Diagnosis small bowel malabsorption syndromes in adults

J. Belaiche, E. Louis

Department of Gastroenterology, CHU Sart Tilman, Liège, Belgium.

Abstract

Patients with malabsorption represent a small proportion of presentations with chronic diarrhea. In spite of some progress, the last twenty years were not very innovating in malabsorption investigations. Supporting history may direct investigations toward either the small bowel or pancreas. Serological testing for celiac disease will determine most cases without invasive investigation, but individuals suspected to have small bowel malabsorption, despite negative celiac serology, should have endoscopic distal duodenal biopsies taken to exclude other rare forms of small bowel enteropathy. This strategy has largely supplanted many older tests of small bowel function. (Acta gastroenterol. belg., **2006**, 69, **31-37**).

Patients with malabsorption represent a small proportion of presentations with chronic diarrhea. Adult malabsorption syndromes include diseases with lipids, proteins, glucids, minerals and vitamins defect of absorption associated with diarrhea. Exsudative enteropathies with lymph and plasma leakage are taken within the same clinical scope.

Mechanisms of malabsorption

An understanding of malabsorption syndromes calls for an approach of physiological processes of digestion -absorption and the location of these functions at different small bowel levels. Most of these processes are achieved at the upper part of the gut, bile salts and vitamin B12 being selectively absorbed at the ileal level.

Nevertheless, ileum can supply to a proximal deficiency and absorb an important quantity of malabsorbed nutriments except for minerals and vitamins exclusively picked up at the proximal level. Conversely jejunum is unable to compensate particular ileal absorptive processes. Following the site of defects, the clinical data are different : a proximal lesion with iron and folates deficiencies is usually free from diarrhea and steatorrhea with regard to an ileal compensation event though a largely extended ileal lesion is responsible of vitamin B12 and bile salts malabsorption and induces diarrhea and sometimes steatorrhea. In case of carbohydrate malabsorption, the colon assumes the fermentation of 50% products via a compensatory mechanism.

Thus, malabsorption syndromes are to be classified following the site of their intra-luminal, mucosal, and post-mucosal anomalies. Luminal phase anomalies related to bilio-pancreatic deficiencies are going to a nutriment hydrolysis failure. Therefore maldigestion is more appropriate than malabsorption. Anomalies of the mucosal step are linked to a lower number and/or reduced functional activity of enterocytes, or an infiltration process of lamina propria. This group includes enteropathies with mucosal lesions and post-surgical small bowel insufficiency and more rarely malabsorption with histological normal mucosa. In such cases the defect is limited to brush border enzyme activities (usually disaccharides) or a lack of an up-take factor (mostly observed during childhood).

Lipids coming from the enterocyte are normally transported by lymphatic vessels. In case of obstacle the patient develops an exsudative enteropathy.

Jejunal motility disorders, with normal mucosa and osmolality, can lead to a malabsorption (sclerodermia, chronic pseudo-obstruction).

Table I. — **Clinical presentation of malabsorption**

Severe malabsorption
Classical manifestations of global malabsorption
Chronic abdominal pain
Deficiencies of specific nutrients and vitamins
Irritable bowel like syndrome
Asymptomatic patient

Dominant clinical data

Symptoms evoking a malabsorption syndrome are mostly chronic diarrhea and complete or specific nutritional deficiency. Digestive symptoms are given in table I.

Abundant liquid unbloody stools indicate a severe enteropathy associated with dehydration, hypokalemia, acidosis, important loss of weight, lower legs oedema, hydrops, pallor, tetany, pelvic and costal pains.

On the opposite, the diagnosis of malabsorption can be asymptomatic and such a syndrome is obvious due to a proximal enteropathy. A typical example is done by an isolated iron deficiency which is the only marker of coeliac disease. The classical data of malabsorption are chronic diarrhea, bloating, and abdominal cramps, loss

Corresponding author : Prof. Jacques Belaiche, Department of Gastroenterology, CHU Sart Tilman, 4000 Liège, Belgium.
E-mail : Jacques.Belaiche chu.ulg.ac.be.

