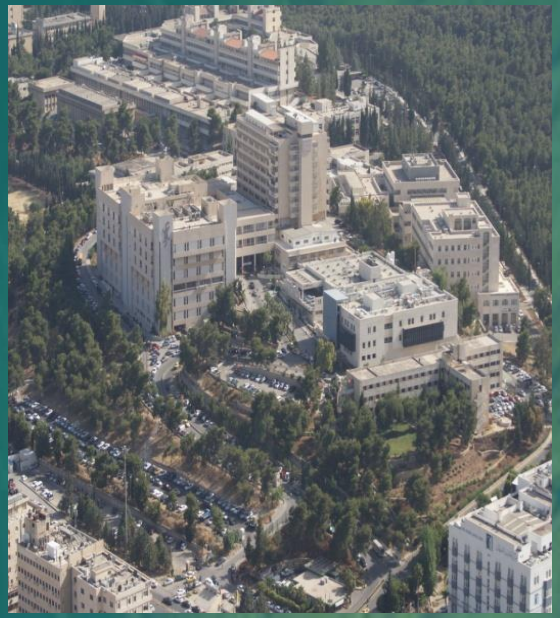
Celiac Disease



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NASPGHAN

North **A**merica **S**ociety of **P**ediatric **G**astroenterology, **H**epatology, **A**nd **N**utrition

content

- Definition
- Pathogenesis
- Epidemiology and risk groups
- Clinical manifestations
- Diagnosis
- Treatment

Definition

Celiac disease is an:

- **immune-mediated enteropathy**
- **caused by a permanent sensitivity to gluten**
-
- **in genetically susceptible individuals.**

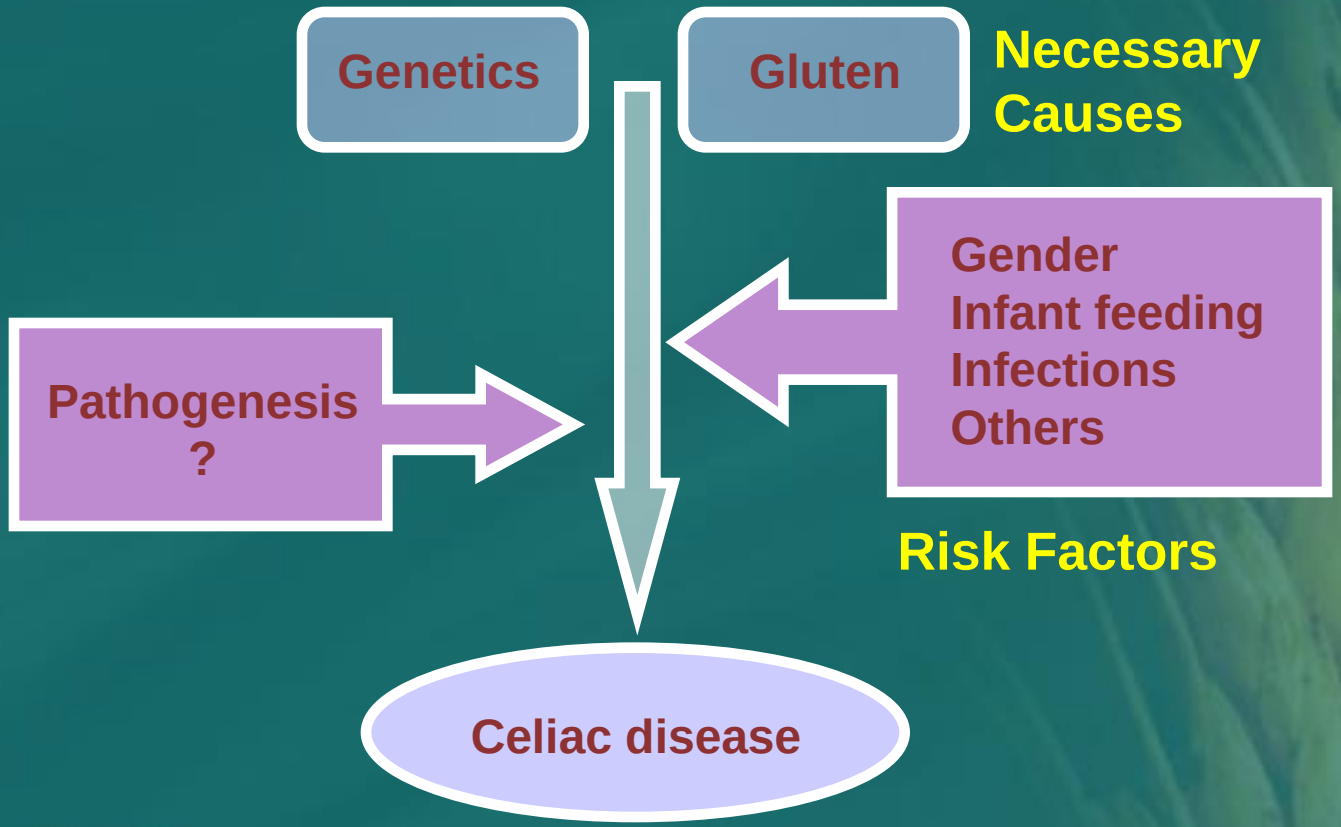
Expanded Definition

- Celiac disease is an autoimmune condition
- Occurs in genetically susceptible individuals
  - DQ2 and/or DQ8 positive HLA haplotype is necessary but not sufficient
- A *unique* autoimmune disorder because:
  - both the environmental trigger (gluten) and the autoantigen (tissue Transglutaminase) are known
  - elimination of the environmental trigger leads to a complete resolution of the disease

Pathogenesis

- Genetic predisposition
- Environmental triggers
  - Dietary
  - Non dietary?

Pathogenesis



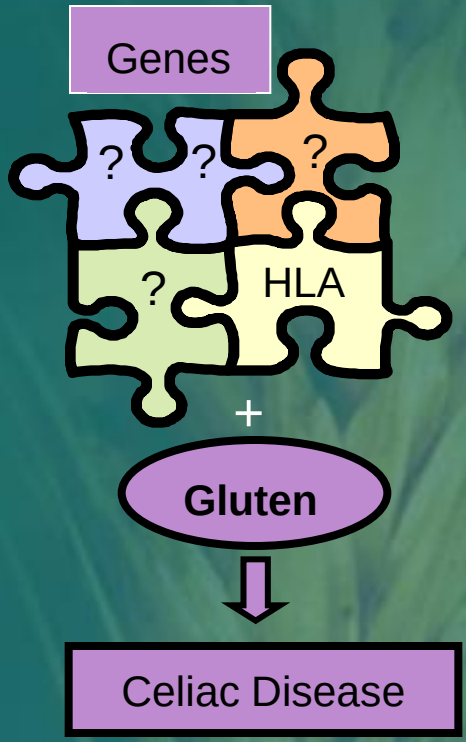
Genetics

- Strong HLA association
- 90 - 95% of patients HLA-DQ2 +ve
- Most of the remainder are HLA - DQ8 +ve

