

Celiac Spru, Tropical Spru, and Whipple's Disease

What's similar, and what's not?

2016

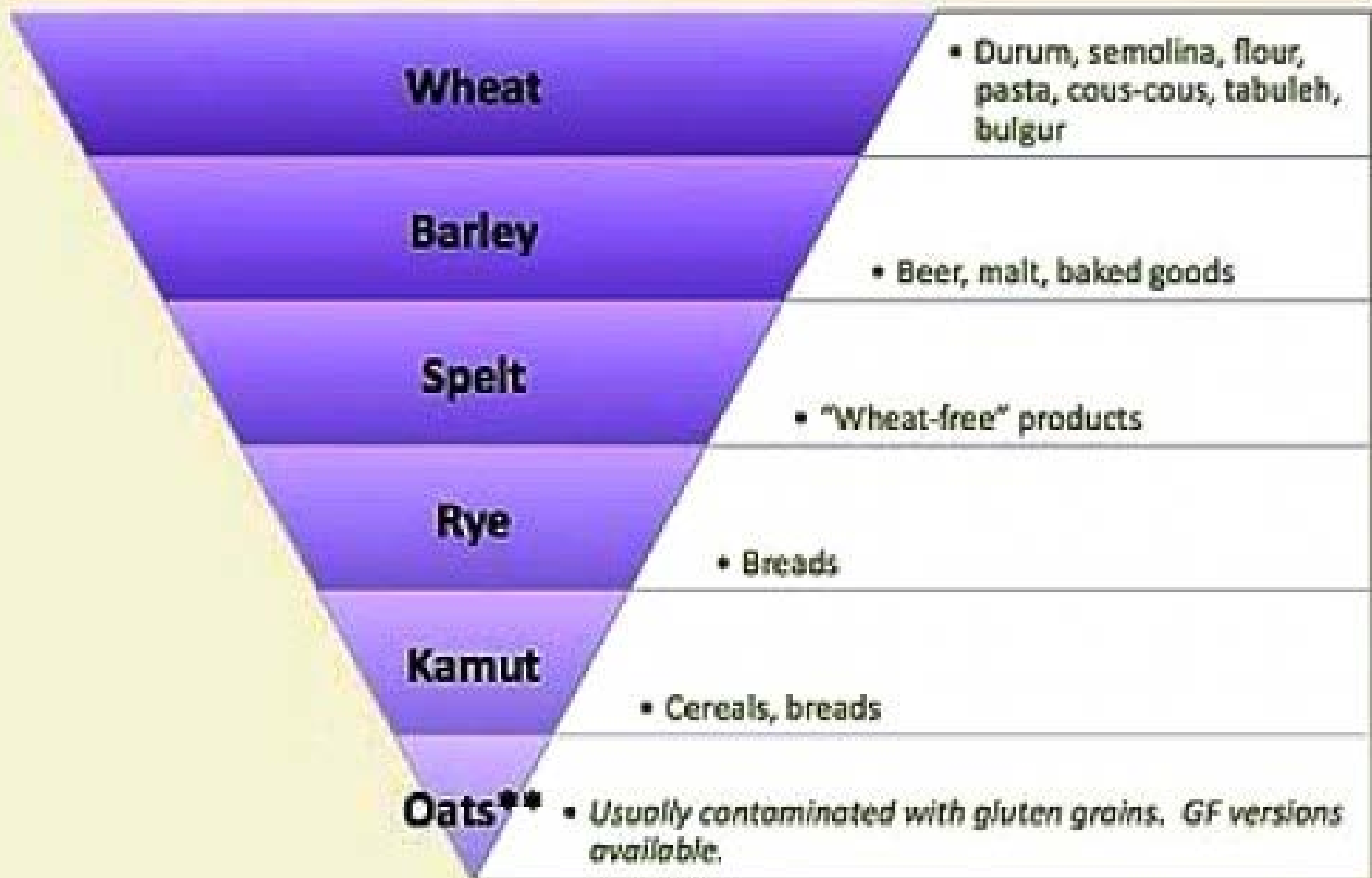
A funny funny patient-2003

23 year old female nursing student only taking keppra for seizures after falling backwards down a waterfall while on a medical mission trip to Guatemala. She reports at least two episodes each of giardia and amoeba, says she can tell the difference by the amount of burps and farts and color of the stool. Now she has culture negative, O and P and WBC negative floating loose stools, inability to gain weight, anorexia, frequent headaches, and fatigue. Albumin 3.2, She is 5'5 and 107 lbs. Most concerned her flatulence will making "hubby hunting difficult"

Coeliac or Celiac Spru or Sprue or “non-tropical” sprue

- “Gluten sensitive enteropathy” – gliadin, a 33 AA alcohol soluble fraction of gluten.
- Immunologically mediated inflammatory response that damages the intestinal mucosa and results in maldigestion and malabsorption
- Strong association with HLA haplotypes DQ2.2, DQ2.5, DQ8 (91-97%)
- Also cell mediated immunity demonstrated by presence of CD8 T lymphocytes in epithelium

Foods Gluten is found in:



Classical symptoms of celiac disease:

Gastrointestinal

- Diarrhea (45-85%)
- Flatulence (28%)
- Borborygmus (35-72%)
- Weight loss (45%)
- Weakness, fatigue (80%)
- Abdominal pain (30-65%)
- Secondary lactose intolerance
- Steatorrhea

Extra-intestinal

- Anemia (10-15%), Fe, B12
- Neurological Sx (8-14%)
- Skin disorders (10-20%)
- Endocrine disturbances including infertility, impotence, amenorrhea, delayed menarche

**Table
1**

NON-CLASSIC PRESENTATIONS OF CELIAC DISEASE

GI

Recurrent abdominal pain
Abdominal discomfort
Loose stools
Lactose intolerance
Pancreatitis
Transaminitis

Non-GI

Constitutional

Short stature
Chronic fatigue

Bone

Osteopenia
Arthritis

Mouth/Dental

Enamel hypoplasia
in permanent teeth
Cavities
Aphthous stomatitis

Skin

Dermatitis herpetiformis
Alopecia areata
Chronic urticaria

Genital

Late-onset puberty
Menstrual abnormalities

Neurological

ADHD
Learning disabilities
Seizures
Cerebellar ataxia
Peripheral neuropathy
Hypotonia
Developmental delay
Headaches

