscopy can be recommended as the best initial test. During sigmoidoscopy, random biopsy specimens should be obtained from the descending colon, the sigmoid colon, and the rectum (e.g., four biopsy specimens taken every 10–20 cm). When results of other diagnostic tests raise a strong suspicion of a colonic process (e.g., when leukocytes or lactoferrin are present in stool),when the presence of inflammatory bowel disease is suggested by specific symptoms or signs, or when biopsy specimens from the distal colon are equivocal, colonoscopy may provide additional helpful information. When there is significant weight loss or gross or occult bleeding to suggest malignancy, or when an abnormality of the terminal ileum or proximal colon has been seen on an imaging study or radiogram, it is appropriate to begin endoscopic evaluation of the colon with a full colonoscopy. However, no prospective study has assessed the utility and costs of limited vs. complete examination of the colon in patients with chronic diarrhea, although it seems that complete colonoscopy would be more expensive and rarely leads to an additional diagnosis.[115]

Chronic disorders that can be diagnosed by inspection of the colonic mucosa include melanosis coli, ulceration, polyps, tumors, Crohn's disease, ulcerative colitis, and amebiasis.[116–118] Diseases in which the mucosa appears normal endoscopically but that can be diagnosed histologically include microscopic colitis (lymphocytic and collagenous colitis), amyloidosis, Whipple's disease, granulomatous infections, and schistosomiasis in its chronic form.

Upper tract endoscopy. Upper endoscopy has become the standard method for obtaining biopsy specimens from the upper small intestine.[119,120] If a small intestinal malabsorptive disorder is strongly suspected, the procedure is probably best performed with an endoscope that allows specimens to be obtained from the distal duodenum and/or proximal jejunum as well as from the proximal duodenum, although duodenal biopsies may be adequate to discover most diffuse mucosal diseases. An aspirate of small intestinal contents can be sent for quantitative aerobic and anaerobic bacterial culture (using techniques used for quantitative urine culture) if bacterial overgrowth is suspected and for microscopic examination for parasites. Diseases that may be diagnosed by small intestinal biopsy include Crohn's disease, giardiasis, celiac sprue, intestinal lymphoma with or without villous atrophy, eosinophilic gastroenteritis, hypogammaglobulinemic sprue (with or without nodular lymphoid hyperplasia), Whipple's disease, lymphangiectasia, abetalipoproteinemia, amyloidosis, mastocytosis, and various mycobacterial, fungal, protozoal, and parasitic infections.[121–123] The presence of steatorrhea or fecal occult blood increases the likelihood of making one of these diagnoses by upper endoscopy.

Radiography

Barium radiography. There have been no formal studies of the utility of radiography in the diagnostic evaluation of chronic diarrhea. However, because most of the small intestine (including most of the terminal ileum) cannot be approached with standard endoscopes, anatomic changes are best assessed with barium radiography. There are situations in which a previously unsuspected diagnosis is made by small intestinal radiography (such as Crohn's disease or jejunal diverticulosis). In other situations, abnormal findings will lead to further investigation and, ultimately, a diagnosis. For example, a "malabsorption pattern" consisting of excess luminal fluid, dilation, and an irregular mucosal surface may lead to a diagnosis of celiac sprue, Whipple's disease, or intestinal lymphoma, although this may be less common with modern barium preparations than in the past.[124] Other diseases that might be diagnosed with small intestinal radiography are carcinoid tumors and scleroderma.

Although it has not been tested specifically in patients with chronic diarrhea, the diagnostic yield of small bowel radiography is about the same whether barium is administered orally ("small bowel follow-through examination") or by an enteroclysis tube, provided that the small bowel follow-through study is performed by a "dedicated" radiologist who personally watches the column of barium and uses fluoroscopy intermittently (rather than a technologist who performs overhead radiographs at some set time intervals).[125,126] Thus, for the study of patients with chronic diarrhea, enteroclysis probably has no special role.

Radiographic studies of the stomach and colon may be complementary to endoscopy and colonoscopy because barium-contrast radiograms can better detect fistulas and strictures. Radiography of the gastrointestinal tract also helps to delineate anatomy after previous surgical resection or bypass.

Mesenteric angiography. Small intestinal ischemia is a rare cause of chronic diarrhea.[127,128] In the appropriate clinical setting, mesenteric or celiac angiography may show evidence of intestinal ischemia caused by atherosclerosis or vasculitis. The utility of magnetic resonance imaging or spiral computed tomographic angiography in this setting is not clear.

Computed tomography. Computed tomography is performed in patients with chronic diarrhea to examine for pancreatic cancer or evidence of chronic pancreatitis in the presence of malabsorption or when the results of pancreatic function tests are abnormal. Inflammatory bowel disease, chronic infections such as tuberculosis, intestinal lymphoma, carcinoid syndrome, and other neuroendocrine tumors are additional diagnoses that can be revealed by computed tomography. In the case of the tumors mentioned last, rapid computed tomography scanning with thin (5 mm or less) sections through the pancreas following a bolus of intravenous contrast is recommended, although the degree to which sensitivity is increased over standard computed tomographic methods is unknown.

