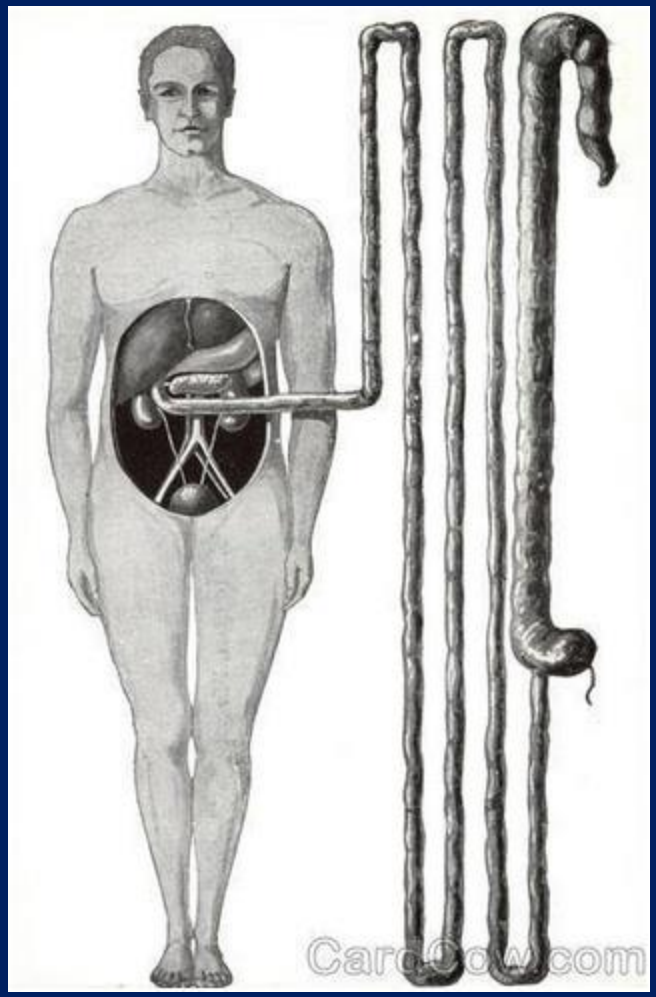
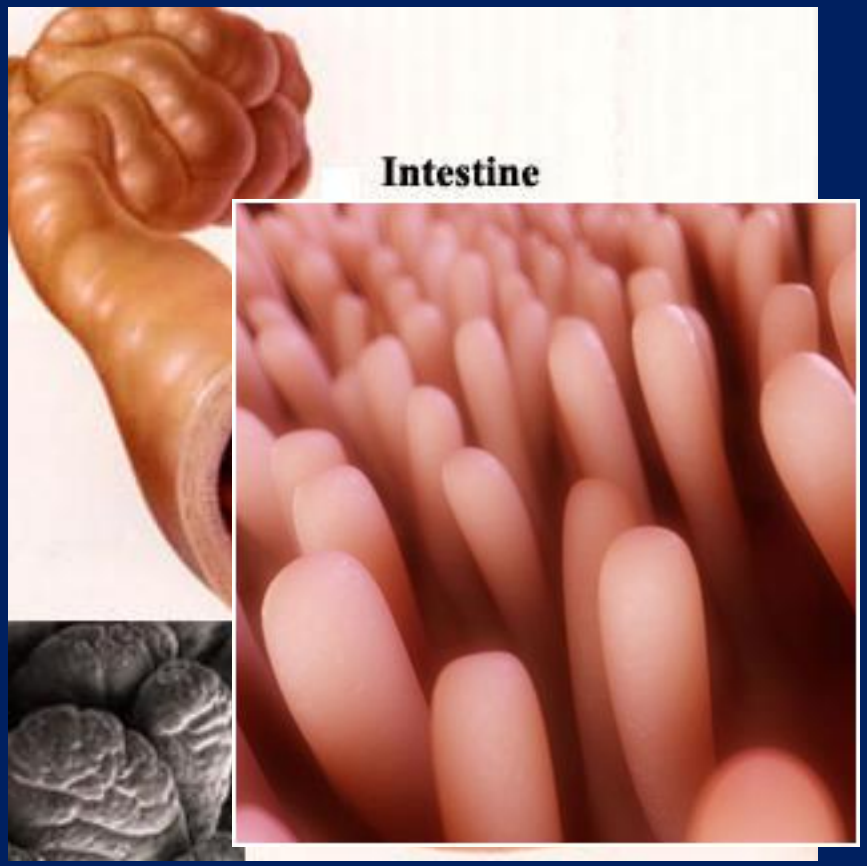
Malabsorption & Celiac Disease

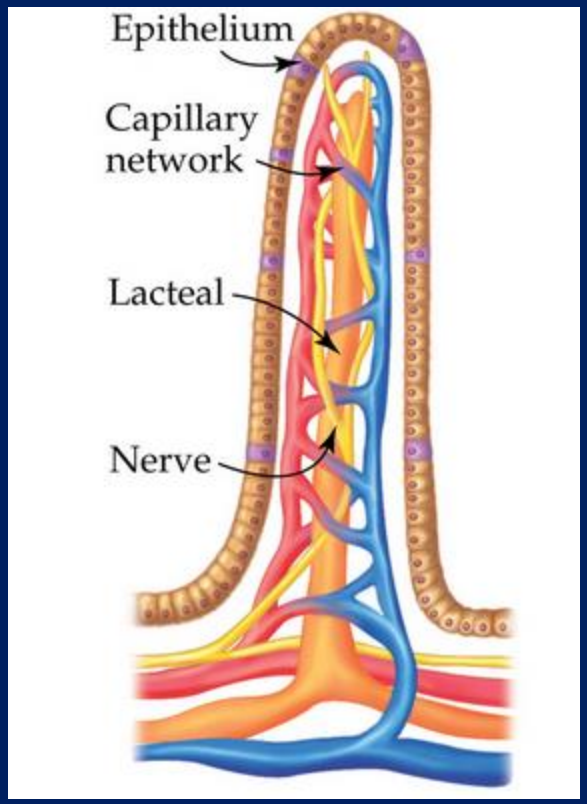
Absorptive Capability

Measured Small Intestine Length = 6 Meters



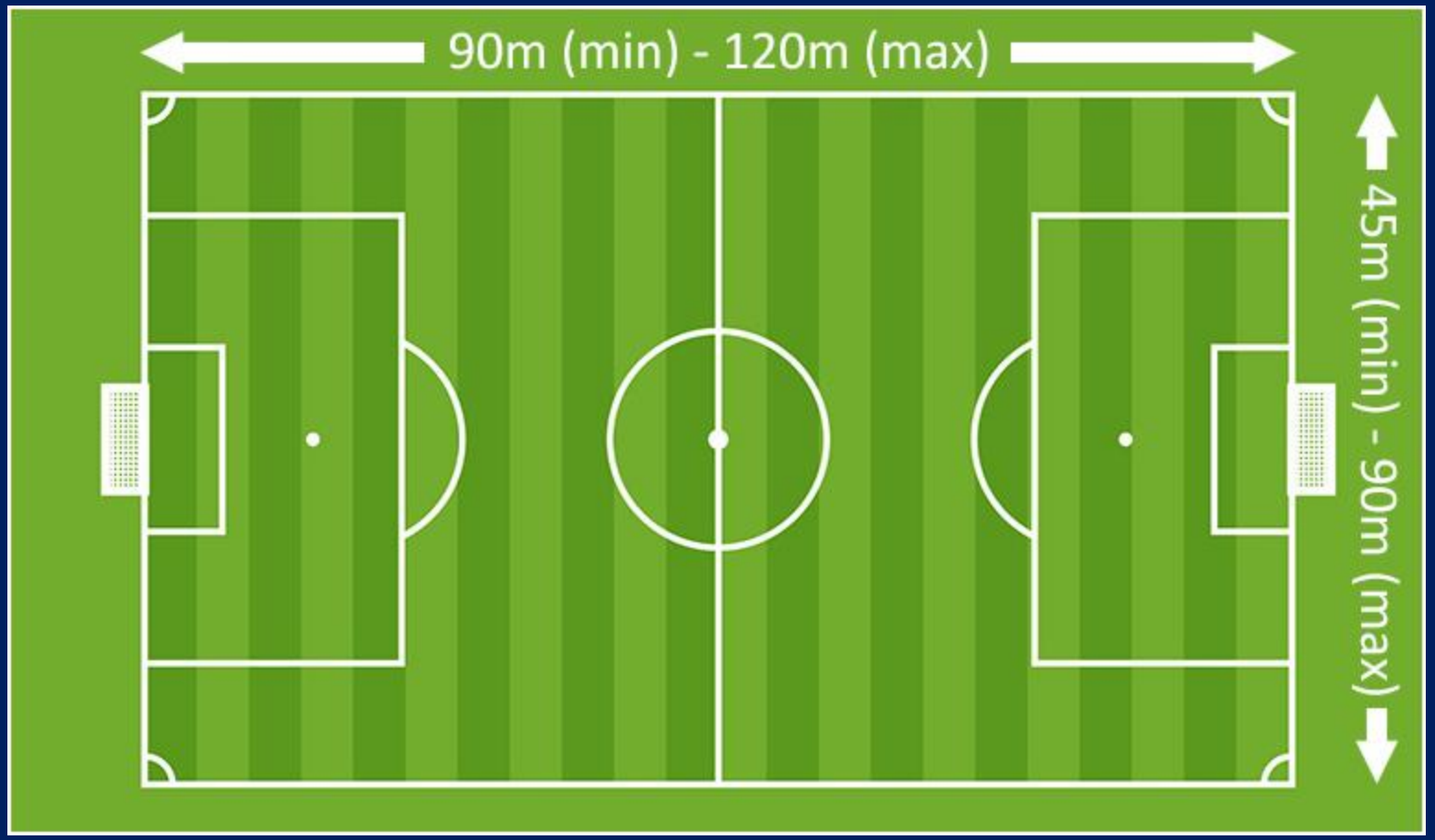
Absorptive Capability





Villi / Mico-Villi

Absorptive Capability



Standard Football Field

Pathophysiology

Malabsorption results from disturbance in at least one of the 3 phases of nutrients digestion & absorption:

1. ***Luminal phase (Defective digestion)***
2. ***Mucosal phase (Defective absorption)***
3. ***Post Absorptive phase (Deranged lymphatics)***

Maldigestion Vs Malabsorption

Maldigestion:

Impaired breakdown of nutrients (absorbable split-procarbohydrates, protein, fat) to ducts (mono-, di-, or oligosaccharides; amino acids; oligopeptides; fatty acids; monoglycerides)

Malabsorption:

Defective mucosal uptake and transport of adequately digested nutrients including vitamins and trace elements.

Malabsorption Syndrome

A clinical term that encompasses defects occurring during the digestion and absorption of food nutrients by the gastrointestinal tract.

Maldigestion Vs Malabsorption

Maldigestion

- Inadequate mixing of food with enzymes (e.g. post-gastrectomy)
- Pancreatic exocrine insufficiency
- Primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
- Bile salt deficiency:
  - Terminal ileal disease (impaired recycling),
  - Bacterial overgrowth (deconjugation of bile salts),
  - Liver disease (cholestatic)
- Specific enzyme deficiencies (e.g. lactase)

Malabsorption

- Inadequate absorptive surface
  - infections/infestations (e.g. Whipple's disease, Giardia)
  - immunologic or allergic injury (e.g. celiac disease)
  - infiltration (e.g. lymphoma, amyloidosis)
  - fibrosis (e.g. systemic sclerosis, radiation enteritis)
  - bowel resection
  - extensive Crohn's disease
- Drug-induced: cholestyramine, ETOH, neomycine
- Endocrine:
  - DM (complex pathogenesis)

Where to start from?!!

The best way to classify the numerous causes of malabsorption is to consider the 3 phases of digestion and absorption.

Maldigestion

Impaired Luminal phase

▼

Defect in the hydrolysis of nutrients

Luminal Phase
"digestion"

- **Pancreatic insufficiency**

  "The most common cause"

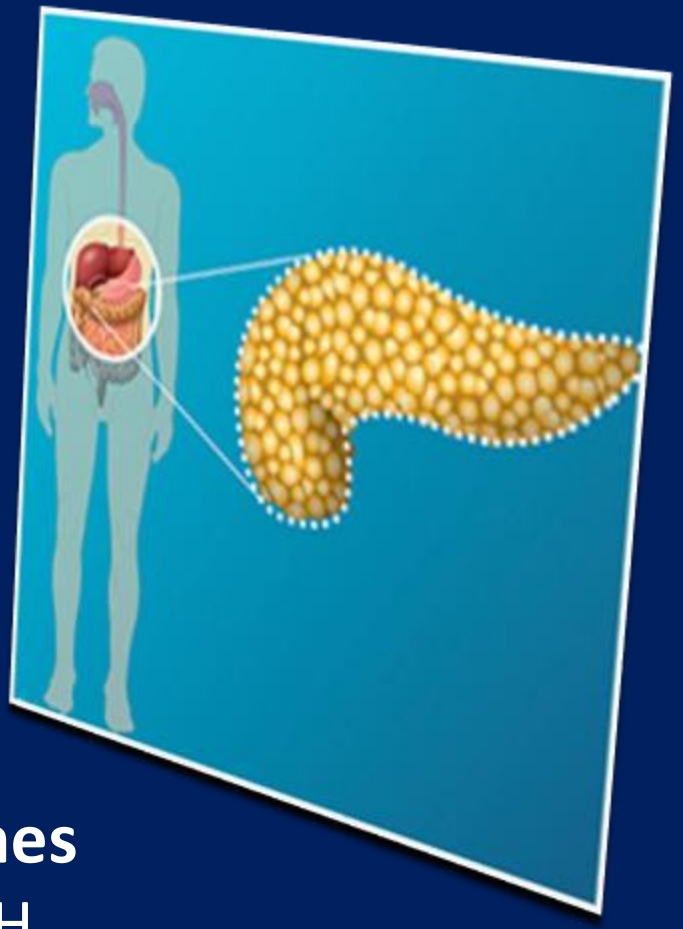
  •Ch Pancreatitis •CF •Post Sx (Gastric/Pancreatic)

  ▼

  ↓↓lipase & ↓↓proteases

  ▼

  lipid & protein malabsorption

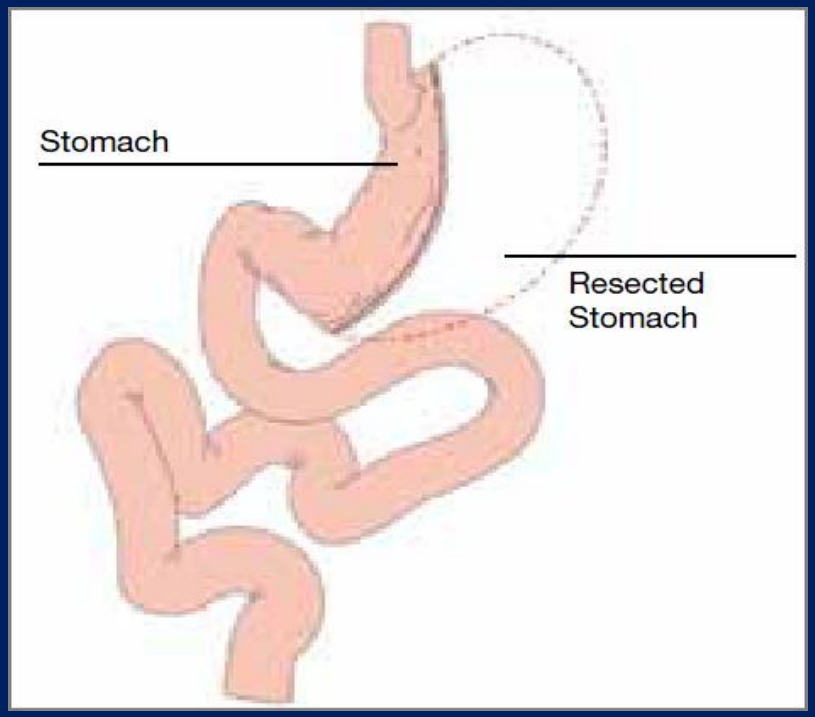


- **Inactivation of pancreatic enzymes**

  by gastric hypersecretion (ZE) → ↓pH

Luminal Phase
"digestion"

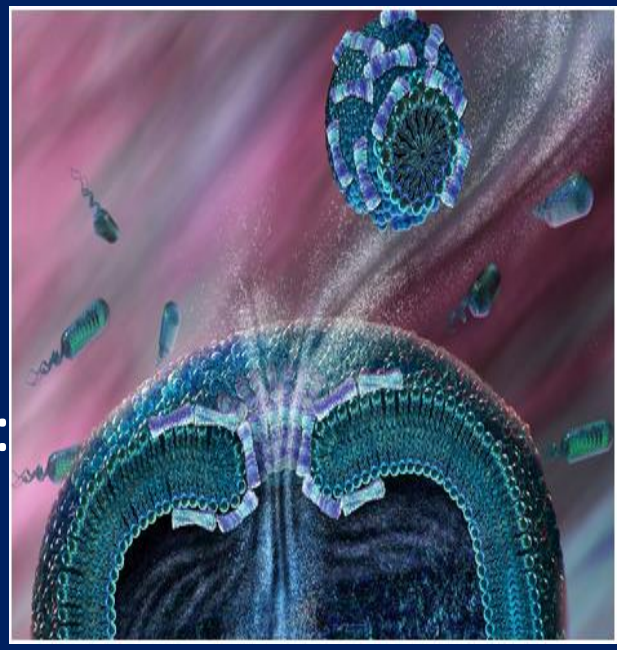
- **Post-Gastrectomy**
  Inadequate mixing of nutrients, bile, and pancreatic enzymes, also causes impaired hydrolysis.



