Celiac Disease

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Advisory Committee/Board Member: Alvine, Inc.
Consultant: Flamentera, Ironwood, Inc, Nexpep, Shire
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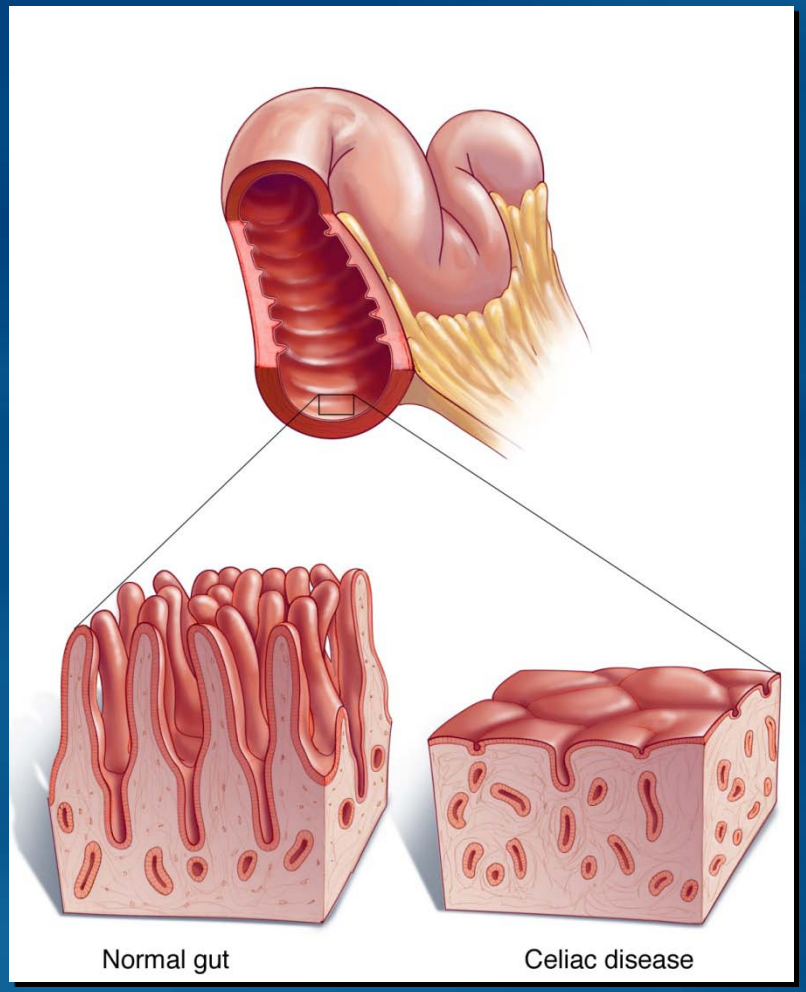
What is Celiac Disease?

- It is a inflammatory state of the small intestine that occurs in genetically predisposed individuals and resolves with exclusion of dietary gluten.