Physiological Tests

Mucosal absorption. Tests of monosaccharide absorption have been used classically to distinguish small intestinal mucosal absorptive defects from pancreatic digestive defects in the setting of malabsorption. In the 1950s, the oral glucose tolerance test was replaced by the D-xylose–absorption test because of better reliability and the lack of interference from endogenous serum glucose.[129,130] Subsequently, an abnormal D-xylose–absorption test result became synonymous with a diseased small intestine (barring confounding renal dysfunction or urine collection problems) and was used to determine who would be served best by capsule biopsies of the small bowel. Today, with the widespread use of endoscopic biopsies, the role of this test has become less clear, although it still yields information about small intestinal absorptive function. Some clinicians still use this test for screening or for following up the response to treatment, but the utility of this approach has not been assessed formally.

Most verification studies of the D-xylose test involve patients with celiac sprue or inflammatory bowel disease of the small bowel.[129,130] Urinary excretion of less than 5 g in the 5 hours following ingestion of 25 g of D-xylose is considered abnormal. A plasma concentration of less than 1.3 mmol/L per 1.73 m^2 body surface area (20 mg/dL for an average adult) 1 hour after a 25-g oral dose is considered abnormal.[131]

Tests of ileal absorptive function. The terminal ileum has evolved three specific and unique absorptive functions: absorption of vitamin B_{12}, absorption of sodium chloride against steep electrochemical gradients, and absorption of bile acids. Disruption of any one of these, particularly of all three, can be seen in patients with diarrhea. Therefore, tests have been developed to assess these specialized ileal absorptive functions.

The time-honored test of vitamin B_{12} absorption is the Schilling test.[132] In patients being evaluated for chronic diarrhea (as opposed to those being evaluated for vitamin B_{12} deficiency or macrocytic anemia), radiolabeled vitamin B_{12} is given with intrinsic factor (the so-called "Schilling II test"). The positive and negative predictive values of the test for ileal dysfunction in a large group of

patients with chronic diarrhea of unknown origin has not been determined. With the widespread availability of colonoscopy, which can visualize the terminal ileum, sophisticated radiographic imaging techniques, and standard barium radiography, the Schilling test is now less important in the investigation of chronic diarrhea than in the past.

The only method developed to study fluid and electrolyte absorption in the ileum is intestinal perfusion. Perfusion of a segment of ileum can be carried out but requires painstaking effort by the patient and investigator to place the tube in the distal small bowel. Alternatively, total gastrointestinal perfusion (with the infusion port in the stomach and the effluent collected from the rectum) can be performed. To assess ileal function, total gut perfusion is carried out first with a balanced electrolyte solution, and then a solution containing a low concentration of sodium chloride compared with plasma, which requires an intact functional ileum for normal active absorption.[133] Although this technique has uncovered specific absorptive defects in patients with ileocolonic resection and rare patients with idiopathic ileal dysfunction, intestinal perfusion is not clinically useful in most cases of chronic diarrhea.[134]

Tests for bile acid malabsorption can be done in two ways. The first method measures the quantity of endogenous bile acids excreted during a quantitative stool collection. The second method involves measurement of the turnover of radiolabeled bile acid. This can be done in two ways. The first involves the use of a gamma camera to detect the retained fraction of an orally administered synthetic radiolabeled bile acid, selena-homocholic acid conjugated with taurine (commonly abbreviated ^{75}Se-HCAT).[135–140] The second involves measurement of fecal recovery of an oral load of [^{14}C]glycocholate during a 48- or 72-hour stool collection and calculation of a retention half-life.[141,142] Measurement of serum concentrations of an intermediate of bile acid synthesis, 7α-hydroxy-4-cholesten-3-one, is an alternate method for evaluating bile acid metabolism, with a reported sensitivity and specificity of 80% and 85%, and positive and negative predictive values of 74% and 98%, respectively, for excessive losses of bile acids from the body.[143,144] These tests are not widely available to clinicians and have been complicated by lack of standardization of reference values.[145] Furthermore, an abnormal test result is not necessarily specific for pathological bile acid malabsorption but may occur as the result of diarrhea per se.[141,142,146,147] Therefore, many clinicians use a therapeutic trial of cholestyramine as an indirect test for the possibility that malabsorbed bile acids are the cause of diarrhea. However, the extent to which a good therapeutic response to cholestyramine denotes the presence of bile acid malabsorption as the main cause of diarrhea is an unsettled issue.[141,142]

Breath tests for physiological testing. Breath tests have found their way into clinical diagnosis mainly for use in patients with chronic diarrhea, abdominal bloating, or pain. The most common tests use probe molecules labeled with ^{14}C or ^{13}C[148] or a nonradioactive fermentable sugar. Metabolism of these substances produces isotopically labeled CO_2 or H_2 that can be detected in expired air.[149–151] The tests and the clinical conditions for which breath tests are used are shown in Table 3.

Tests for lactose malabsorption. In the past, except for therapeutic trial of a lactose-free diet, the standard diagnostic test for hypolactasia had been the oral lactose tolerance test.[152] In this test, an oral load of lactose is given, followed by sequential measurement of serum glucose. An increase in serum glucose concentration indicates that lactose has been hydrolyzed and absorbed by the mucosa. However, random fluctuations in endogenous serum glucose concentrations limit sensitivity and specificity[153,154]; therefore, the lactose tolerance test has been replaced with lactose breath hydrogen testing. This test exploits the fact that lactose malabsorbed by the small intestine in lactase-deficient individuals is fermented rapidly in the colon to organic acids and gases, including hydrogen.[155,156] The latter is then absorbed and excreted by the lungs into the breath, where it is collected in a balloon or bag and measured by gas chromatography or other methods.