Hematological

Iron deficiency anemia
Folate deficiency anemia

Hypoplasia of dental enamel- common in childhood onset celiac



**Dermatitis Herpetiformis-maculopapular,
pruritic, extensor surfaces of extremities and
back, trunk, neck, buttocks**



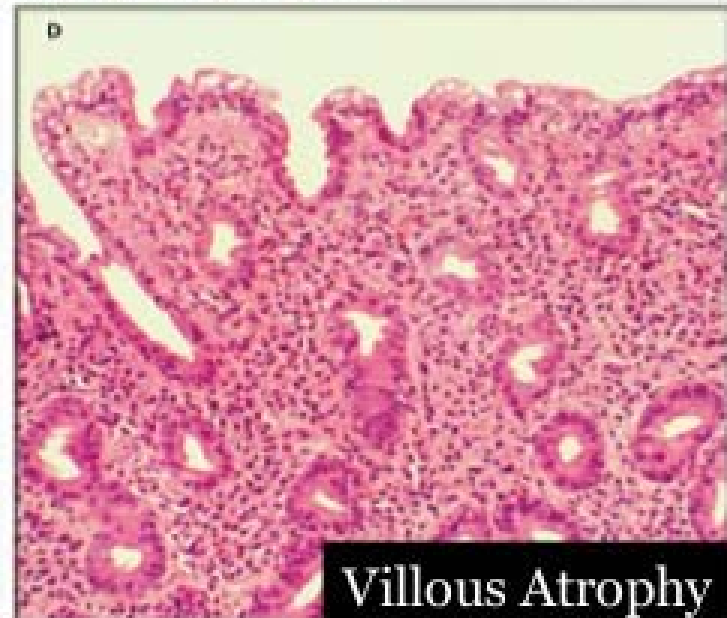
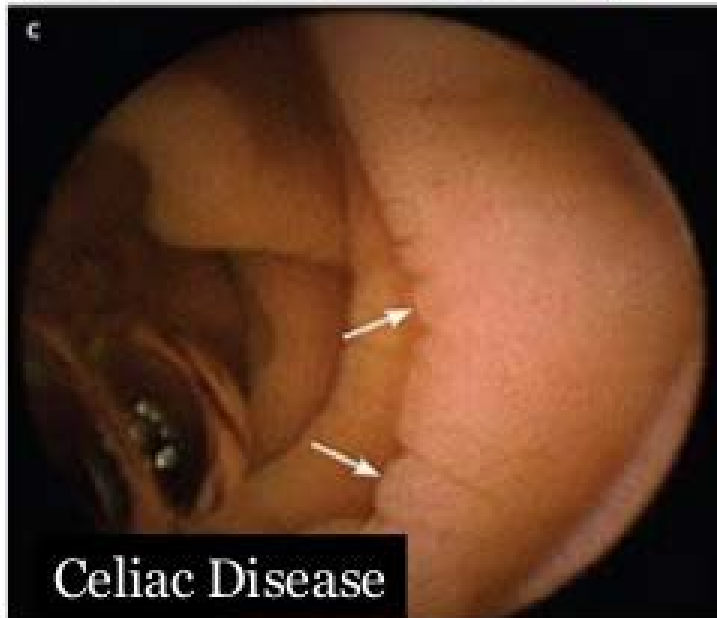
Diagnosis of Celiac Disease

- IgA antibodies to TTG first and best test; if under 2 years of age may need IgG ab to TTG
- Check total IgA antibodies because 3-5% patients are IgA deficient
- Antiendomerial antibodies have higher sensitivity than antigliadin antibodies; antigliadin antibodies can regress with gluten free diets
- Endoscopic biopsy still considered confirmatory however recent guidelines suggest if a patient has HLA haplotypes and TTG antibodies with classical symptoms then bx not necessary for dx

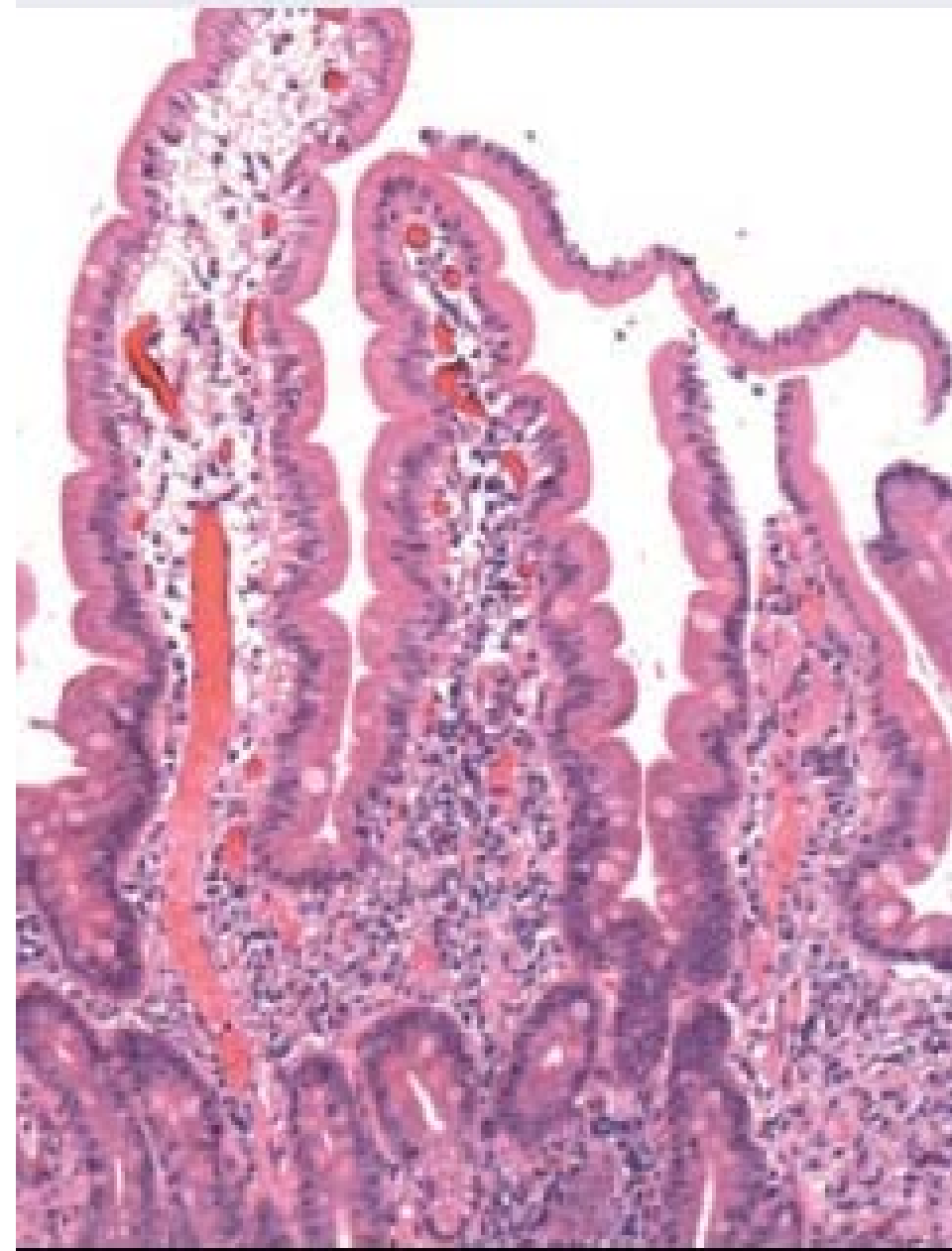
Epidemiology of Celiac Sprue

- US: 1/3000 persons = 3 million
- Europe = 3 million
- Under-diagnosed in most affected people; therefore true incidence about 1% Western population (Europe, Australia, Irish, Finnish- now with migration increasingly seen in Africa, Asia and the Middle East)
- Bimodal age distribution 8-12 months and 3-4th decade; prevalence in >60 yrs is 20%

