

# The Surgical Pathology of Malabsorption

## (How not to sprue-up a small bowel biopsy)

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### Malabsorption-Definition.

- A. The term malabsorption is used to encompass broadly any type or degree of dysfunction in uptake of any substance that is normally absorbed (or retained) by the small intestine. "Malabsorption" in this sense can be caused by a wide variety of disorders affecting the small intestine.
  
- B. The malabsorption syndrome more narrowly describes the constellation of clinical findings that includes diarrhea and steatorrhea and variable secondary changes, such as weight loss and evidence of vitamin deficiencies resulting from reduced absorption of nutrients.

### Introduction:

All too often endoscopic biopsies of the small bowel to rule out malabsorption are taken from the two worst places to evaluate villous architecture, either the duodenal bulb or the terminal ileum. Although both sites are the easiest for endoscopists to biopsy, they are the least reliable in terms of evaluating small bowel architecture. In a perfect world, only distal duodenal or proximal jejunal biopsies would be sent for such evaluation, and perfectly oriented sections would magically emerge from every histology lab. The harsh reality is that the deck is stacked against the pathologist from the beginning and diagnostic errors are easy to make if one is not familiar with anatomic variations incumbent upon this region of the gut. The combinations of peptic duodenitis or prominent peyer's patches and tangential sections can easily lead to misdiagnoses. It is important to realize that the vast majority (>90% in my practice) of small bowel biopsies are normal.

While there are several different approaches to classifying small bowel biopsy changes, the most problematic cases for surgical pathologists are those that involve non-specific inflammatory changes. The poster child for this is, of course, celiac disease.

CELIAC DISEASE (Synonyms): gluten-induced enteropathy, celiac sprue, "non tropical sprue"

1. A well-characterized entity in which epithelial injury caused by dietary wheat gluten (and more particularly, its alcohol-soluble fraction, gliadin) accounts for the malabsorption.
2. The cardinal features in patients with symptomatic celiac disease during different stages of therapy with a gluten-free diet (GFD) are:
  - a. Before gluten-free diet:
    - Clinical and lab evidence of the malabsorption syndrome
    - Flat jejunal biopsy (Absent or severely blunted villi) with:  
Surface epithelium that is thinned, injured  
Intraepithelial lymphocytes increased at surface
      - Chronic inflammation increased in lamina propria
      - Crypt mitoses increased; crypts elongated ("hyperplastic").
    - Some patients may have normal villi with increased IELs**
  - b. Gluten-free diet – short term (1wk-3 mos)
    - Marked clinical improvement
    - Diminished surface epithelial injury
    - Reduced number of intraepithelial lymphocytes
    - Villi return - partially
  - c. Gluten-free diet - Long Term (greater than 3 mos.)
    - Villi gradually become normal
    - Mitotic hyperactivity gradually subsides
    - Chronic inflammation much diminished
  - d. Gluten restored to diet
    - Rapid return of all lesions and malabsorption.
    - Early increase in intraepithelial lymphocytes and injury to epithelium over villi
3. Diagnostic approaches to celiac disease.
  - a. Endoscopic biopsy of the distal duodenum (preferably beyond the bulb to avoid confounding peptic disease) is usually satisfactory, but an even more distal specimen may be needed at times.
  - b. Serum anti-reticulin, anti-endomysial, and anti-gliadin antibodies; these are used to screen and to check on effectiveness of a GFD. Anti- endomysial antibodies have historically been the most sensitive and specific for celiac disease. Antibodies to tissue

transglutaminase (a closely related factor to anti-endomysial antibodies) may now be the single most sensitive and specific test for celiac disease.