Luminal Phase
"digestion"

- **Impaired Micelle formation**

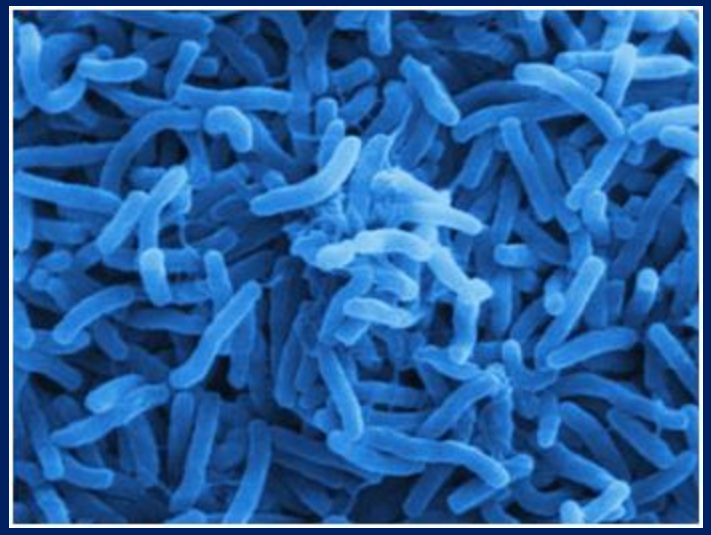
  Impaired micelle formation causes a problem in fat solubilization and subsequent fat malabsorption.



- **Decreased bile salt synthesis/secretion**:
  Liver diseases, Biliary obstruction, Drugs (cholestyramine)
- **Impaired enterohepatic bile circulation**
  Ileal resection/disease
- **Bile salt deconjugation**
  (SIBO)

Luminal Phase

"digestion"

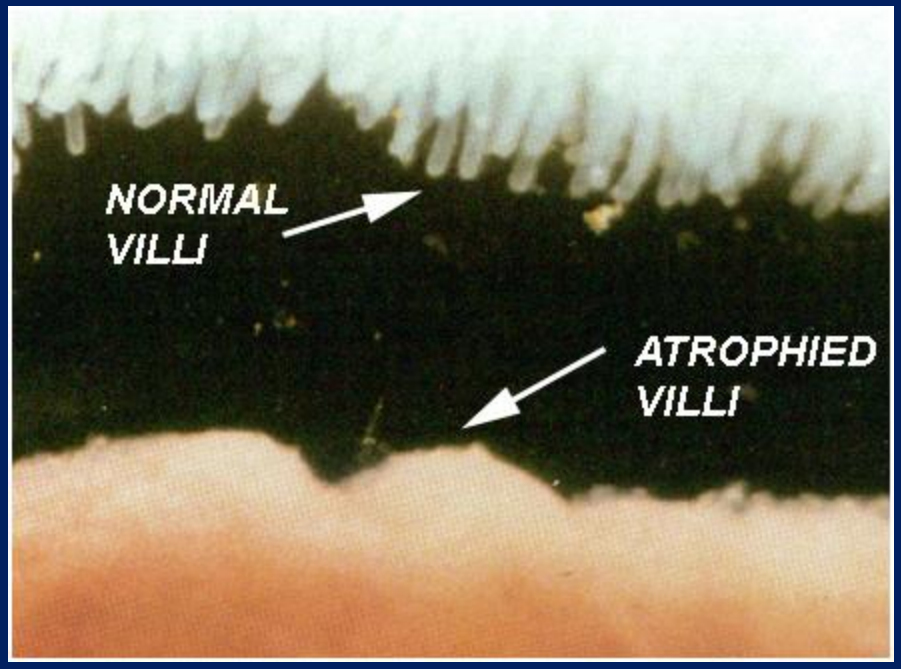


Bile Salts Deconjugation:

- Stasis of intestinal content caused by a motor abnormality (eg, scleroderma, diabetic neuropathy, intestinal obstruction),
- Anatomic abnormality (eg, small bowel stricture, ischemia, blind loops),
- Small bowel contamination from enterocolonic fistulas can cause bacterial overgrowth

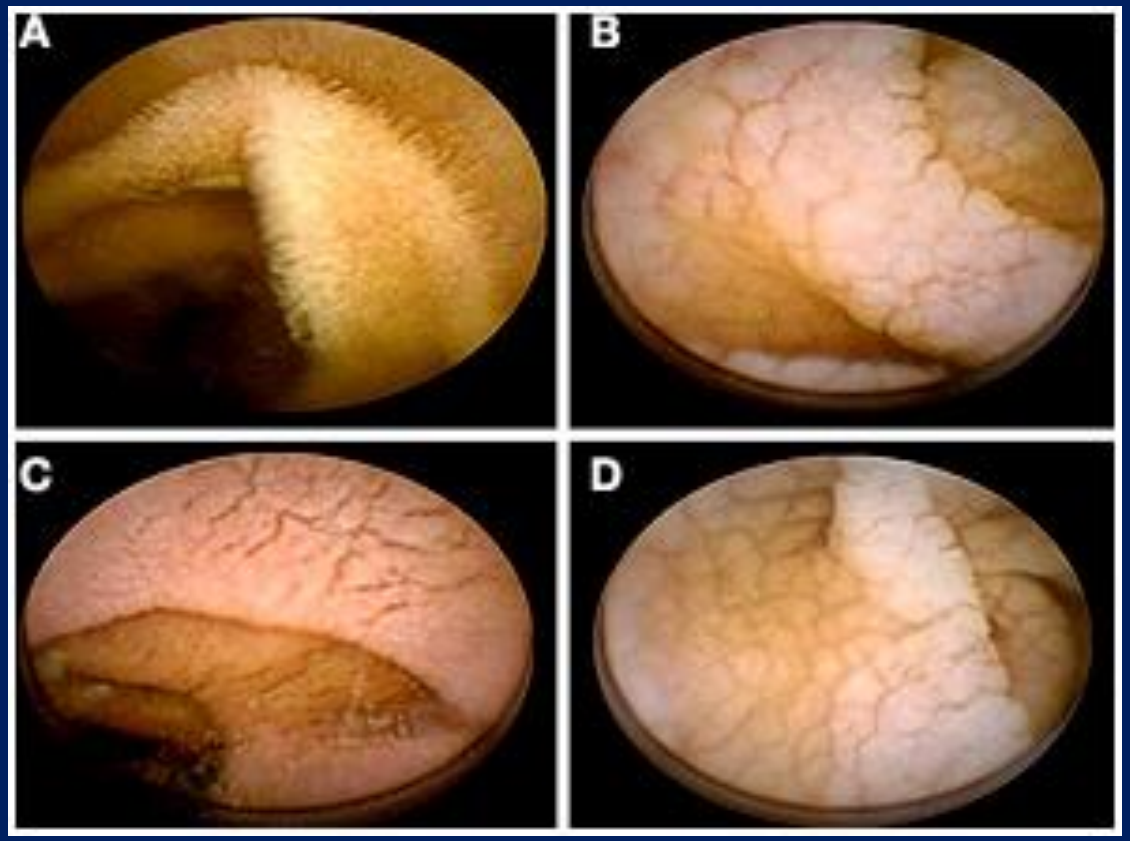
Mucosal phase

- Mucosal damage: (Villous Atrophy)



Mucosal phase

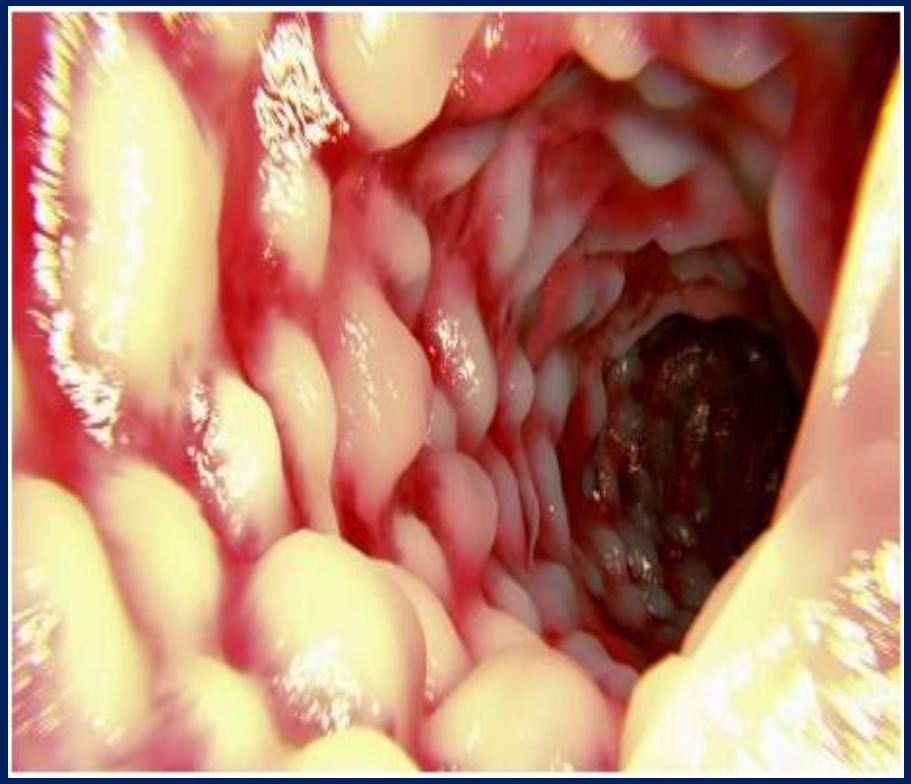
- Mucosal damage: (Villous Atrophy)