The exact methodological procedure used depends on whether maximal sensitivity or specificity is desired. Tests using larger doses of lactose (e.g., 50 g) are more sensitive but less specific for clinically significant dietary lactose intolerance, whereas smaller doses (e.g., 12.5 g) are more specific but less sensitive. As a compromise, a 25-g test dose is frequently used.

Table 3. Breath Tests That May be Applied to Patients With Chronic Diarrhea

Agent administered	Substance measured in breath	Condition assessed
Lactose	H_2	Lactase deficiency
Sucrose	H_2	Sucrase deficiency
Glucose	H_2	Bacterial overgrowth of small intestine
Lactulose	H_2	Bacterial overgrowth of small intestine; determination of orocecal transit time
^{14}C-xylose	^{14}C	Bacterial overgrowth of small intestine
^{14}C-glycocholate	^{14}C	Bacterial overgrowth of small intestine

An increase in breath hydrogen of 20 ppm above baseline within 4 hours usually has been set as the cutoff for a positive test result, although Strocchi et al.[157] found maximal diagnostic accuracy with a 12.5-g test dose using an 8-hour test period. The lengthier test is less practical for patients who may become irritated with medical tests requiring prolonged fasting. (Breath hydrogen testing usually requires a 12-hour pretest fasting period to ensure that baseline fasting breath hydrogen levels are low.)

As many as 10% of individuals do not possess an intestinal bacterial flora capable of producing hydrogen gas; they will not produce a hydrogen signal in response to malabsorbed carbohydrate.[158] In such individuals, a negative breath hydrogen test result may represent a false negative.

Tests for bacterial overgrowth. Bacterial overgrowth of the small intestine occurs in some children and in some elderly adults with nonspecific gastrointestinal complaints. Some of these patients do not have specific syndromes that would predispose them to such colonization.[159–161] The true importance of bacterial overgrowth of the small intestine as a cause of chronic diarrhea is unknown. Cases clearly exist, especially when disorders that diminish intestinal motility are present.[162,163]

The gold standard for diagnosis of bacterial overgrowth has been quantitative culture of an aspirate of luminal fluid; more than 10^6 organisms/mL in either aerobic or anaerobic conditions is the criterion for a positive culture. However, the clinical importance of a positive culture is difficult to assess because some asymptomatic individuals have $>10^6$ organisms/mL. Nevertheless, in patients with chronic diarrhea, a positive jejunal culture ($>10^6$ organisms/mL) can be considered evidence of clinically significant bacterial overgrowth in the upper small intestine. This evidence becomes more credible if the patient responds to treatment with an appropriate antibiotic.

Problems with use of jejunal cultures as a test for bacterial overgrowth include lack of standardization of the collection method and the requirement for intubation of the upper gastrointestinal tract (with an endoscope or fluoroscopically placed tube). Various breath tests have been proposed as noninvasive tests for small intestinal bacterial overgrowth. These tests rely on some of the same general principles outlined in the preceding sections.

Because bacteria in the upper small intestine deconjugate bile acids, making them inadequate for micellar formation and fat absorption (the primary mechanism by which bacterial colonization of the small intestine results in diarrhea), a breath test using [^{14}C]glycocholate has been developed.[164,165] The radiolabeled conjugated bile acid is deconjugated by the bacteria, and the ^{14}C in the side chain is metabolized to $^{14}CO_2$, which is exhaled. However, this test has never received widespread acceptance in the United States, probably because of problems with both false positives (in patients with ileal resection or dysfunction) and false negatives.[166,167] At least one group of investigators overseas has reported satisfaction with this test, albeit almost 20 years ago.[168]

Another ^{14}C-breath test using [^{14}C]xylose as a fermentable substrate also has been proposed. When a xylose dose of 25 g was used (a dose that also allows assessment of small bowel absorptive function), the test suffered from poor specificity because xylose is not completely absorbed by the normal small intestine and could reach the colon, where colonic bacteria could produce $^{14}CO_2$ during a 2–3-hour test period.[169] Reducing the dose of xylose from 25 g to 1 g was one method of avoiding this problem.[169,170] However, sensitivity and specificity, initially both reported to be 100%, subsequently have varied between 65% and 90% and between 59% and 62%, respectively.[170,171] [^{14}C]Xylose breath testing is not offered at most medical centers.

A widely available alternative breath test uses nonradioactive glucose and measures breath hydrogen excretion as the signal. In this test, 50–100 g of glucose is administered in water by mouth, followed by measurement of breath hydrogen concentration at 15–30-minute intervals for 2–4 hours. Because even a diseased small intestine should be able to absorb this load of glucose completely, false-positive results (from colonic fermentation) should be less frequent than in tests that use 25 g of xylose. An increase in breath hydrogen concentration of more than 12–20 ppm above baseline is considered a positive result. As in other breath tests, sensitivity and specificity vary widely, in this case from 62% to 93% and from 78% to 100%, respectively.[167,172,173]

Another breath test using nonradioactive lactulose also has been used. In this version, breath hydrogen excretion is monitored after ingestion. Although it would seem to have the same limitations as xylose in that colonic fermentation would result in a low specificity (e.g., 44% in one study[173]), 100% specificity has been reported.[174] This conclusion is tentative because, as in most clinical studies of breath tests, the number of patients enrolled was relatively small.

