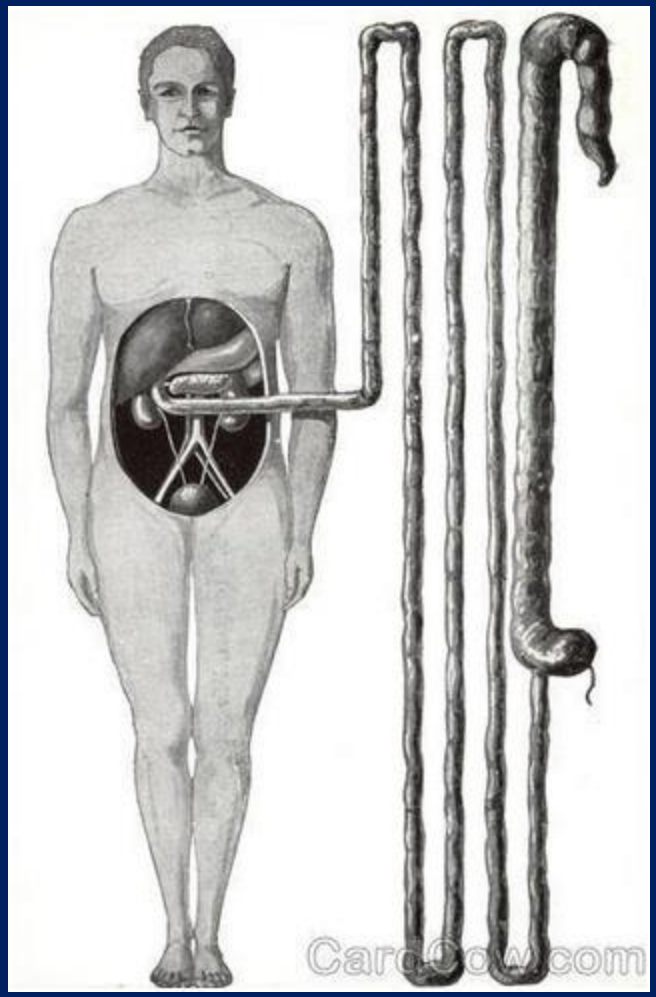
Malabsorption & Celiac Disease

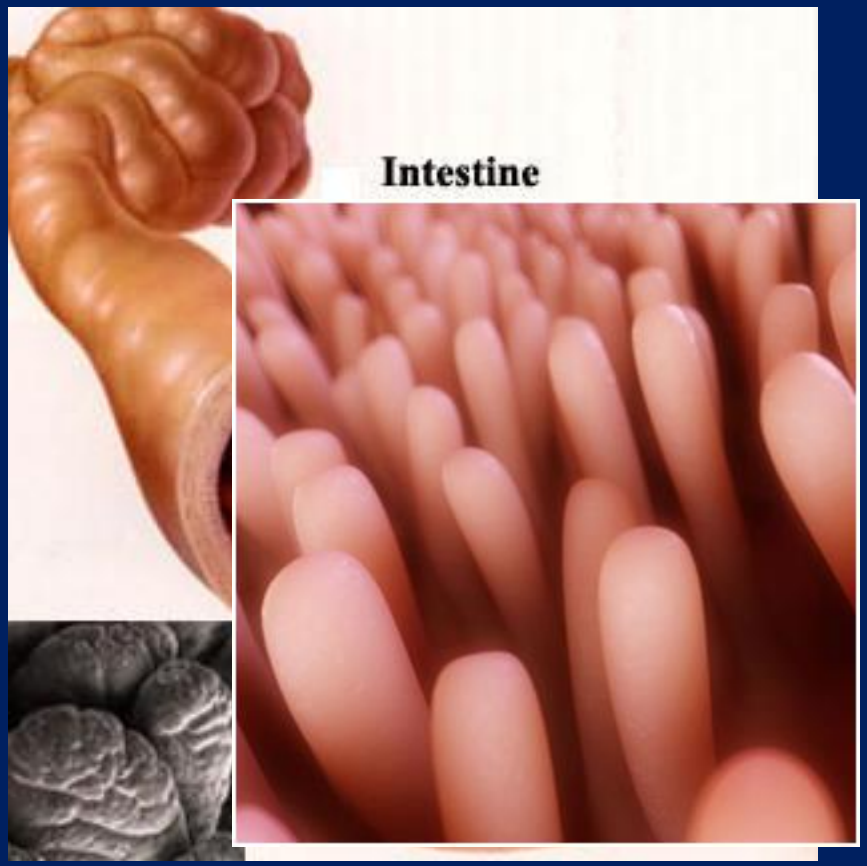
Eyad Swaity, MD
American Board, MRCP GI
Consultant Gastroenterology & Hepatology
Division of Gastroenterology - Jordan University Hospital

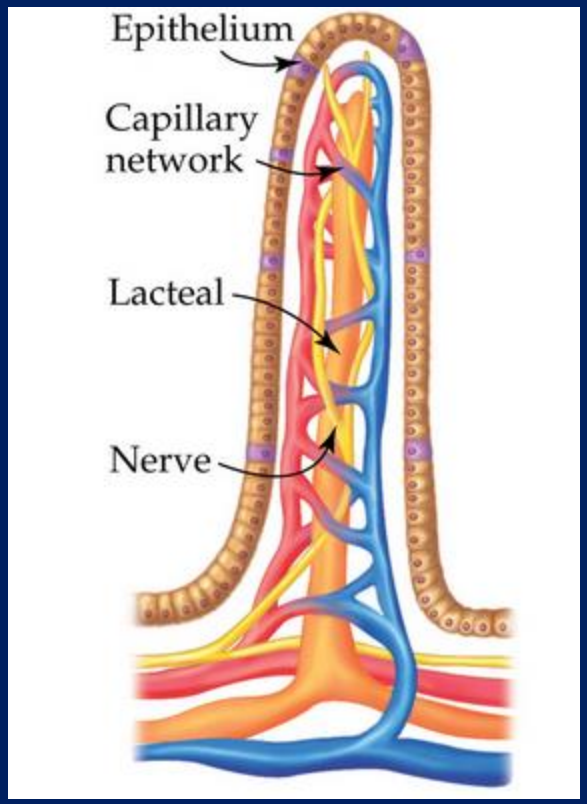
Absorptive Capability

Measured Small Intestine Length = 6 Meters



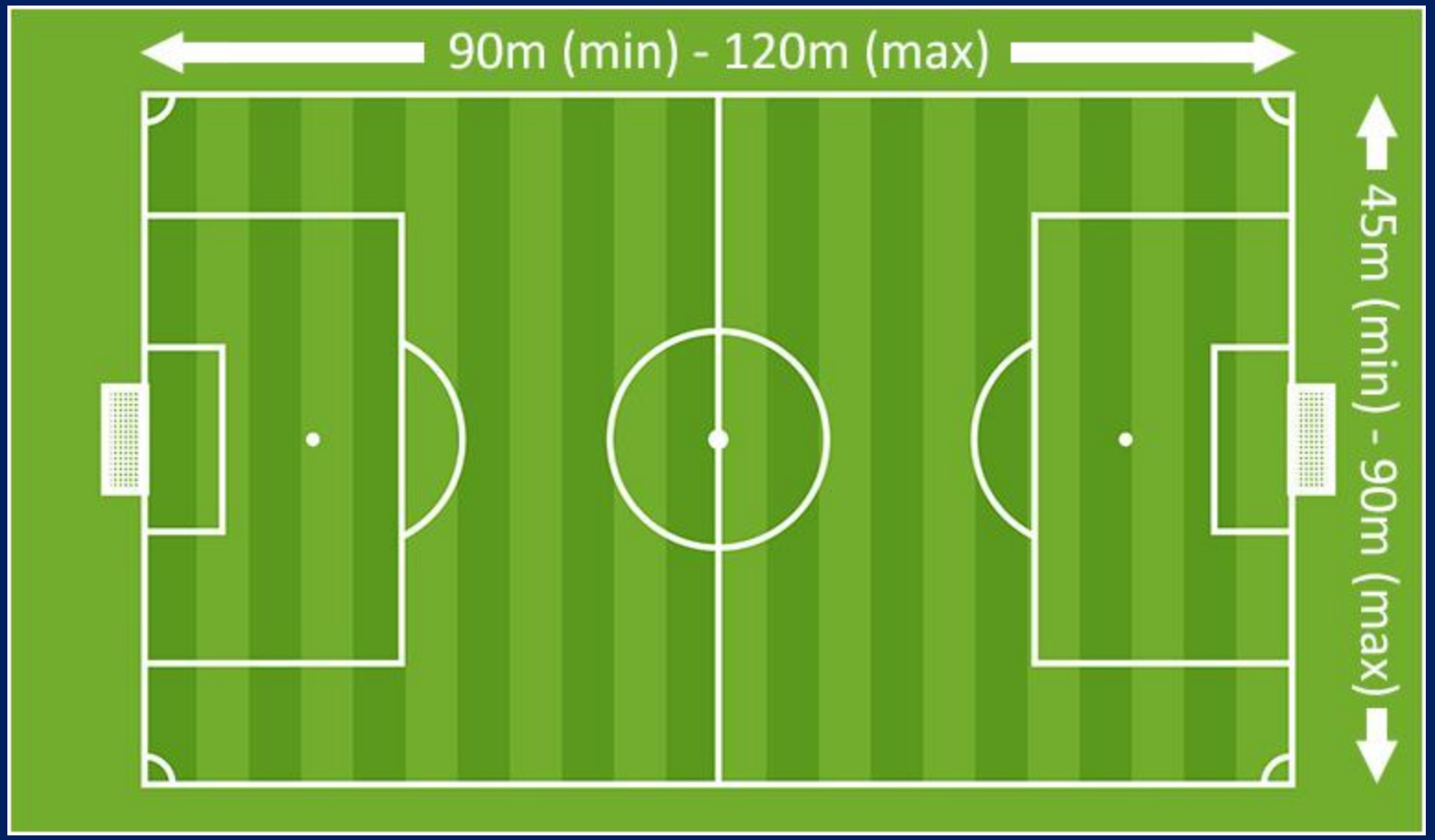
Absorptive Capability





Villi / Mico-Villi

Absorptive Capability



Standard Football Field

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.

The digestion or absorption of a single nutrient component may be impaired, as in lactose intolerance due to lactase deficiency.

However, when a diffuse disorder, such as Celiac disease or Crohn's disease, affects the intestine, the absorption of almost all nutrients is impaired.

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)

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)***

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"

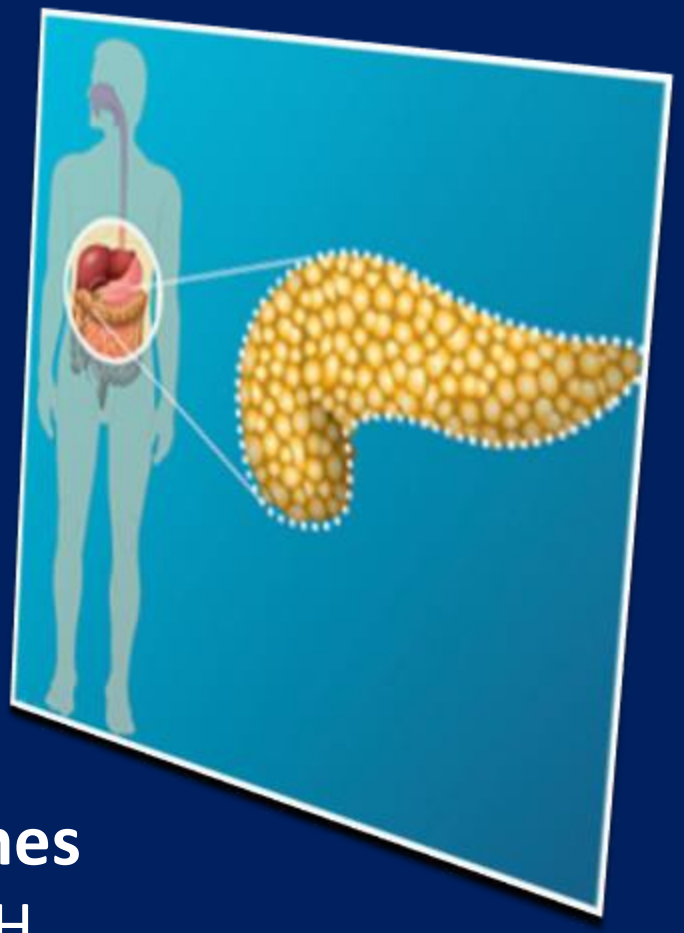
  •Ch Pancreatitis •CF •Post Sx (Gastric/Pancreatic)