- c. Unequivocal evidence of improvement on a GFD is needed for a definitive diagnosis of symptomatic celiac disease.
4. Pathogenesis. The mechanism(s) by which gluten injures the epithelium have not been fully established. However, immunologic, genetic, and environmental factors all seem to be important
- a. Immune mechanisms: Multiple observations favor the conclusion that celiac disease is an autoimmune disorder occurring in the context of a combination of genetic and environmental factors, including the following:
    - i. Serum antibodies to gluten and its gliadin fraction are virtually always present in active celiac disease. A recent study showed subepithelial deposition of activated complement, IgG and IgM in proportion to circulating anti-gliadin levels, suggesting humoral epithelial injury. Anti-reticulin antibodies also correlate with disease activity, and have diagnostic specificity.
    - ii. Presence of numerous intraepithelial lymphocytes, chiefly in the injured surface epithelium (these are mostly T cells, but with a high proportion gamma/delta types). This is highly consistent with cell-mediated injury that is somehow facilitated by gluten.
    - iii. Steroid Rx can cause patient improvement comparable to that with a GFD.
    - iv. Patients with celiac diseases show a highly significant excess of other autoimmune diseases (e.g. insulin dependent diabetes mellitus)
  - b. Genetic factors. These include:
    - i. A strong tendency for celiac disease to run in families (11-22% occurrence in first degree relatives). Also a high (70%) concordance for celiac diseases in identical twin pairs.
    - ii. A high correlation between celiac disease and presence of HLA-B8, DR3 (DR17), DR7, and DQ2 histocompatibility loci. The strongest association (95%) is with a specific HLA DQ2 molecule that is seen in only 20-30% of the general population. The genetics seem to be "complex" and a multigenic HLA associated susceptibility is favored.
    - iii. Overlap with the blistering skin condition dermatitis herpetiformis (DH), including similar mucosal alterations, and

overlap in HLA markers, and improvement in the skin lesions on a GFD.

- c. Environmental factor(s). It seems likely that an environmental factor is a necessary precondition, along with appropriate genetic make-up and gluten ingestion, for an individual to develop celiac disease. Support for this conclusion comes from:
  - i. The fact that only one member of an identical twin pair is sometimes affected by celiac disease.
  - ii. Evidence of a possible role for viral infection: In one study serologic findings of prior exposure to an adenovirus (Type 12) were unusually common. In addition, a Type 12 adenovirus antigen shares an amino acid sequence with gliadin. Although more recent studies have not confirmed a direct correlation between celiac diseases and adenovirus12, the concept remains an attractive paradigm.
- d. General hypothesis of celiac diseases pathogenesis (simplified): Gluten + Specific HLA Receptor + environmental factor (? viral infection) --> Sensitization --> Autoimmune susceptibility to gluten --> Lymphocyte/lymphokine induced epithelial injury = Celiac disease.

5. Variant and related forms of celiac disease. These include:

- a. Latent celiac diseases. This term is applied to persons who are asymptomatic for malabsorption but who nevertheless show evidence of gluten sensitivity. This can be accompanied by small bowel mucosal changes and it is important for pathologists to be aware that these changes can fall anywhere along a long spectrum of severity. In some persons with latent celiac disease, the mucosal lesion approaches that seen in the full-blown symptomatic disorder while individuals at the other extreme show normal mucosa. A common denominator among these patients can be elevated anti-gliadin antibody production.
- b. Dermatitis herpetiformis. (See 4.-b-iii, above)
- c. "Collagenous sprue" A probable variant manifestation of celiac disease in which a flat small intestinal biopsy also shows a thick subepithelial collagen band.

6. Important complications of celiac disease include:

- a. Refractory celiac disease and refractory ("unclassified") sprue.

The common denominator of "refractory celiac disease" is late failure to respond to a gluten-free diet. I limit use of "refractory sprue" to those patients with flat biopsies who have never shown gluten sensitivity and for whom the relevance of gluten is

therefore unproven. Others also use "refractory sprue" to cover those with celiac diseases. Refractory celiac disease is sometimes seen with peptic duodenitis and distinctive radiological changes ("bubbly bulb"). Refractory sprue cases often have a poor prognosis and many feel these cases are lymphoproliferative disorders. Loss of CD8 staining and/or T-cell gene rearrangements can be helpful in proving clonality.

- b. Small intestinal ulceration (with or without refractory celiac disease).
- c. Malignancy: These include primary intestinal lymphoma - "enteropathy-associated T cell lymphoma" or EATCL. It may present clinically as refractory celiac disease or sprue. Other tumor types are: small intestinal adenocarcinoma, and squamous carcinoma of the esophagus.