An elevated concentration of hydrogen in breath after overnight fasting also has been proposed as an insensitive but specific marker of small intestinal bacterial overgrowth.[172,175] This elevated hydrogen concentration may also be seen in patients with malabsorption syndrome.

Finally, an abnormal Schilling II test result (radiolabeled B_{12} given with intrinsic factor) that normalizes

after therapy with broad-spectrum antibiotics has also been considered as a test for small intestinal bacterial overgrowth (the so-called Schilling III test).[176,177] However, this approach is indirect because it requires a positive result from parts I or II of the Schilling test before it can be applied, and in many cases it evolves out of investigation of vitamin B_{12} deficiency rather than diarrhea per se. The clinical utility of this approach has not been tested.

Tests of pancreatic exocrine function. Intubation tests are still considered the gold standards for pancreatic function testing. In these tests, a tube is placed under fluoroscopic guidance with an aspiration port in the distal duodenum; another port is used to drain gastric juice from the stomach. After secretin and/or cholecystokinin is administered intravenously[178–180] or a test meal is eaten,[181,182] duodenal fluid is aspirated for measurement of bicarbonate concentration and output and pancreatic enzyme levels. Although these tests are time-honored and direct in their principles, they require intestinal intubation, and several technical difficulties limit their application. These include the need for correct placement of the drainage tube and adequate aspiration of duodenal fluid, contamination of fluid by bile and gastric juice, the need for accurate assay of the fluid for bicarbonate and enzyme concentrations, and the need to establish clinically useful limits of normal and abnormal. This form of pancreatic function testing rarely is done anymore.

Several noninvasive tests of pancreatic exocrine function have been developed to make this evaluation more acceptable to patients and physicians. Two types have received some degree of acceptance, the bentiromide test and measurement of pancreatic enzymes in stool.

The bentiromide test relies on the presence of enough chymotrypsin in the duodenal lumen to digest the peptide bond in the bentiromide reagent (*N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid). This releases para-aminobenzoic acid, which is absorbed by the mucosa and excreted in the urine.[183–185] Urinary excretion of less than 85 mg of para-aminobenzoic acid (50% of the amount contained in 500 mg of bentiromide) in 6 hours has been set as the threshold for a positive test result.[184] As with other tests involving urinary excretion of a test substance, renal insufficiency and the potential for incomplete urine collection are confounding factors capable of causing false-positive results (i.e., reducing urinary recovery for reasons unrelated to inadequate pancreatic function). In one study, the sensitivity of the test was 80%; the specificity was 95%.[184]

Because of their simplicity and diagnostic accuracy, measurements of fecal concentrations of the pancreatic enzymes chymotrypsin, trypsin, lipase, and elastase have been developed as tests of pancreatic function.[186–190] The fecal chymotrypsin test has been the most widely applied. Its sensitivity is approximately 80%, but its specificity is approximately 90%, perhaps because of problems with preservation of the enzyme's activity during intestinal transit or after its passage and dilution of the enzyme by fecal water in the setting of diarrhea. Although calculation of "output" seemingly would solve the problem of dilution, the method involves measurement of the enzyme's activity rather than its true concentration; this may explain why calculation of output by multiplication by stool weight proved to be less accurate than concentration in one study.[191]

The newest in a long line of enzymatic tests of pancreatic function is measurement of the concentration of the enzyme elastase in feces using an ELISA method.[190] In this test, the amount rather than the activity of the enzyme is measured and is expressed in concentration terms (usually micrograms of enzyme per gram of stool). In a comparative study, fecal elastase outperformed fecal chymotrypsin in terms of both sensitivity and specificity. However, like all of its predecessors,[192] measurement of fecal elastase must stand the test of time.

Breath tests have been developed for determination of exocrine pancreatic insufficiency using [^{14}C]triolein.[193–195] Detection of $^{14}CO_2$ in expired air requires sufficient pancreatic lipase activity to hydrolyze the labeled fatty acid from its glycerol backbone, absorption of the fatty acid by the small intestinal mucosa, metabolism of the labeled fatty acid to $^{14}CO_2$ in the body, and excretion of $^{14}CO_2$ in the breath. Thus abnormalities of small intestinal absorption, fatty acid metabolism, and pulmonary function could interfere with the appearance of the isotope in breath, even if pancreatic function were normal. Perhaps for these reasons, the promise and excitement accompanying early reports of this method have waned over the years. A new modification of breath testing for assessment of fat absorption that combines more intense ^{14}C labeling, use of a unique fatty acid, and a dual method that separates digestive and absorptive function was reported recently in abstract form.[196] More information about the clinical utility of this test must be obtained.

Tests for Gastrointestinal Food Allergy

Allergy to food antigens may be the cause of chronic diarrhea in some patients, but documentation of this has been difficult. Reports have described detection of antibodies to food in feces[197,198] or small intestinal secretions.[199] Validation studies in larger groups of patients with chronic diarrhea are needed before the value of these tests is apparent. Serum antibody testing and

skin testing are not of proven value in detection of gastrointestinal food allergies.

Recommended Approach to Patients With Chronic Diarrhea

Systematic outcomes research to evaluate various clinical approaches to chronic diarrhea has not been reported. Publications relevant to management are of two types: recommendations by experts informed by clinical experience[14,200–205] and reports of series of patients with chronic diarrhea from medical centers with an interest in this problem.[15,16,115,206,207] Both types of publications are subject to referral bias and may or may not be applicable to patients with chronic diarrhea seen in different settings. The following recommendations represent our synthesis of this information as colored by our clinical experience (Figures 1 and 2).