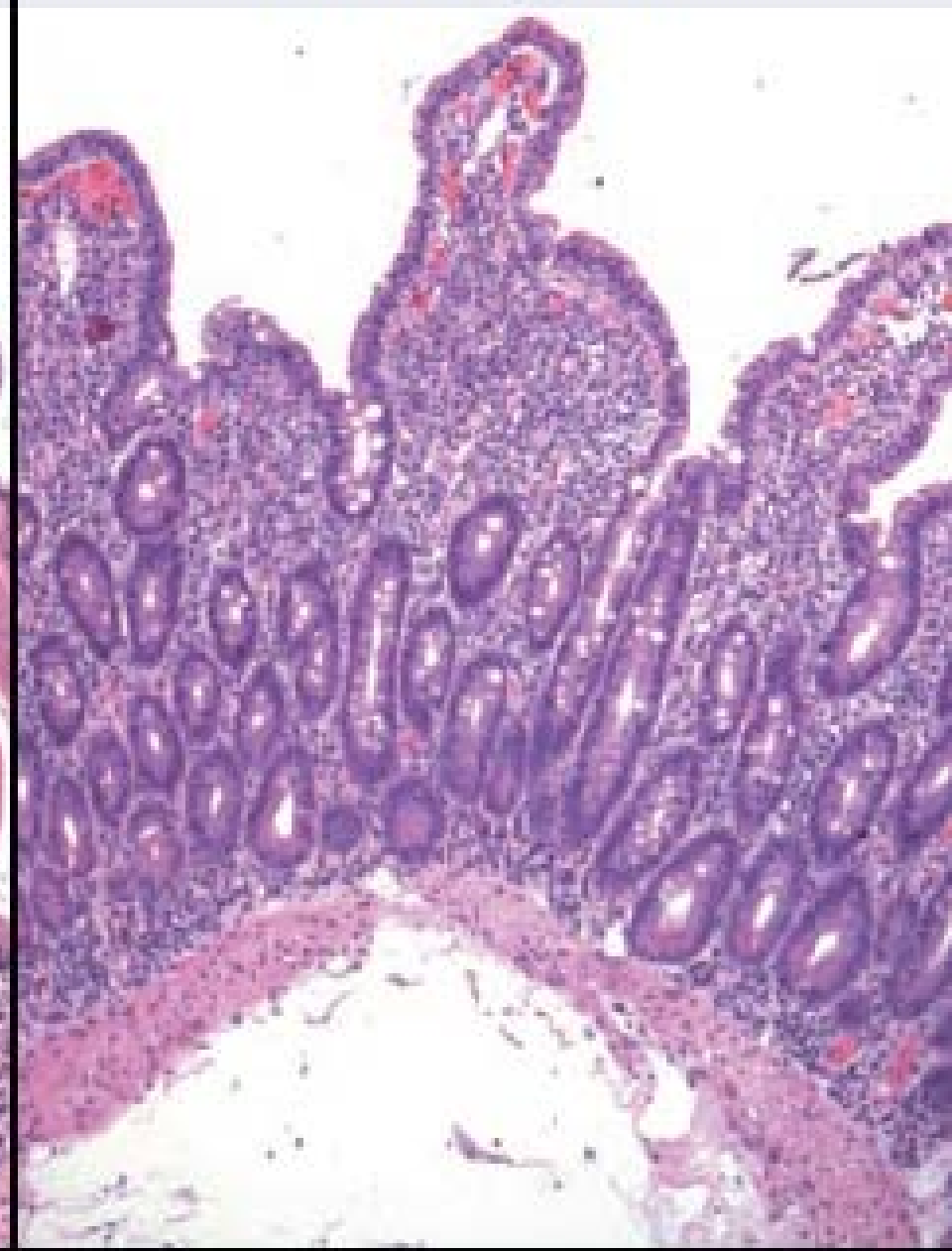
Endoscopy & Biopsy in Celiac Disease

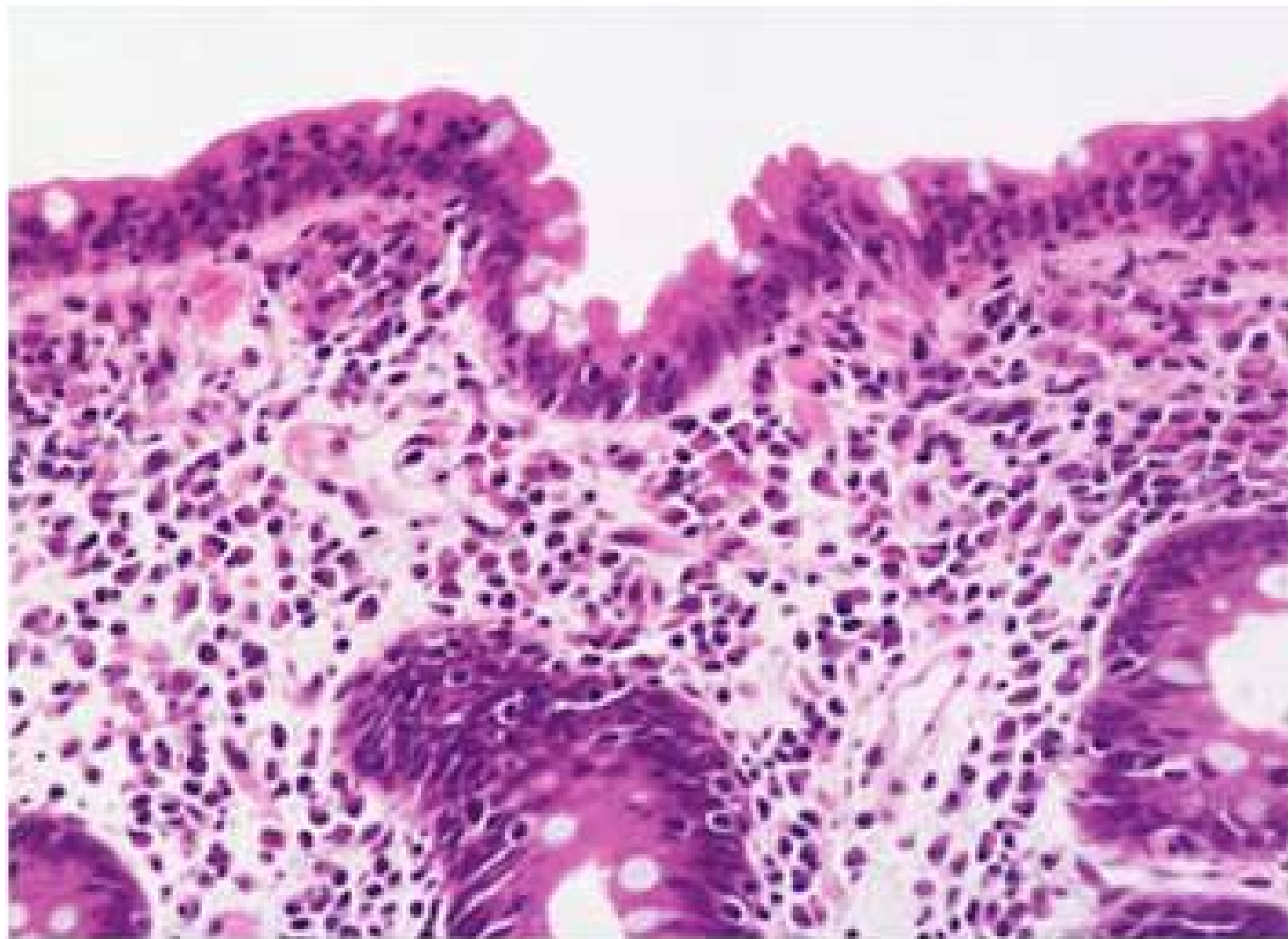


**Normal duodenal
mucosa**



**Duodenal mucosa
in celiac disease**







at a glance

Celiac Disease

Treatment of Celiac Disease

- Gluten restriction curative in 95%
- Refractory in 5%- use corticosteroids, poor outcome
- Involve dietician, support groups, on-line recipes, read labels including medications, cosmetics, etc.
- *Although rare, remember there is increased risk of lymphoma and adenocarcinoma of the pancreas, esophagus, small bowel, biliary tract, including T and B cell non-Hodgkins lymphoma

Whipple's Disease-rare 1/1 million

- Described in 1907 in a 35 yr old medical missionary by George Hoyt Whipple
- Suspected infectious etiology, bacteria seen by EM until causative agent definitely identified in 1992 as *Tropheryma Whipplei*. In 2003, original patient dx confirmed from study of archived tissues at Hopkins
- Readily present in the environment, we are unsure of human transmission. Some people with the bacterium do not have the disease
- Immune susceptibility suspected as 87% cases are in Males of White or N. European descent.
- Recent studies show defective TH1 lymphocytes, with decreased CD 11 B (integrin alpha) expression important for macrophages to destroy intracellularly ingested *T. Whipplei* bacteria.
- Seen most in farmers and outdoor workers with frequent contact with sewage and waste water.