  ▼

  ↓↓lipase & ↓↓proteases

  ▼

  lipid & protein malabsorption

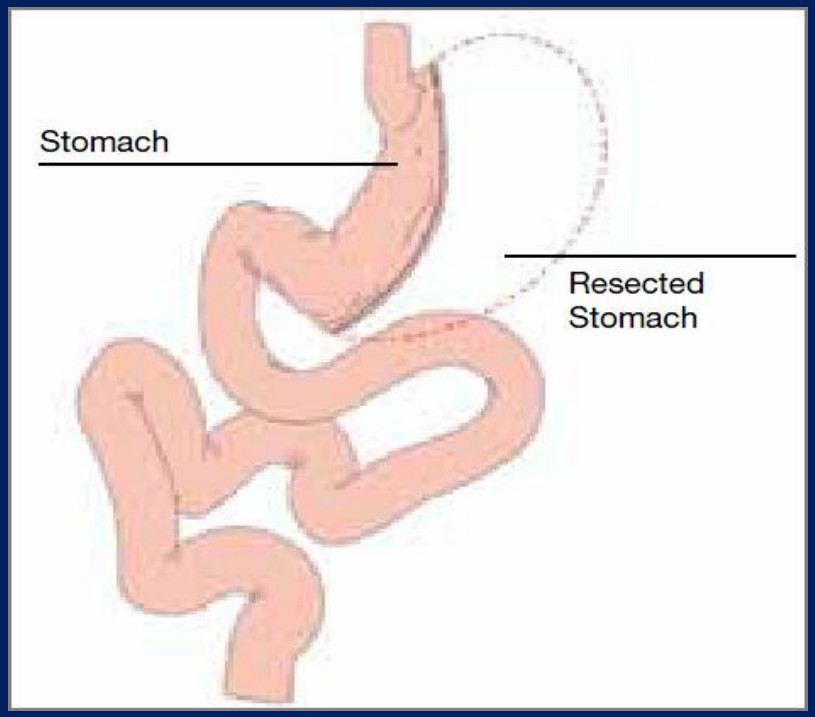


- **Inactivation of pancreatic enzymes**

  by gastric hypersecretion (ZE) → ↓pH

Luminal Phase
"digestion"

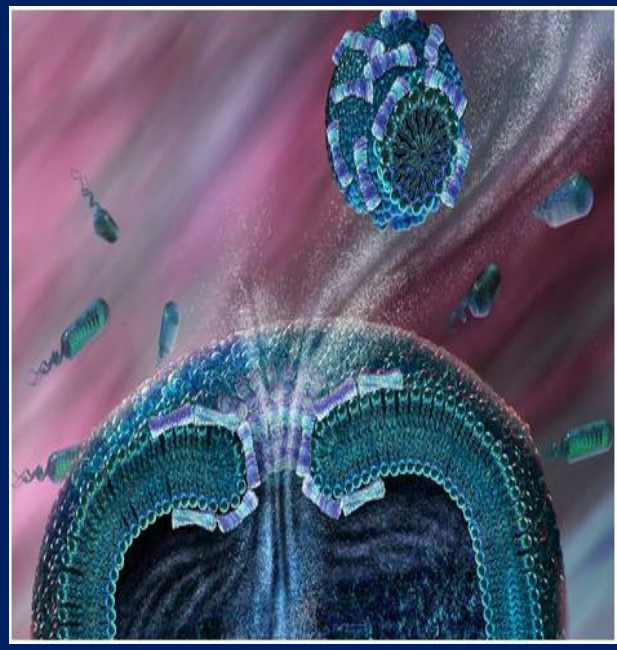
- **Post-Gastrectomy**
  Inadequate mixing of nutrients, bile, and pancreatic enzymes, also causes impaired hydrolysis.



Luminal Phase
"digestion"

- **Impaired Micelle formation**

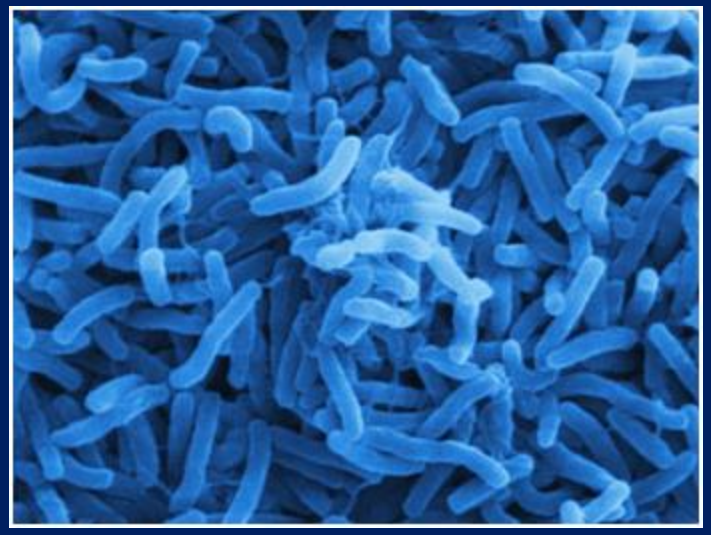
  Impaired micelle formation causes a problem in fat solubilization and subsequent fat malabsorption.



- **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"

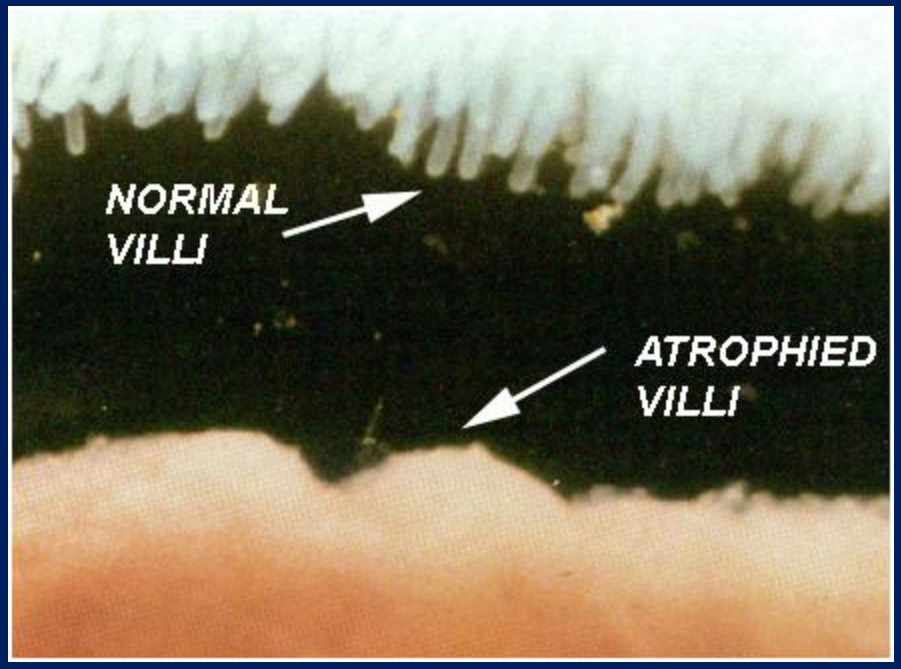


Bile Salts Deconjugation:

- 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

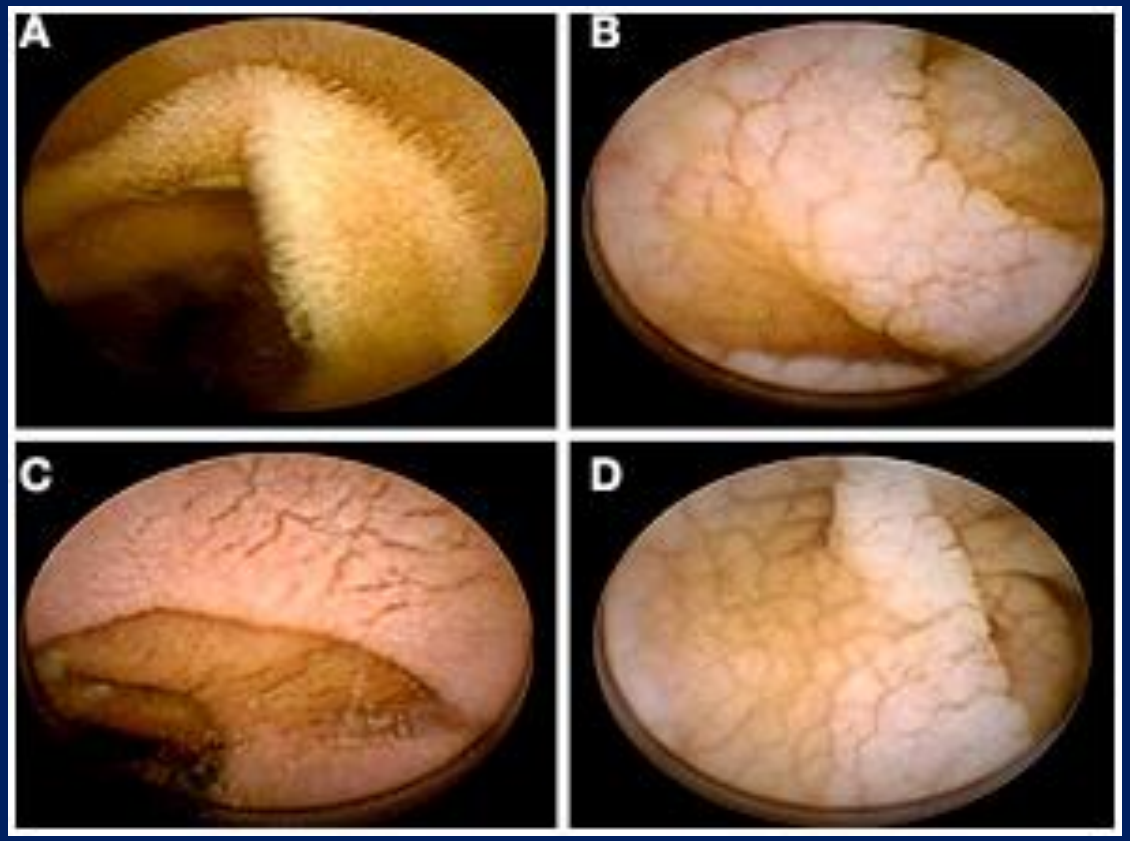
Mucosal phase

- Mucosal damage: (Villous Atrophy)

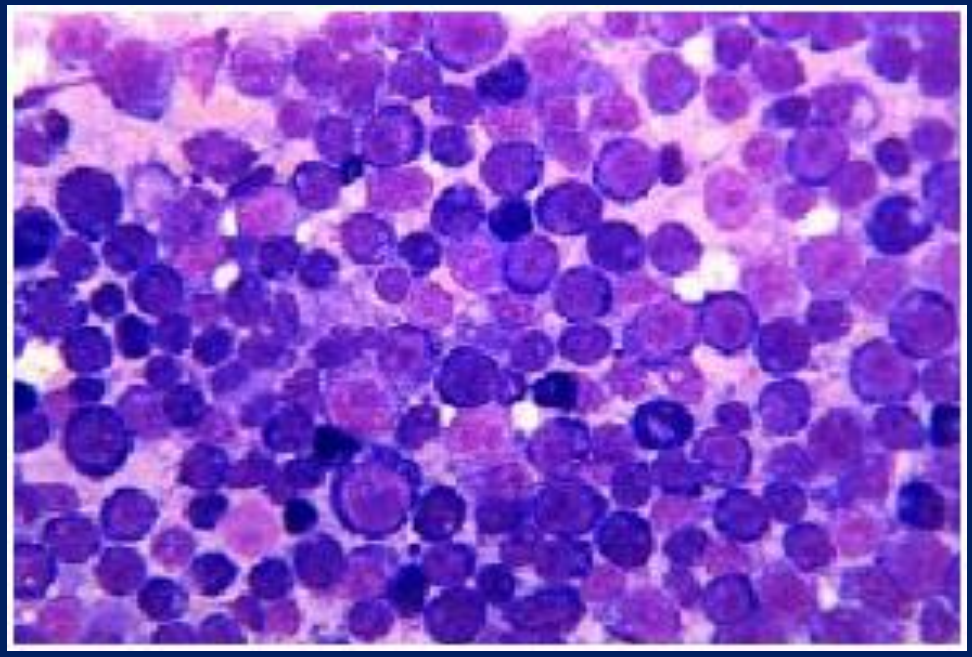


Mucosal phase

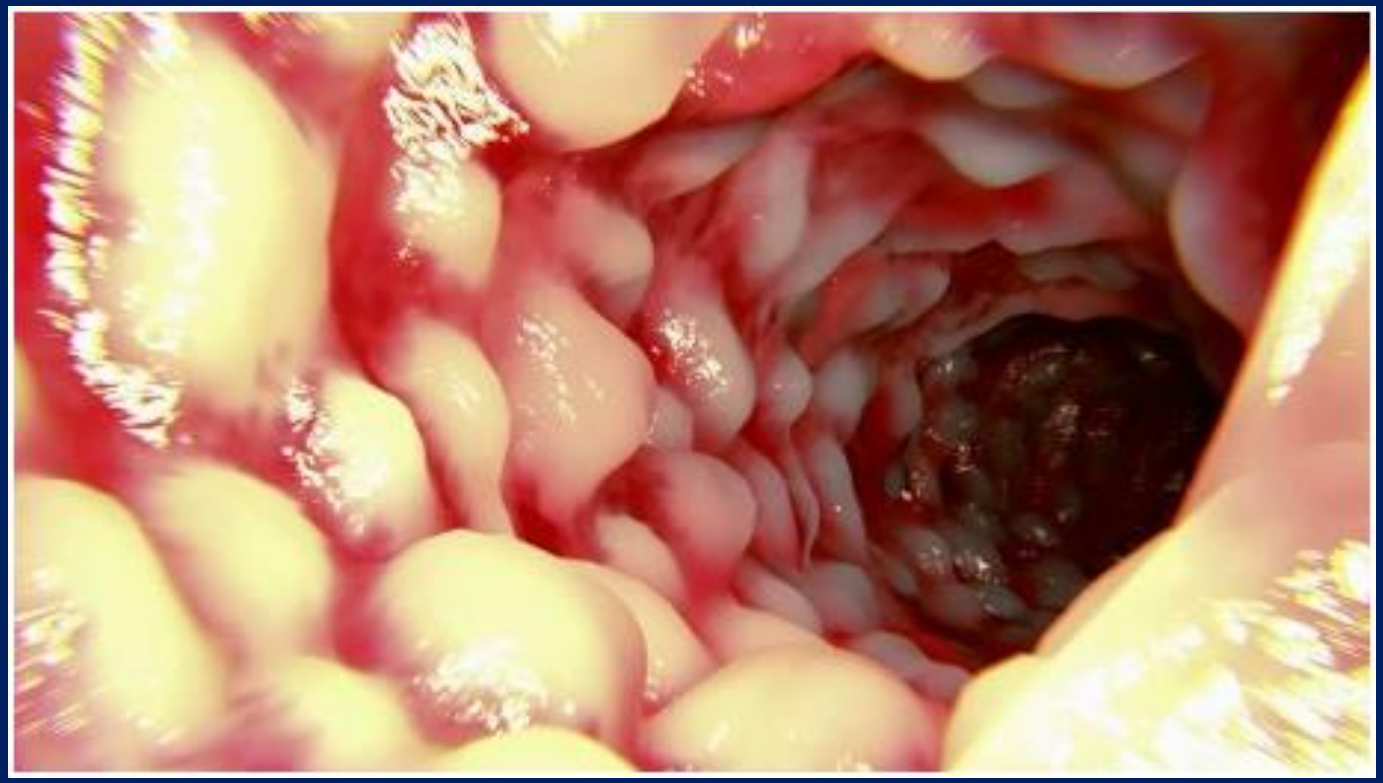
- Mucosal damage: (Villous Atrophy)