Medical History

Some specifics of a thorough medical history can guide appropriate evaluation of the patient with chronic diarrhea (Table 4). First, it must be understood what specific symptoms have led the patient to complain of diarrhea (e.g., stools are too loose or watery, fragment in the toilet, are too frequent, or are associated with urgency). Detailed questioning about all characteristics of the stools themselves is a necessity. Although a specific diagnosis rarely is produced by this line of questioning, the information helps the physician understand the magnitude of the problem and allows the patient to know that his or her problem is being taken seriously. Patients sometimes are embarrassed by discussing diarrhea, particularly if fecal incontinence is present. This symptom should always be inquired about directly because it rarely is volunteered.

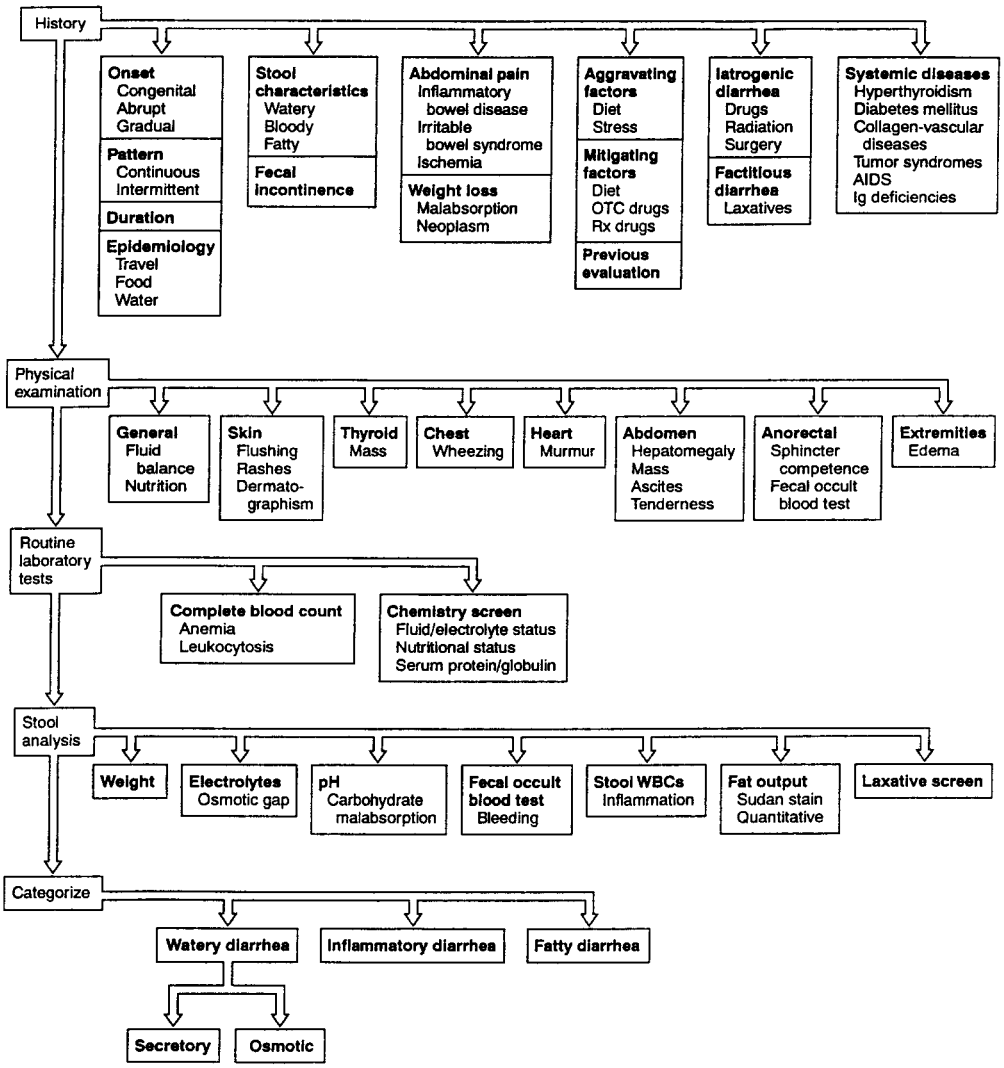

Figure 1. Flow chart or ''mind map'' for evaluation of chronic diarrhea. Initial efforts should be directed to classification of chronic diarrhea based on history, physical examination, basic laboratory test results, and stool analysis.