Table II. — **Clinical consequences of malabsorption**

Symptoms and signs	Malabsorbed nutrient
Weight loss with normal appetite	Calories
Asthenia	Multifactorial
Pale and voluminous stool, steatorrhea	Fat
Anemia	Iron, folic acid, vitamin B12
Osteomalacia	Calcium, vitamin D
Paresthesia, tetany	Calcium, magnesium
Hyperkeratosis, night blindness	Vitamin A, carotene
Edema, anasarca	Protein
Pellagra	Niacin
Bruising, bleeding tendency	Vitamin K
Poor taste, acrodermatitis, poor wound healing	Zinc
Amenorrhea, sterility	Multifactorial

of weight contrasting with high caloric intake, steatorrhea and sometimes signs of deficiency related to a impeded intake of vitamins or minerals. The list is given in table II. An excellent instance is an osteomalacia leading to coeliac disease diagnosis. At opposite, the clinical picture can be suggesting functional bowel disorders such as IBS when diarrhea and bloating contrast with an excellent being state (1). Then a selective malabsorption by primary lactase deficiency has to be suspected. In spite of a frequency of lactase deficiency in around 30% of adults, symptoms of lactose intolerance are exceptional. This diagnosis could be frequently a wrong way. Other inducers are to be inquired : malabsorbed sugars, sweetening products untolerated in case of overload. Now, the first step of the coeliac disease diagnosis is to look about serological testing for all patients presenting with diarrhea.

Diagnostic approach

The clinical inquiry and biological data are the first step of the diagnosis followed by functional and morphological investigations, to confirm the malabsorption and its origin.

1. *Clinical inquiring*

Table III gives the data of the diagnosis approach. A deficiency is an exclusive sign of malabsorption. An occult intestinal bleeding is the most frequent cause of anemia with iron deficiency and an absence of diarrhea does not exclude a malabsorption syndrome. A normal transit is observed in 10% of adult coeliac patients (“dry” presentation).

2. *First biological balance*

A basic screen for evidence of malabsorption should include full blood count, iron, ferritin, vitamin B12, folate, calcium and magnesium metabolism, albuminemia Thyroid function tests should also be performed at this stage. When anemia from double origin is evidenced a malabsorption is very likely. This display of etiologic biological data is given in table IV.

3. *Leading functional investigations*

The more uses are : fecal fat out-up, D-xylose test and Schilling test. Other functional tests are devoted to specific disturbances : hydrogen breath test after glucose load or absorption test of ^{75}Selenium homotaurocholate.

Three day collection of stools for measurement of unabsorbed fat has been the standard test for malabsorption for decades and continue to be the reference method. To avoid drawbacks an intake of 60 g lipids (butter) has to be applied 3 days before the test and the further 3 days of stool collection. Normally the daily lipid excretion is $\geq$ 6 g. However, there are several limitations to the technique including difficulty in collecting complete three day samples. Alternative methods of assessing fat malabsorption have been developed which rely on single stool analysis of fat content. Fecal fat concentration (g fecal fat/100 g wet stool weight) is reported to correlate well with total fat excretion. Others methods for estimation of fecal fat in stool are semiquantitative and give a moderate correlation with quantitative methods. The stool steatocrit involves separating a fecal homogenate by centrifugation into a lipid, water, and solid phase. Fecal acidification much improves this method with a better correlation with three day fecal fat (2). Sudan III staining of stools has also been used as a qualitative test for fat malabsorption and more recently has been adapted to give a quantitative result (3). Both stool steatocrit and Sudan III stool staining may be considered to be useful simple semiquantitative tests in the investigation of fat malabsorption although it is questionable whether they are superior to a visual assessment of stool for fat.

Breath tests for fat malabsorption offer an attractive alternative to stool tests. ^{14}C-triolein absorption has been used as an alternative to fecal fat. Sensitivies of 85-100% have been reported with specificity > 90% using a fat load of about 20 g, although lower sensitivity has been reported when fecal fat is only 7-14 g/day. The test is inappropriate in patients with diabetes, liver disease, or obesity.

Fat absorption tests based on stable isotopes have also been developed using a variety of ^{13}C-substrates : ^{13}C-Hiolein, ^{13}C mixed chain triglyceride, ^{13}C-cholesteryl octanoate. Breath test gives an information about only the stool lipid concentration but neglects the out-up. When steatorrhea is over 30 g/24 h an exocrine pancreatic origin is very likely. Otherwise in case of proximal enteropathy an ileal compensatory mechanism can explain a low out-up or an absence of steatorrhea. Motor diarrhea without any absorptive dysfunction may be associated with a mild steatorrhea (< 14 g/24 h).