Whipple's Disease Presentation

Systemic Involvement

- GI tract
- Brain
- Joints
- Eyes
- Skin
- Heart
- Lungs

Sign's and Symptoms

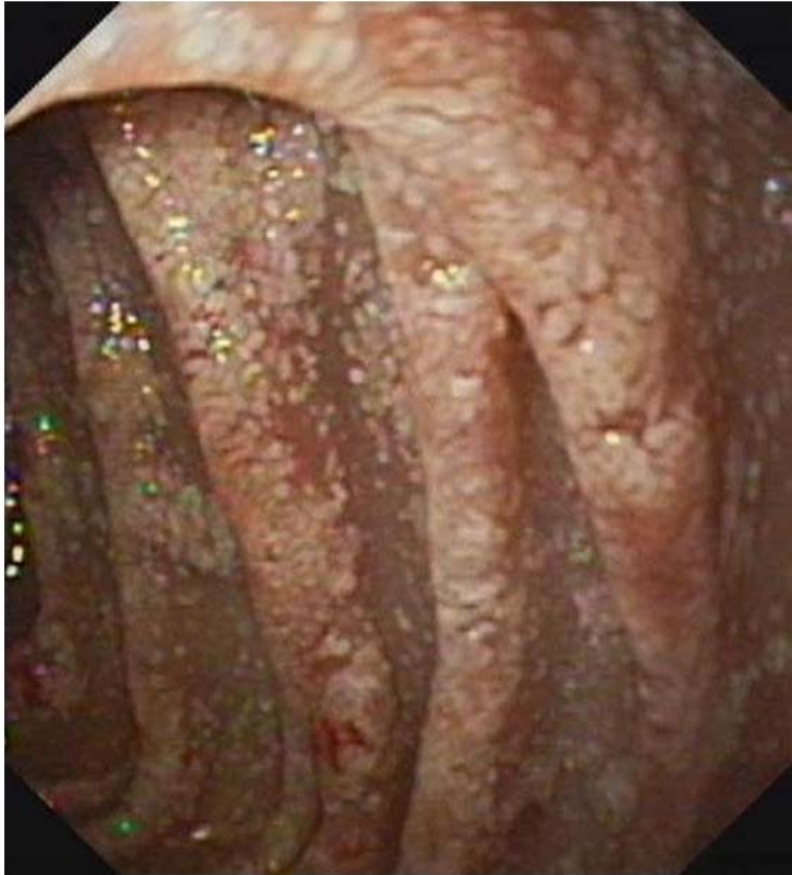
- Diarrhea, Steatorrhea
- Fever, migratory arthropathy
- Weight Loss, hypoalbumin
- Lower Extremity edema
- Splenomegaly, enlarged LN
- Hyperpigmentation of Skin
- Chest pain, cough
- Fatigue, anemia
- Visual impairment, nystagmus, memory loss, seizures, gait disturbance, "oculomasticatory myorhythmia"



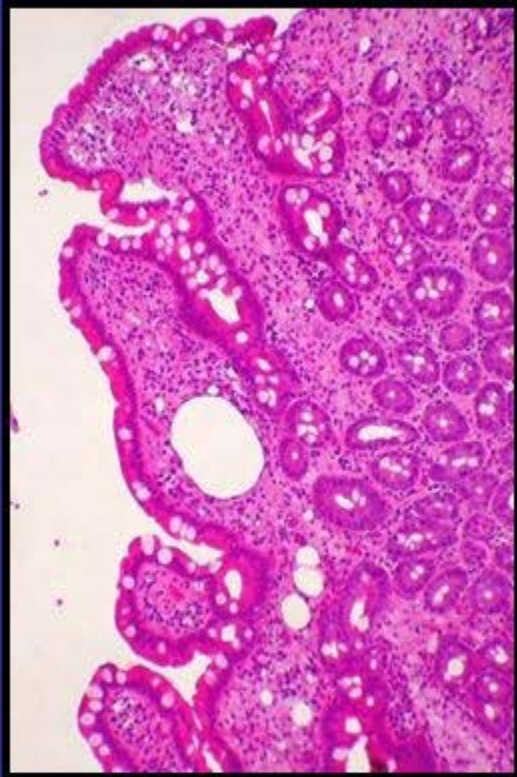
Whipple's Diagnosis

- Small bowel biopsy with “foamy macrophages” containing PAS positive staining organisms seen best on Electron Microscopy
- PCR for spinal fluid, synovial fluid, vitreous fluid
- PCR also positive in the saliva and stool, sensitive but not specific because also found in asymptomatic carriers. **PCR negative stool study most likely rules it out.

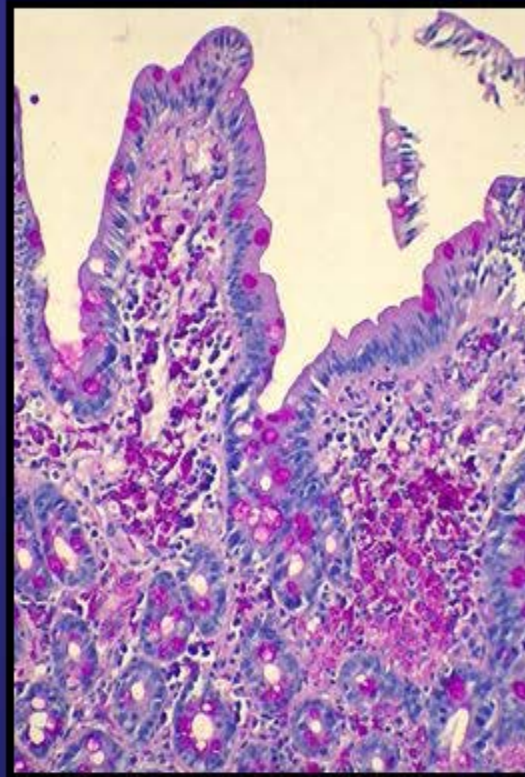
**Whipple's Disease initially referred to as
“intestinal lipodystrophy”
due to yellow appearance of villi**



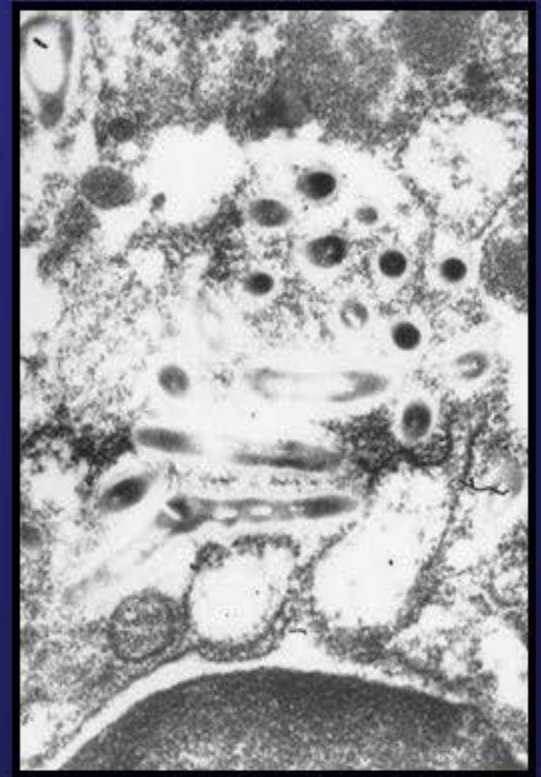
Whipple's Disease (Duodenum)