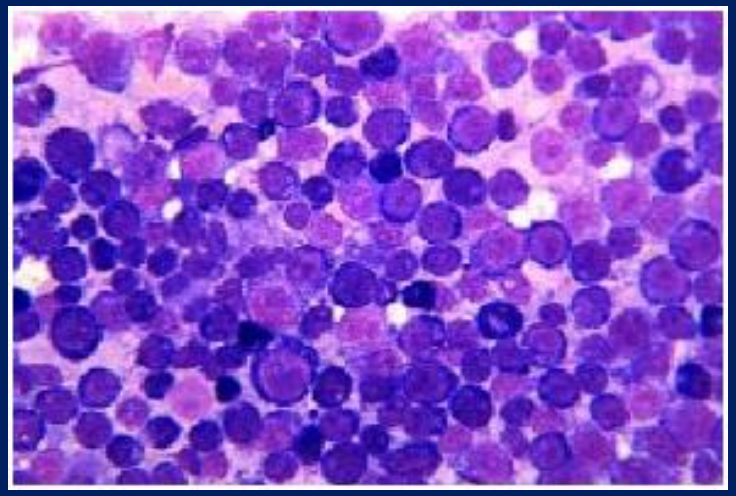


Celiac

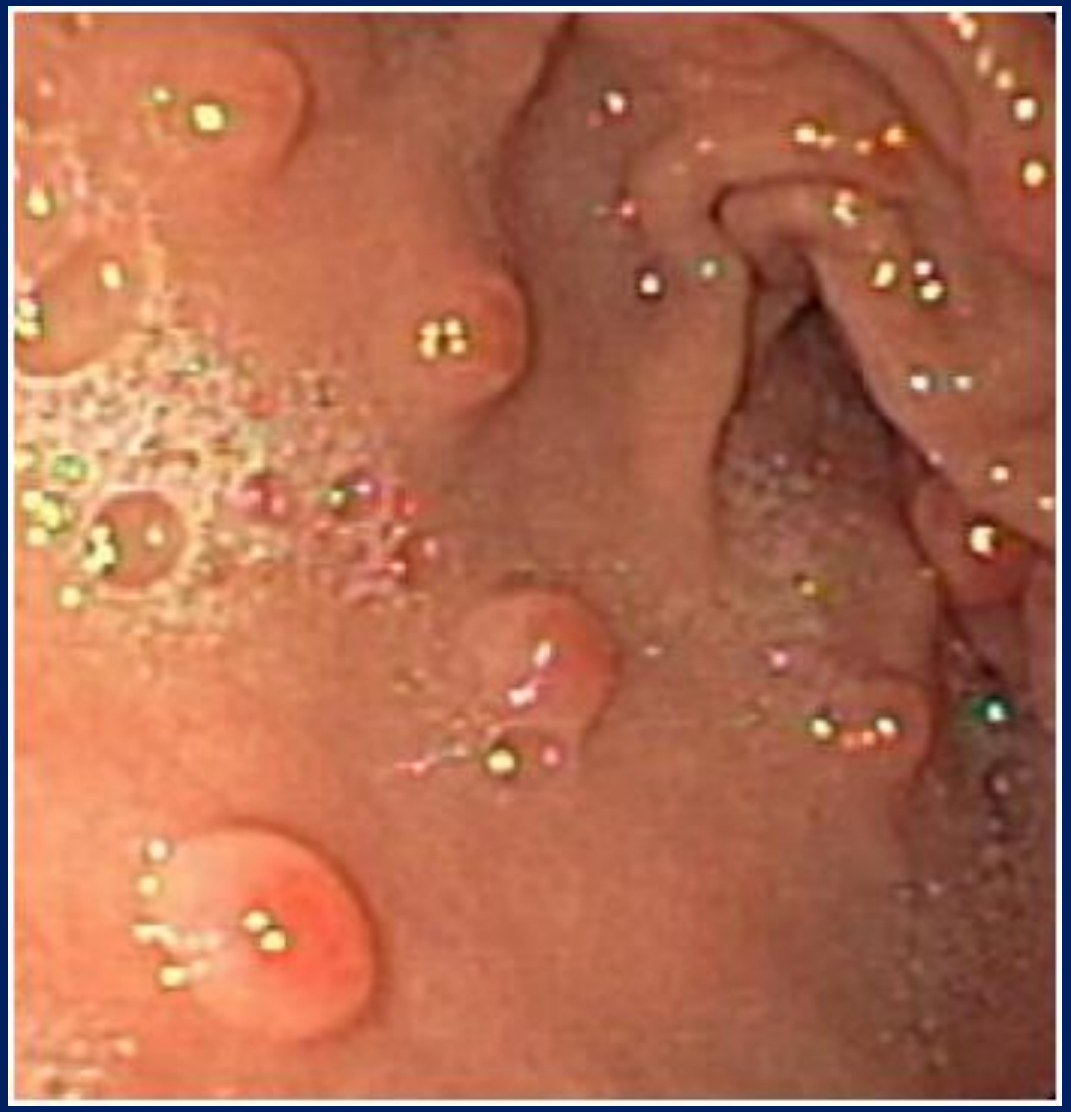
c

Intestinal Lymphoma

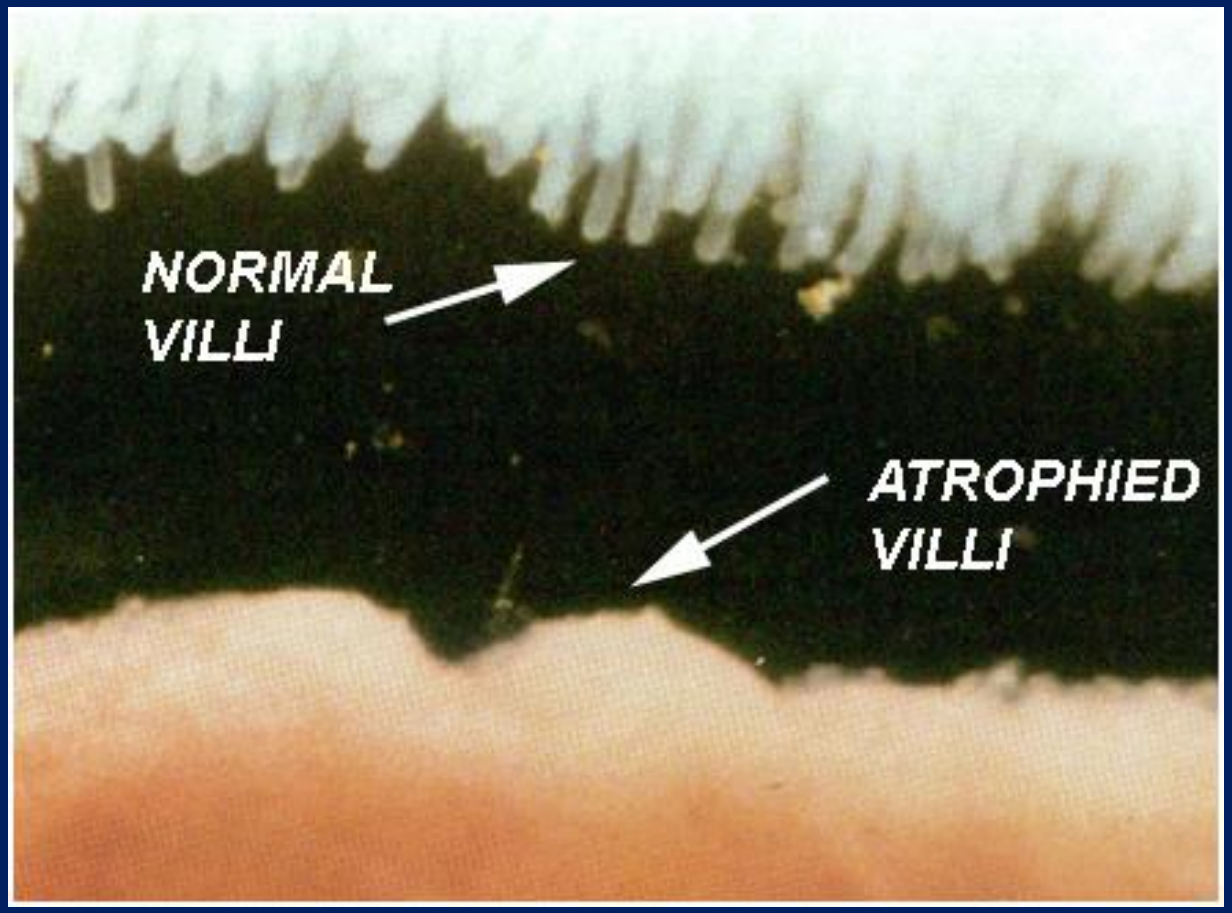




Crohn's

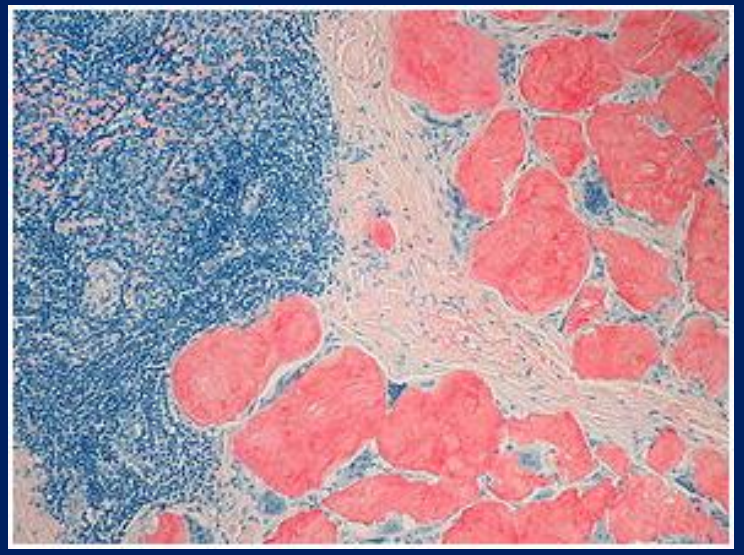


Eosinophilic enteritis

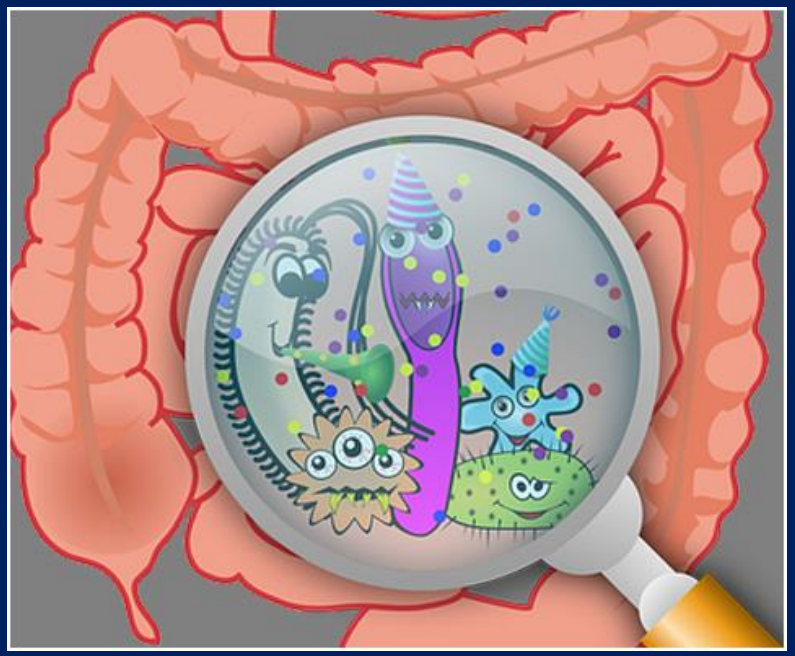