Table III. — **Symptoms due to primary disease**

Presentation	Disease
Chronic diarrhea, malabsorbed nutrient, aphta, positive family history of gluten sensitivity, dermatitis herpetiformis ; thinness	Celiac disease
Abdominal pain, tender mass in the right lower quadrant, aphta, perianal lesion, extra-intestinal manifestations, thinness	Crohn's disease
Recurrent sinus infections, pulmonary infections, otitis media	Selective IgA deficiency, common variable immuno-deficiency
Polyarthritis with pigmentation, lymphadenopathy, fever, neurologic symptoms	Whipple's disease
Young people, Mediterranean patient, poor hygiene, weight loss, clubbing	IPSID*, lymphoma
Stay in the Caribbean, south India, south-east Asia	Tropical sprue
Toxicomania, homosexuality, blood transfusions Urticaria Pigmentosa, hepatomegaly, splenomegaly Scleroderma, CRST Neuropathy, liver and spleen enlargement Bone marrow transplantation Abdominal radiation	SIDA Mastocytosis Systemic sclerosis Amyloidosis Graft-versus-host disease Radiation enteritis

* IPSID : Immuno Proliferative Small Intestinal Disease.

Table IV. — **"Screening" blood tests**

Laboratory features	Etiologic orientation
Hematologic : Iron deficiency : microcytosis ± anemia Folic acid deficiency : macrocytosis ± anemia Iron + folic acid deficiency	Duodenal or duodenojejunal mucosa disease
B12 deficiency : macrocytosis ± anemia Howell-Jolly bodies ± thrombocytosis	Pernicious anemia, bacterial overgrowth, ileal disease Splenic atrophy : celiac disease
Calcium and magnesium metabolism : Hypocalcemia, hypophosphoremia, increase alkaline phosphatase, hypo-magnesemia, vitamin D deficiency	Duodenal or duodenojejunal mucosa disease
hypoproteinemia	Malabsorption or protein-losing enteropathy
Prothrombin time prolonged :Vitamin K deficiency	Small-bowel mucosa disease, cholestasis

Prior to the advent of endoscopic biopsy, assessment of small bowel mucosa function was primarily achieved by quantifying absorption of the inert sugar D-xylose. Despite literature supporting a good correlation with histological abnormalities, it is sensitive rather than specific, and the analytic performance of the test is poor in routine practice. As such it is becoming largely superseded by access to small bowel histology obtained at endoscopy and/or serological tests for celiac disease. Nevertheless, in current practice, the D-xylose test remains sometimes useful to differentiate normal subjects and enteropathies and in case of steatorrhea solely to look about a possible exocrine pancreatic deficiency.

Schilling test using B12 vitamin and with/or without intrinsic factor gives information about physiological condition on B12 vitamin absorption. Without intrinsic factor the test is abnormal after total gastrotectomy or Biermer anemia. It is also abnormal in bacterial overgrowth, ileopathies and ileal resection but repeated with intrinsic factor and after antibiotics the test returns to the normal.

4. *Other functional intestinal investigations*

Their use is not common.

Bile acid malabsorption can be assessed by breath test with 75 selenium homotaurocholate (^{75}Se-HCAT). The ^{75}Se-HCAT investigates the ileal function and it is more sensitive than the Schilling test. Value less than 15% suggest bile acid malabsorption. This can also be used to assess the functional integrity of the terminal ileum in cases where localized disease is suspected. Patients with Crohn's disease or other terminal ileal abnormality or resection are particulary at risk of bile acid malabsorption but the condition has also been well documented following cholecystectomy, post-infectious diarrhea, and idiopathic diarrhea.

Hydrogen breath testing is based on the ability of some bacteria to ferment carbohydrates with an end product of hydrogen, which is not produced by mammalian cells. Breathed out hydrogen results from fermentation of sugars due to a bacterial overgrowth or from colonic H_2 production in case of selective sugar

Table V. — **Specific diagnoses made by small intestinal mucosal biopsy**

Diagnostic allways obtained with certainty by small intestinal biopsy
Collagenous sprue
Wipple's disease
Mycobacterium avium-intracellulare
IPSID* and lymphoma
Abetalipoproteinelia
Cryptosporidium and Isospora
Diagnostic obtained with fair certainty by small intestinal biopsy
Celiac disease
Tropical sprue
Diagnostic some times obtained with certainty by small intestinal biopsy
Lymphangiectasia
Eosinophilic gastroenteritis
Giardiasis
Strongyloidiasis
Crohn's disease
Amyloidosis