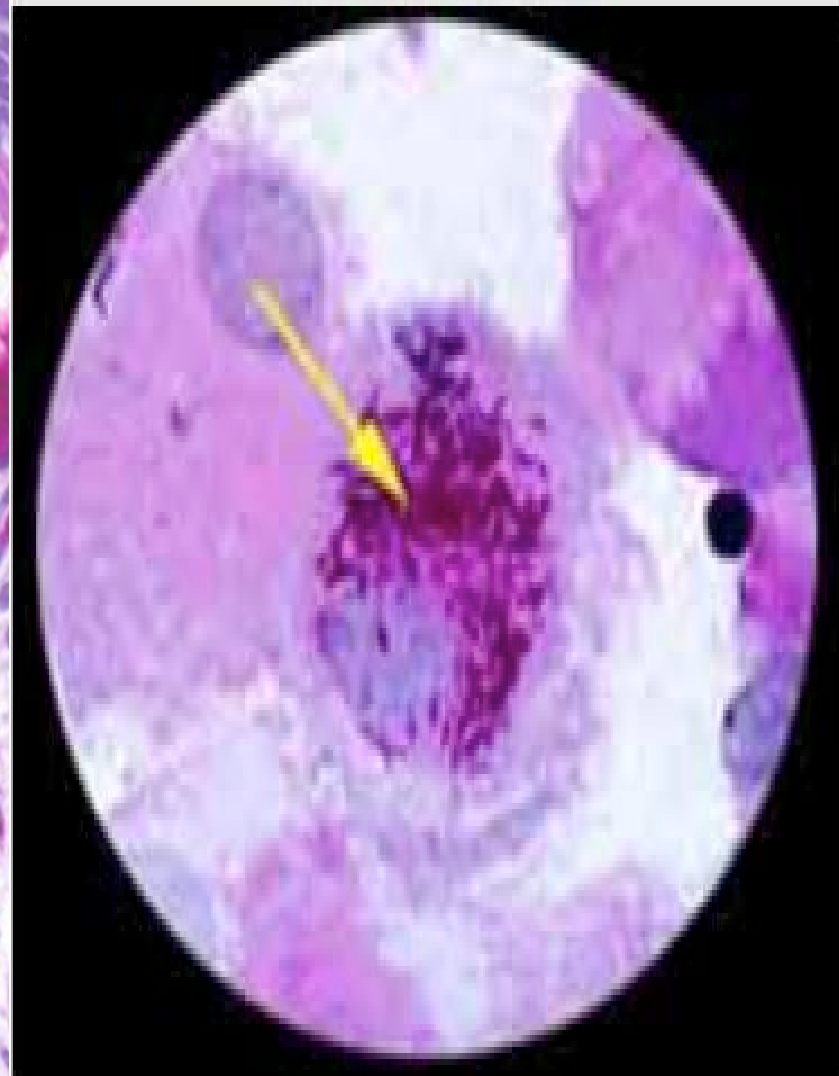
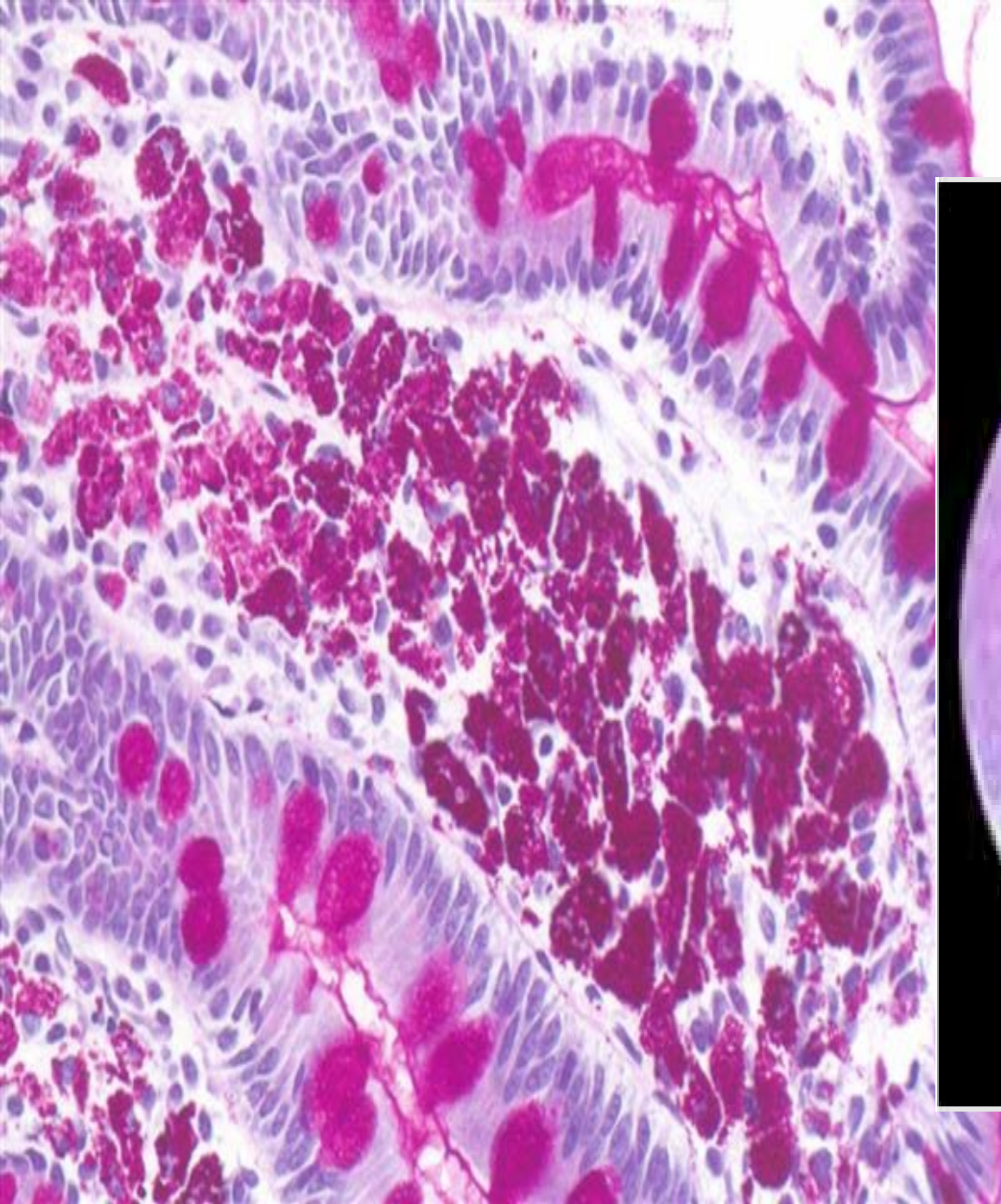
Low Power
H & E