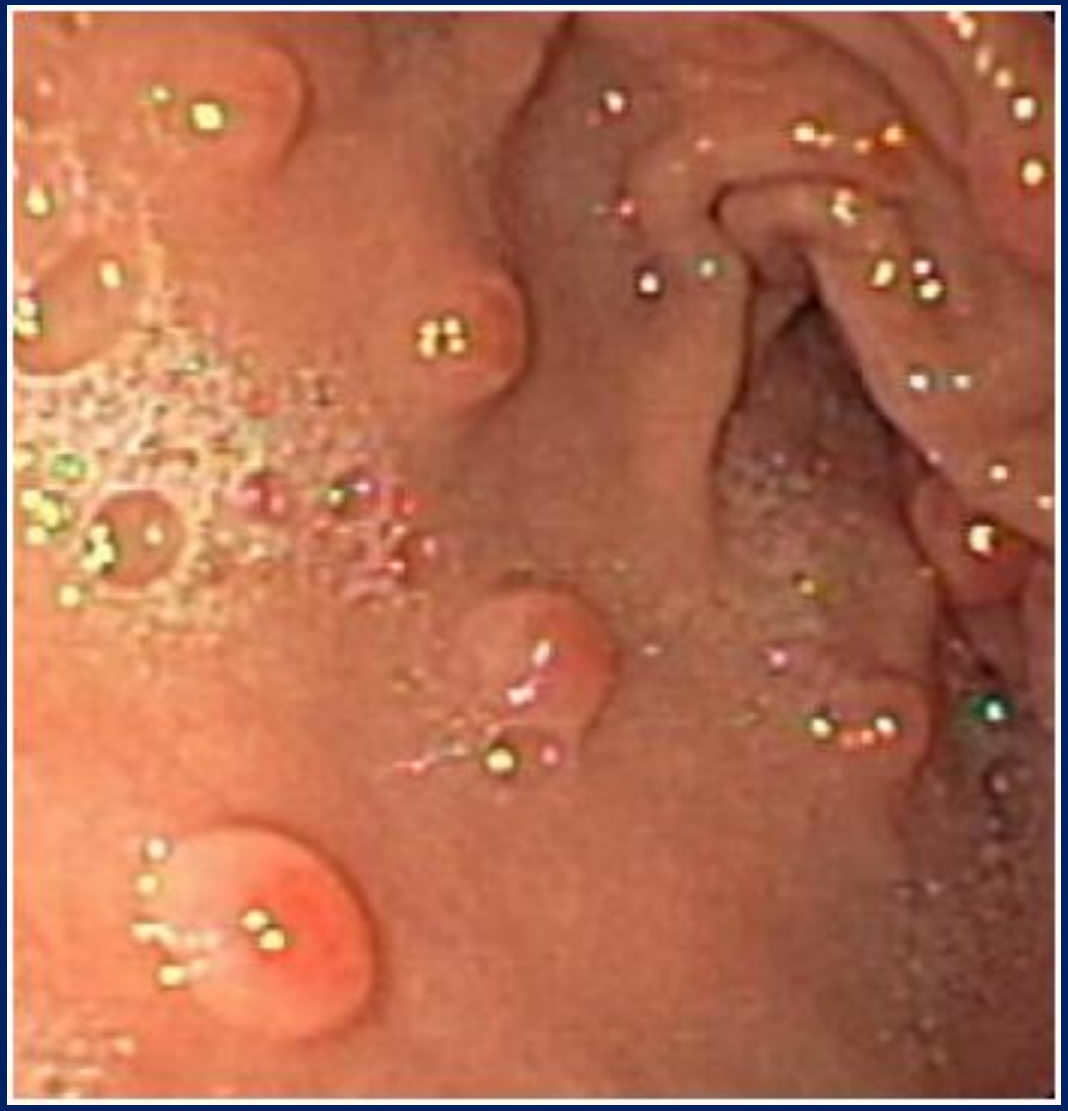
Celiac



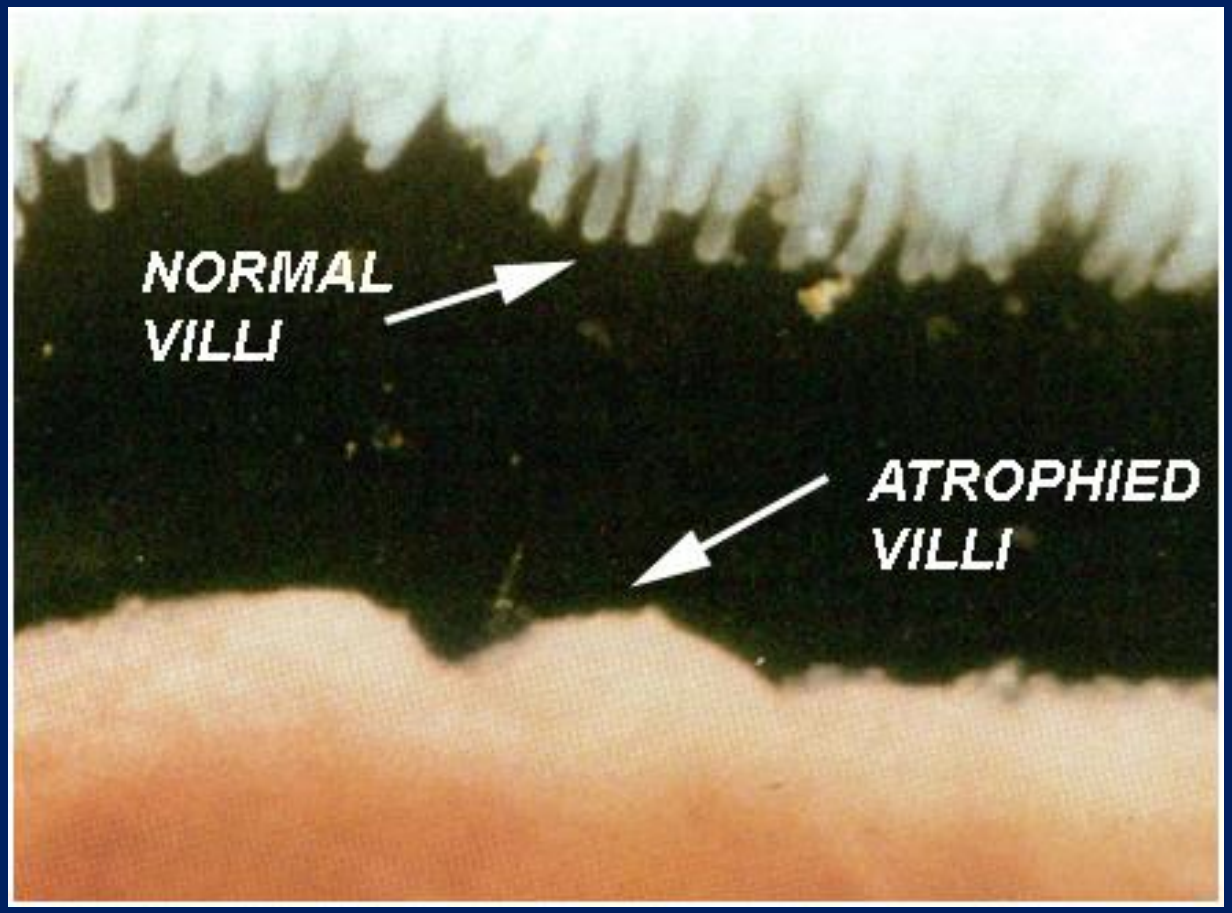
Intestinal Lymphoma



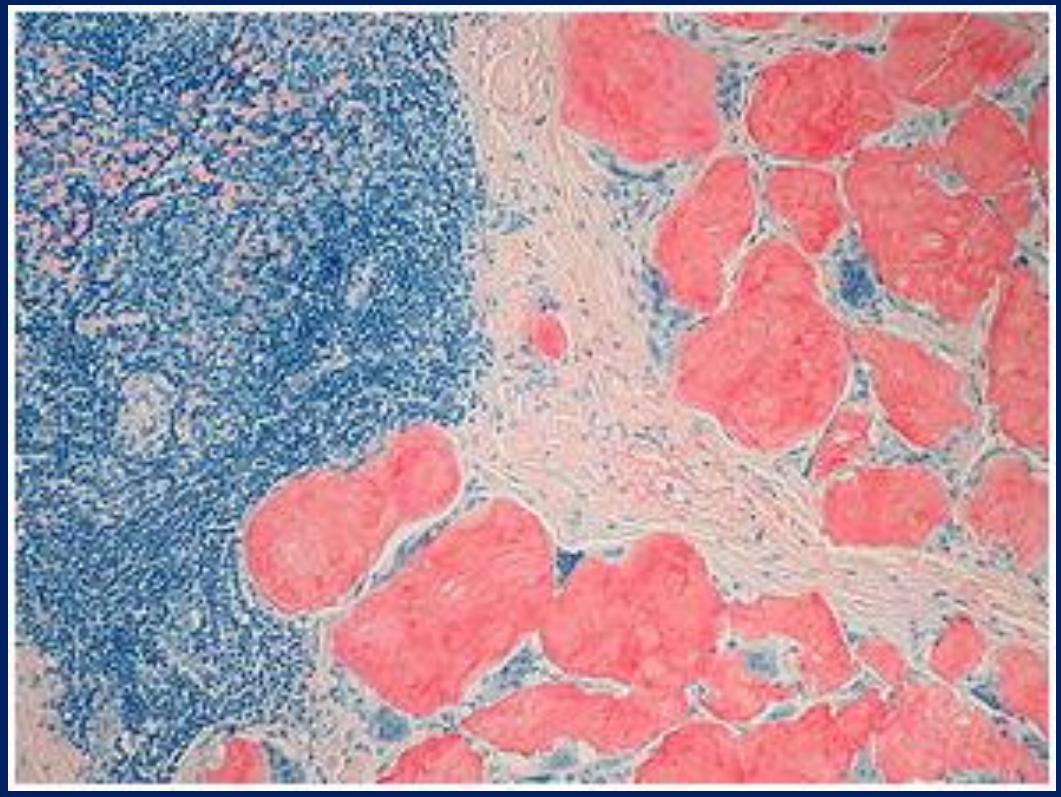
Crohn’s



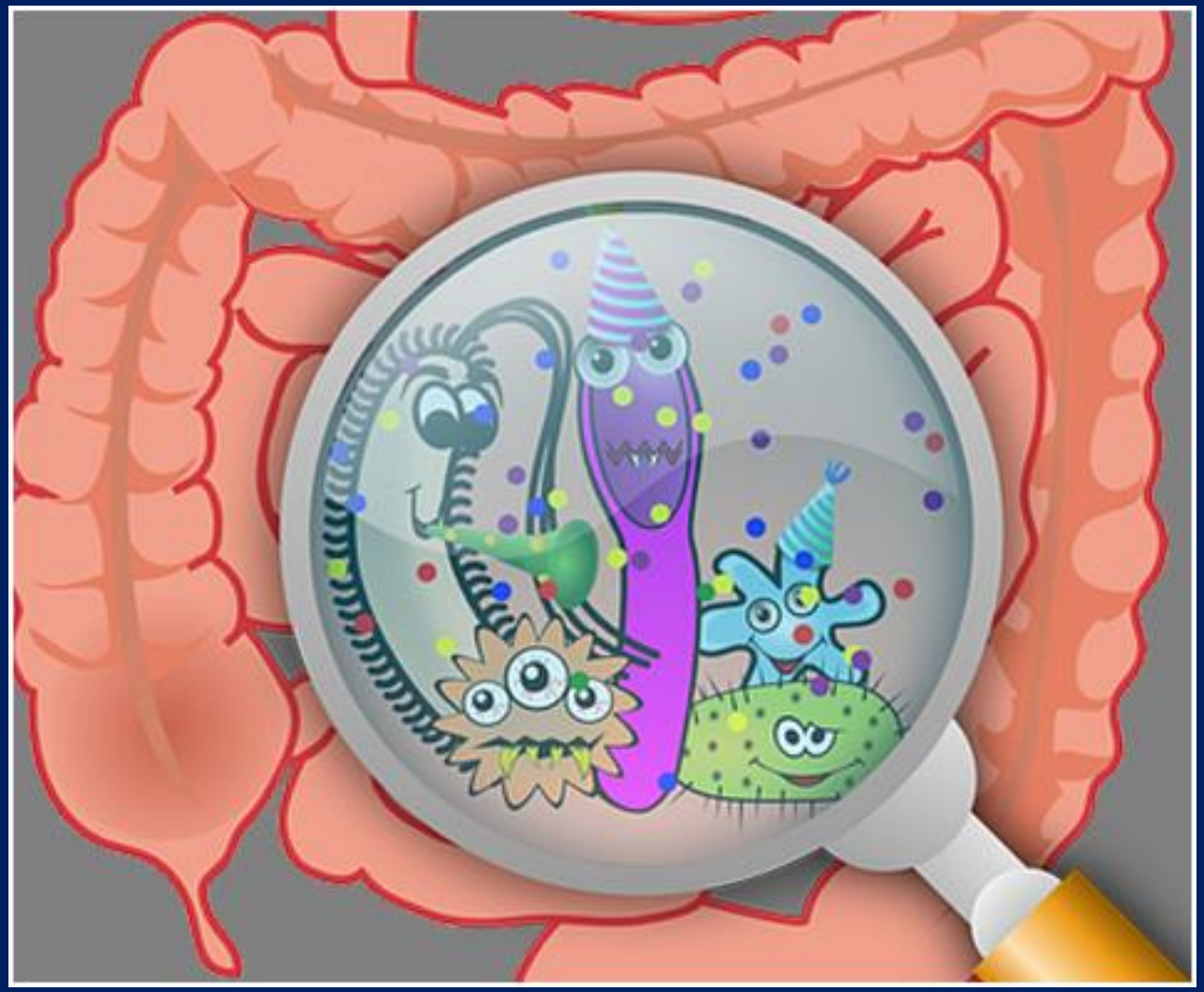
Eosinophilic enteritis


NORMAL
VILLI
ATROPHIED
VILLI

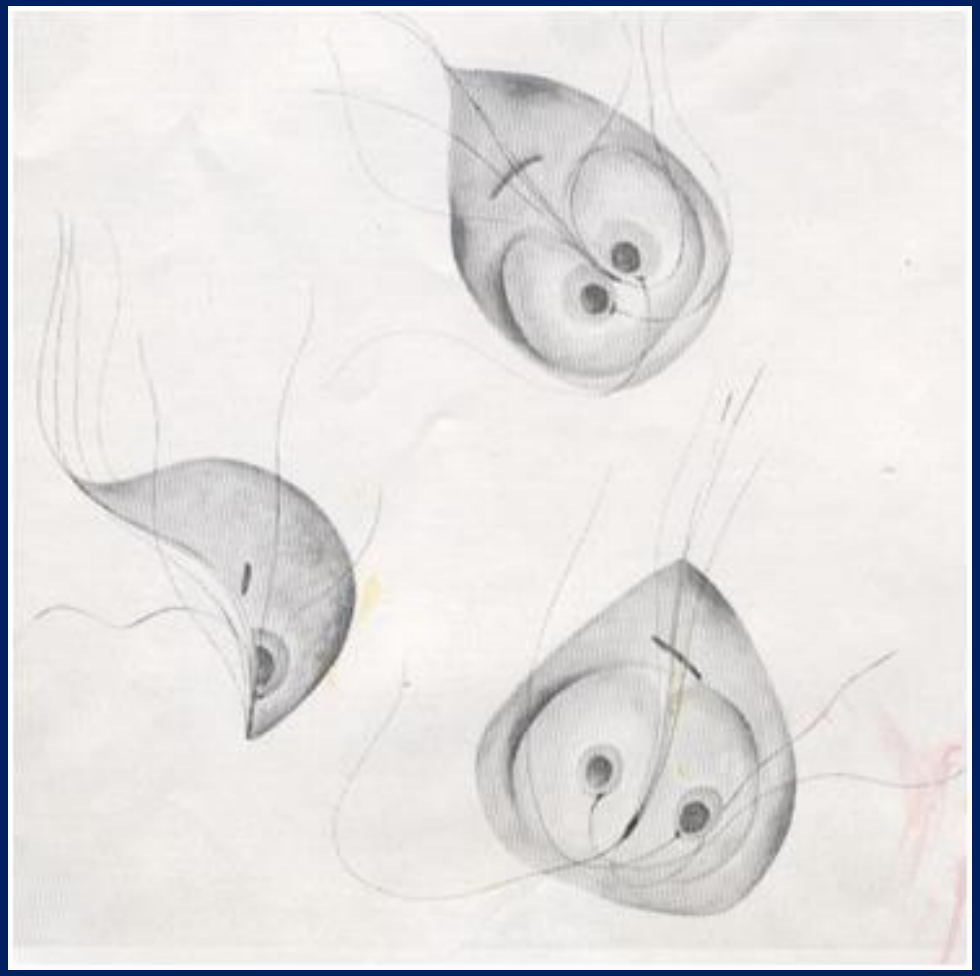
Common Variable ImmunoDeficiency



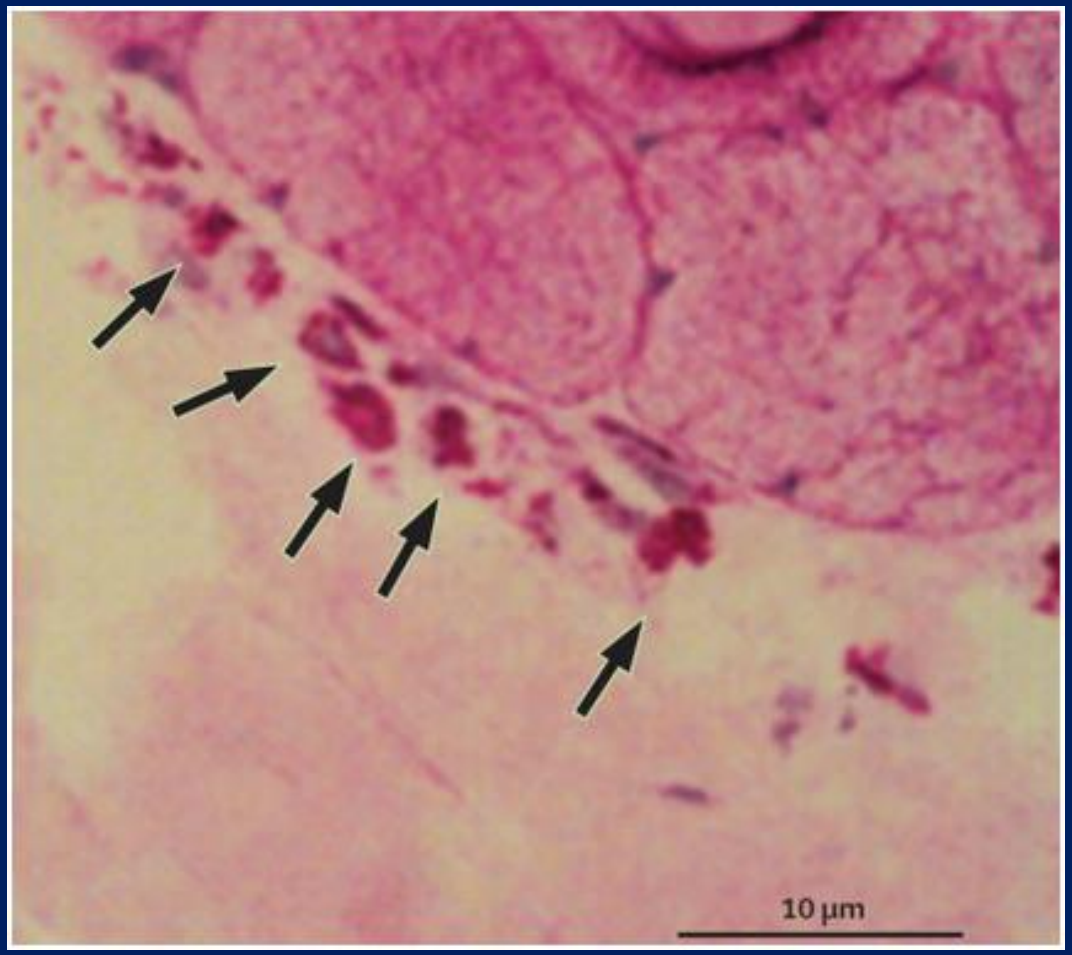
Amyloidosis



SIBO

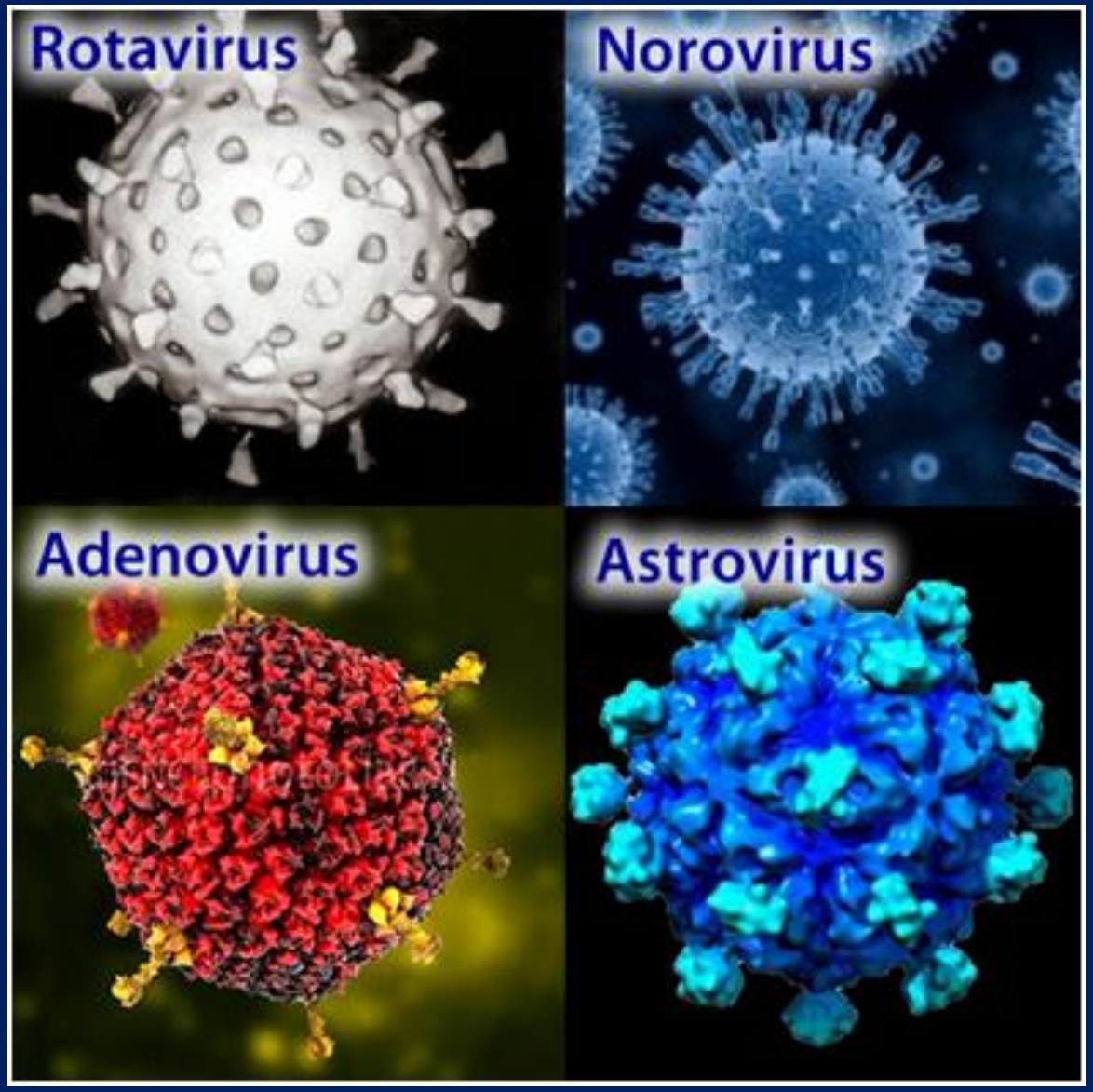


Giardiasis

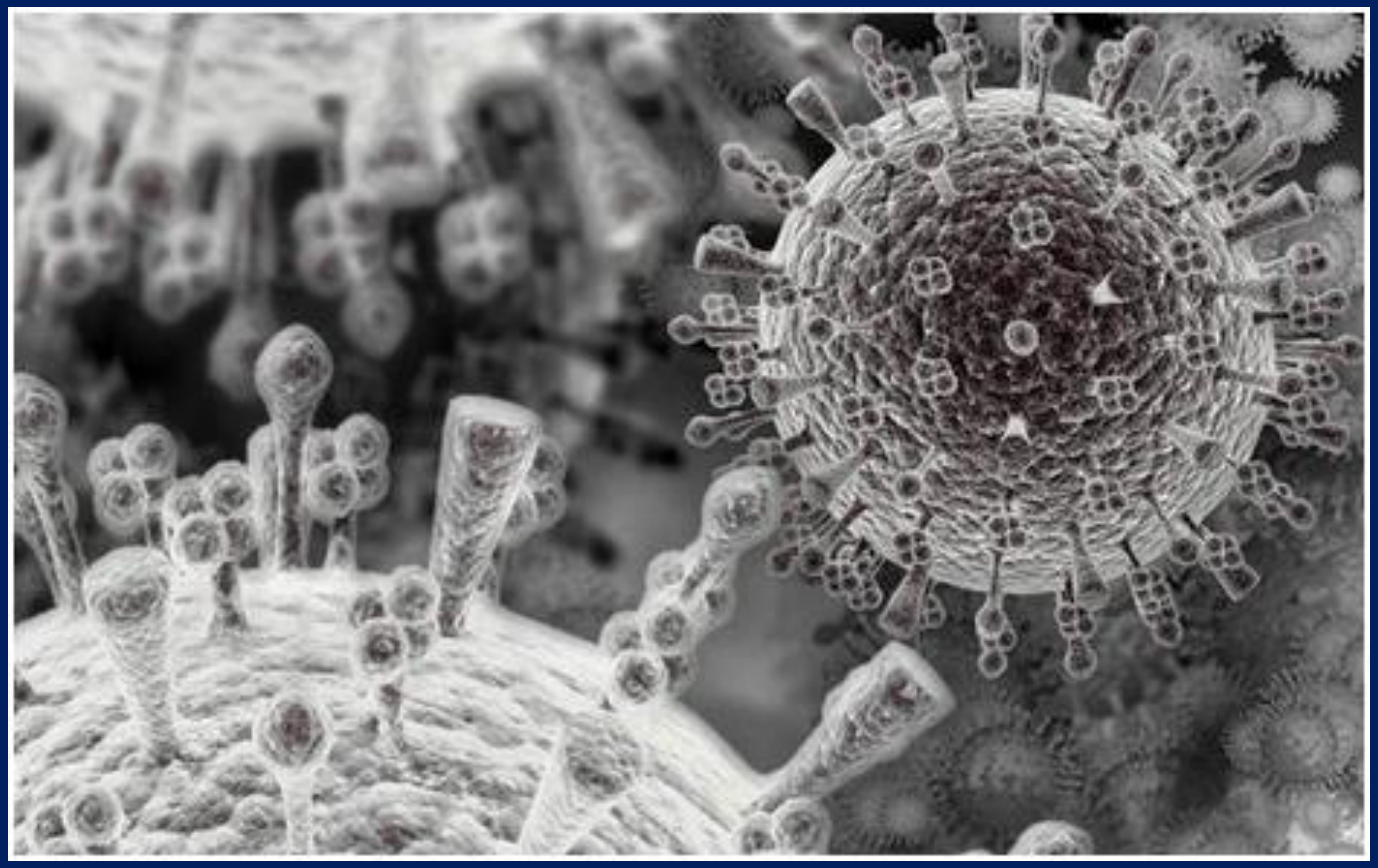

10 µm

Whipple’s