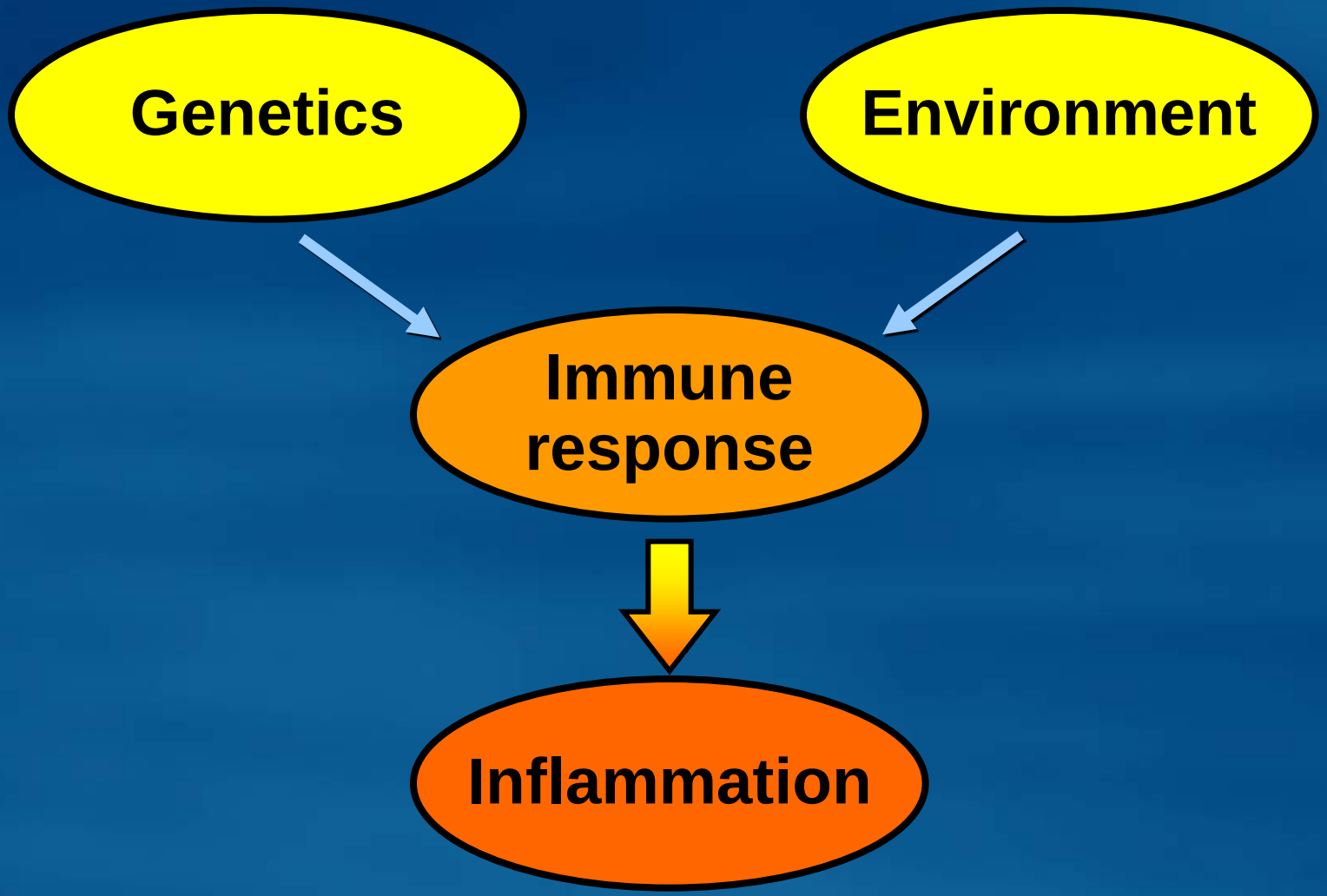
Evolutionary Collision

Wheat

Human Immune System

Kasorda, 1992

Pathogenesis of Celiac Disease



Genetics of Celiac Disease

- Strong family predisposition

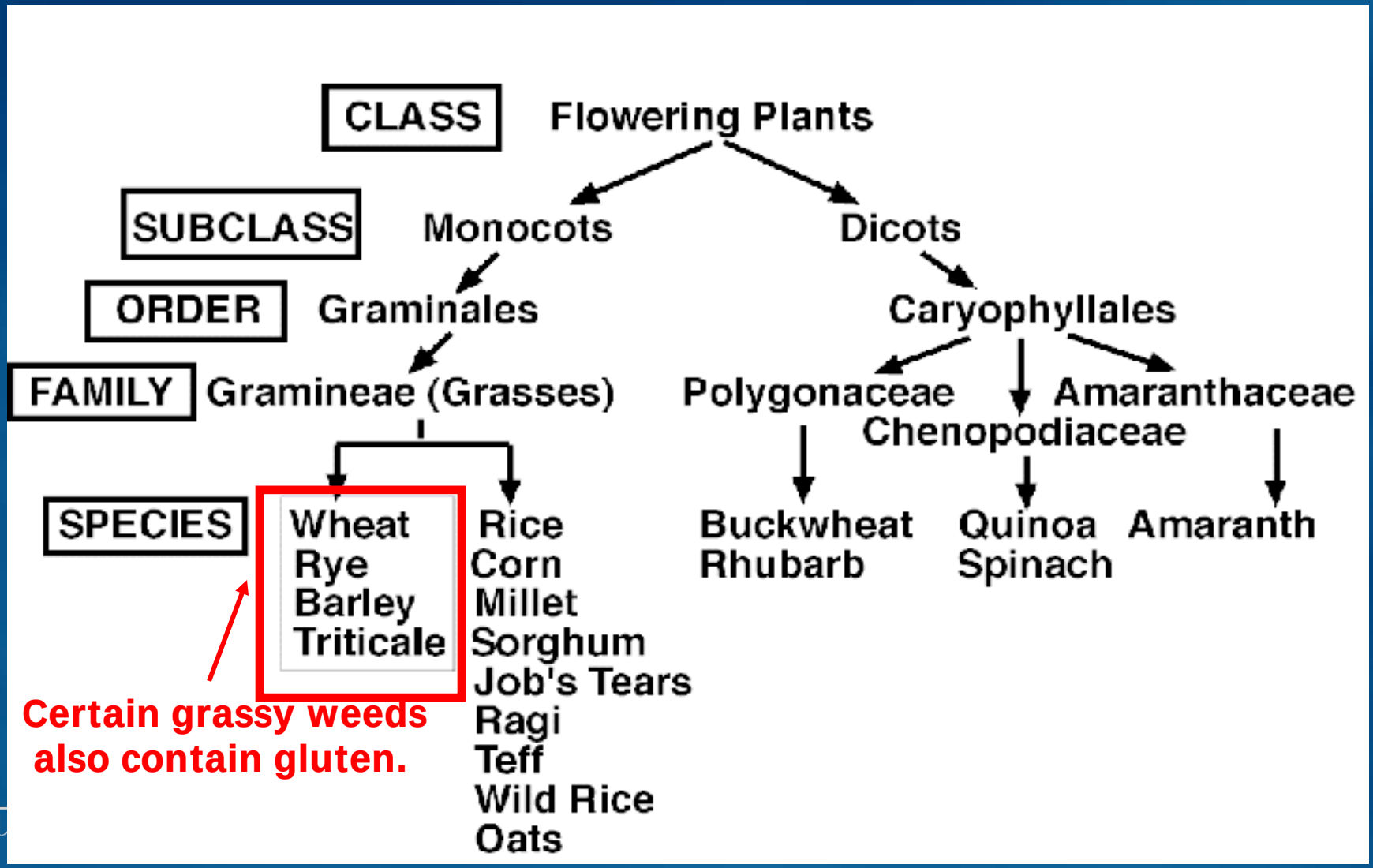
  Monozygous twins (80%), siblings (10%) kids (5-10%)