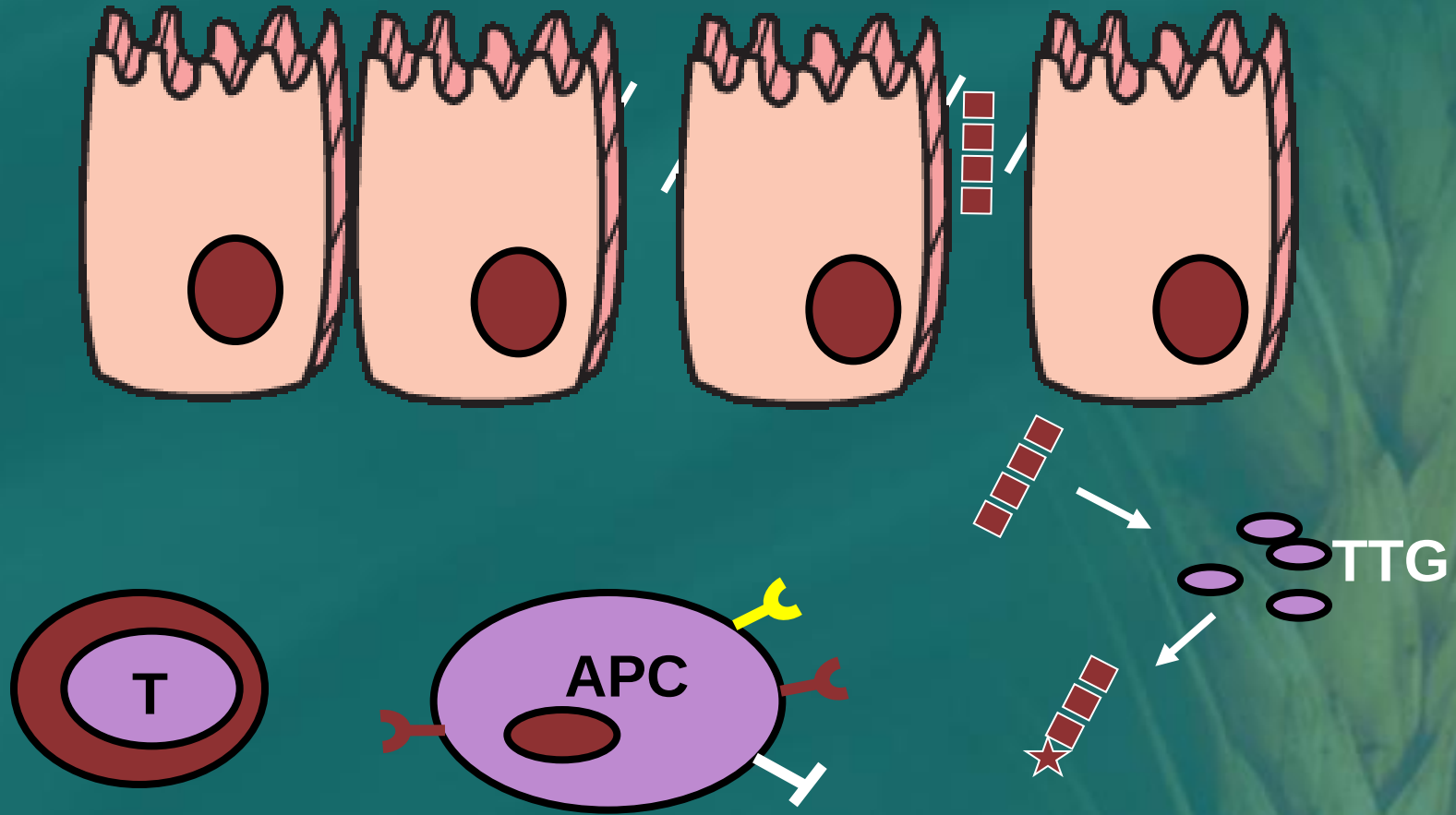
Genetics

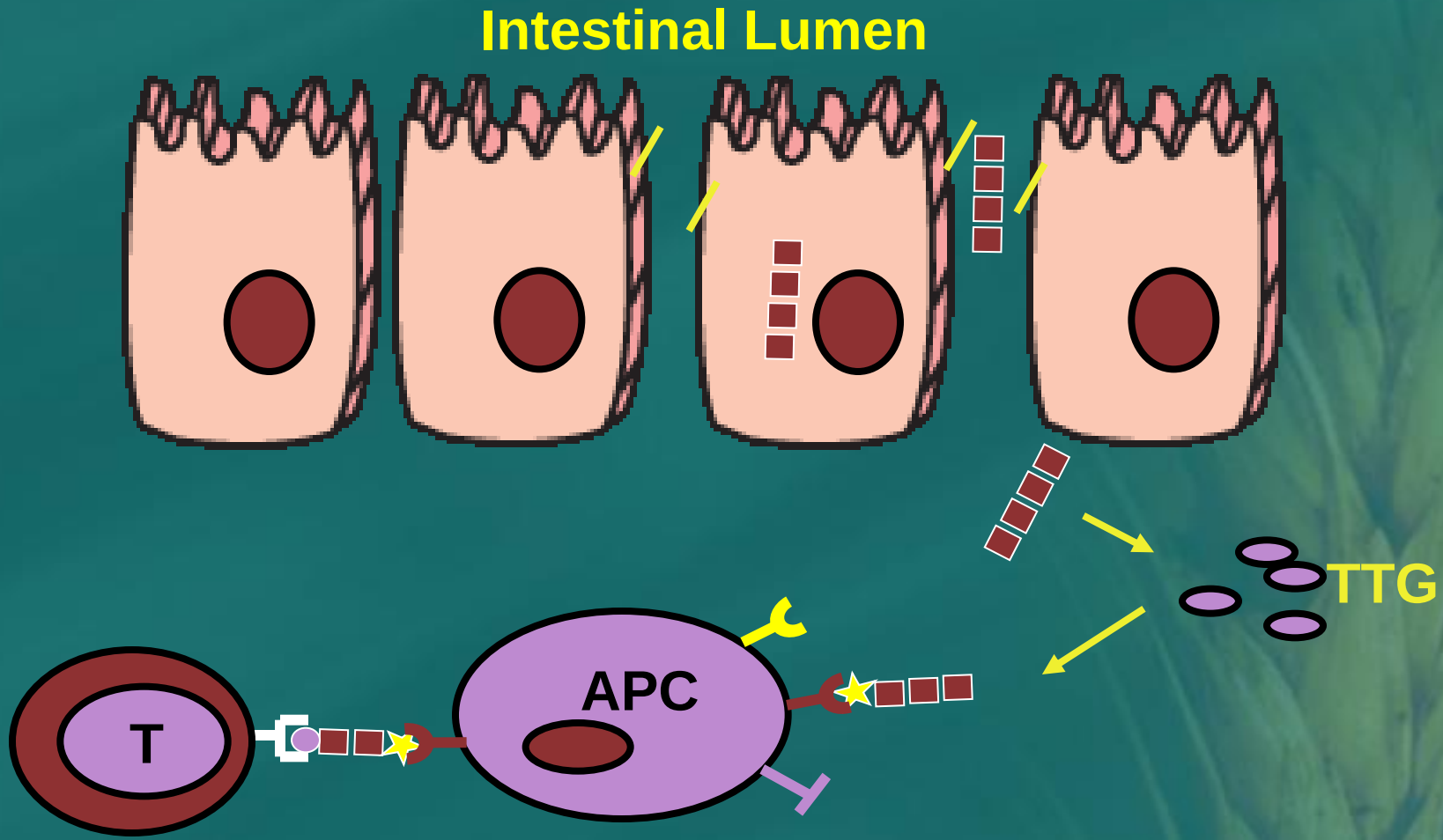
- Several genes are involved

- HLA-DQ2 and / or DQ8 genes are necessary **(No DQ2/8, no Celiac Disease!)**
- but not sufficient for the development of the disease

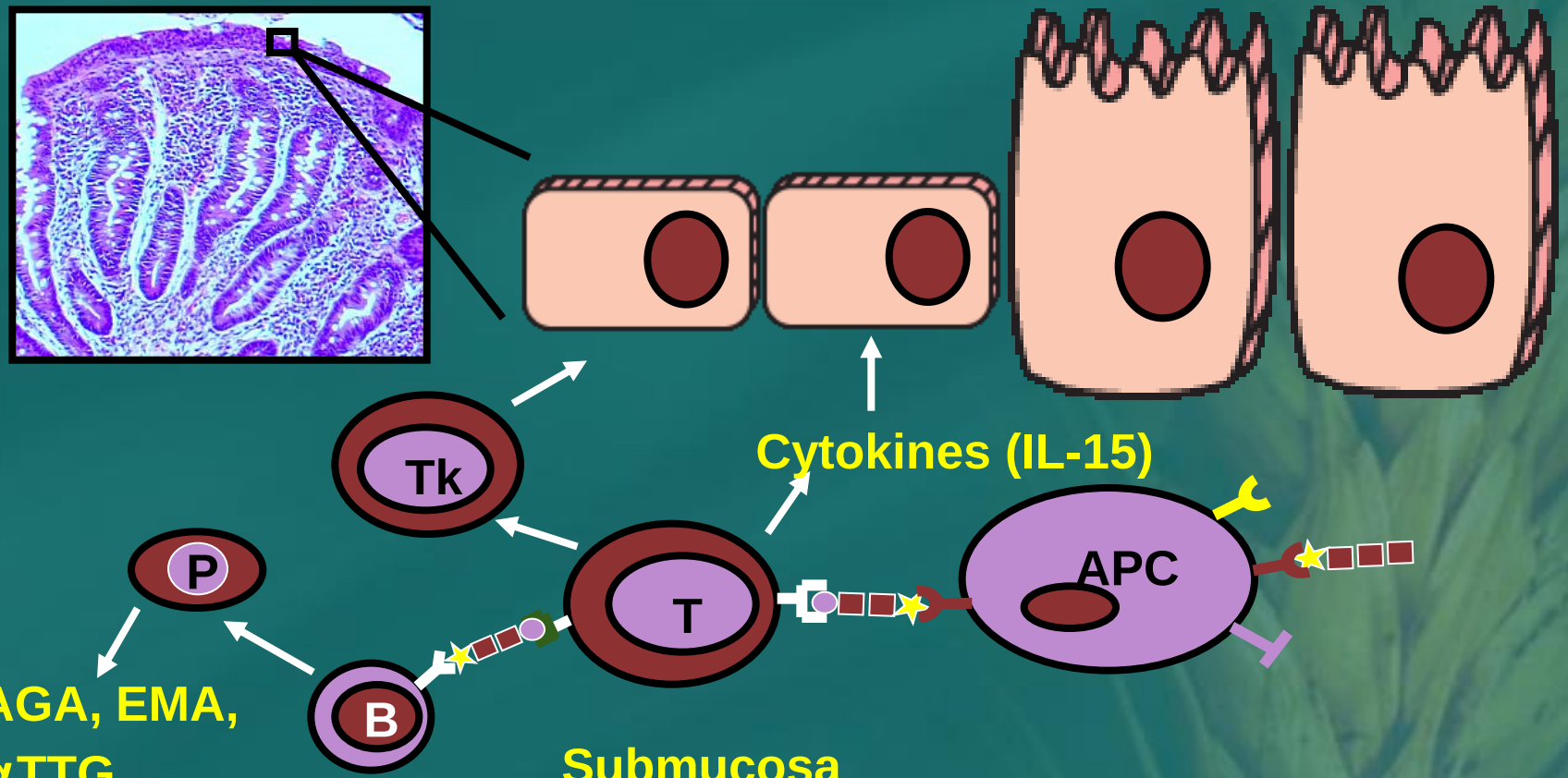


Intestinal lumen




Intestinal Lumen
TTG
APC
T
Submucosa

Intestinal lumen



Epidemiology

Epidemiology

The “old” Celiac Disease Epidemiology:

- A rare disorder typical of infancy
- Wide incidence fluctuates in space (1/400 Ireland to 1/10000 Denmark) and in time
- A disease of essentially European origin

Celiac Disease Prevalence Data

Geographic Area	Prevalence on clinical diagnosis*	Prevalence on screening data
Brasil	?	1:400
Denmark	1:10,000	1:500
Finland	1:1,000	1:130
Germany	1:2,300	1:500
Italy	1:1,000	1:184
Netherlands	1:4,500	1:198
Norway	1:675	1:250
Sahara	?	1:70
Slovenia	?	1:550
Sweden	1:330	1:190
United Kingdom	1:300	1:112
USA	1:10,000	1:133
Worldwide (average)	1:3,345	1:266