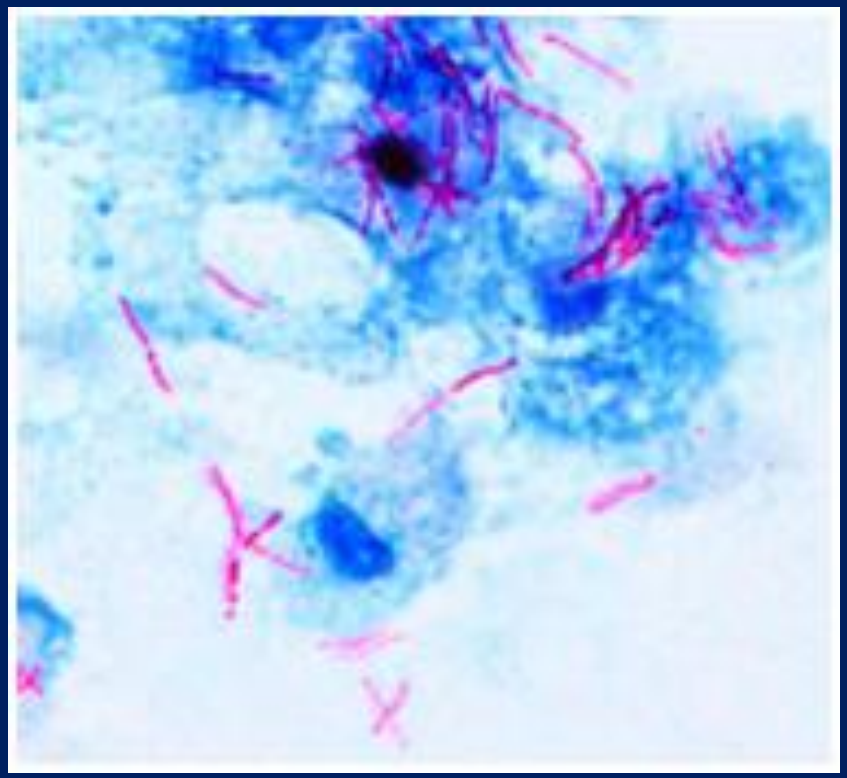
Tropical Sprue


Rotavirus
Norovirus
Adenovirus
Astrovirus

Viral GE

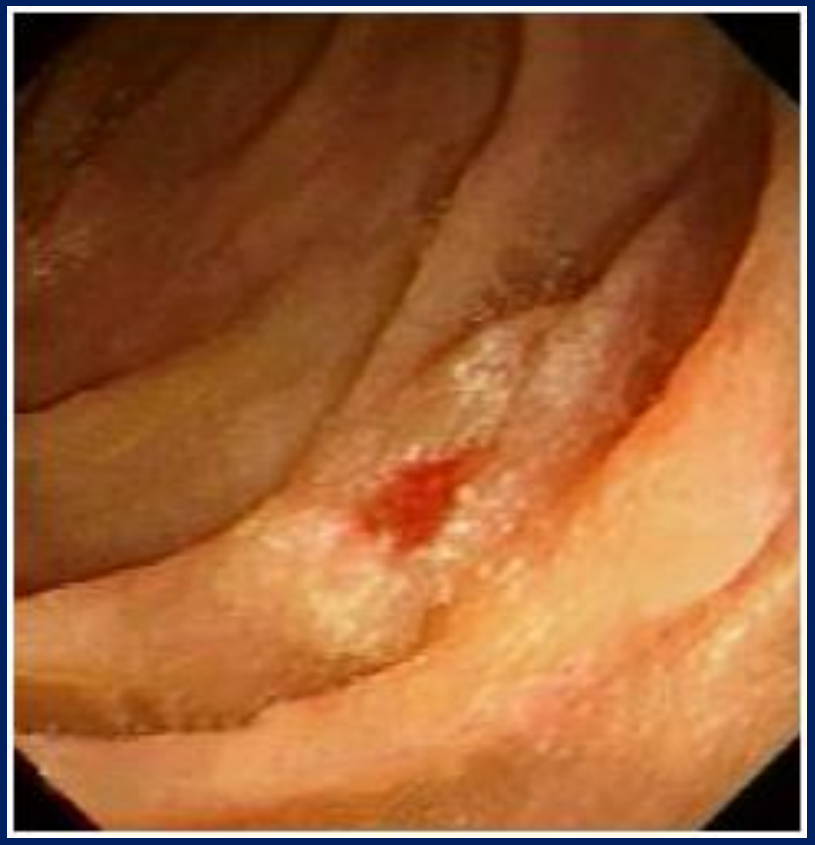


AIDS Enteropathy



Intestinal TB

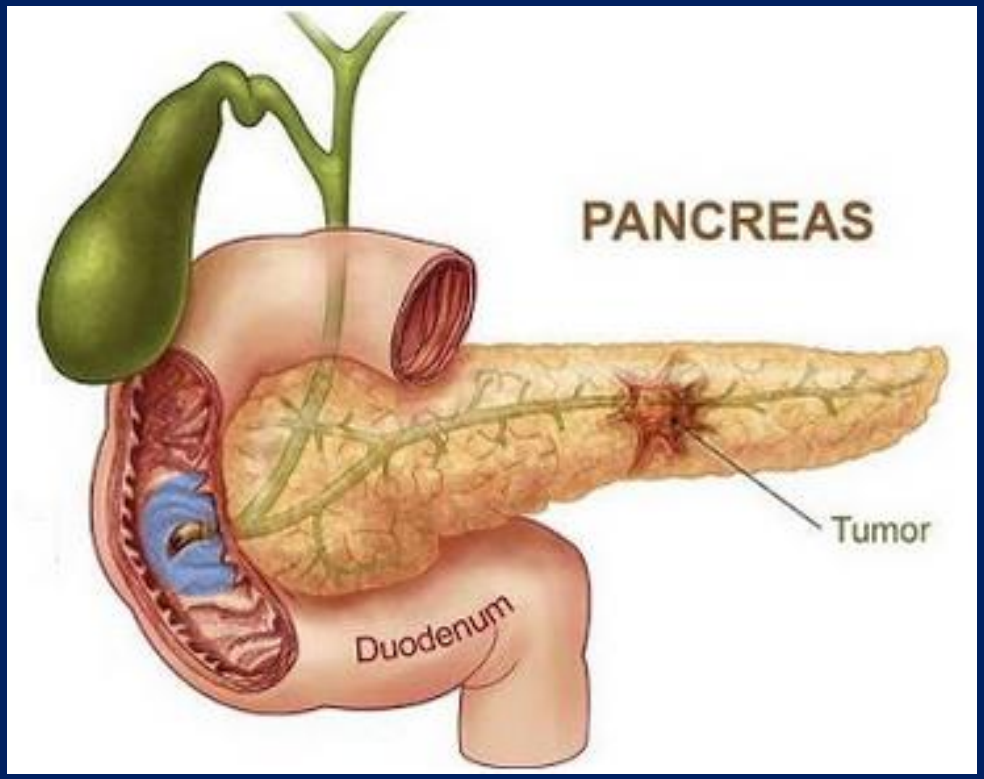

CVS
NEW!
Extra Strength
PAIN RELIEF
CAPLETS
ACETAMINOPHIN
CVS
NEW!
Extra Strength
PAIN RELIEF
CAPLETS
ACETAMINOPHEN
TYLENOL
$8.49

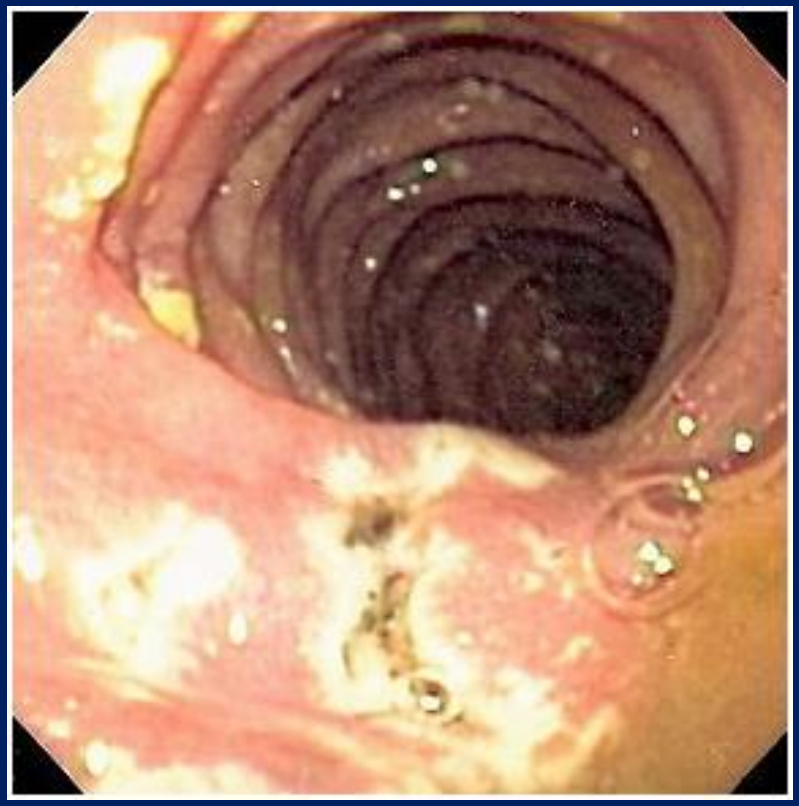


NSAIDs


Angiotensin
Receptor
Blockers
ARBs

Olmesartan


PANCREAS
Tumor
Duodenum



Zollinger Ellison syndrome

Mucosal phase

- Mucosal damage: (Villous Atrophy)

  Celiac disease, Intestinal Lymphoma

  Crohn's disease (CD), Eosinophilic enteritis, Auto-Immune Enteropathy (AIE), Common variable immunodeficiency, Amyloidosis

  SIBO, Giardiasis, Whipple's disease, Tropical sprue, Viral GE, AIDS enteropathy, Intestinal TB

  NSAIDs, Olmesartan

  ZE synd (Gastrinoma)

▼

↓surface area, ↓absorption/secretion

Mucosal phase

- **↓Brush border Enzymes:**
  - Disaccharidase deficiency (**Lactase**,**Trehalase**, **Sucrose**) can lead to disaccharide malabsorption.