#### REFERENCES (Celiac disease):

1. Baer, AX, Bayless, T.M., and Yardley, J.H. Intestinal ulceration and malabsorption syndromes. *Gastroenterology* 79:754-765, 1980.
2. Bayless, T.M., Kapelowitz, R.F. and Shelley, W.M., et. al.: Intestinal ulceration - a complication of celiac disease. *New Eng. J. Med.* 276:996-1002, 1967.
3. Falchuk, Z.M., Gebhard, R.L., Sessoms, C. and Strober, W.: An in vitro model of gluten-sensitive enteropathy. Effect of gliadin on intestinal epithelial cells of patients with gluten-sensitive enteropathy in organ culture. *J. Clin. Invest.* 53:487-500, 1974.
4. Gebhard, R.L., Falchuk, Z.H., Katz, S.L., Sessoms, C., Rogentine, G.N., Strober, W.: Dermatitis herpetiformis. Immunological concomitants of small intestinal disease and the relationship to histocompatibility antigens. *J. Clin. Invest.* 54:98, 1974.
5. Swinson, C.M., Slavin, G., Coles, E.C., Booth, C.C.: Coeliac disease and malignancy. *Lancet* 1:111-115, 1983.
6. Holdstock, G., Eade, D.E., Isaacson, P., and Smith, C.L. Endoscopic duodenal biopsy in coeliac disease and duodenitis. *Scand. J. Gastroenterol* 14:717, 1979.
7. Jones, B., Bayless, T.M., Hamilton, S.R., and Yardley, J.H.: The bubbly bulb and celiac disease. *Am. J. Roentgen.* 142:119, 1984.
8. Kagnoff, M.F.: Immunology and disease of the gastrointestinal tract. In: Sleisinger, M.H. and Fordtran, J.S.: *Gastrointestinal disease*. Philadelphia, Saunders, 1993, 5th Ed., pgs. 45-86.

9. Katz, A.J., Falchak, Z.M.: Definitive diagnosis of gluten-sensitive enteropathy: Use of an in vitro organ culture model. *Gastroenterology* 75:695-700, 1978.
10. Rubin, C.E., et al: Studies of celiac disease. I. Apparent identical and specific nature of duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue. *Gastroenterology* 38:28-49, 1960.
11. Samloff, I.M., David, J.S., and Schenk, E.A.: A clinical and histochemical study of gluten-free diet. *Gastroenterology* 48:1 55, 1965.
12. Trier, J.S., Falchak, Z.M., Carey, M.C., et al: Celiac sprue and refractory sprue (clinical conference). *Gastroenterology* 75:307-31 6, 1978.
13. Unsworth, D.J., Leonard, N.L., Fry, L.: Antireticulin and antigliadin antibodies in dermatitis herpetiformis and celiac disease. In: Beutner EH, Chorzelski TC, Kumar V (eds): *Immunopathology of the Skin*, ed 3. New York, John Wiley & Sons Inc., 1987, Chap 25.
14. Weinstein, W.M., Saunders, D.R., Tytgat, G.N., et al: Collagenous sprue an unrecognized type of malabsorption. *New Eng. J. Med.* 283:1297-1301, 1970.
15. Whitehead, R.: Primary lymphadenopathy complicating idiopathic steatorrhea. *Gut* 9:569-575, 1948.
16. Yardley, J.H., Bayless, T.M., Norton, J.H., et al: Celiac disease: A study of the jejunal epithelium before and after a gluten-free diet. *New Eng. J. Med.* 267:1173-1179, 1962.
17. Yardley, J.H.: Malabsorption disorders. In: Ming SC, Goldman H (ed s.): *Pathology of the gastrointestinal tract*. Philadelphia, Saunders, 1992, Chap 29.
18. Halstensen, T.S., Hvatum, M., Scott, H., Fausa, O., Brandtzaeg, P.: Association of subepithelial deposition of activated complement and immunoglobulin G and M response to gluten in celiac disease. *Gastroenterology* 102:751-759, 1992.
19. Arranz, E., Ferguson, A.: Intestinal antibody pattern in celiac diseases: Occurrence in patients with normal jejunal biopsy histology. *Gastroenterology* 104:1263-1272, 1993.
20. Marsh, M.N.: Gluten sensitivity and latency: Can patterns of intestinal antibody secretion define the "silent majority?" *Gastroenterology* 104:1150-1153, 1993.
21. Lawler, M., Humphries, P., O'Farrelly, C., Hoey, H., Sheils, O., Jeffers, M., O'Briain, D.S., Kelleher, D.: Adenovirus E1A gene detection by polymerase chain reaction in both the normal and celiac duodenum. *Gut* 35:1226-1232, 1994.
22. Collin, P., Reunala, T., Pukkala, E., Kyrilainan, O., Pasternack, A.: Coeliac disease-associated disorders and survival. *Gut* 35:1215-1218, 1994.
23. Catassi, C., Ratsch, I-M, Fabianai, E., Rossini, M., Bordicchia, F., Candela, F., Coppa, G.V., Giorgi, P.L.: Coeliac disease in the year 2001 exploring the iceberg. *Lancet* 343:200-203, 1994.