*based on classical, clinical presentation

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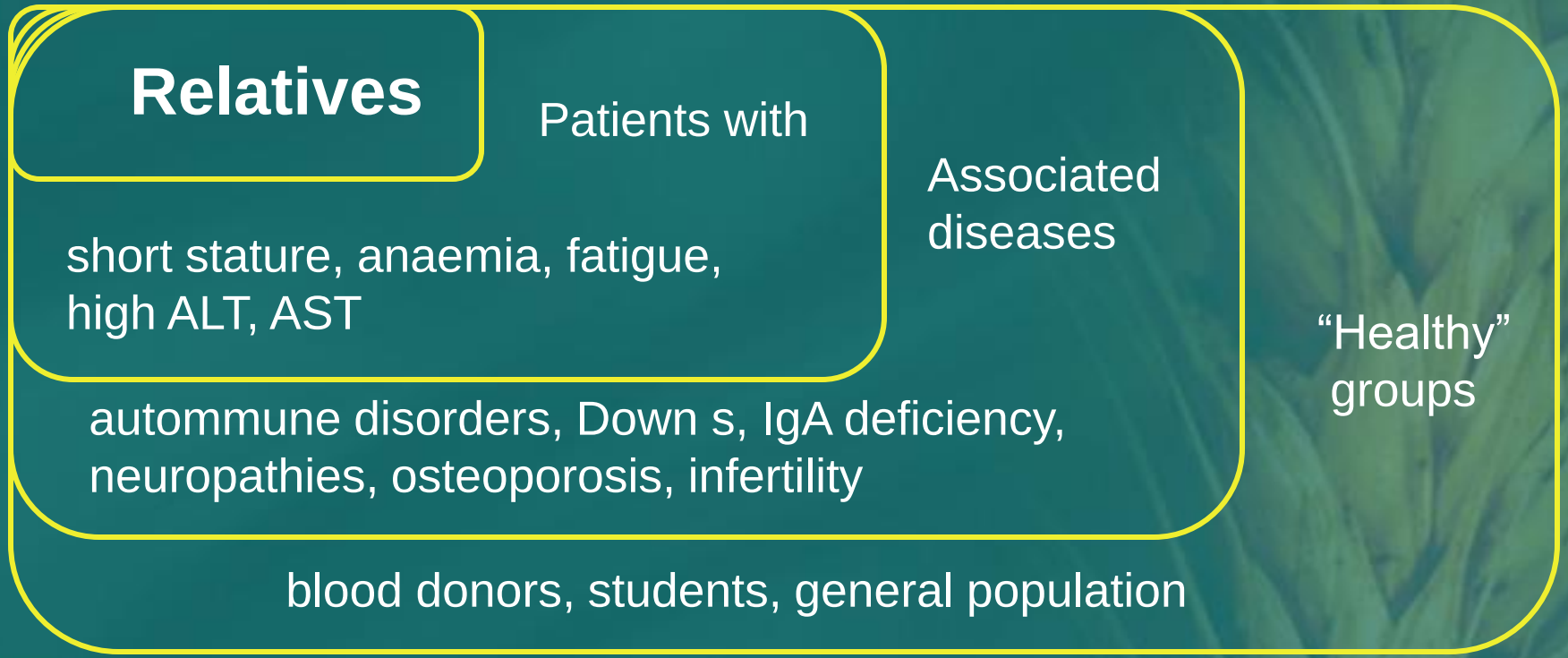
Fasano & Catassi, *Gastroenterology* 2001; 120:636-651.

“Mines” of Celiac Disease Were Found Among:



Relatives

- Healthy population: 1:133
- 1st degree relatives: 1:18 to 1:22
- 2nd degree relatives: 1:24 to 1:39

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Fasano, et al, *Arch of Intern Med*, Volume 163: 286-292, 2003

Genetic Disorders

- Down Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8.2%
- IgA Deficiency: 7%
  - Can complicate serologic screening

Prevalence of Celiac Disease is Higher in Other Autoimmune Conditions

Type 1 Diabetes Mellitus:	3.5 - 10%
Thyroiditis:	4 - 8%
Arthritis:	1.5 - 7.5%
Autoimmune liver diseases:	6 - 8%
Sjögren's syndrome:	2 - 15%
Idiopathic dilated cardiomyopathy:	5.7%
IgA nephropathy:	3.6%

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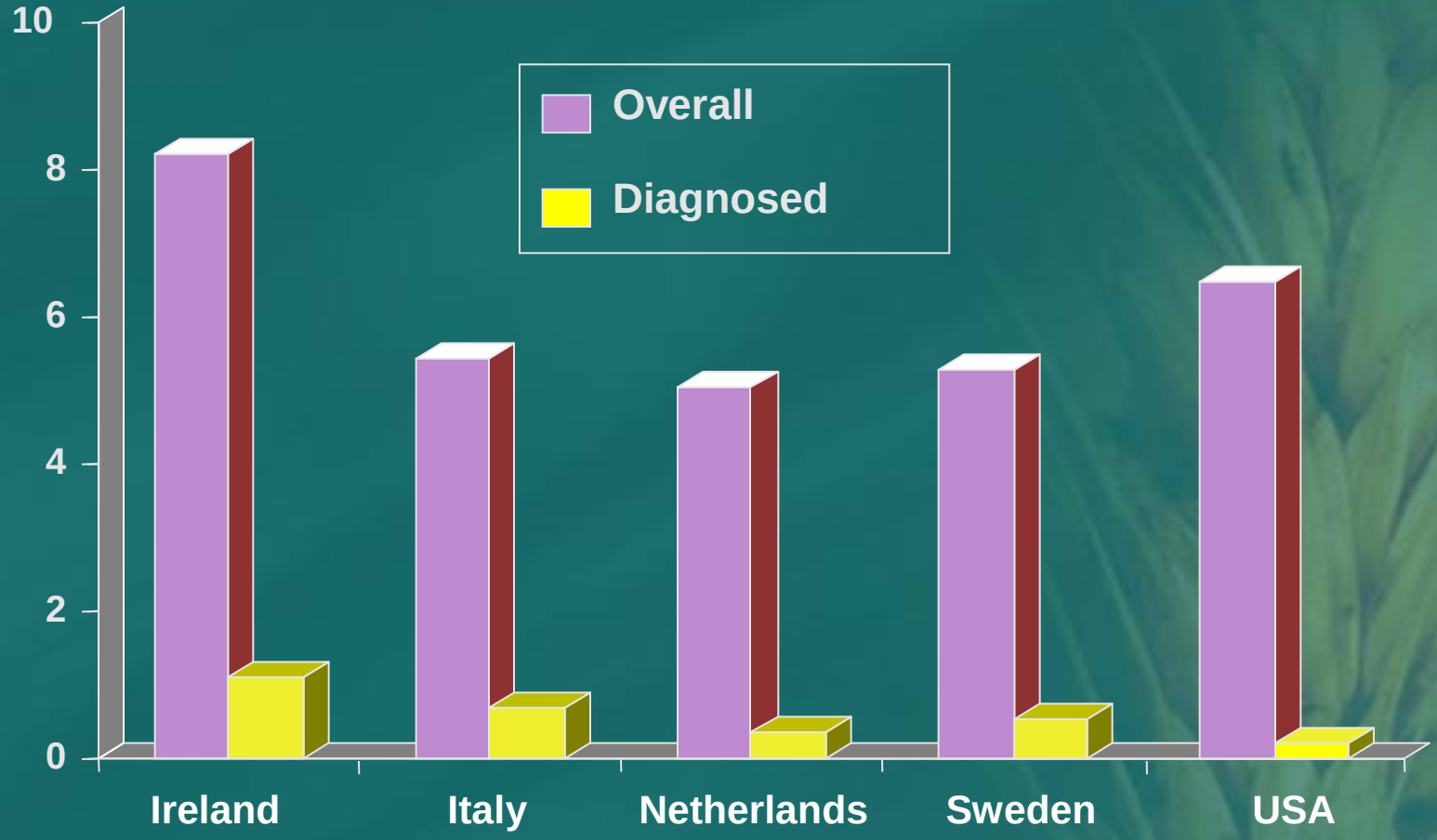
Celiac Disease Icebergs