  ►Lactase deficiency, either Congenital or Acquired, is the most common form of disaccharidase deficiency.

  ►Acquired lactase deficiency can be due to acute gastroenteritis (rotavirus or giardia infection), chronic alcoholism, celiac sprue, radiation enteritis, regional enteritis, or AIDS enteropathy.

Mucosal phase

- Immunoglobulin A (IgA) deficiency (most common immunodeficiency) is due to decreased or absent serum and intestinal IgA, which clinically appears similar to celiac disease and is unresponsive to a gluten-free diet.

- Acrodermatitis enteropathica is an autosomal recessive disease with selective inability to absorb zinc, leading to villous atrophy and acral dermatitis.

Post Absorptive Phase
"Lymphatics"

- Obstruction of the lymphatic system:

  -Congenital

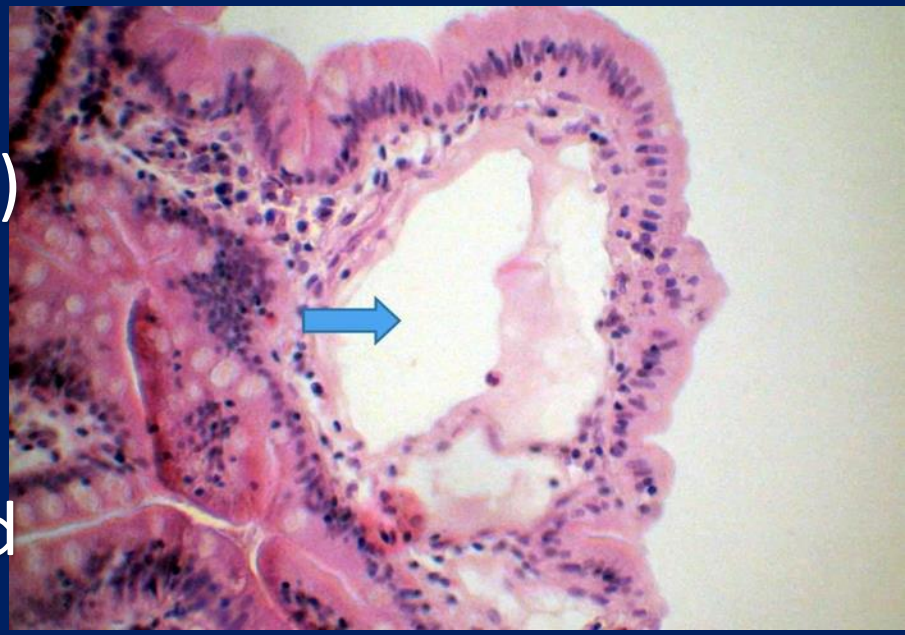
  (Intestinal Lymphangiectasia)

  -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.

Diarrhea can be classified according to 4 categories:

- **Secretory diarrhea**

  is characterized by isotonic stool and persists during fasting.

- **Osmotic diarrhea**

  due to the excessive osmotic forces exerted by unabsorbed luminal solutes. The diarrhea is over 100 mOsm more concentrated than plasma and abates with fasting.

- **Malabsorptive diarrhea**

  follows generalized failures of nutrient absorption and is associated with **steatorrhea** and is relieved by fasting.

- **Exudative diarrhea**

  2ry inflammatory disease & characterized by purulent, bloody stools that continue during fasting.

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

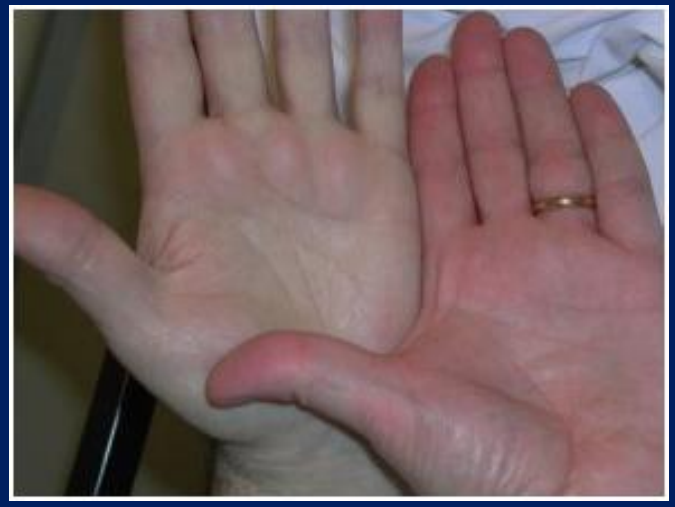
Bacterial fermentation of unabsorbed food substances releases gaseous products, such as hydrogen and methane, causing flatulence.

Flatulence often causes uncomfortable abdominal distention and cramps.

Edema

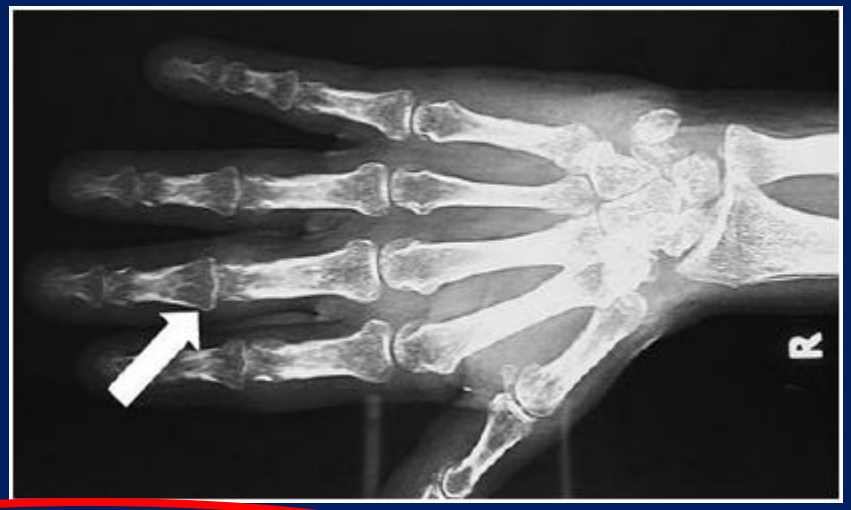
- Hypoalbuminemia from chronic protein malabsorption or from loss of protein into the intestinal lumen causes peripheral edema.
- Extensive obstruction of the lymphatic system, as seen in intestinal lymphangiectasia, can cause protein loss.
- With severe protein depletion, ascites may develop.

Anemia

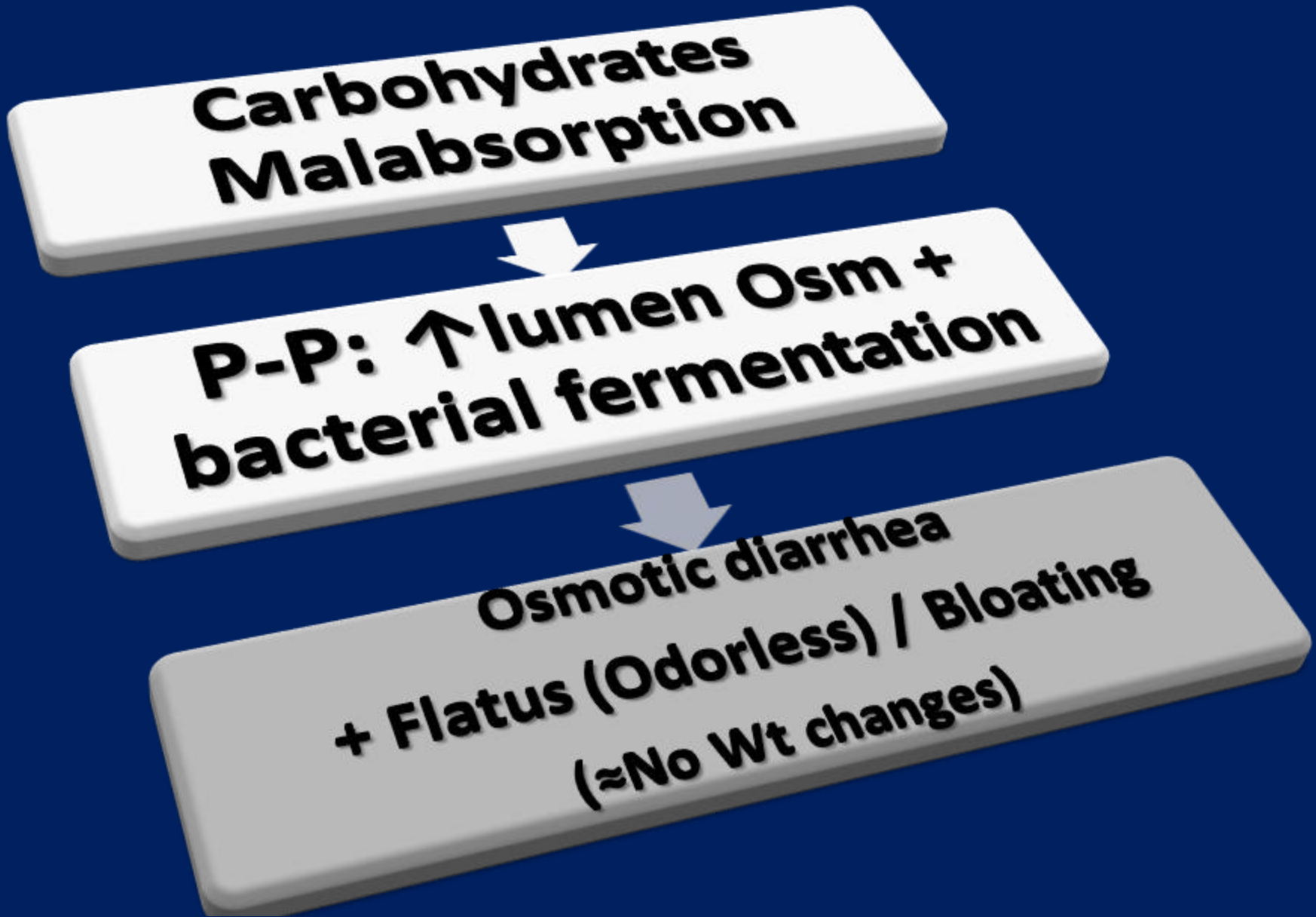


- Depending on the cause, anemia resulting from malabsorption can be either microcytic (iron deficiency) or macrocytic (vitamin B-12 deficiency).
- Iron deficiency anemia often is a manifestation of celiac disease.
- Ileal involvement in Crohn disease or ileal resection can cause megaloblastic anemia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


Carbohydrates Malabsorption
P-P: ↑lumen Osm + bacterial fermentation
Osmotic diarrhea
+ Flatus (Odorless) / Bloating
(≈No Wt changes)

Carbohydrate Malapsorbtion

Etiology

Lactase deficiency:

(Most common **Æ** of carbohydrate malabsorption)

- S/P intestinal resection
- Mucosal disease
- Post-infectious GE syndrome (Viral/Bacterial)
- Changing diet from Eastern → Western Diet

Carbohydrates Malabsorption

Workup

- **Stool Osmotic gap**

>100 (Osmotic Diarrhea)

Carbohydrates Malabsorption

Workup

- **Stool Osmolality:**
  - **Normally shall equal that of plasma Osmolality**
  - **Shall be measured; if not → will considered ≈290**
  - **Stool gap: is normally a minimal difference 2ry to some ⊖ charged particles ≈ 50 – 100**

So …

Stool gap =

(Measured) (or ≈**290**) - (Calculated) **[stool (Na^+ + K^+) x2]**

Carbohydrates Malabsorption

Workup

- **Stool Osmotic gap**

>100 (Osmotic Diarrhea)

- **Stool pH**

<6 (Fermentation)

- **Lactase DNA Assay**

- **Breath testing w/H_2**

  (↑fermentation of unabsorbed carbohydrate by bacteria) = Malabsorption


Fat Malabsorption
Greasy foul smell Diarrhea
↓Wt
fat-soluble Vit def (ADEK)

Fat Malabsorption

Workup

Pancreatic

Vs

Small Bowel

(D-Xylose test)

25g D-xylose po →

serum level @1hr &/or urine collection level x5hrs

N. Serum level: > 20mg/dL
N. Urine level: ≥ 4g

↓level

(≤20mg/dL)

(Small Bowel Disease)

- SBBx
- SB Cx
- SB Imaging

↑level

(≈45mg/dL)

(Normal) or

(Pancreatic Insufficiency)

(1) Imaging:

•X-Ray (Calcifications) •CT •MRCP •EUS

(2) pancreatic function:

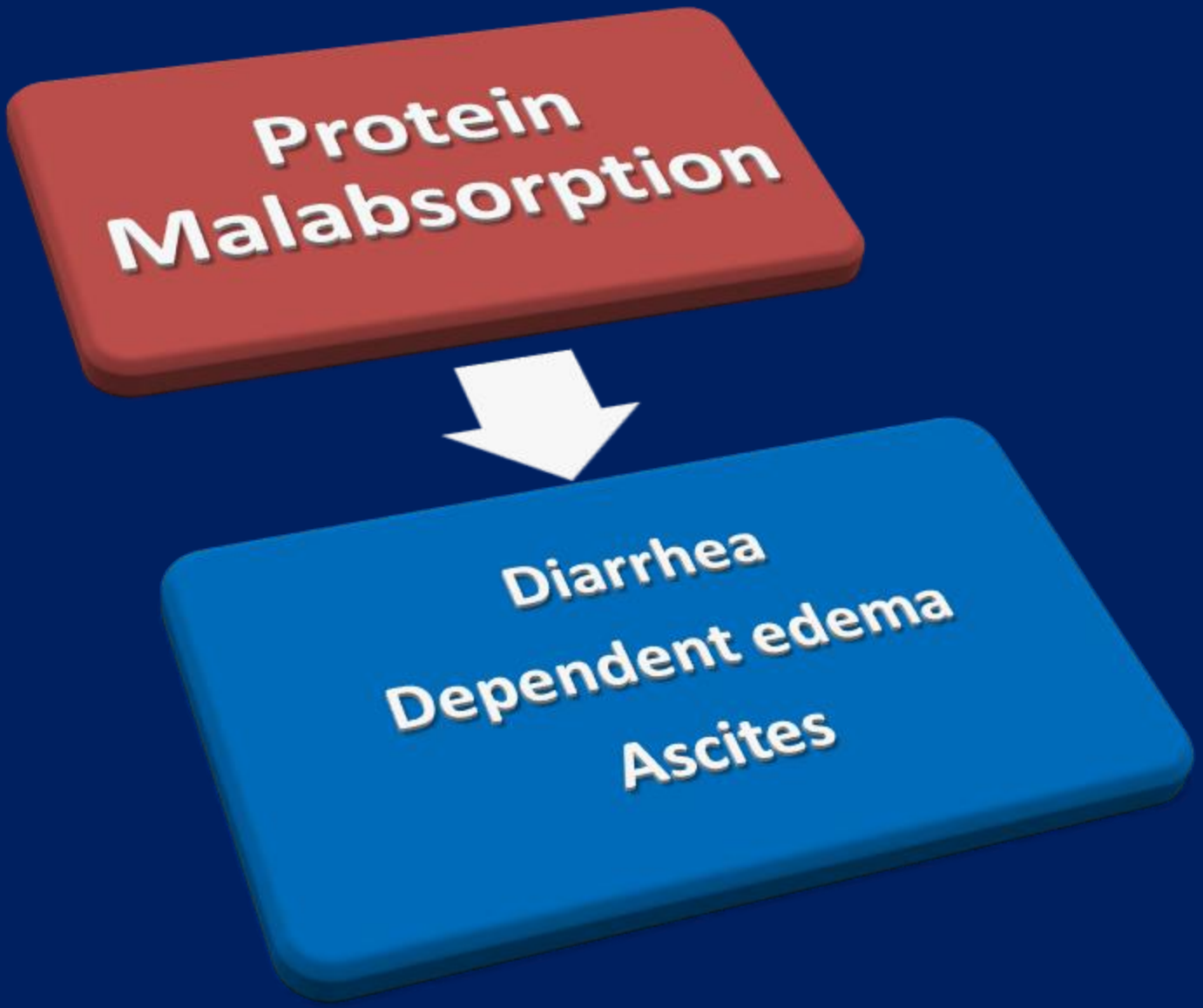
•**Secretin** (measure **HCO_3**)

•**CCK** (measure **lipase/trypsin**)

(3) Alternatively:

empiric trial of pancreatic enzymes w/Quantify of fecal fat before & after

TNC-CDAAR
TUFTS • BROWN • JOHNS HOPKINS


Protein Malabsorption
Diarrhea
Dependent edema
Ascites

Protein Malabsorption Workup

- **Serum:**
  - **↓ Protein**
  - **↓ Albumin**
  - **↓ IgG (except IgE (short half-life/rapid Re-Synth))**
  - **↓ WBC/Lymph (w/Lymphangiectasia)**
- **Stool:**
  - **↑ α 1-Antitrypsin "A1A" (↑ α 1-Antitrypsin Clearance)**
    - A1A: not digested, absorbed or secreted by intestine

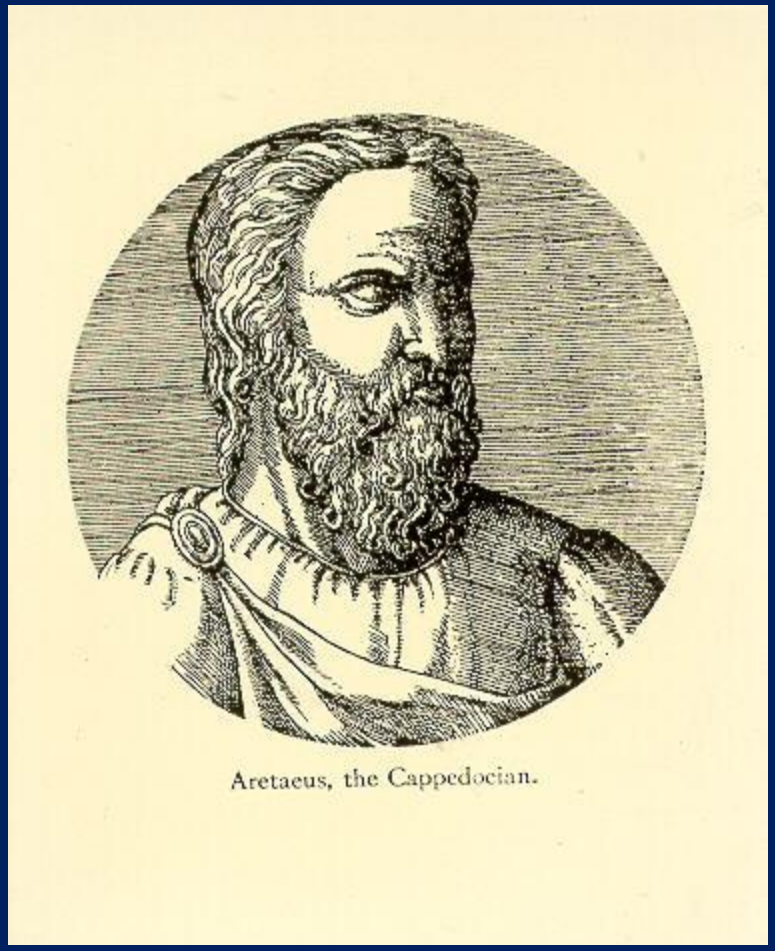
Treatment

Treating the cause


Celiac Disease

- Aretaeus from Cappadochia (now Turkey) in the 2nd century AD described a chronic malabsorptive condition

- He named this disorder "koiliakos" which is Greek for "suffering in the bowels."


Aretaeus, the Cappedocian.

- During World War II, celiac children improved during the food shortages when bread was unavailable.
- After the war, symptoms reoccurred when bread and cereals were reintroduced.
- Dutch pediatrician Willem K Dicke recognized and confirmed this association between cereal grains and malabsorption.

Origin of the Term Celiac

Celiac Disease

Pain in the belly

Greek
Koiliakos
=
Issues of the Hollow part (Abdomen)

▼

Latin
Coeliacus “with K”

▼

Modern Latin
Coeliacus “with C”

▼

English UK
Coeliac

▼

English USA
Celiac

Also known as

Celiac sprue

Non - tropical sprue

Gluten intolerance

Gluten-sensitive enteropathy

Pathophysiology

Celiac disease

is …

an immune disorder,

that is …

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

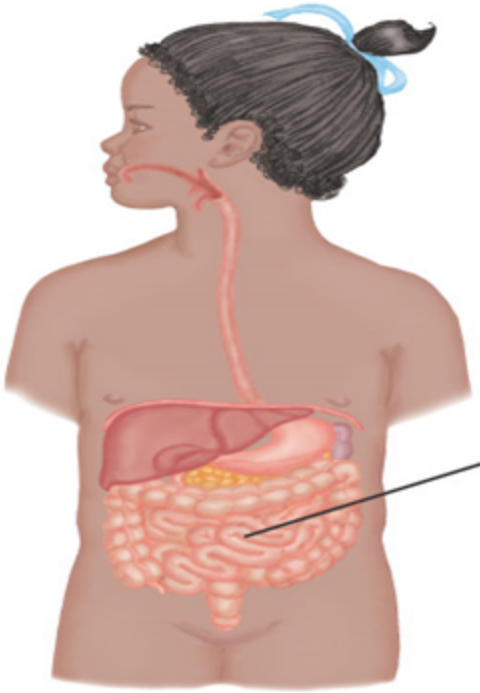
in …

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

↓

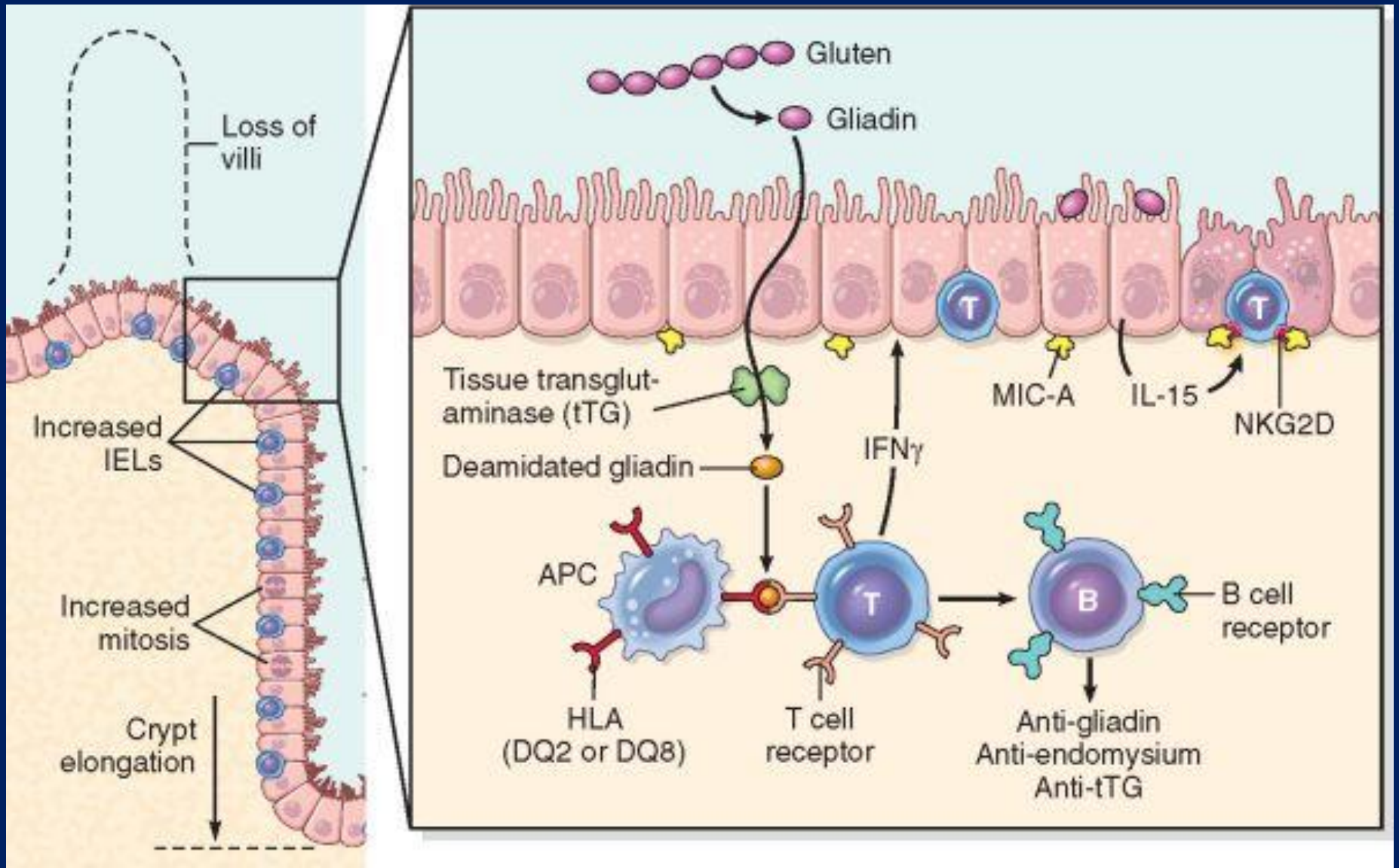
Severe dehydration
and diarrhea

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)

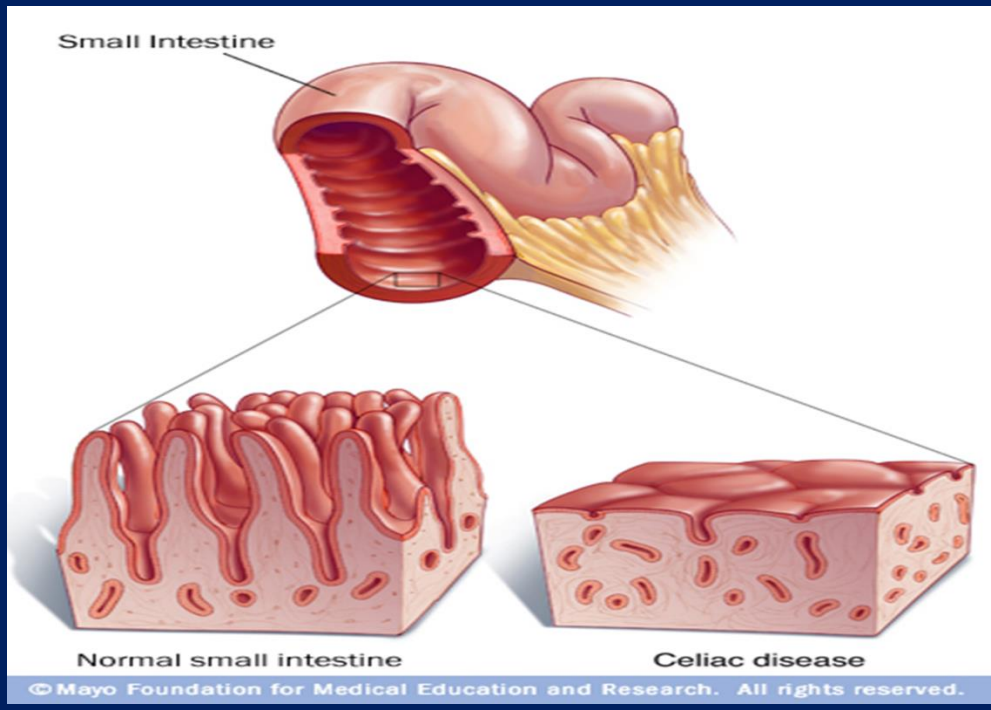
Histopathology:

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*.