24. Cronin, C., Shanahan, F.: A significant step in the celiac puzzle. *Gastroenterology* 1998;114:1338-40.
25. Colin P. New diagnostic findings in Coeliac disease. *Ann Int Med* 31:399-405, 1999.
26. Farstad IN, Johansen F-E, Vlatkovic L, Johansen J et al. Heterogeneity of intraepithelial lymphocytes in refractory sprue: potential implications of CD30 expression. *Gut* 51:372-378, 2002.

### TROPICAL SPRUE (POST-INFECTIVE TROPICAL MALABSORPTION)

1. Definition (Baker and Mathan): "Intestinal malabsorption of unknown etiology, occurring among residents in, or visitors to, the tropics". Despite the fact that a single etiologic agent has not been identified, there is much evidence that an infection initiates and sustains tropical sprue: a) It occurs in certain specific geographic areas (eg, West Indies, Indian subcontinent) and enteric infections are common in these locations. b) In some areas it is epidemic. c) Aerobic enterobacteria colonize the patient's small intestine and these may be toxin producing. (Note that this differs from the stasis syndrome in which anaerobic bacterial overgrowth is central (see below)). d) Recovery after treating tropical sprue with broad-spectrum antibiotics is usually rapid and dramatic. e) Some have postulated that a Protozoan infection such as cyclospora may play a role.

The important role played by infection in tropical sprue has led to the alternative designation "Post-infective tropical malabsorption".

2. Other factors such as epithelial damage may also contribute to the condition. Along with diarrhea and malabsorption, folate, and sometimes B-12 deficiencies are commonly present. In severe tropical sprue there can be resulting diminution in epithelial mitosis accompanied by nuclear enlargement - changes that are the epithelial counterpart to maturational derangements in the marrow and macrocytic anemia (megaloblastic changes). Genetic or ethnic predisposition has also been suggested.
3. The mucosal lesion in tropical sprue is of "nonspecific" type with epithelial blunting, chronic inflammation, etc. A completely flat biopsy like that often seen in celiac disease is rare in tropical sprue, but epithelial dysfunction, as in celiac disease, is central to pathogenesis. Unlike celiac disease, in which mucosal changes are greatest in the proximal small bowel, lesions in the ileum are as prominent as those in the jejunum in tropical sprue. This fits well with the resulting secondary B-12 and folate deficiency states (which are not common in celiac disease). Intraepithelial lymphocytes are increased in tropical sprue, although they may be more numerous in the crypts than in the villi.

## REFERENCES (Tropical Sprue):

1. Baker, Z.7. and Mathan, V.I.: Syndrome of tropical sprue in India. *Am. J. Clin. Nutr.* 21:984, 1968.
2. Schenk, E.A., Samloff, I.M. and Klipstein, F.A.: Morphologic characteristics of jejunal biopsy in celiac disease and tropical sprue. *Am. J. Path.* 47:765,1965.
3. Swanson, V.L. and Thomassen, R.W.: Pathology of the jejunal mucosa in tropical sprue. *Am. J. Path.* 46:511,1965.
4. Swanson, V.L., Wheby, M.S. and Bayless, T.M.: Morphologic effects of folic acid and vitamin B-12 on the jejunal lesion of tropical sprue. *Am. J. Path.* 49: 167, 1966.
5. Trier JS, Donnelly SM. Case records of the Massachusetts General Hospital. *New Engl J Med* 322:1067-1075,1990.
6. Wheby, M.S., Swanson, V.L. and Bayless, T.M.: Comparison of ileal and jejunal biopsies in tropical sprue. *Am. J. Clin. Nutr.* 24:117-123,1971.
7. Cook GC. Aetiology and pathogenesis of postinfective tropical malabsorption (tropical sprue). *Lancet* 1:721-723,1984.
8. Cook GC. Postinfective malabsorption (includes tropical sprue). In: Bouchier AD, Alan RN, Hodgson JF, Deighley M RB, eds. *Gastroenterology. Clinical practice and science.* Philadelphia, Saunders. 1993. Pgs.522-537
9. Cook GC. "Tropical sprue": Some early investigators favored an infective cause, but was a coccidian protozoan involved? *Gut*; 40:428-429.