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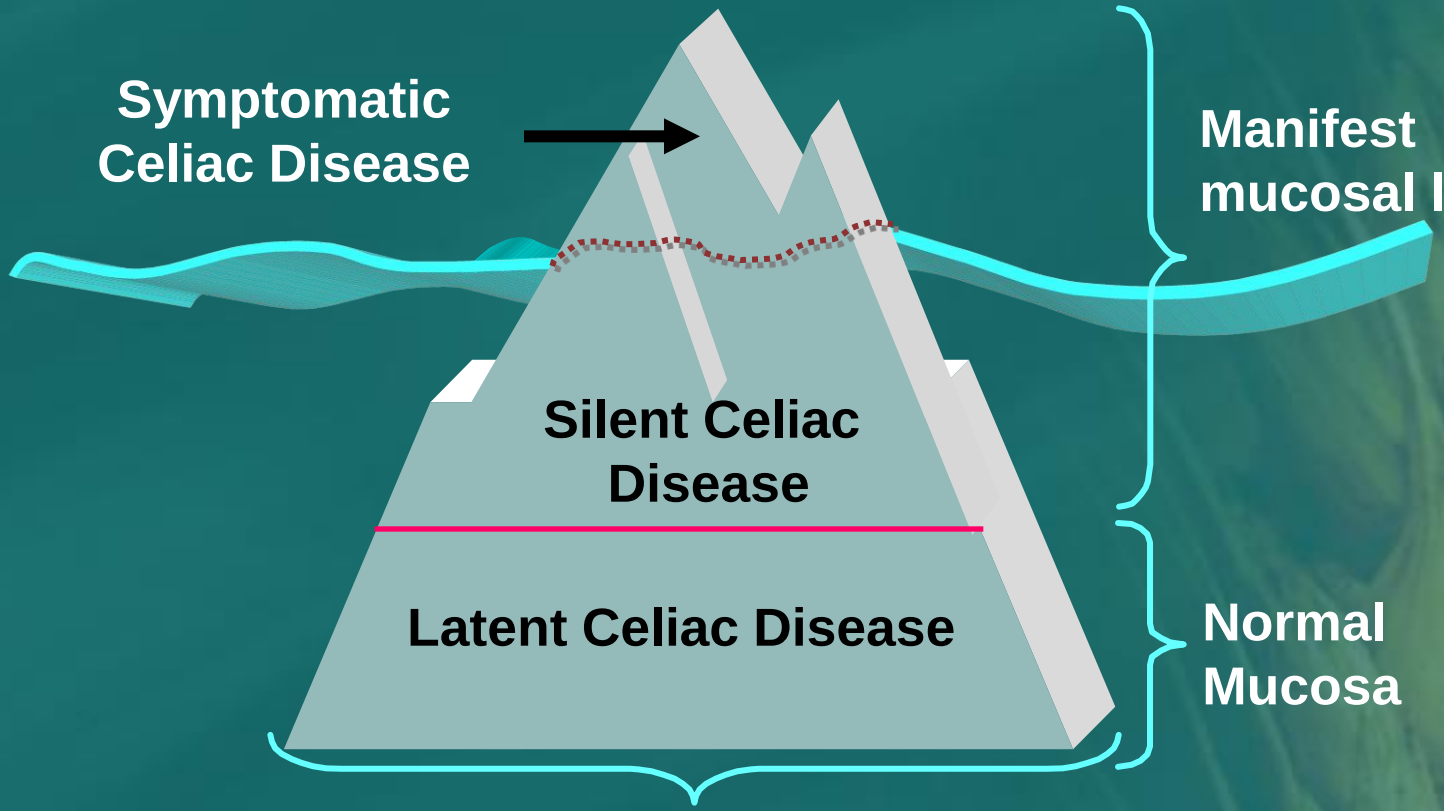
Clinical Manifestations

Clinical Manifestations

- **Gastrointestinal *(“classical”)***
- **Non-gastrointestinal *(“atypical”)***

- **Asymptomatic**

The Celiac Iceberg



Genetic susceptibility: - DQ2, DQ8
Positive serology

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1: Gastrointestinal Manifestations ("Classic")

Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

Rarely: Celiac crisis

Typical Celiac Disease

2: Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

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Listed in descending order of strength of evidence

Dermatitis Herpetiformis

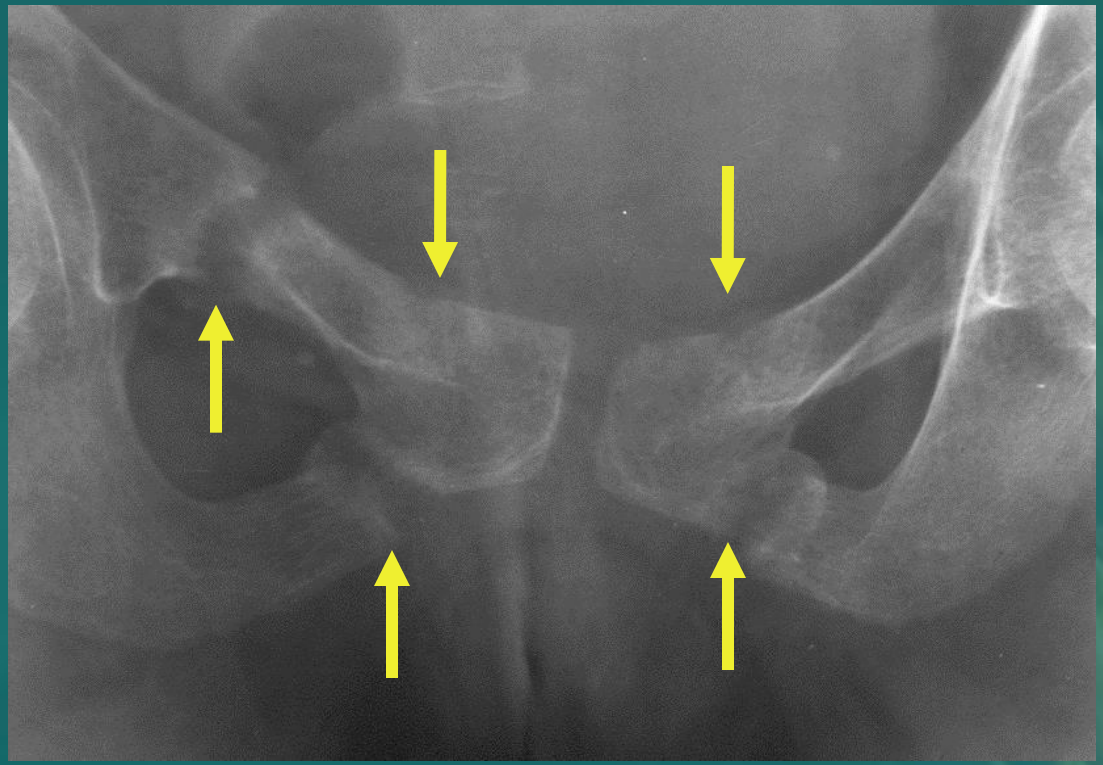
- Erythematous macule > urticarial papule > tense vesicles
- Severe pruritus
- Symmetric distribution
- 90% no GI symptoms
- 75% villous atrophy
- Gluten sensitive