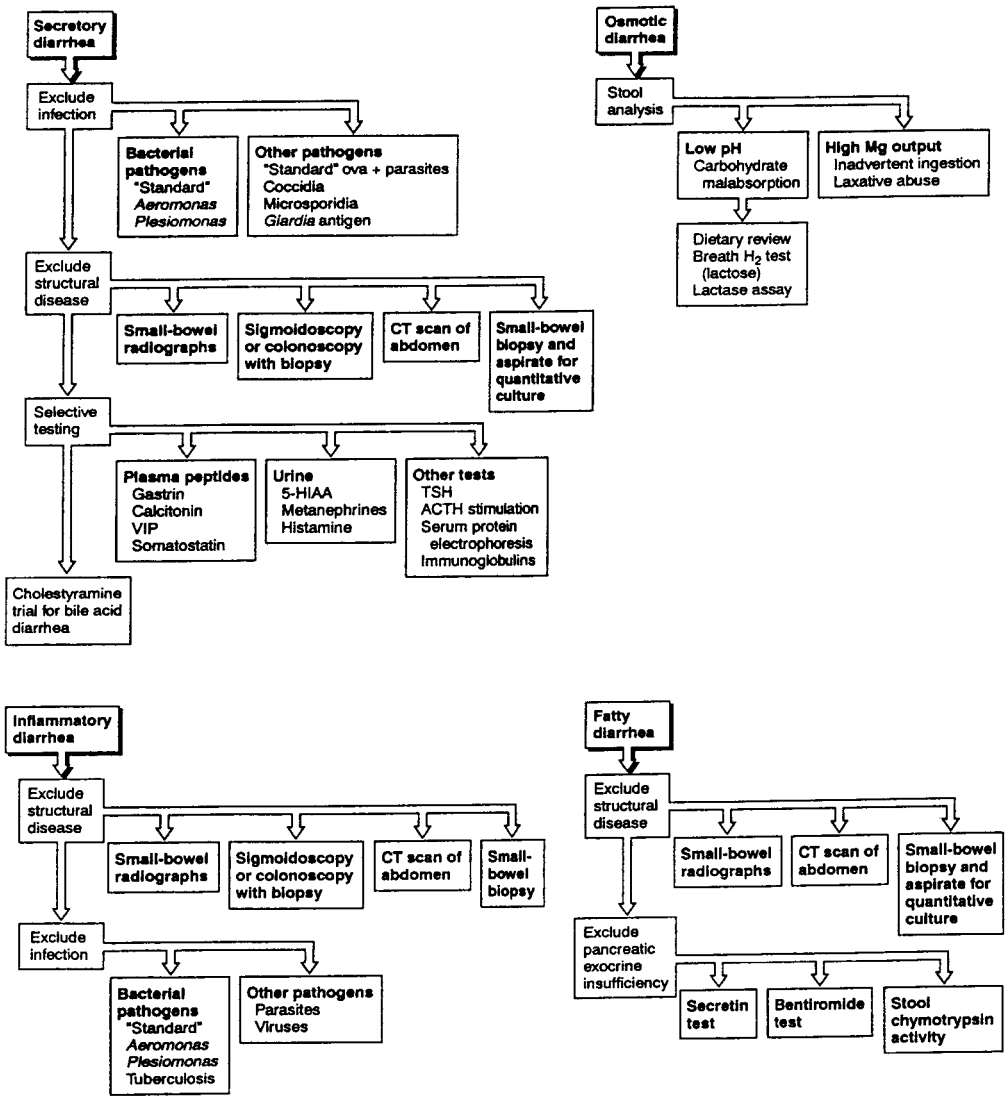

Figure 2. Flow charts or ''mind maps'' for further evaluation of secretory diarrhea (*top left*), osmotic diarrhea (*top right*), inflammatory diarrhea (*lower left*), and fatty diarrhea (*lower right*). It is not necessary to perform every test in a given pathway once a diagnosis is reached. TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; 5-HIAA, 5-hydroxyindole acetic acid.

The characteristics of the stool may suggest a potential pathophysiological mechanism (e.g., malodorous, floating, greasy stools containing food particles suggesting malabsorption; or gross blood suggesting inflammation or neoplasm). The patient's perception of the volume of diarrhea may help to localize the disease process in the gastrointestinal tract. Diarrhea that is watery and voluminous suggests a disorder of the small bowel or proximal colon, whereas frequent, small-volume diarrhea may be associated with disorders of the left colon or rectum. The latter disorders are often accompanied by tenesmus and passage of dark, mushy stools that may contain mucus, pus, or blood.

Fever or weight loss may herald a diagnosis of inflammatory bowel disease, amebiasis, intestinal lymphoma, other malignancies, Whipple's disease, tuberculosis, other enteric infections, or thyrotoxicosis.

The patient's medical history may be important. Seronegative spondyloarthropathy may precede the recognition of inflammatory bowel disease by many years. A history of diabetes, thyroid problems, and other autoimmune phenomena may be pertinent. Previous surgery to the gastrointestinal or biliary tracts may be the cause of diarrhea. Other diseases associated with diarrhea include rheumatic diseases with or without vasculitis, immunoglobulin deficiency, and peptic ulcer disease if caused by the Zollinger–Ellison syndrome or systemic mastocytosis.

All current medications (including "over-the-counter" drugs), nutritional supplements, illicit drugs, alcohol,

Table 4. Implications of Some Aspects of Medical History

Line of questioning	Clinical implication
Onset	
Congenital	Chloridorrhea, Na^+ malabsorption
Abrupt	Infections, idiopathic secretory diarrhea
Gradual	Everything else
Family history	Congenital absorptive defects, IBD, celiac disease, multiple endocrine neoplasia
Dietary history	
''Sugar-free'' foods	Sorbitol, mannitol ingestion
Raw milk	Brainerd diarrhea
Exposure to potentially impure water source	Chronic bacterial infections (e.g., *Aeromonas*), giardiasis, cryptosporidiosis, Brainerd diarrhea
Travel history	Infectious diarrhea, chronic idiopathic secretory diarrhea
Weight loss	Malabsorption, pancreatic exocrine insufficiency, neoplasm, anorexia
Previous therapeutic interventions (drugs, radiation, surgery, antibiotics)	Drug side effects, radiation enteritis, postsurgical status, pseudomembranous colitis
Secondary gain from illness	Laxative abuse
Systemic illness symptoms	Hyperthyroidism, diabetes, vasculitis, tumors, Whipple's disease, IBD, tuberculosis, mastocytosis
Intravenous drug abuse, sexual promiscuity	AIDS
Immune problems	AIDS, Ig deficiencies
Abdominal pain	Mesenteric vascular insufficiency, obstruction, IBS
Excessive flatus	Carbohydrate malabsorption
Leakage of stool	Fecal incontinence
Stool characteristics	
Blood	Malignancy, IBD
Oil/food particles	Malabsorption, maldigestion
White/tan color	Celiac disease, absence of bile
Nocturnal diarrhea	Organic etiology