- HLA association DQ2 and DQ8 required but not sufficient

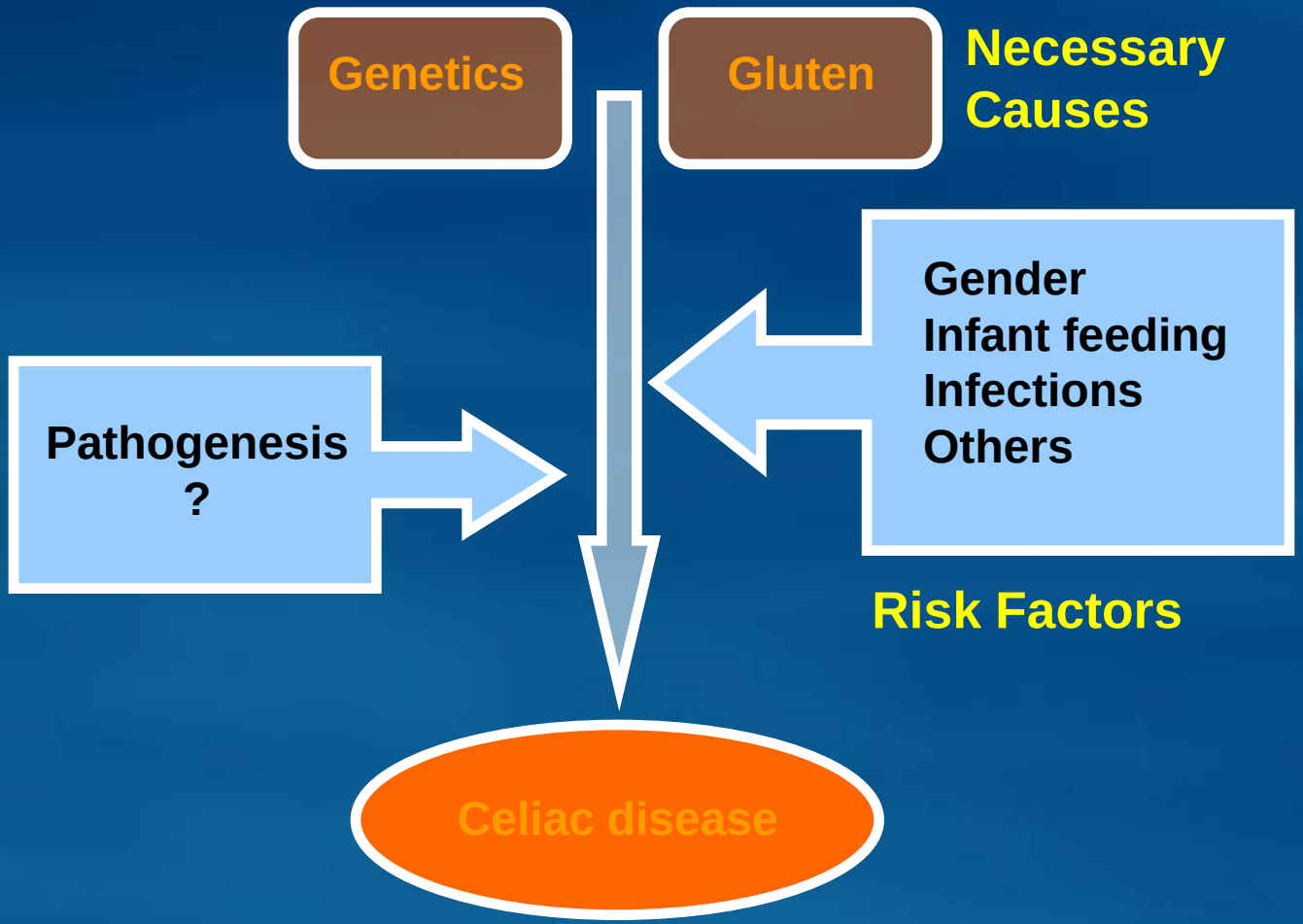
- Non HLA genes suspected but not confirmed