* IPSID : Immuno Proliferative Small Intestinal Disease.

malabsorption. In the first situation 50 g of glucose is used, with a 80% sensitivity and a specificity not far from 90%, for the second one the unabsorbed sugar - mostly lactose- is given in the same conditions. Sometimes the basal H_2 is very high due to continuous fermentation or a background amount of malabsorbed sugars and jeopardizes the test. Then a second similar test can be tried after a 24 hrs period fasting with a return of basal H_2 to zero or a low value (< 20 ppm). In addition, a false negative result may occur in those individuals whose bacterial flora are not hydrogen producers. Approximately 2-25% of patients (depending on the population studied) do not have H_2 producing bacteria.

Stool culture is not useful in immunocompetent Western populations but stool cultures should be considered, particularly where there is a history of travel to high risk areas. Protozoan infections, such as giardiasis and amoebiasis are most likely to result chronic infections. Examination of three fresh stools for ova, cysts, and parasites remains the mainstay of diagnosis and has a sensitivity of approximately 60-90% for detection of theses organisms. Stool examination is also mandatory in case of immunodeficiency to research for cryptosporidiosis, coccidosis, and microsporidiosis.

5. *Morphologic investigations*

They are only going to a safe etiologic diagnosis with the use of endoscopy and biopsies, X-rays examination and more recently wireless capsule enteroscopy.

Upper gastrointestinal endoscopy and small bowel enteroscopy let to biopsy sampling under visual control. The same advantage is available at the colon and mostly at the end of ileum. Small bowel enteroscopy with intestinal biopsy is beneficial in most cases of malabsorption believed to be due to small bowel disease. Table V gives the overview of the diseases diagnosed by intestinal biopsy.

Table VI. — **Disorders associated with abnormal small intestinal X-ray**

Small intestinal diverticulosis
Surgically created blind loops (end-to-side anastomosis)
Crohn's disease
Radiation
Lymphoma
Gastrocolic or jejunocolic fistula
Intestinal bypass
Scleroderma
Idiopathic intestinal pseudo-obstruction

The small bowel barium follow through or barium enteroclysis have a lower interest with regard to endoscopy. Most of the focal lesions associated to malabsorption are related to small bowel bacterial overgrowth (Table VI). It is likely that a negative result offers a reasonably reliable exclusion of macroscopic small bowel disease.

Results of preliminary study suggest that wireless capsule enteroscopy is a novel and potentially clinically useful method of directly visualizing and diagnosing small-bowel lesions in patients with inflammatory bowel disease that can be missed by traditional endoscopic and radiological procedures (4).

Strategy of a diagnostic inquiry

There are no validated guide-lines for a diagnostic inquiry. The best way is to avoid a "carpet bombing system" with "unsalted investigation" for everybody. The approach will be gradual and critical. After anamnesis, physical examination, with help of first range biological data, it is possible to suspect one type of enteropathy, a sufficient reason to ask for upper GI tract endoscopy with biopsies. When endoscopy is inconclusive with biopsies normal, functional investigations are required for a further ongoing approach. When steatorrhea is alone and D-xylose test normal, a pancreatic deficiency is the first hypothesis, but an association with motility disorders is possible as it was previously said (Fig. 1). Exceptionally the cause of malabsorption remains unexplained, classified "out of rules" they call for a strict follow-up.

Principal causes of small bowel malabsorption

Table VII gives the principal causes of malabsorption and their diagnostic indications.

Diseases associated with villous atrophy after vital staining with methyl blue show scalloped folds of the mucosa with a typical mosaic pattern. Coeliac disease is the most common cause of villous atrophy in the Western world. Serological screening studies using IgA antiendomysium antibodies (EMA) or antigliadine antibodies have shown a prevalence of 1:200 and 1:559 in European and North American populations. Coeliac disease is frequently presenting with diarrhea due to steatorrhea and malabsorption. Many individuals are