and caffeine used by the patient should be noted. Patients should be asked specifically about new medicines, magnesium-containing products, and any antibiotics taken within the preceding 6–8-week period.

A detailed dietary history should be obtained with special attention to recent changes; special diets; "sugar-free" foods, gums, or mints (which may contain poorly absorbable sugar alcohols); fiber intake; and consumption of raw seafood or shellfish. The patient's usual intake of fruits, fruit juices, vegetables, milk products, and beverages containing high concentrations of sugar or caffeine should also be estimated.

The family history may disclose others with diarrhea or familial diseases associated with diarrhea, such as congenital absorptive defects, inflammatory bowel disease, celiac sprue, IBS, and multiple endocrine neoplasia. A careful social history should be obtained including details of recent travel, type of residential area (urban vs. rural), living conditions, sources of drinking water, occupation, sexual preference, and sexual activity. Patients living in rural settings may be exposed to farm animals that can harbor bacterial pathogens (such as *Salmonella* or *Brucella*). Consumption of well water or raw milk also may cause infections, sometimes associated with epidemics of chronic diarrhea. Health-care workers may be at risk for nosocomial enteric infections (including *Clostridium difficile*) and factitious diarrhea . A discrete but direct inquiry into the patient's sexual practices must be made. Anal intercourse is a risk factor for proctitis due to gonorrhea, herpes simplex, *Chlamydia*, syphilis, and amebiasis, as well as routine bacterial pathogens. Promiscuous or unprotected sexual activity is a risk factor for HIV infection and the multitude of causes of diarrhea associated with the acquired immunodeficiency syndrome (AIDS).[200–205]

Because functional disorders are very common and may be associated with diarrhea, factors suggestive of IBS should be sought. These include a long history (usually beginning in the second or third decade) of intermittent abdominal pain associated with alteration of bowel habits (classically diarrhea alternating with constipation or passage of pellet-like stools), passage of nonbloody mucus, and symptoms exacerbated by emotional stress. Factors that argue against IBS include a recent onset of diarrhea without a long history (especially in a middle-aged or older person), lack of abdominal pain, nocturnal diarrhea (especially if associated with incontinence), weight loss (particularly greater than 5–10 pounds), stools containing gross or occult blood, fecal weight greater than 400–500 g/day, and abnormal blood test results (e.g., low hemoglobin, low albumin, or high erythrocyte sedimentation rate).[15,16,208,209] Finally, it is important to determine whether the patient is seeking help mainly because of fear of a potentially dangerous problem (such as cancer) or primarily for relief of symptoms.

Physical Examination

In most cases of chronic diarrhea, results of physical examination are normal or nondiagnostic. In some cases, however, important clues to the diagnosis may be found including mouth ulcers, signs of severe atherosclerosis, lymphadenopathy, signs of autonomic failure, and rashes, flushing, or hyperpigmentation of the skin. It is important to determine the volume status of the patient; in all instances, it is more important to correct dehydration and electrolyte depletion than to establish a definitive diagnosis.

Further Evaluation

In some cases, findings from the patient's history and physical examination may point strongly to a particular diagnosis, and specific, confirmatory tests can be ordered or a trial of empirical therapy may be warranted. In many cases, particularly those in which a partial evaluation has already been carried out without defining a diagnosis, a quantitative stool collection is the best choice for further evaluation. This allows appreciation of stool weight, examination for the presence or absence of steatorrhea, and classification of an osmotic or nonosmotic (secretory) process. These characteristics, in combination with facets of the history and physical examination, can narrow down the possible diagnoses (Table 5). The diagnostic evaluation then can be directed in an efficient fashion. Although this approach is rational, it has not been tested formally in practice or by clinical simulation. The efficacy of repeated evaluations also has not been studied. In our opinion, there is little to be gained from repeated investigations once a thorough evaluation has been concluded.

Table 5. Major Causes of Chronic Diarrhea Classified by Typical Stool Characteristics