- Down's Turner's and William's syndrome

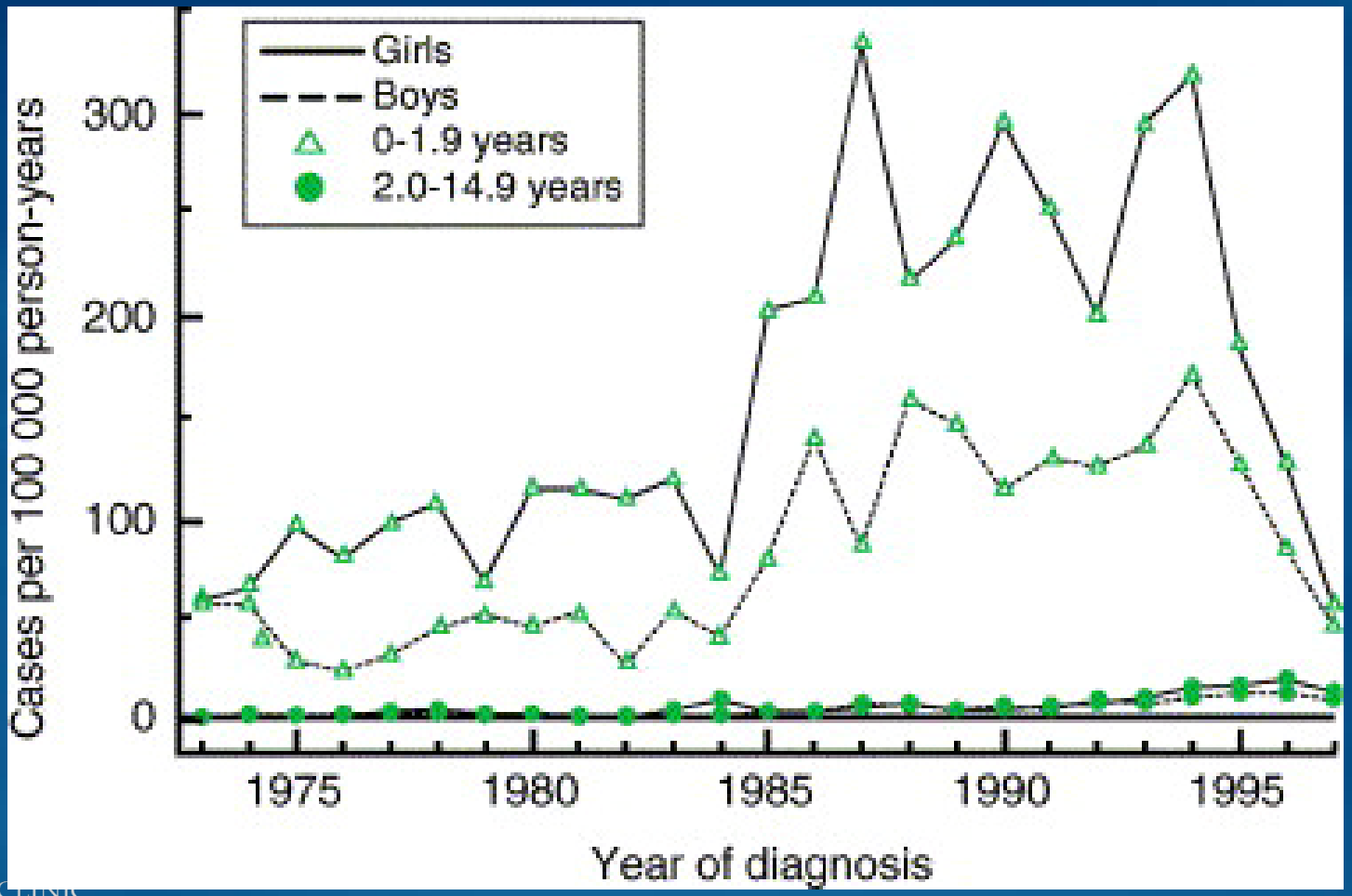
Gluten Is The Seed Storage Protein In Wheat, Rye, Barley, And Triticale



Pathogenesis



The Swedish Epidemic



Swedish Epidemic

- Delayed gluten introduction from 4 to 6 months of age
- Weaning finished before cereals started
- Increased gluten in baby foods > 6 months of age

- Epilogue: the rate of celiac in the epidemic cohort is now 3% at age of 18!