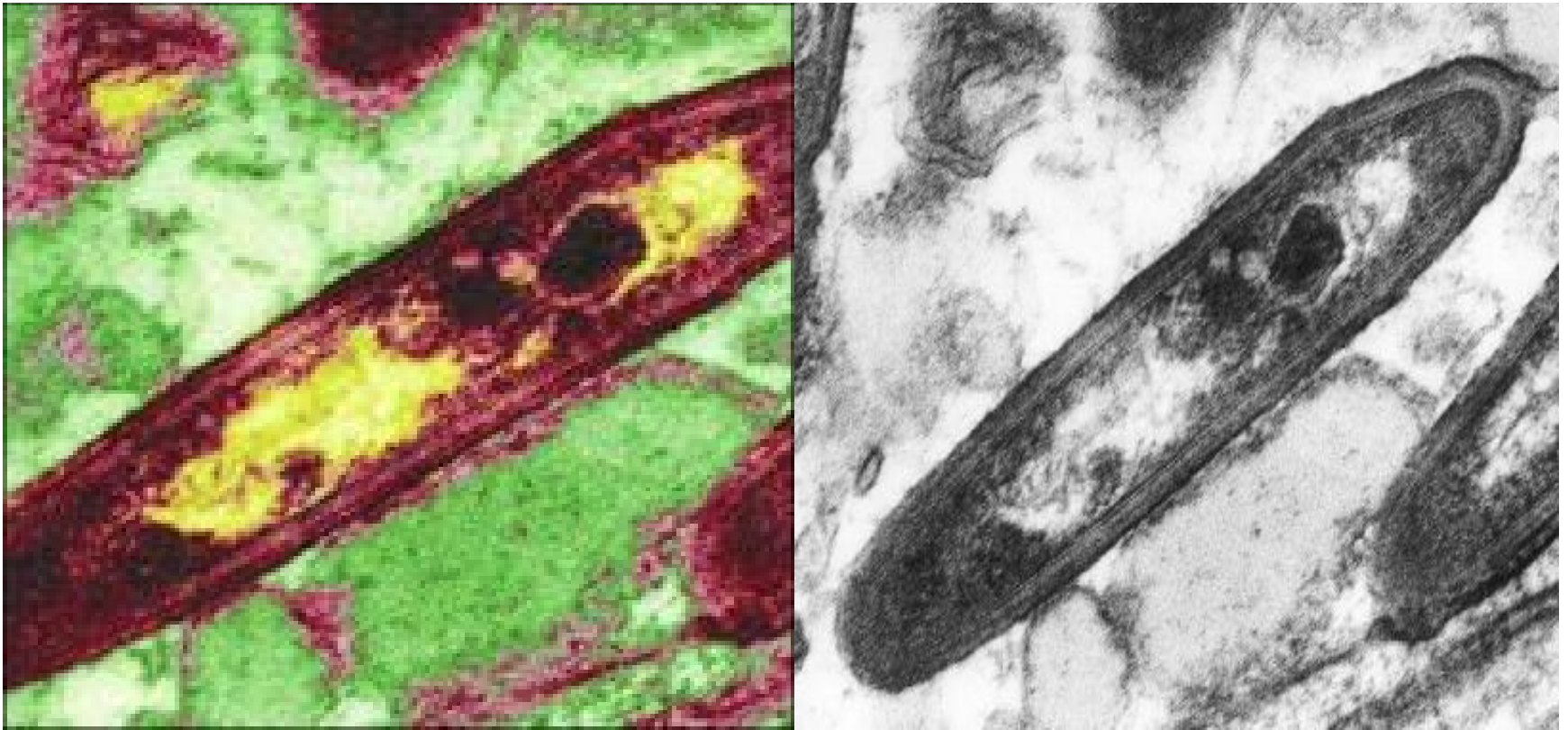
Low Power
PAS



EM

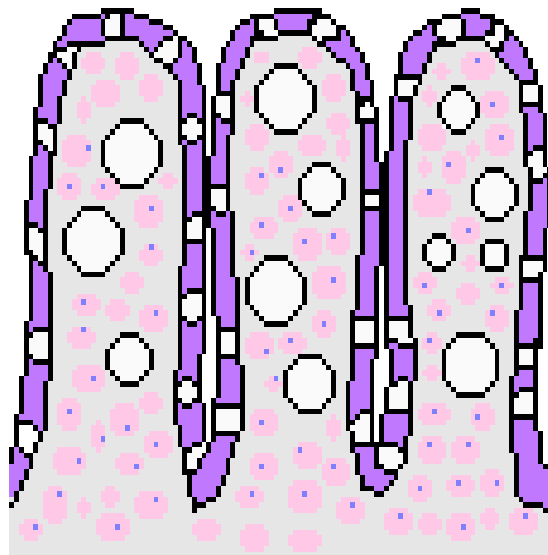


Tropheryma Whipplei- One of actinomycetes -Distant relative to MAI, mycobacterium paratuberculosis

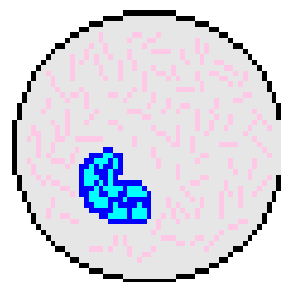


Whipple's disease

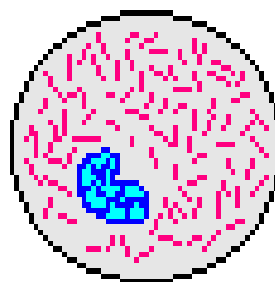
Easy to diagnose and treat -- if you think of it.



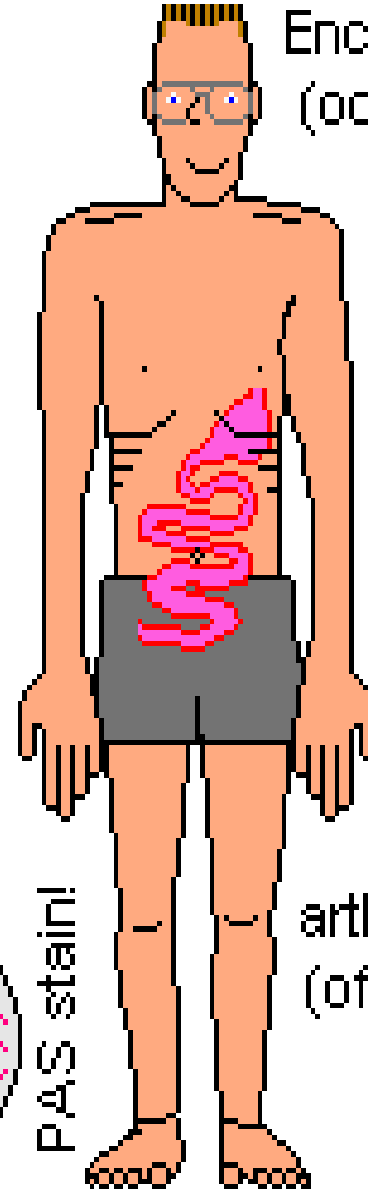
Bacteria-laden macrophages and lipid pools in the mucosa



Tropheryma whipplei bacilli within the macrophages



PAS stain!