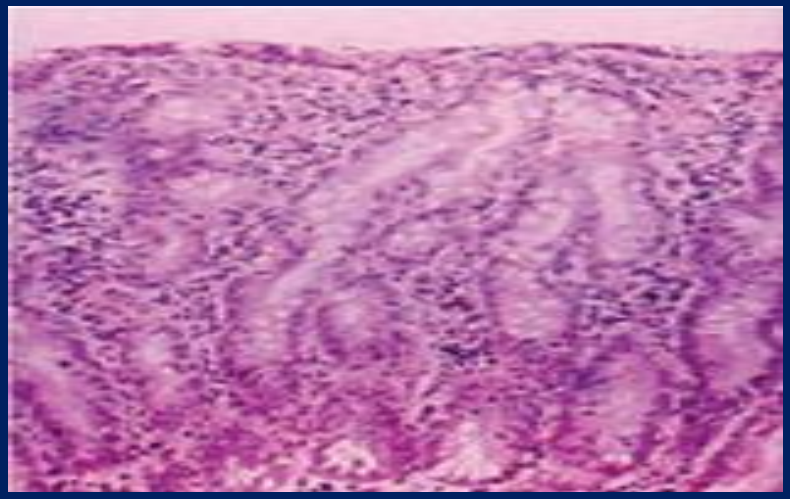
Genetic Testing:

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



Normal

Pathology



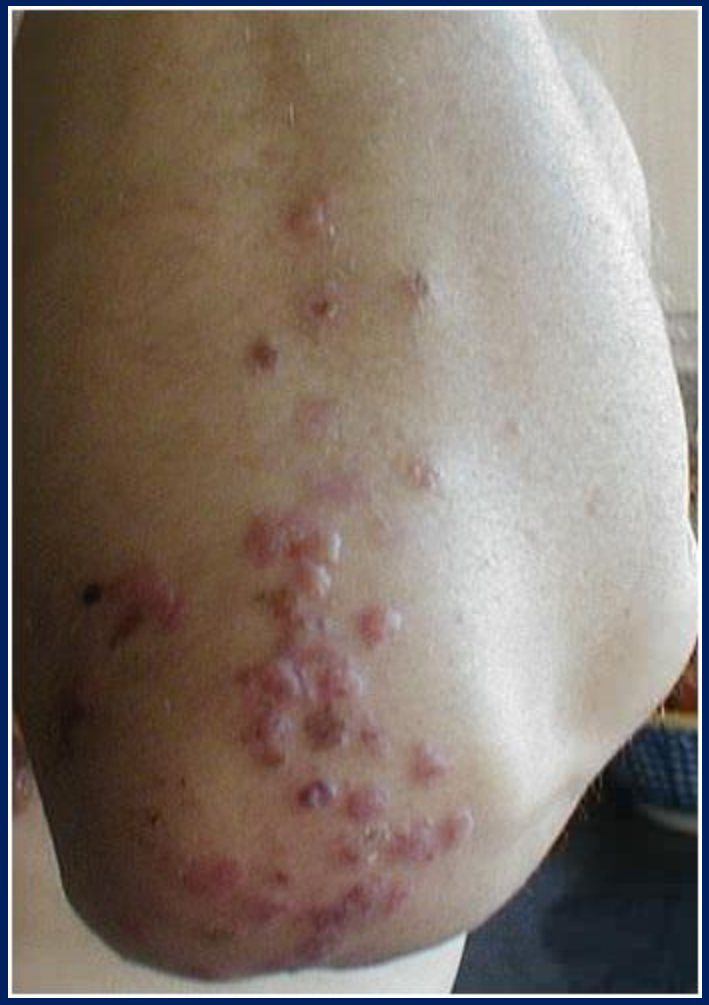
Symptoms & Signs

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

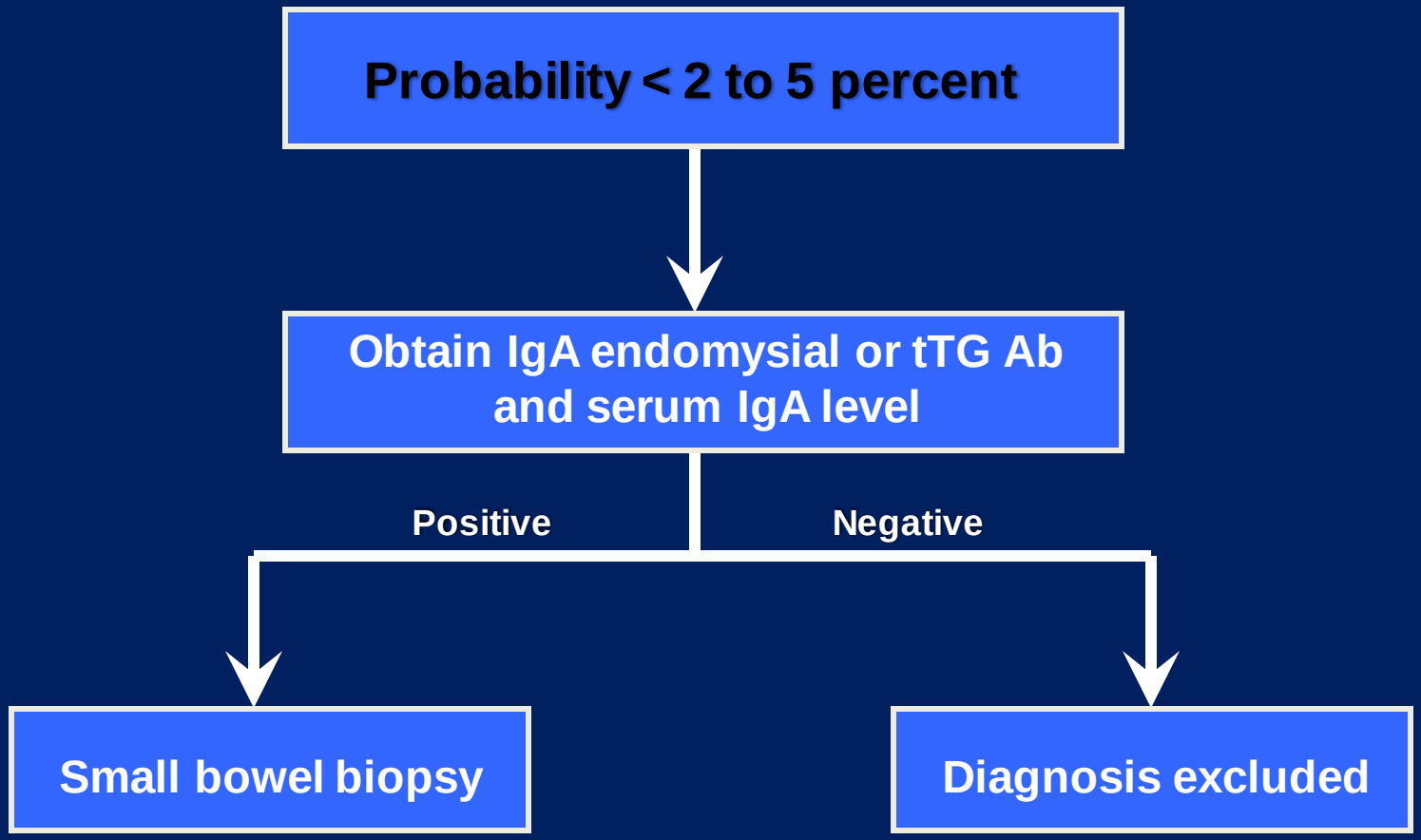
-Abnormal LFTs
-Dermatitis Herpetiformis
-Hypo-Splenism (Splenic)
-Osteopenia/OP/Enamel defects, Arthropathy (Non-erosive, polyarticular, symmetrical, large joint) (Non-Migratory)
-Peripheral neuropathy (Symmetrical & distal), Ataxia (Cerebellar), Epilepsy (Bilat parieto-occipital calcifications), Depression/anxiety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

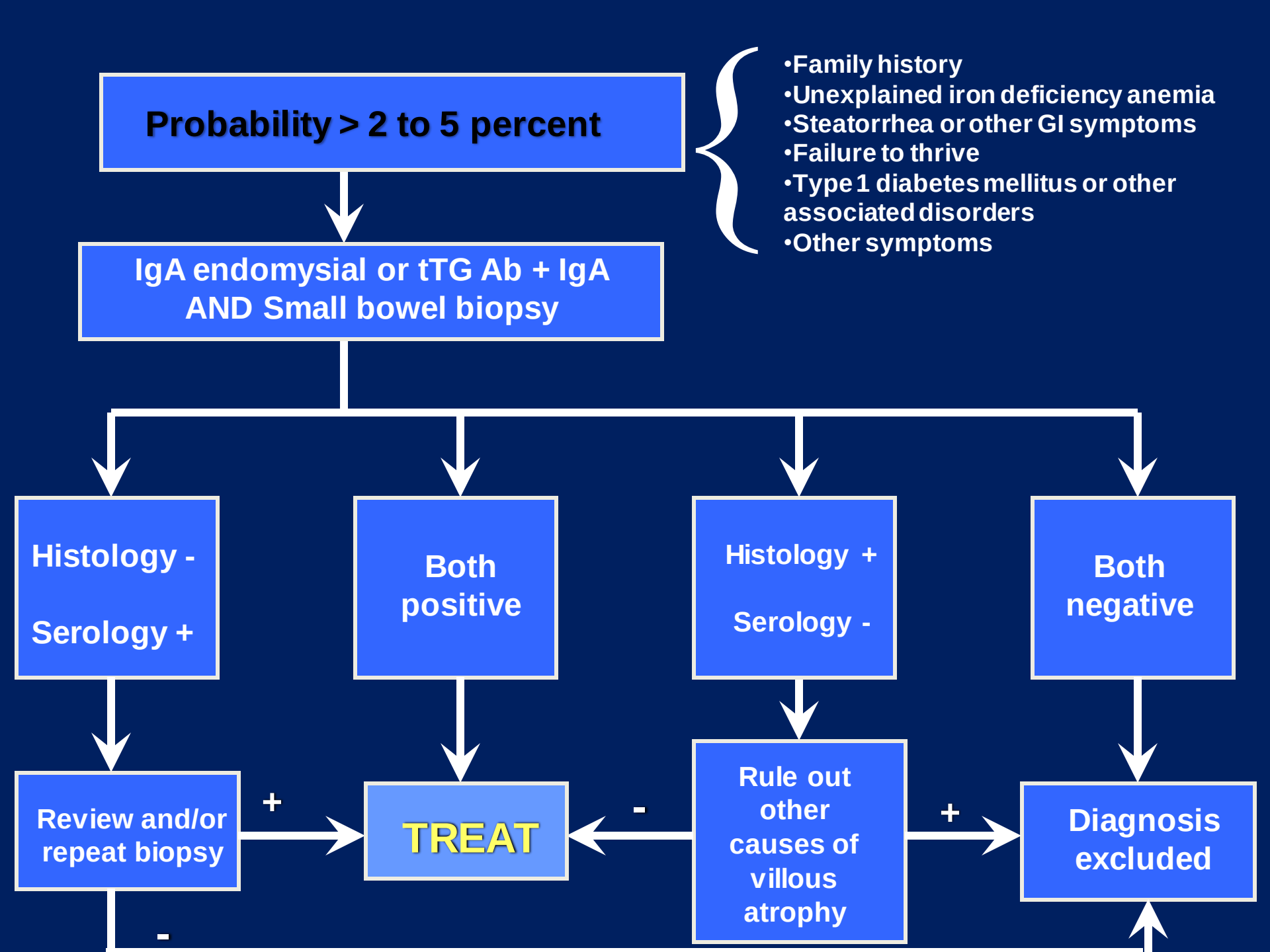


Diagnosis: Gluten Rechallenge

- 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 and/or repeat biopsy
+
TREAT
-
Rule out other causes of villous atrophy
+
Diagnosis excluded
-