NORMAL
VILLI
ATROPHIED
VILLI

Common Variable ImmunoDeficiency

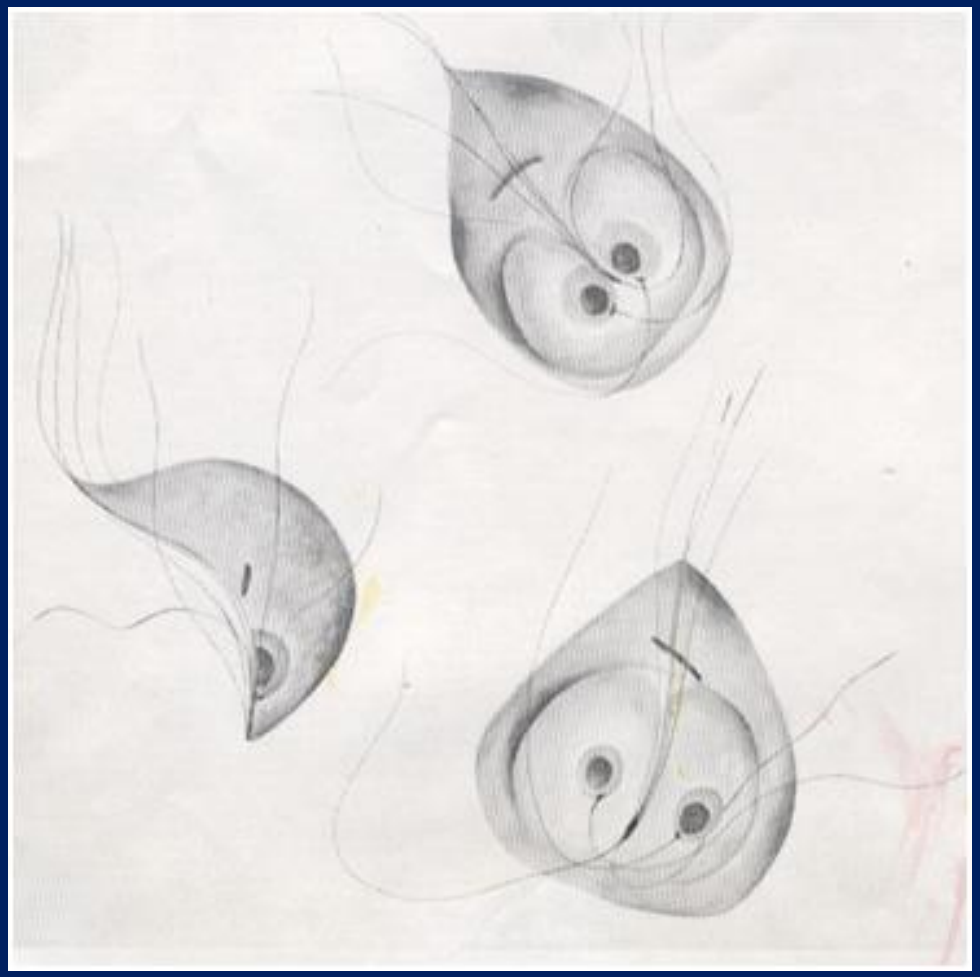
Amyloidosis



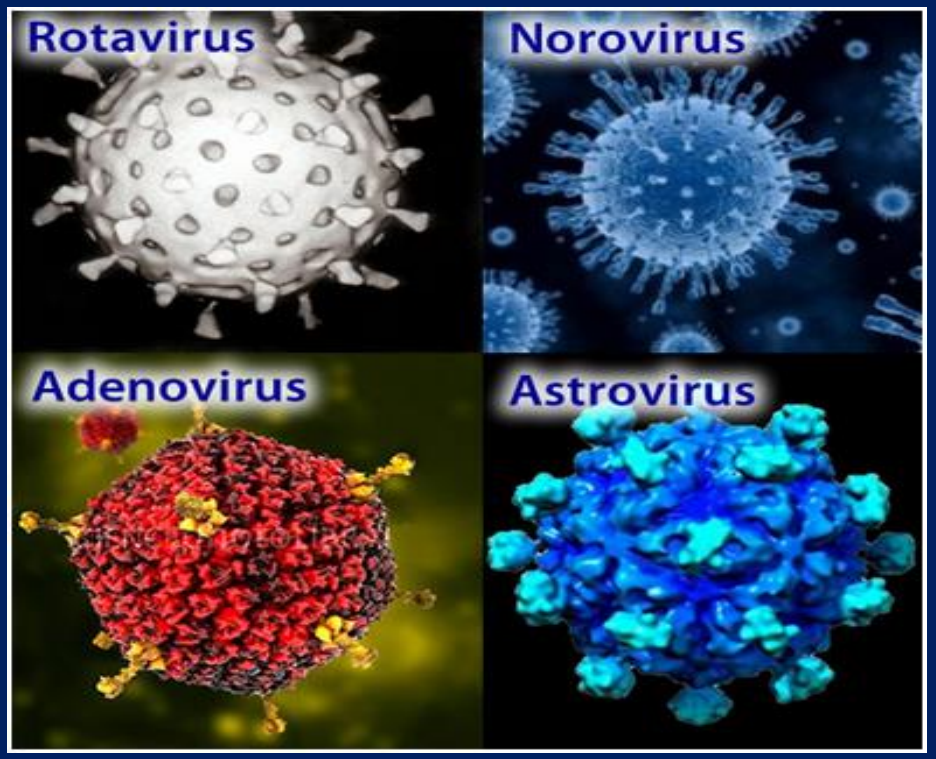
SIBO



Giardiasis



Viral GE



Post Absorptive Phase
"Lymphatics"

- Obstruction of the lymphatic system:

  -Congenital

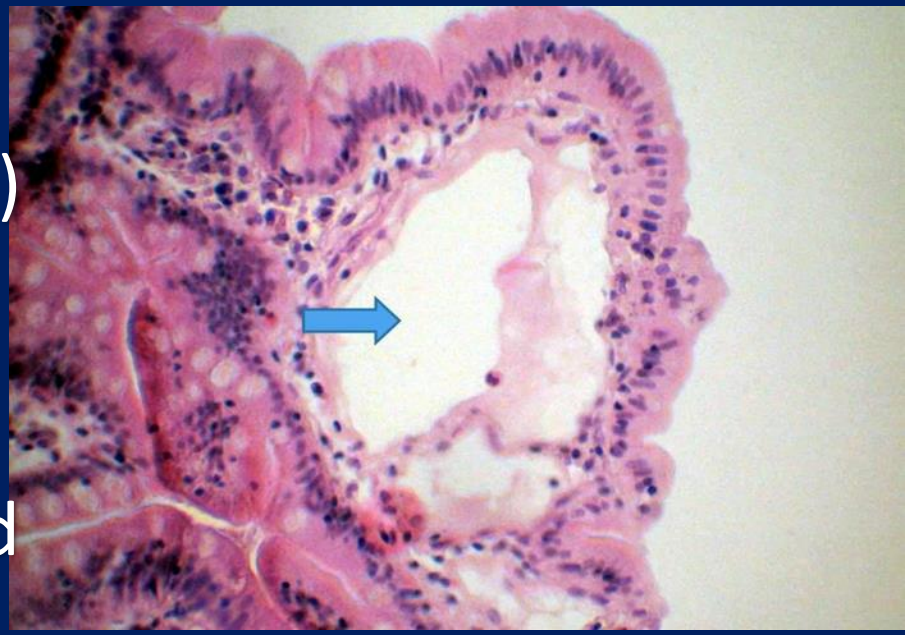
  (Intestinal Lymphangiectasia)

  -Acquired

  Whipple disease, neoplasm (lymphoma), TB, CHF, Constrictive Pericarditis, Rad Tx, Retroperitoneal Fibrosis

  ▼

  impairs the absorption of chylomicrons & lipoproteins



Pathophysiology of Clinical Manifestations of Malabsorption

Symptom or Sign	Mechanism
Weight loss/malnutrition	Anorexia, malabsorption of nutrients
Diarrhea	Impaired absorption or secretion of water and electrolytes; colonic fluid secretion secondary to unabsorbed dihydroxy bile acids and fatty acids
Flatus	Bacterial fermentation of unabsorbed carbohydrate
Glossitis, cheilosis, stomatitis	Deficiency of iron, vitamin B12, folate, and vitamin A
Abdominal pain	Bowel distention or inflammation, pancreatitis
Bone pain	Calcium, vitamin D malabsorption, protein deficiency, osteoporosis
Tetany, paresthesia	Calcium and magnesium malabsorption
Weakness	Anemia, electrolyte depletion (particularly K^+)
Azotemia, hypotension	Fluid and electrolyte depletion
Amenorrhea, decreased libido	Protein depletion, decreased calories, secondary hypopituitarism
Anemia	Impaired absorption of iron, folate, vitamin B12
Bleeding	Vitamin K malabsorption, hypoprothrombinemia
Night blindness/xerophthalmia	Vitamin A malabsorption
Peripheral neuropathy	Vitamin B12 and thiamine deficiency

Diarrhea

- Diarrhea is the most common symptomatic complaint
- Diarrhea is defined as an increase in stool mass, frequency, or fluidity, typically greater than 200 g per day.

Steatorrhea

- Steatorrhea is the result of fat malabsorption.
- The hallmark of steatorrhea is the passage of pale, bulky, and malodorous stools.
- Such stools often float on top of the toilet water and are difficult to flush. Also, patients find floating oil droplets in the toilet following defecation.

Weight loss & fatigue

- Weight loss is common and may be pronounced; however, patients may compensate by increasing their caloric consumption, masking weight loss from malabsorption.

- The chance of weight loss increases in diffuse diseases involving the intestine, such as celiac disease and Whipple disease.

Flatulence & abdominal distention

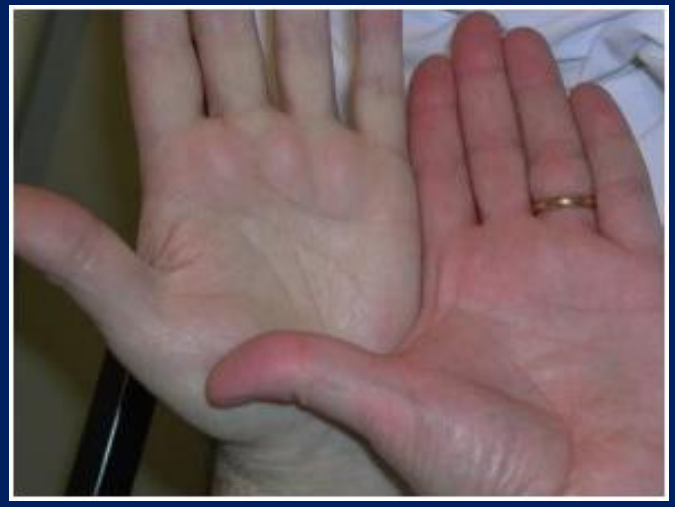
Bacterial fermentation of unabsorbed food substances releases gaseous products, such as hydrogen and methane, causing flatulence.

Flatulence often causes uncomfortable abdominal distention and cramps.

Edema

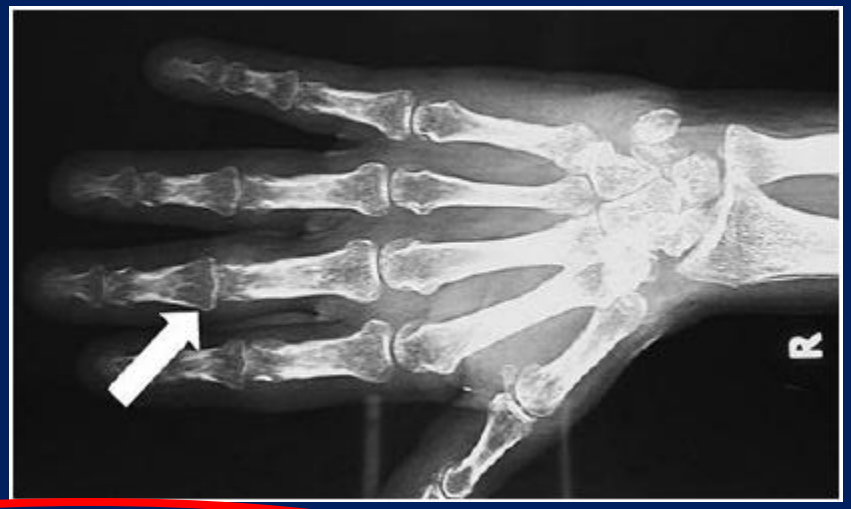
- Hypoalbuminemia from chronic protein malabsorption or from loss of protein into the intestinal lumen causes peripheral edema.
- Extensive obstruction of the lymphatic system, as seen in intestinal lymphangiectasia, can cause protein loss.
- With severe protein depletion, ascites may develop.

Anemia



- Depending on the cause, anemia resulting from malabsorption can be either microcytic (iron deficiency) or macrocytic (vitamin B-12 deficiency).
- Iron deficiency anemia often is a manifestation of celiac disease.
- Ileal involvement in Crohn disease or ileal resection can cause megaloblastic anemia due to vitamin B-12 deficiency.

Metabolic defects of bones



- Vitamin D deficiency can cause bone disorders, such as osteopenia or osteomalacia.
- Bone pain and pathologic fractures may be observed.
- Malabsorption of calcium can lead to secondary hyperparathyroidism.


Celiac Disease

Pathophysiology

Celiac disease

is …

an immune disorder,

that is …

triggered by an environmental agent (gliadin component of gluten),

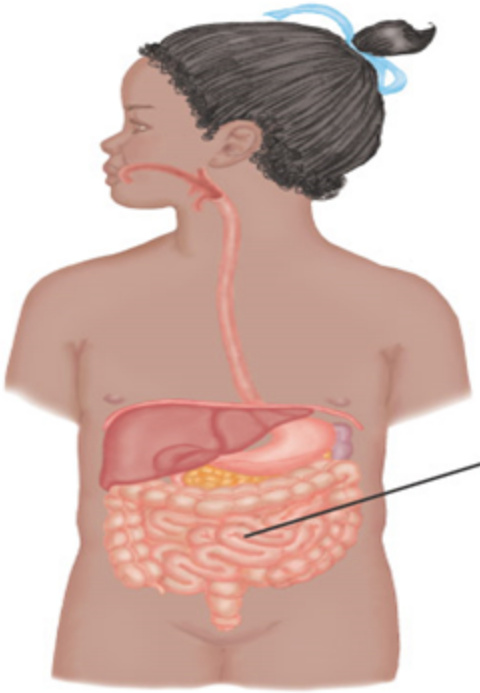
in …

genetically predisposed individuals.