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Typical Celiac Disease

Steatorrhea

This also happens with liver disease

The “Old” Disease

- A rare disorder typical of infancy
- Everyone had diarrhea/steatorrhea
- Wide incidence fluctuations in space (1/400 Ireland to 1/10,000 Denmark) and in time
- A disease of essentially European origin
- That was rare in North America

Talley, AJG,1994

Presentations of Celiac Disease

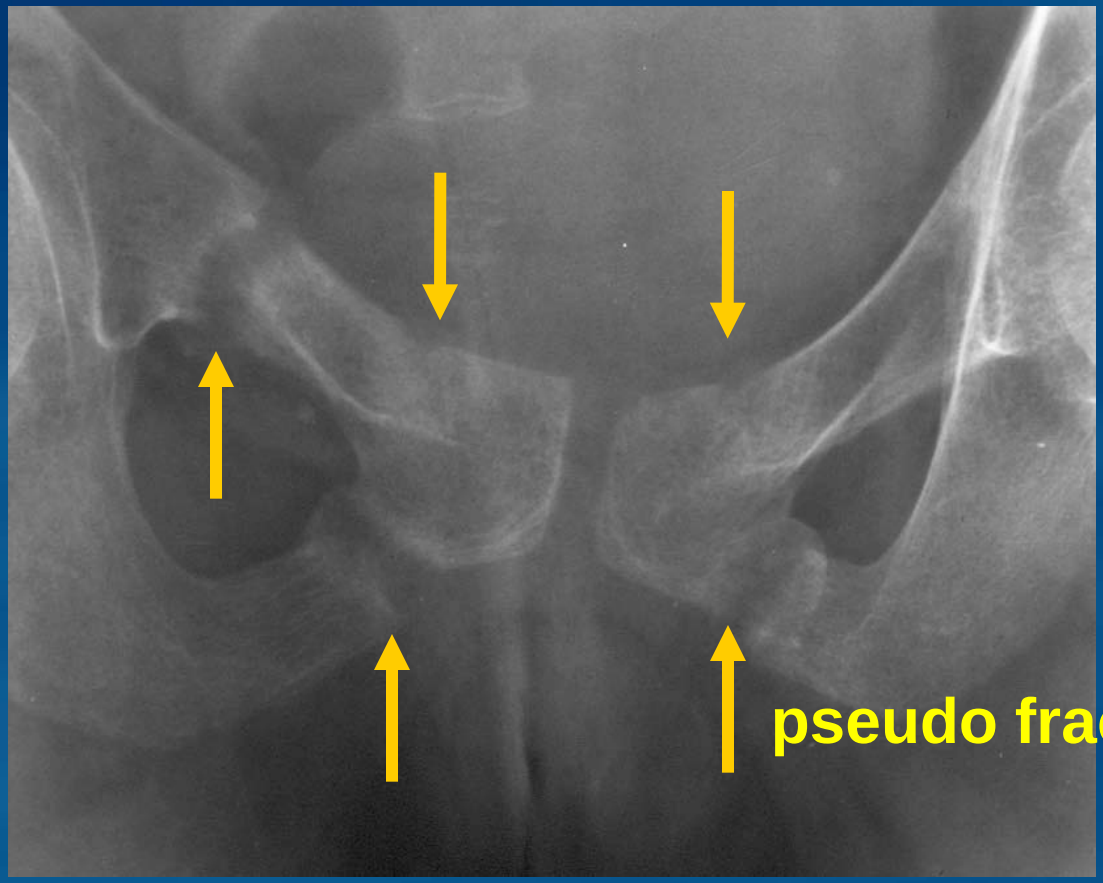
- Classic malabsorptive syndrome(25%)
  diarrhea, steatorrhea, weight loss, multiple deficiencies
- Monosymptomatic (50%)
  Anemia, diarrhea, lactose intolerance, constipation
- Acute Abdomen (rare)
  abdominal pain, intussception, vomiting, obstruction perforation, lymphoma
- Non-GI presentations(25%)
  Infertility, bone disease, neurological disease, short stature, brittle diabetes, chronic fatigue, abnormal LFTS