Table VII. — **Common causes of intestinal malabsorption**

Diagnosis	Diagnostic test
Villous atrophy	
Celiac disease	Serologic tests, response to a gluten-free diet
Tropical sprue	Stay in endemic tropical area, antibiotic's response
Selective IgA deficiency	Serum electrophoresis and immunoelectrophoresis
Giardia lamblia	Small intestinal biopsies, duodenal aspiration, stool
Lamina propria infiltration	
Whipple's disease	Small intestinal biopsies, PCR detection of *Tropheryma whipplei*
? Heavy chain disease (*IPSID)	Small intestinal biopsies, incomplete IgA heavy chain in serum or secretion
Lymphoma	Small Intestinal X-ray, small intestinal biopsies
Eosinophilic gastroenteritis	Small intestinal biopsies
Amyloidosis	Small intestinal biopsies
Crohn's disease	Ileocoloscopy with biopsies, small intestinal X-ray
Lactase deficiency	Lactose/Hydrogen breath test
Bacterial overgrowth	Previous abdominal surgery, small intestinal X-ray, Glucose/Hydrogen breath test ; antibiotic's response

* IPSID : Immuno Proliferative Small Intestinal Disease.

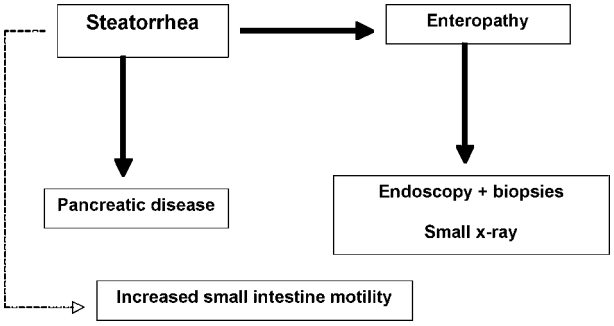

Fig. 1. — Approach to a patient with steatorrhea

Table VIII. — **Main disorders to consider in the differential diagnosis of villous atrophy**

Celiac disease
Dermatitis herpetiformis
Selective IgA deficiency
Common variable immunodeficiency
Tropical sprue
Collagen sprue
Refractory sprue
IPSID
Crohn's disease
Giardiasis
Strongyloidiasis
Ileal villous atrophy
Drugs

however asymptomatic. As such, there is a strong case for routine serological testing for coeliac disease for all patients presenting with diarrhea. The recent identification of tissue transglutaminase (tTG) as the autoantigen of EMA has led to the development of commercial ELISA kits for the detection of anti-tTG antibodies. Reliance on serological testing for coeliac disease should be tempered with the knowledge that the condition is associated with selective IgA deficiency, which will give rise to false negative serum IgA antibodies tests. Selective igA deficiency occurs in 1/500-1/700 of the general population but in 2,6% of patients with celiac disease. A recent study has shown that both IgG antiendomisium and IgG anti-tTG antibodies may be suitable alternative serological means of diagnosing celiac disease but are not suitable for monitoring the response to dietary modifications. Antiendomisium igA antibodies, in contrast, disappear following adequate treatment with a gluten free diet (5). The two steps diagnosis takes in account at first positive serological tests for coeliac disease and few months later a clinical, serological and histological positive response to gluten free diet. Villous atrophy is no only the result of coeliac disease, other factors are candidates : antibiotics, (polymixin, bacitracin), anti-metabolite drugs (methotrexate, colchicin) and biguanides (Table VIII).

The duodenal mucosa of patients with Whipple disease is pathognomonic : villous pattern is disorganized, and the mucosa and the chorion are showing an infiltration by macrophages with a characteristic PAS positive material in their cytoplasm. The responsible bacteria (tropheryma whipplelii) is now recognized and the diagnosis can be assessed by molecular biology applied on biopsic material or blood. This last approach is especially useful in case of neurological manifestations without intestinal involvement (6).

The ? chain disease is the main pathology of IPSID (Immuno Proliferative Small Intestinal Disease). Evoking clinical and epidemiological data are given in the table. A serum immuno-electrophoresis with immuno-selection assesses the diagnosis on the evidence of an incomplete IgA. Following the stage of the disease, histology shows a lamina propria infiltration by mature plasmocytes to in worse conditions a diffuse infiltration of immunoblastic lymphoma. Recently infection by campylobacter jejuni was evidenced at the initial stage, a lymphome prone status as we know for *Helicobacter pylori* at the gastric level (7).