Osmotic diarrhea
Mg^{2+}, PO_4^{-3}, SO_4^{-2} ingestion
Carbohydrate malabsorption
Fatty diarrhea
Malabsorption syndromes
Mucosal diseases
Short bowel syndrome
Postresection diarrhea
Small bowel bacterial overgrowth
Mesenteric ischemia
Maldigestion
Pancreatic exocrine insufficiency
Inadequate luminal bile acid
Inflammatory diarrhea
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Diverticulitis
Ulcerative jejunoileitis
Infectious diseases
Pseudomembranous colitis
Invasive bacterial infections
Tuberculosis, yersinosis, others
Ulcerating viral infections
Cytomegalovirus
Herpes simplex
Amebiasis/other invasive parasites
Ischemic colitis
Radiation colitis
Neoplasia
Colon cancer
Lymphoma
Secretory diarrhea
Laxative abuse (nonosmotic laxatives)
Congenital syndromes (chloridorrhea)
Bacterial toxins
Ileal bile acid malabsorption
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Microscopic (lymphocytic) colitis
Collagenous colitis
Diverticulitis
Vasculitis
Drugs and poisons
Disordered motility
Postvagotomy diarrhea
Postsympathectomy diarrhea
Diabetic autonomic neuropathy
Hyperthyroidism
IBS
Neuroendocrine tumors
Gastrinoma
VIPoma
Somatostatinoma
Mastocytosis
Carcinoid syndrome
Medullary carcinoma of thyroid
Neoplasia
Colon carcinoma
Lymphoma
Villous adenoma
Addison's disease
Epidemic secretory (Brainerd) diarrhea
Idiopathic secretory diarrhea

Empirical Therapy of Chronic Diarrhea

Empirical therapy is used in three situations: (1) as temporizing or initial treatment before diagnostic testing, (2) after diagnostic testing has failed to confirm a diagnosis, and (3) when a diagnosis has been made, but no specific treatment is available or specific treatment fails to effect a cure. An empirical trial (e.g., antibiotic therapy) could be considered as initial therapy if the prevalence of bacterial or protozoal infection is high in a community or in a specific situation. A successful trial would eliminate the need for a more extensive evaluation. For example, a case of chronic diarrhea in a daycare worker might be treated empirically with metronidazole for suspected giardiasis. No utility analysis of this approach is available for most situations likely to be faced in the United States. One study from Mexico published in 1974 studied the effectiveness of empirical amoxicillin in the treatment of "chronic" diarrhea in patients of low socioeconomic status; 96% were asymptomatic by the third day.[210] It is unlikely that similar success would meet empirical antibiotic therapy in most patients with chronic diarrhea in the United States, because chronic diarrhea is less likely to be caused by bacterial infection in the United States.

Symptomatic therapy for undiagnosed or poorly responsive chronic diarrhea can involve a variety of agents.[211] Natural and synthetic opiates are the most widely used, but other agents, such as bile acid–binding agents, bismuth, and medicinal fiber, are sometimes used. Many of these agents were introduced to medicine before the era of randomized, controlled trials, and only the most modern have been the subjects of proper studies. Nevertheless, a considerable body of experience guides the use of these agents.

Opium has been used for 2500 years to control diarrhea and remains a highly potent remedy. Most cases of diarrhea, except for high-volume secretory states, respond to a sufficiently high dose of opium or morphine. Codeine is somewhat less potent, and the synthetic opioids diphenoxylate and loperamide are clearly less potent. Because of the potential for abuse, these drugs, with the exception of loperamide, are controlled substances in the United States. In practice, patients with

chronic diarrhea seldom abuse these agents, and it is unusual to require ever higher doses to control diarrhea once an effective dose is reached. Potent narcotics are probably underused in the treatment of severe chronic diarrhea. Lesser opioids, such as diphenoxylate and loperamide, are satisfactory for control of less severe diarrhea and ought to be tried before resorting to more potent drugs. The prodrug loperamide-*N*-oxide and the enkephalinase inhibitor acetorphan are under development and may have some therapeutic advantages over currently available agents.[212–214]

The somatostatin analogue octreotide has proven effectiveness in carcinoid tumors and other peptide-secreting tumors, dumping syndrome, and chemotherapy-induced diarrhea. It has had limited success in patients with AIDS-associated diarrhea and short bowel syndrome.[211] Octreotide does not seem to have any advantage over opiates in the treatment of chronic idiopathic diarrhea and probably should be a second-line agent for this indication because of the need for administration by injection and its expense.

Intraluminal agents include adsorbants, such as clays, activated charcoal, and binding resins; bismuth; and stool modifiers, such as medicinal fiber.[211] Few controlled studies have been conducted with these agents, and results have been equivocal. Cholestyramine and other similar binding resins have reduced stool weight in European studies in which patients with chronic idiopathic diarrhea have had a high frequency of bile acid malabsorption.[135–139,215] In an American series, cholestyramine had little effect in these patients, even when bile acid malabsorption was present.[141] Bismuth subsalicylate has been shown to be effective in acute travelers' diarrhea, but its effectiveness in chronic diarrhea is unproven.[216] Stool modifiers, such as psyllium, may alter stool consistency but do not reduce stool weight.[217]

Oral rehydration solutions that include glucose or other nutrients and salt are useful for repletion of body fluids.[211] Cereal-based oral rehydration solutions have gained acceptance in recent years. They can be life-saving therapy for dehydrating, acute secretory diarrheas, such as cholera, but have limited application in most chronic diarrheal states and have not been well studied in these situations. Although these solutions increase net salt and water absorption, they are not designed to reduce stool weight, and diarrhea (defined by stool weight or frequency) may worsen with their use.

Directions for Future Research

Study of clinical outcomes in patients with chronic diarrhea has been fragmentary. Utility parameters are available for some diagnostic tests, but in the absence of solid epidemiological data about the prevalence of different causes of chronic diarrhea, these cannot be applied accurately to clinical decision making. Algorithmic management is untested, and the economic aspects of different approaches to the diagnosis and treatment of chronic diarrhea are unstudied. Opportunities for clinical research in patients with chronic diarrhea are voluminous.

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