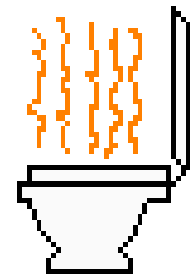


Encephalopathy (occasionally)

Lymphadenopathy (same morphology as gut)

Malabsorption and diarrhea

arthritis (often)



steatorrhea

Whipple's Disease Treatment

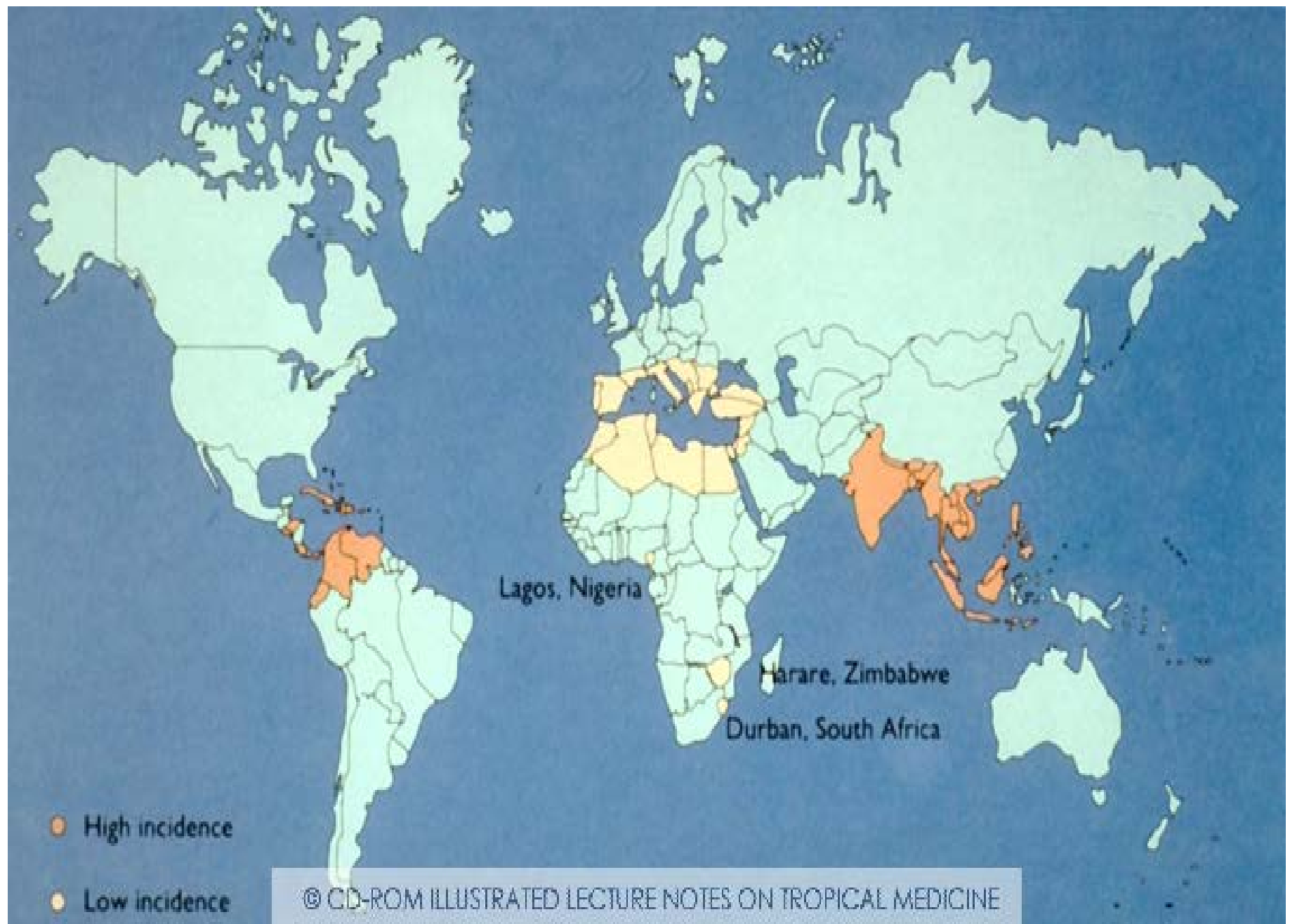
Antibiotics for 1-2 years: (Relapse rate 40% if course is shortened). Response rate good, sx reduction in 1-2 weeks and gone by 1 month.

- Mild disease (no neurological symptoms) use Septra DS twice daily 1-2 years with nutrient replacement: folic acid, calcium, iron, magnesium, vitamin D
- Severe disease and neurological sx: Favor 12-18 months doxycycline with hydrochloroquine (plaquenil) AND septra, AND micronutrient replacement as above. Can also start with 2-4 weeks IV Rocephin for severe CNS disease then switch to oral abx as above



Tropical Spru

wiseGEEK



Tropical Sprue = Environmental enteropathy = Tropical malabsorption

- Cause unknown, likely the result of persistent or recurrent bacterial, viral, amoeba or parasitic infection.
- Associated with folic acid deficiency, altered intestinal motility, and persistent small bowel intestinal bacterial overgrowth
- Found within 30 degrees of the equator, especially seen in Caribbean, South America, India, SE Asia.
- Recent travel to these areas are key historical factors, *travel related risk unknown

Tropical Sprue (Post Infectious Sprue)

- In people living in or visiting tropics
 - Endemic in Puerto Rico and parts of Caribbean
- Symptoms appear months or even years after visit
- Pathogenesis related to bacterial infection superimposed on pre-existing small intestine injury
- All parts of small intestine equally involved
- Small intestine may appear near normal
- Difficult to differentiate from celiac disease
- Responds to antibiotics