Grain protein exists in four forms:

- Prolamins
- Glutenins
- Globulins
- Minor albumins

} Glutens



Gluten:
protein in wheat, rye,
oats, and barley

↓

Breaks down into gliadin
in small intestine

↓

Celiac disease:
inability to digest gliadin

↓

Accumulation of glutamine;
toxic effect on mucosal cells

↓

Atrophy of villi

↓

Malabsorption

↓

Fat, calorie, carbohydrate,
and vitamin deficiencies

Celiac crisis

↓

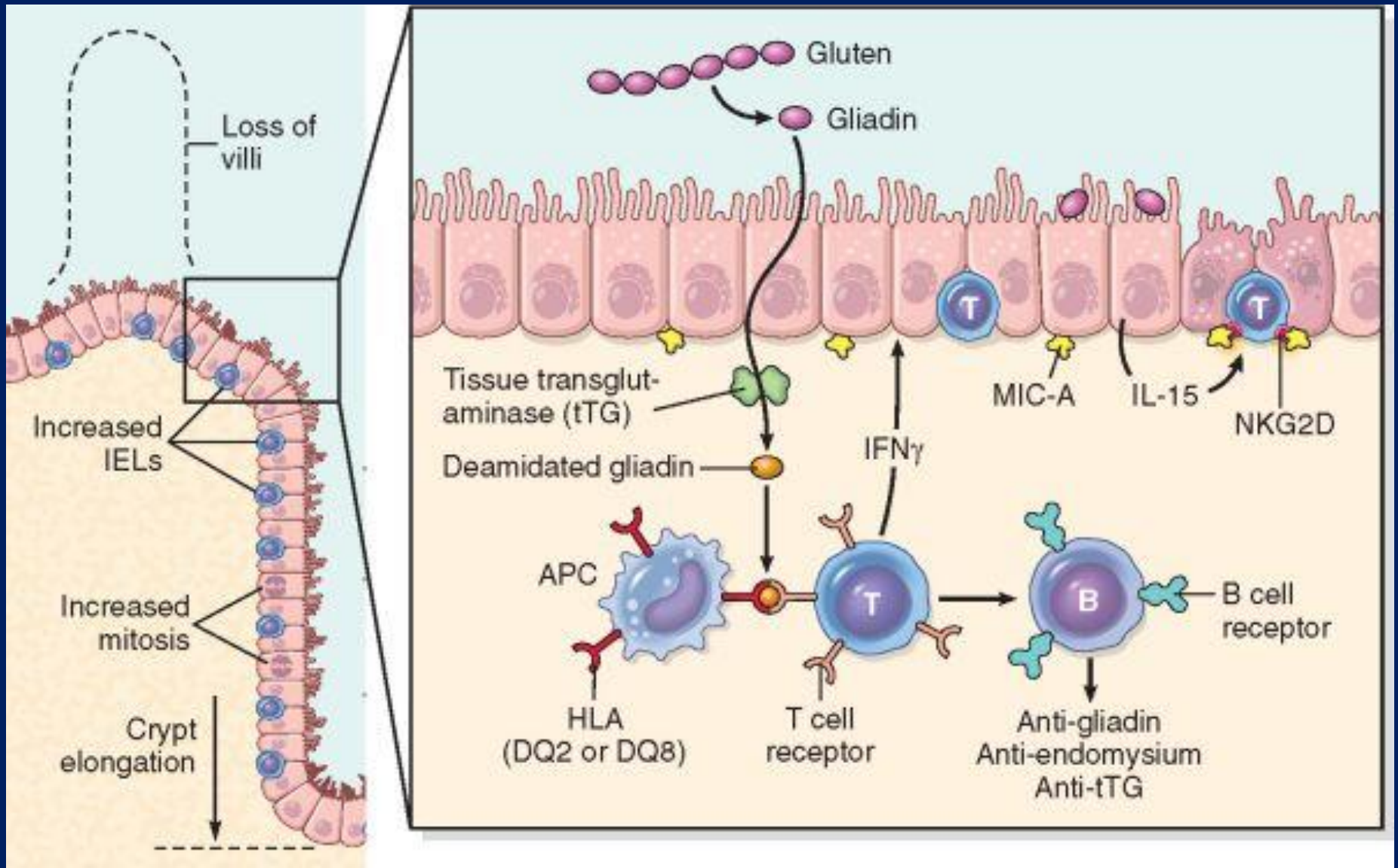
Severe dehydration
and diarrhea

Pathophysiology

- Similarities between gliadin proteins and certain enteral pathogens may result in the immunologic response to antigens in gluten.

- Gliadin-sensitive T cells in genetically predisposed individuals recognize gluten-derived peptide epitopes and develop an inflammatory response which produces mucosal damage

Pathogenesis of Celiac Disease



- Genetic factors play an important role- there is significantly increased risk of celiac among family members
- A close association with the HLA-DQ2 and/or DQ8 gene locus has been recognized
- HLA-DQ2 is found in 98 percent of celiac patients from Northern Europe.
- However, ~25% of “normal” individuals in this population will also demonstrate HLA-DQ2

Risk Factors for Celiac Disease

People suffering from other immune diseases and certain genetic disorders are more likely to have celiac disease. Some disorders associated with celiac include:

- Rheumatoid arthritis
- Type 1 diabetes
- Thyroid disease
- Autoimmune liver disease
- Addison's disease
- Sjogren's disease
- Lupus
- Down syndrome
- Turner syndrome
- Lactose intolerance
- Intestinal lymphoma

Malignant diseases are more frequent in patients with long-term untreated classical CD.

Small-bowel adenocarcinoma, esophageal and oropharyngeal squamous-cell carcinoma, and non-Hodgkin's lymphoma occur more often in CD patients than in healthy control individuals.

Diagnosis of Celiac: Serologic Testing

- Some of the serologic tests used to diagnose celiac:
- IgA and IgG antigliadin antibodies
- IgA endomysial antibodies
- IgA and IgG tissue transglutaminase antibodies
- Anti reticulin antibodies (no longer used)

Histopathology:

The only definitive test is small intestinal biopsy taken endoscopically (the proximal duodenum is maximally affected).

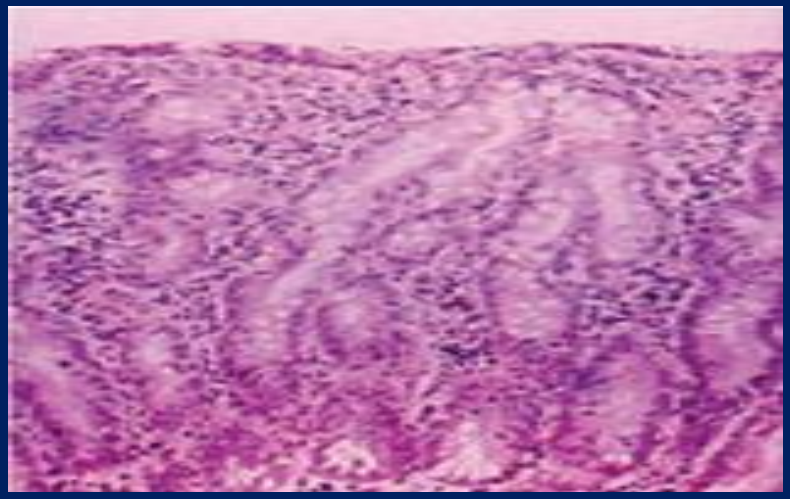
It shows *subtotal or total villous atrophy* with *Intraepithelial Lymphocytic infiltration*.

Genetic Testing:

HLA-DQ2 and HLA-DQ8 markers in >90% CD patients

Normal

Pathology



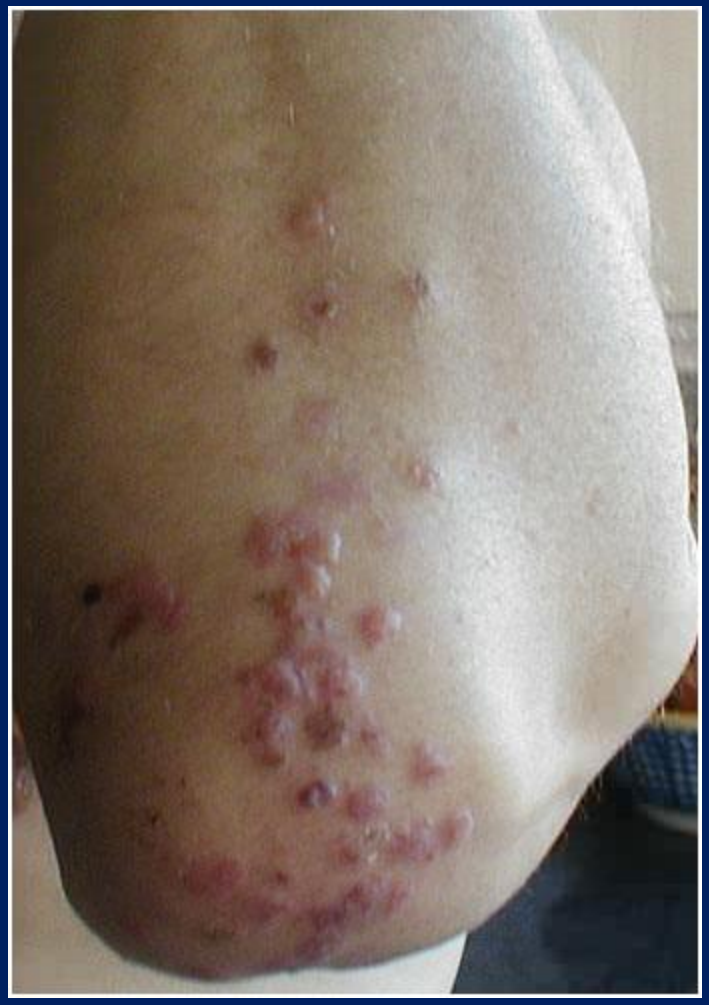
Symptoms & Signs

Intestinal (Classic)

Ch Diarrhea (can be steatorrhea/osmotic/ or watery), edema, Flatulence, distention, ↓wt, ↓appetite, Abd pain, N&V, Constipation, Aphthous stomatitis, Angular cheilosis