Garioch JJ, et al. *Br J Dermatol*. 1994;131:822-6.
Fry L. *Baillieres Clin Gastroenterol*. 1995;9:371-93.
Reunala T, et al. *Br J Dermatol*. 1997;136-315-8.

Dental Enamel Defects

Involve the secondary dentition
May be the only presenting sign of Celiac Disease

Osteoporosis

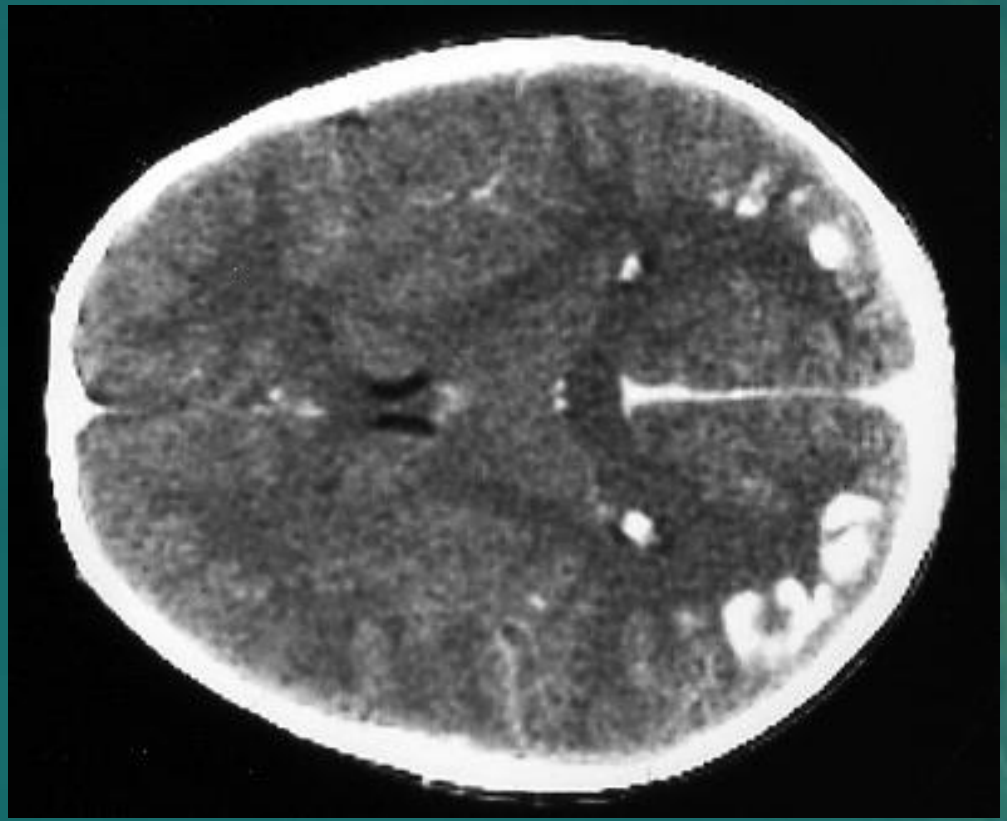


Low bone mineral density improves in children on a gluten-free diet.

Recurrent Aphtous Stomatitis

By permission of C. Mulder, Amsterdam (Netherlands)

CT Scan Showing Occipital Calcifications in a Boy with Celiac Disease and Epilepsy



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Celiac Disease Complicated by Enteropathy-Associated T-cell Lymphoma (EATL)

By permission of G. Holmes, Derby (UK)

3 :Asymptomatic

Silent ⟷ **Latent**

- **Silent:**
  No or minimal symptoms, "damaged" mucosa and positive serology

  Identified by screening asymptomatic individuals from groups at risk such:

  - **First degree relatives**
  - **Down syndrome patients**
  - **Type 1 diabetes patients, etc.**

3 – Asymptomatic

Silent **Latent**

- **Latent: *No symptoms, normal mucosa***
  - **May show positive serology. Identified by following in time asymptomatic individuals previously identified at screening from groups at risk. These individuals, given the "right" circumstances, will develop at some point in time mucosal changes (± symptoms) e.g DM pts**

Major Complications of Celiac Disease

- Short stature
- Dermatitis herpetiformis
- Dental enamel hypoplasia
- Recurrent stomatitis
- Fertility problems
- Osteoporosis
- Gluten ataxia and other neurological disturbances
- Refractory celiac disease and related disorders
- Intestinal lymphoma

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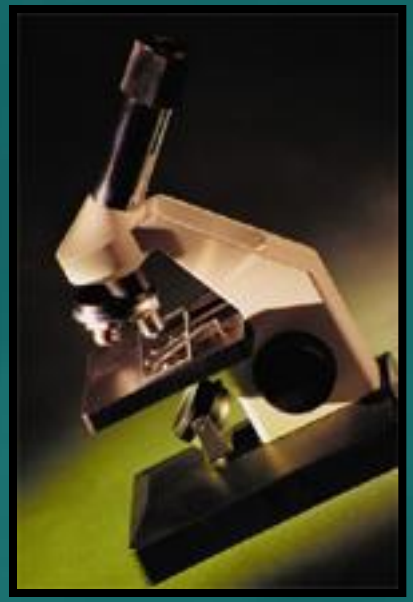
Diagnosis

Diagnosis



Diagnostic principles

- **Confirm diagnosis before treating**
  - **Diagnosis of Celiac Disease mandates a strict gluten-free diet for life**
    - **following the diet is not easy**
    - **QOL implications**
- **Failure to treat has potential long term adverse health consequences**
    - **increased morbidity and mortality**

1: Serological Tests

Role of serological tests:

- **Identify symptomatic individuals who need a biopsy**
- **Screening of asymptomatic "at risk" individuals**
- **Supportive evidence for the diagnosis**
- **Monitoring dietary compliance**

Serological Tests

- Antigliadin antibodies (AGA)
- Antiendomysial antibodies (EMA)
- Anti tissue transglutaminase antibodies (TTG)
  - first generation (guinea pig protein)
  - second generation (human recombinant)
- HLA typing

The Changing Celiac Epidemiology

The availability of sensitive serological markers made it possible to discover Celiac Disease even when the clinical suspicion was low.

Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97

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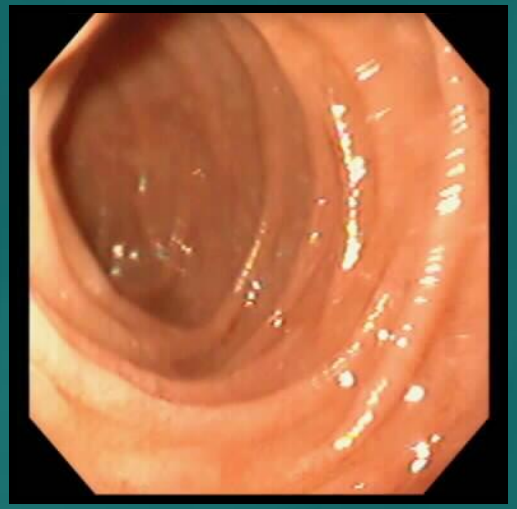
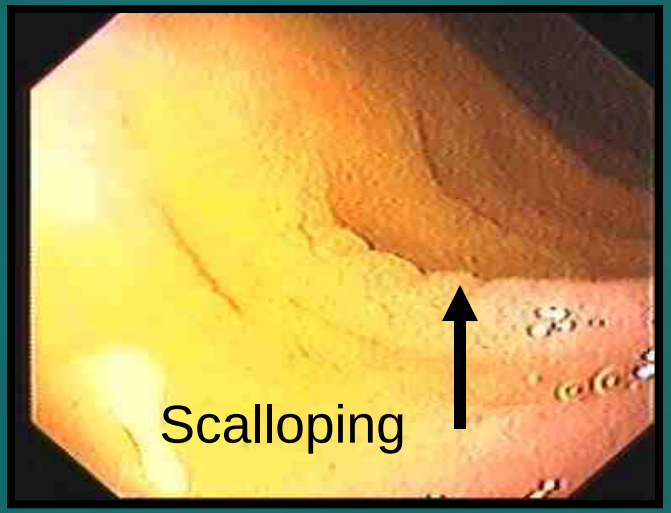
Farrell RJ, and Kelly CP. Am J Gastroenterol 2001;96:3237-46.

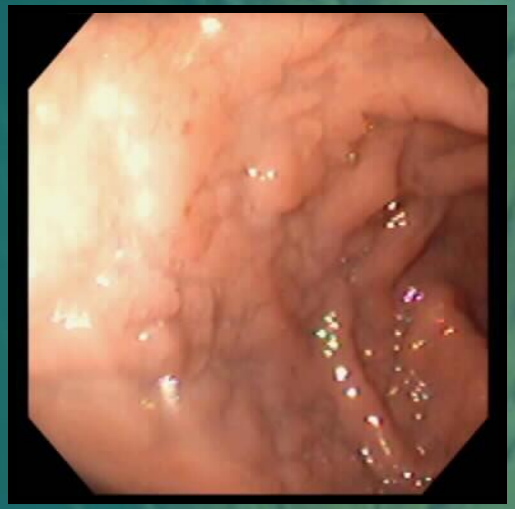
Endoscopic Findings



Normal Appearing

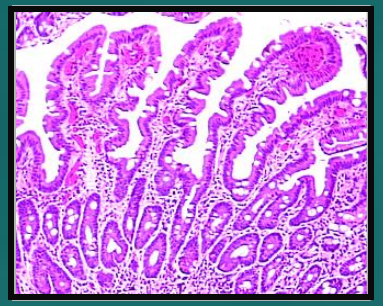


Scalloping

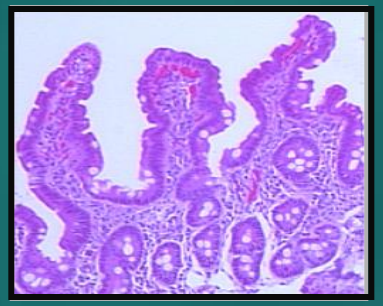


Nodularity

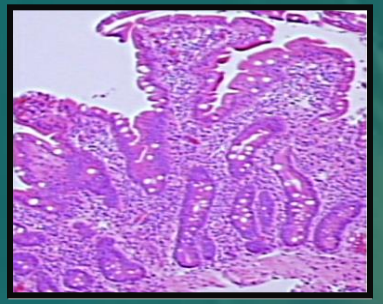
Histological Features



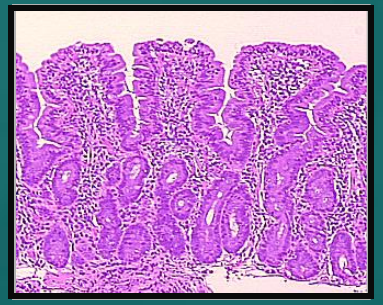
Normal 0



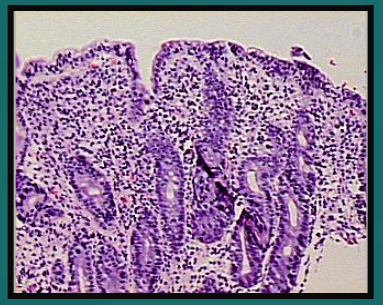
Infiltrative 1



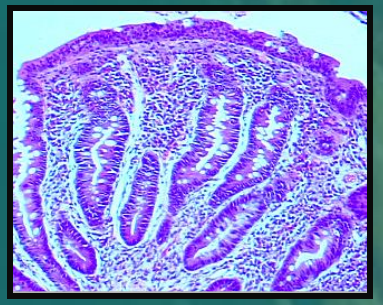
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

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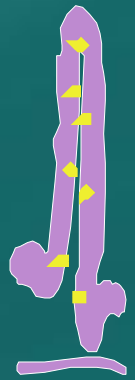
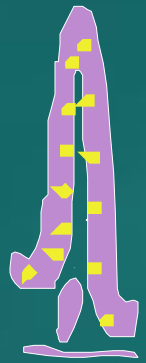
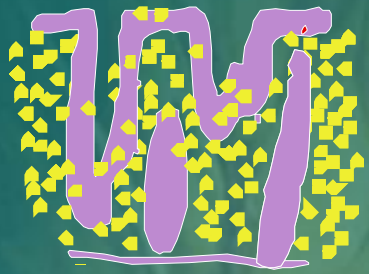
Horvath K. Recent Advances in Pediatrics, 2002.