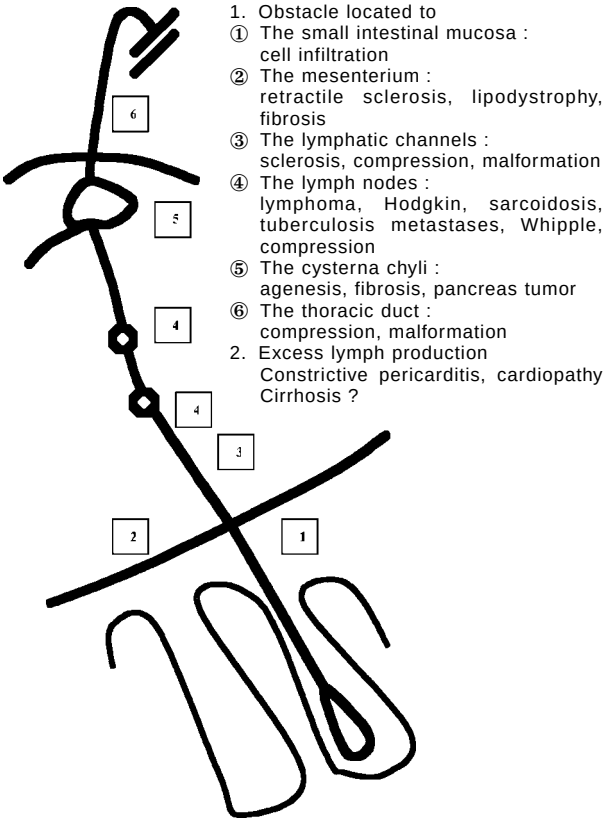

Fig. 2. — Causes of intestinal lymphangiectasia

Lactase, the enzyme responsible for hydrolysis of dietary lactose, is located in the microvilli of small intestinal enterocytes. Lactase deficiency may occur as a rare primary congenital defect or secondarily of small bowel disease such as celiac disease, gastroenteritis, or non-steroidal anti-inflammatory drug use.

The diagnosis of small bowel chronic bacterial colonization is well known and many features are predisposing : bowel stenosis, blind loop, duodeno-jejunal diverticulosis, intestinal dysmotility syndromes associated with systemic disease (diabetes, sclerodermia, intestinal pseudo-obstruction) or fistula by-pass between stomach, colon, small bowel. In such pathologies, D-xylose and B12 vitamin absorption may be impaired. In case of bacterial colonization, a therapeutic trial with antibiotics shows a return to the normal after a 10 days therapy.

Exsudative enteropathies

The predominant feature of these enteropathies is a leakage of lymph or proteins coming from the interstitial layer of submucosa (8). Hypoproteinema goes with hypoalbuminemia and /or hypogammaglobulinemia. The diagnosis is evoked face to a diarrhea with simple sloping edema or worse an anasarca sometimes with chylous ascitis. Exsudative enteropathy diagnosis is assessed by a significant increase of alpha-1-antitrypsin fecal clearance whose normal value does not exceed 12 ml/24 hrs for a normal subject.

The diagnosis is easy when ulcerative lesions (ulcus, digestive tumors, inflammatory bowel diseases) are explaining exsudation but in case of lymphatic origin the approach is more difficult. It is necessary to look for chylous ascitis, lymphopenia, hypocholesterolemia and hypotriglyceridemia. Any impediment to lymphatic return (increased pressure in cardiac right cavities and superior vena cava) cirrhosis, portal hypertension, mesenteric tumors or inflammatory processes are able to induce and exsudative enteropathy (Fig. 2). Lymphangiectasia (lymphatic dilatations) enlarging the tips of the villi or the submucosal layer are visible on biopsy samples. Tumoral lesions of lymphatic system and pancreas are predominant. Primitive intestinal lymphangiectasia or Waldmann disease is more seldom and must be taken in mind when edema was present in childhood, hard and infiltrative asymetric in 20% of the cases. The best diagnostic approach, after anamnesis, and clinico-biological data, is supported by abdominal echography, thoraco-abdominal tomo-densitometry, pancreatic echoendoscopy or eventually bi-pedious lymphography.

Conclusion

Patients with malabsorption represent a small proportion of presentations with chronic diarrhea. In spite of some progress, the last twenty years were not very innovating in malabsorption investigations. Supporting history may direct investigations toward either the small bowel or pancreas. Serological testing for celiac disease will determine most cases without invasive investigation, but individuals suspected to have small bowel malabsorption, despite negative celiac serology, should have endoscopic distal duodenal biopsies taken to exclude other rare forms of small bowel enteropathy. This strategy has largely supplanted many older tests of small bowel function.

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