Extra Intestinal

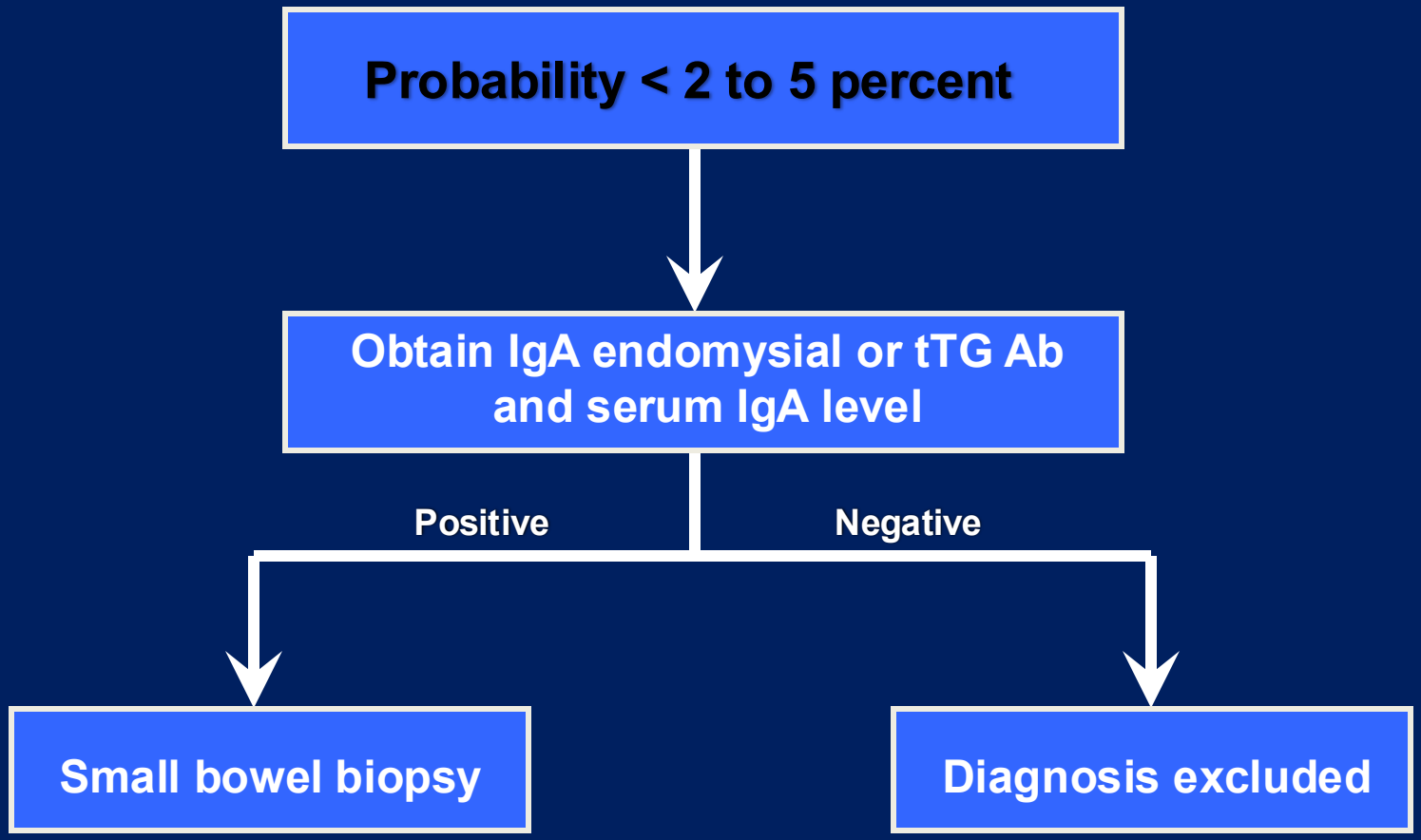
-Abnormal LFTs
-Dermatitis Herpetiformis
-Hypo-Splenism (Splenic)
-Osteopenia/OP/Enamel defects, Arthropathy (Non-erosive, polyarticular, symmetrical, large joint) (Non-Migratory)
-Peripheral neuropathy (Symmetrical & distal), Ataxia (Cerebellar), Epilepsy (Bilat parieto-occipital calcifications), Depression/anxiety
-Infertility (M & F)

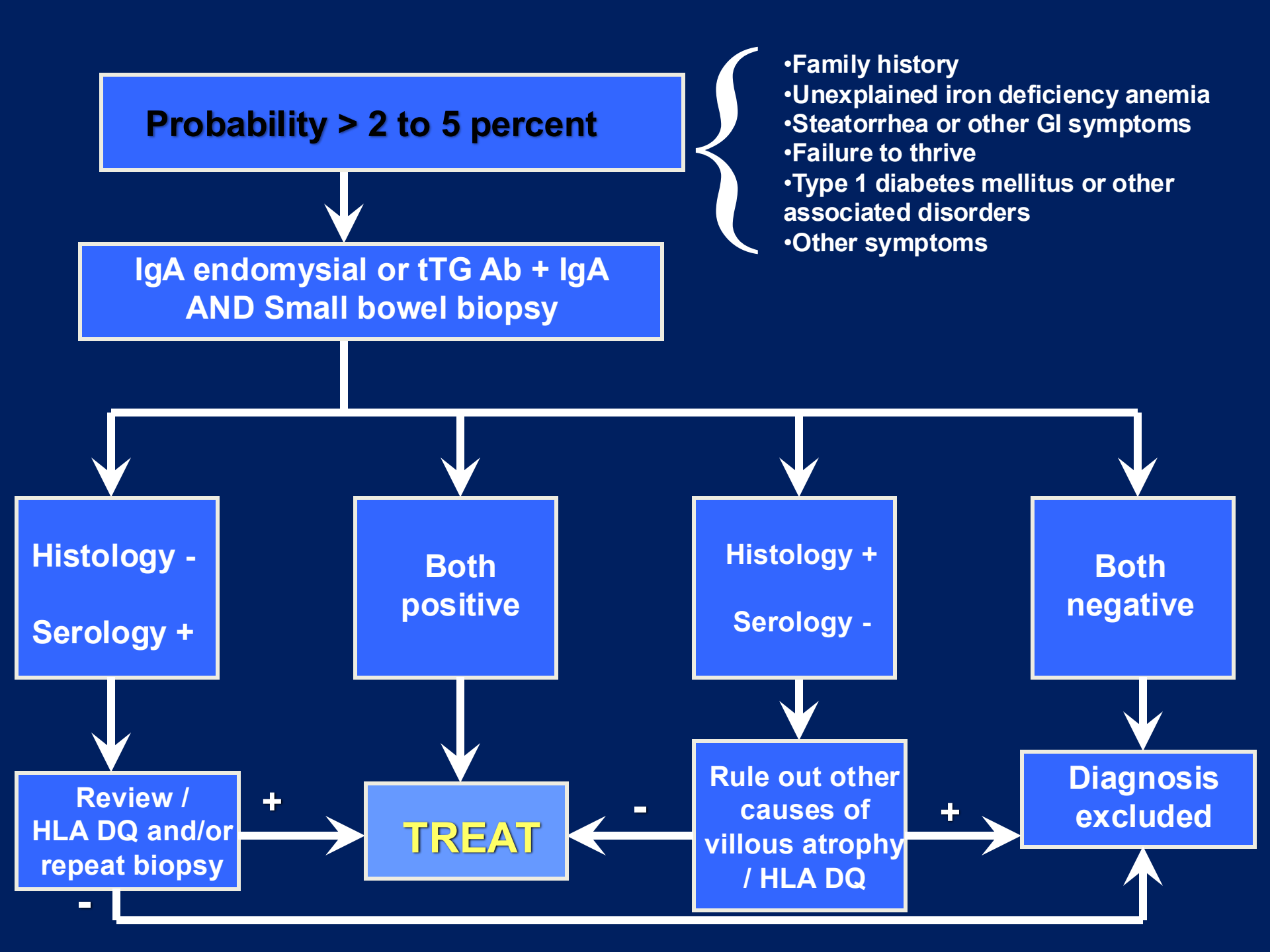


Diagnosis: Gluten Rechallenge

- Gluten Rechallenge- improvement in symptoms and histology with gluten avoidance with a documented return of these features upon gluten reintroduction.
- May be performed by consuming 10 g of gluten per day (an amount contained in four slices of regular bread) for four to six weeks.
- One hazard of rechallenge is development of fulminant diarrhea, with dehydration, acidosis, and other metabolic disturbances ("gliadin shock").

Diagnosis of Celiac Disease




Probability > 2 to 5 percent
•Family history
•Unexplained iron deficiency anemia
•Steatorrhea or other GI symptoms
•Failure to thrive
•Type 1 diabetes mellitus or other associated disorders
•Other symptoms
IgA endomysial or tTG Ab + IgA AND Small bowel biopsy
Histology -
Serology +
Both positive
Histology +
Serology -
Both negative
Review / HLA DQ and/or repeat biopsy
+
TREAT
-
Rule out other causes of villous atrophy / HLA DQ
+
Diagnosis excluded
-