Tropical Sprue signs and symptoms

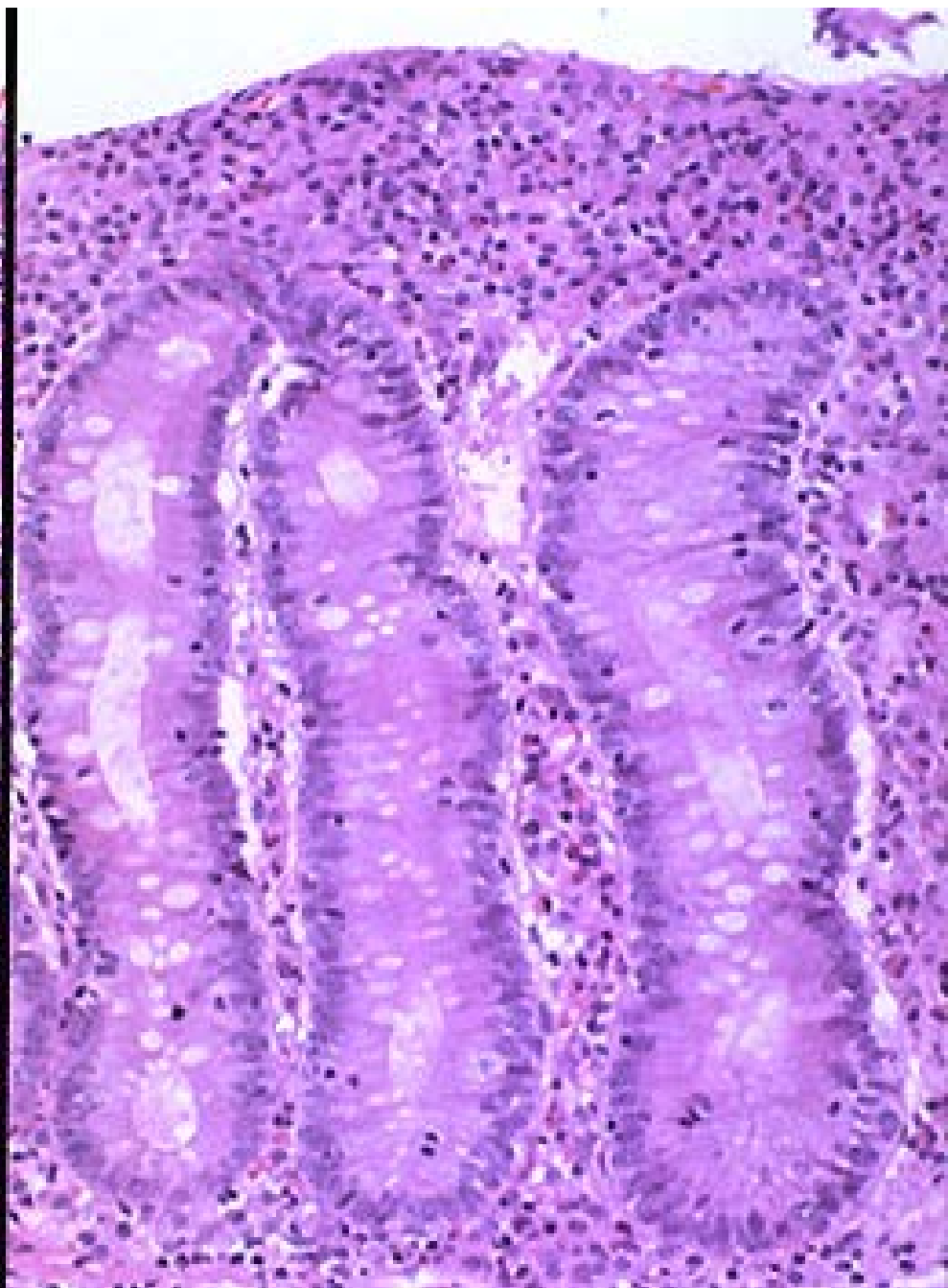
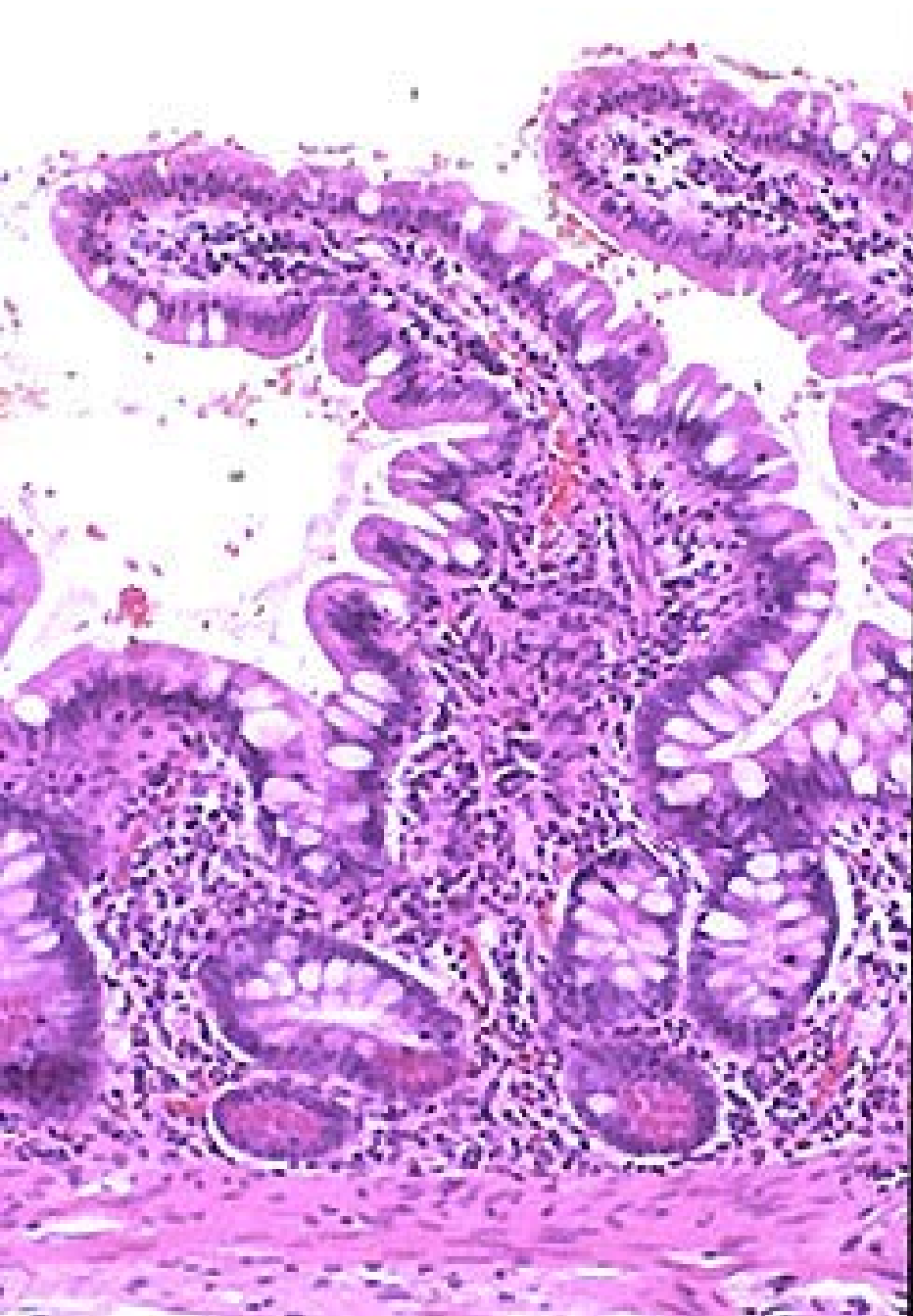
- Usually heralded by acute diarrhea, fever, malaise, then becomes chronic with diarrhea, steatorrhea, weight loss, anorexia, malaise
- Nutritional deficiencies including low levels fat soluble vitamins (A,D,E,K), and B12, and folate
- Low albumin, and calcium
- May see thickened small bowel folds on imaging
- DDX: TB, parasitic infection HIV/AIDS, IBD or chronic pancreatitis

Tropical Spru Prevention

- Boiled or bottled water when traveling to equatorial regions
- Peel fruits (bananas, oranges)
- Unsure if prophylactically taking xifaxan, septra, cipro, bismuth, etc. can reduce risk but likely (no clinical trials).

Tropical Spru Treatment

- Septra DS 3-6 months (or longer) WITH folic acid, and B-12 supplementation. Evaluate and treat for fat soluble vitamin deficiencies (ADEK). Also check calcium and Mg
- Relapses not uncommon and if so, retreat
- May need folic acid and B-12 replacement indefinitely



True or False?

- Persistently elevated IgA endomesial and TTG antibodies after 1 year of gluten restriction may indicate poor compliance with diet
- Malabsorption occurs in celiac spru, tropical spru, and Whipple's disease and small intestinal bacterial overgrowth
- Gastrointestinal symptoms are distinctly different in celiac vs. tropical spru, vs. Whipple's Disease
- Skin lesions are not seen in tropical spru, are most common in Whipple's disease, and occur most often on the palms and soles in celiac spru
- The endoscopic and histologic appearance is most similar for celiac and tropical spru
- Antibiotics can cure both celiac and tropical spru
- Micronutrient deficiencies are least common in tropical spru, compared to celiac and Whipple's.

Which Disease?

- A negative stool PCR may exclude this disease
- Antibiotic treatment can reverse most of the signs and symptoms within 1-2 weeks
- Foamy macrophages seen in intestinal biopsies
- Prevalence in white farmers suggests genetic predisposition
- Whipple's Disease

Which Disease?

- Elevated liver enzymes
- Associated with other autoimmune diseases such as thyroid or type I diabetes
- Predisposed to GI cancers
- Multi-organ involvement including skin, liver, pancreas, CNS
- Celiac spru

Which disease?

- Dr. Mehta is particularly at risk.....
- Tropical sprue

My funny funny patient-2013

- Duodenal biopsies showed mild villous blunting and increased plasma cells and lymphocytes.
- Treated as “tropical spru” with septri-DS and folic acid plus MVI for 6mo; relapsed at 1 year and retreated, continued on folate and MVI
- Says she’s “fat now” at 130 pounds, married with children, happy, still about the funniest person I’ve ever met “Remember me, I used to have the worst farts?”

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