Patterns of Mucosal Immunopathology

Type 0	Type 1	Type 2	Type 3
			
Normal	**Infilitrative**	**Hyper plastic**	**Flat destructive**
Celiac Diseae (latent)	Celiac Giardiasis Milk intolerance Tropical sprue Marasmus GVHR	Celiac Giardiasis Milk intolerance Tropical sprue Marasmus GVHR	Celiac Giardiasis Milk intolerance Tropical sprue Marasmus GVHR

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Marsh, *Gastroenterology* 1992, Vol 102: 330-354

Treatment

- **Only treatment for celiac disease is a gluten-free diet (GFD)**
  - **Strict, lifelong diet**
  - **Avoid:**
    - **Wheat**
    - **Rye**
    - **Barley**

Sources of Gluten

- **OBVIOUS SOURCES**
  - **Bread**
  - **Bagels**
  - **Cakes**
  - **Cereal**
  - **Cookies**
  - **Pasta / noodles**
  - **Pastries / pies**
  - **Rolls**

Sources of Gluten

- POTENTIAL SOURCES
  - Candy
  - Communion wafers
  - Cured Pork Products
  - Drink mixes
  - Gravy
  - Imitation meat / seafood
  - Sauce
  - Self-basting turkeys
  - Soy sauce

Other Items to Consider

- Lipstick/Gloss/Balms
- Mouthwash/Toothpaste
- Play Dough
- Stamp and Envelope Glues
- Vitamin, Herbal, and Mineral preparations
- Prescription or OTC Medications

Barriers to Compliance

- Ability to manage emotions – depression, anxiety
- Ability to resist temptation – exercising restraint
- Feelings of deprivation
- Fear generated by inaccurate information

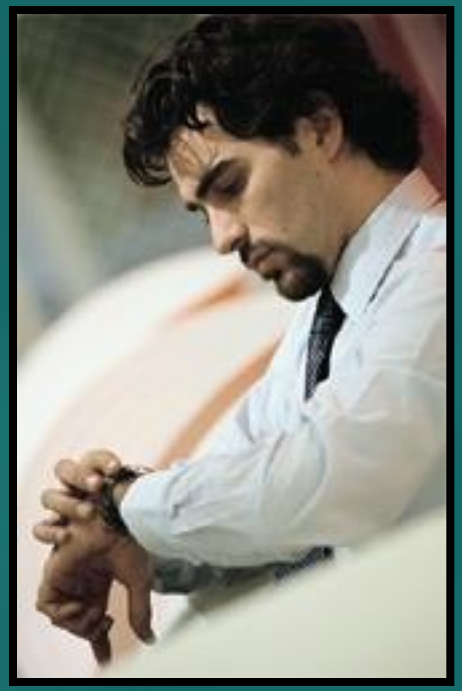
Dietary Adherence: A Common Problem

- Only 50% of Americans with a chronic illness adhere to their treatment regimen including:
  - diet
  - exercise
  - medication
- Dietary compliance can be the most difficult aspect of treatment

Barriers to Compliance

- Social Events – Not wanting to look/be different
- Support of Family and Friends – “Just a little bit – it won’t hurt you”

Barriers to Compliance

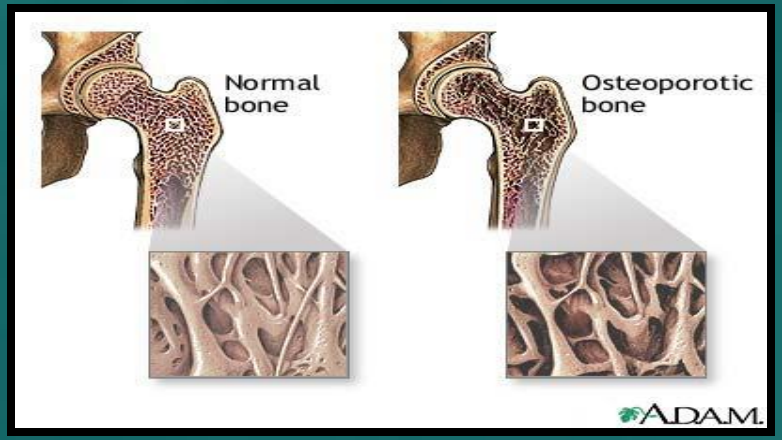


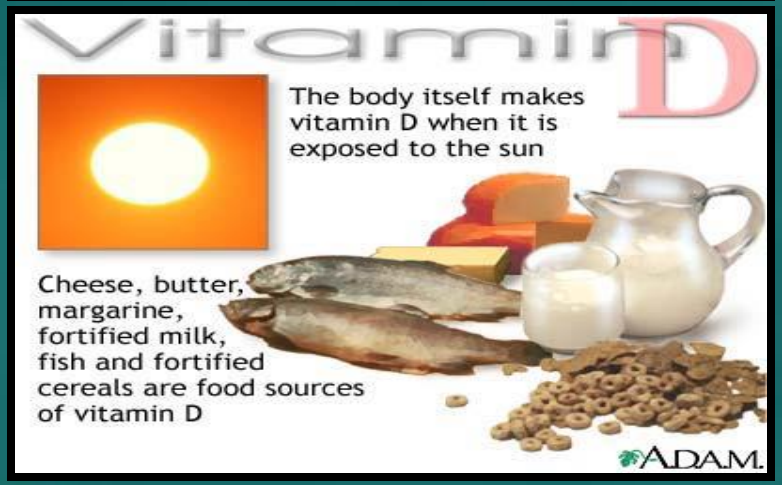
- Time pressure – time to plan, prepare food is longer
- Planning – work required to plan meals
- Competing priorities – family, job, etc.
- Assessing gluten content in foods/label reading
- Eating out – avoidance, fear, difficult to ensure food is safe

Bone Disease in Celiac Disease

- Arthritis
- Osteoporosis
- Osteopenia
- Osteomalacia
- Rickets

Calcium and Vitamin D Requirements





- 800 to 1200 mg/day of Calcium for low bone mineral density (LBMD) in males
- 1200-1500 mg/day of Calcium for treatment of LBMD in females
- 400 IU of Vitamin D daily
- Up to 2/3 of patients on a gluten-free diet have suboptimal calcium intake

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Lactose Intolerance & Celiac Disease: Incidence

- Secondary lactase deficiency is estimated to be 20-40%
- Increasing lactose Intolerance with delayed diagnosis
- Increased incidence in patients with GI symptoms in Celiac Disease
- Decrease calcium and vitamin D intake in lactose intolerance

Lactose Intolerance & Celiac Disease: Treatment

- Gluten free diet
- Temporary lactose-reduction
- Lactase enzymes
- Lactose-free milk
- Gluten-free milk substitute
- Supplement with calcium & vitamin D where appropriate

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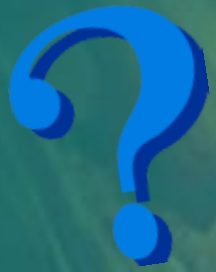
Prevention & Future Directions

Celiac Disease-Diagnosis: The Future

- Non biopsy diagnosis
  - Characteristic clinical subgroups
  - Refined (standardized) serological tests
  - Use of HLA typing
  - Discovery of biomarkers
  - Specific gene identification

Thank you

Questions?



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