Dermatitis Herpetiformis

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

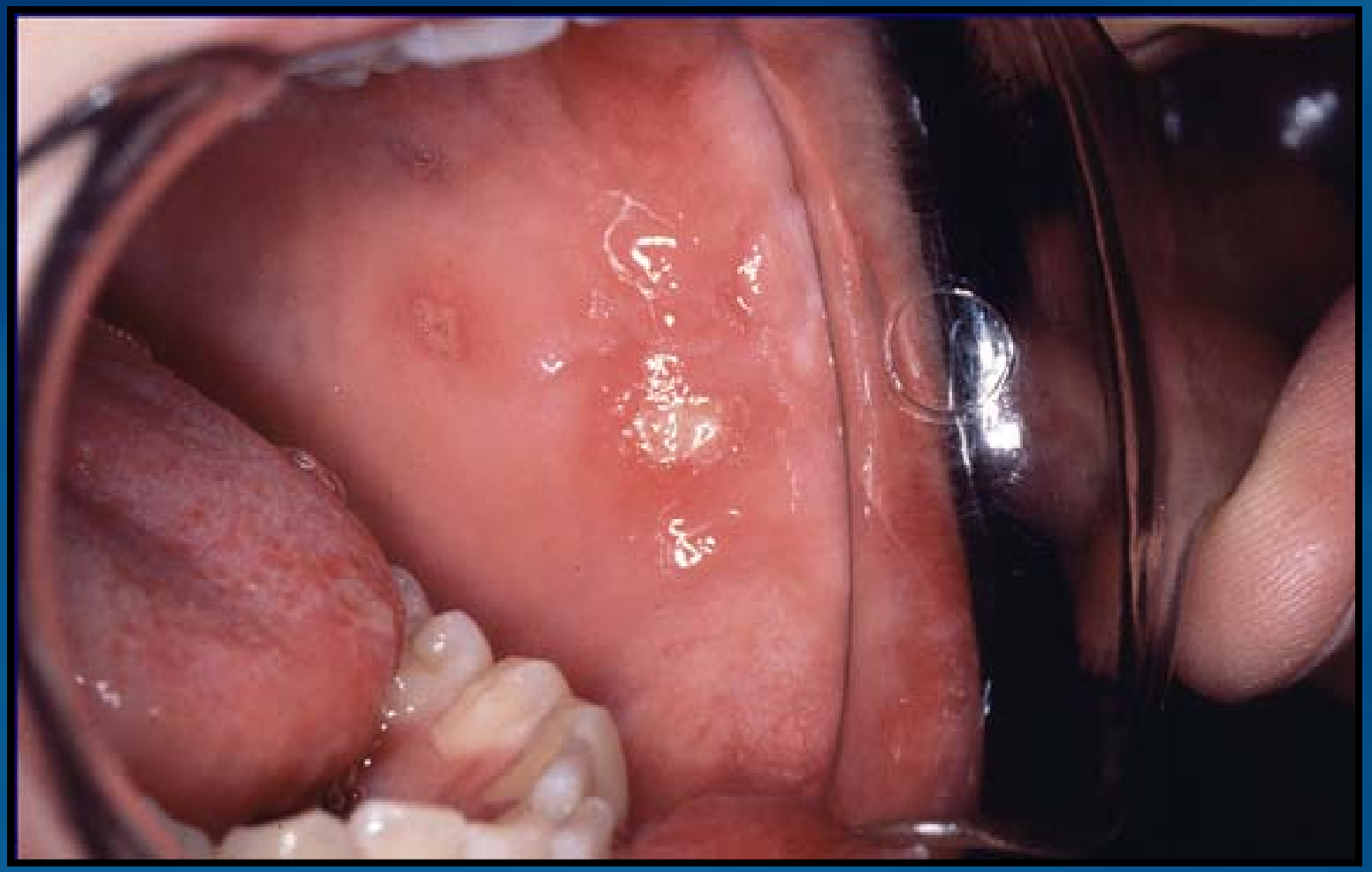
Garioch JJ, et al. *Br J Dermatol*. 1994;131:822-6.
Fry L. *Baillieres Clin Gastroenterol*. 1995;9:371-93.
Reunala T, et al. *Br J Dermatol*. 1997;136-315-8.

Osteoporosis/Osteomalacia



Low bone mineral density improves on a gluten-free diet. In fact it will not improve without it!