## STASIS (BLIND-LOOP) SYNDROME / BACTERIAL OVERGROWTH

1. The causes of stasis in the small bowel include motor/neural disorders such as diabetic neuropathy and scleroderma as well as structural lesions such as diverticula and surgical anastomoses.
2. The pathophysiology of stasis is largely due to anaerobic bacteria that deconjugate bile salts, deplete vitamin B12 and damage surface epithelium.
3. Stasis in the small bowel (regardless of the underlying etiology) may result in abnormal inflammatory changes in the mucosa (although some patients with malabsorption may have normal biopsy findings). As with most small bowel disorders, the histologic features are non-specific. There is generally mild to moderate villus blunting which may be accompanied by an increase in lamina propria mononuclear cells and focal neutrophilic infiltrates in the epithelium. At low-power these

changes may mimic partially developed or partially treated celiac disease. Stasis/bacterial overgrowth typically lacks the intense intraepithelial lymphocytosis of celiac disease. These findings may be focal/patchy. Since the appropriate clinical history is often lacking in these cases, one should think of this diagnosis whenever a small bowel looks “a little funny”.

#### REFERENCES (Scleroderma and Stasis (Blind-Loop) Syndrome):

1. Ament, M.E., Shimoda, S.S., Saunders, D.P. and Rubin, C.E. 1972. Pathogenesis of steatorrhea in three cases of small intestinal stasis syndrome. *Gastroenterology* 63:728.
2. Cave DR, Compton CC, et al. A 21-year-old man with progressive gastrointestinal stasis, hepatomegaly, and a neurologic disorder – familial visceral myopathy. *Case records of the Massachusetts General Hospital. New Engl J Med* 322:829-841, 1990.
3. Glanella, R.A., Rout, W.R., and Toskes, P.P. Jejunal brush border injury and impaired sugar and amino acid uptake in the blind-loop syndrome. *Gastroenterology* 67:965, 1974.
4. Goldstein, F. Mechanisms of malabsorption and malnutrition in the blind-loop syndrome. *Gastroenterology* 61:780, 1971.
5. Hendel L, Kobayashi T, Petri M.: Ultrastructure of the small intestinal mucosa in progressive systemic sclerosis (PSS). 95:41-46, 1987.
6. Krishnamurthy S, Schuffler, M.D.: Pathology of neuromuscular disorders of the small intestine and colon. *Gastroenterology* 93:610-639, 1987.
7. Schuffler M.D., Beegle R.G.: Progressive systemic sclerosis of the gastrointestinal tract and hereditary hollow visceral myopathy: Two distinguishable disorders of intestinal smooth muscle. *Gastroenterology* 77:664-671, 1979.

\*Much if not most of the information in this handout was originally compiled by John H. Yardley, M.D.

## Sprues Blues

Gather round people  
I'm talkin to you  
Tell you a story  
bout that evil  
bout that evil  
bout that evil  
sprue

ain't no mystery baby  
no it ain't  
just an allergy to  
wheat and grain  
too much bread and you'll  
feel the pain

Ouch

If you don't know what to do  
When you're diagnosing sprue  
Those plaintive lawyers will get you  
baby  
And leave you feeling blue

Activated T cells  
In your mucosa  
Your small bowel won't work  
like its supposed ta  
Those villi shrink when  
They're exposed ta

Gluten

If you don't know what to do  
When you're diagnosing sprue  
Be carefull in the bulb  
Where those peptic juices spew

Serum antibodies  
To TTG  
And a family  
History  
A flat gut biopsy  
You will see

Sprue

If you don't know what to do  
When you're diagnosing sprue  
Look for all those IELs  
So you won't get sued

Stop eating gluten and  
You will see a  
Marked improvement in  
Diarrhea  
Time to start livin  
carb free ah

Can you say Atkins?

If you don't know what to do  
When your diagnosing sprue  
Send your favorite GI pathologist  
A consult or two

That's the story  
Its all true  
Don't you forget  
Bout that evil  
Bout that evil  
Bout that evil  
Sprue