Recurrent Aphtous Stomatitis



By permission of C. Mulder, Amsterdam (Netherlands)

Fe-Deficient Anemia Resistant to Oral Fe

- Most common non-GI manifestation in some studies Murray, CGH, 2003
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- 5-15% of patients undergoing endoscopy for fe deficiency anemia have celiac disease Vogelsang, 98; Grisolano, 2004
- 30-50% of patients getting EGD for anemia do not get duodenal biopsies! Harewood, 2003

Celiac Disease: Acute Abdomen

- Mimic partial small bowel obstruction
- Perforation
- Stricture
- Lymphoma
- Intussusception

Abnormal Liver Blood Tests

- Incidental elevated serum transaminases (ALT, AST)
  - Up to 9% may have silent Celiac Disease
  - Liver biopsies in these patients showed non-specific reactive hepatitis
  - Liver enzymes normalize on gluten-free diet
- Occasionally severe liver disease

Rubio-Tapia et al. Liver international, 2008

RubioTapia and Murray, Hepatology, 2007

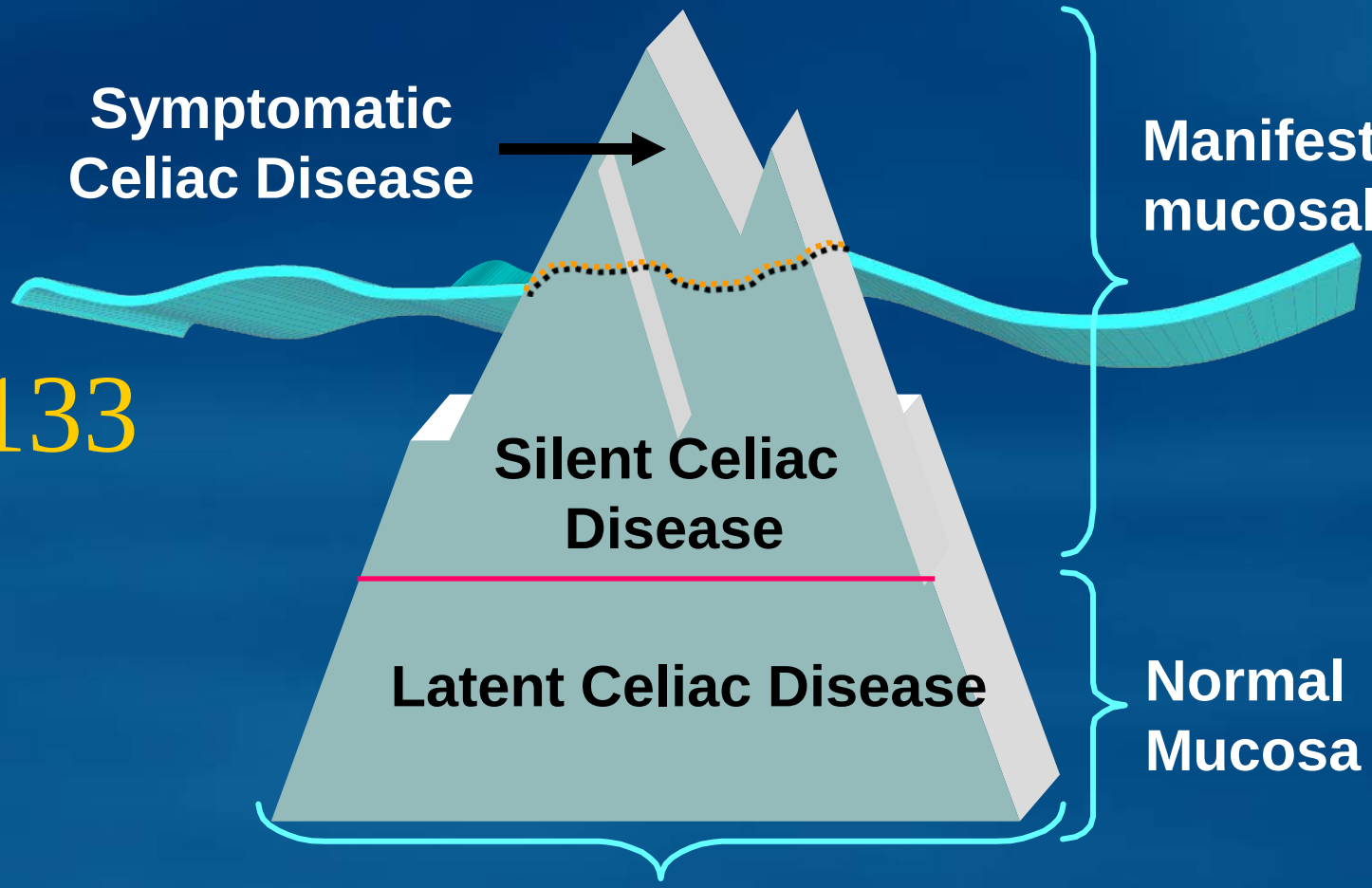
Celiac Disease and other liver diseases

- PBC 2-10%
- PSC case reports
- PSC in prior dx of CD HR 4.4
- AIH variable 3-8%
- Hep C 2% (may be triggered by interferon treatment
- No increased risk of transplantation

Who Gets Celiac Disease?

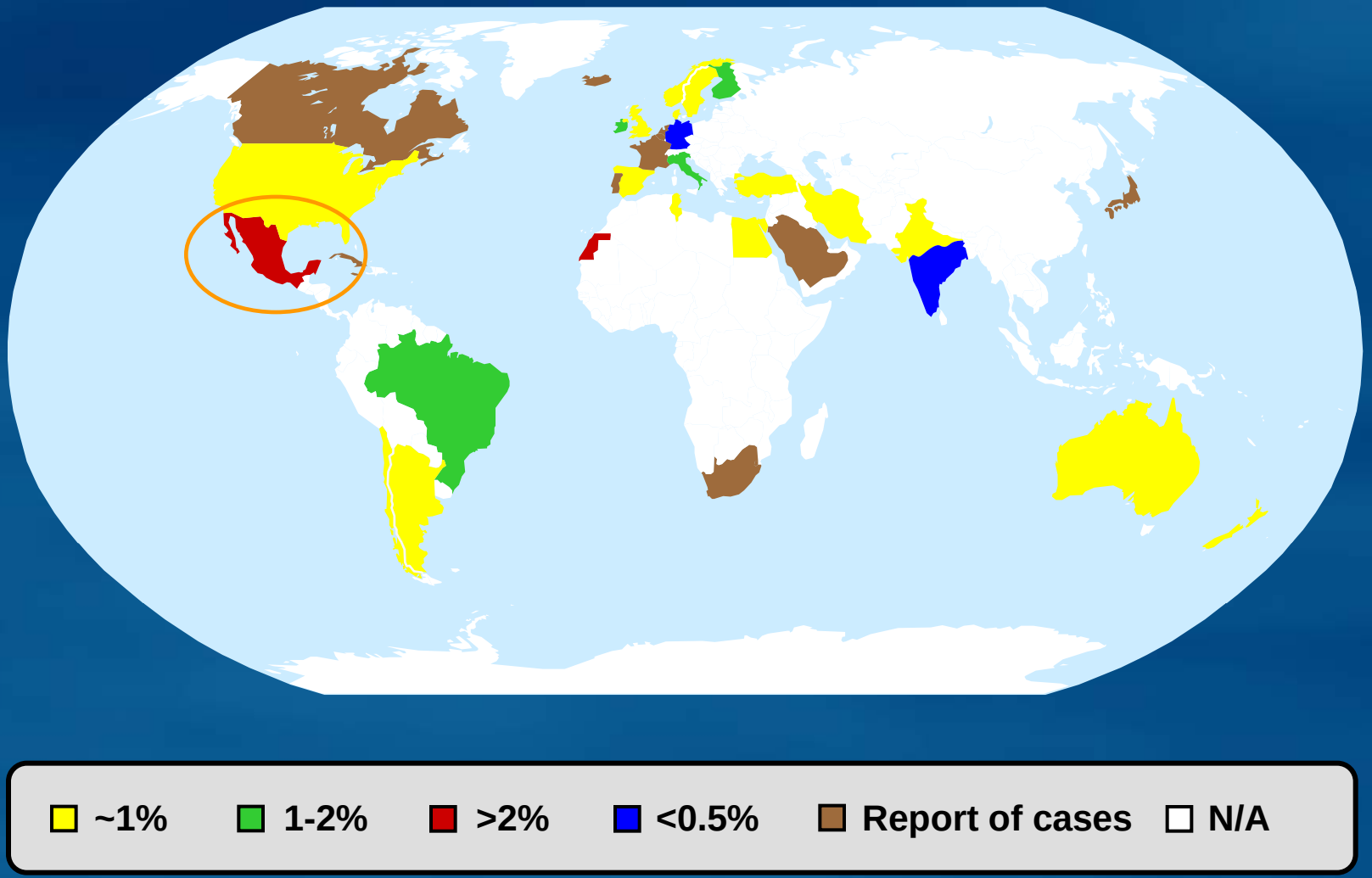
- Adults >> children, female > males
- Worldwide, mostly Caucasians
- Any age including elderly
- People with other immune disorders
  - Type one diabetes mellitus
  - Sjogren's syndrome
  - Thyroid disease
  - Lupus, Addison's disease
- Family members of celiacs

The Celiac Iceberg



Genetic susceptibility: - DQ2, DQ8
Positive serology

World Map Indicating Prevalence of Celiac Disease



*Reilles-Troche JM. Ramirez-Iglesias MT. **Rubio-Tapia** A. Alonso-Ramos A. Velazquez A. Uscanga LF. Journal of Clinical Gastroenterology. 40(8):697-700, 2006*

How Do You Find It?

Diagnostic Tests

Diagnostic Criteria

- Villous atrophy with chronic inflammation in the proximal small intestine while eating gluten
- Objective clinical response to a gluten free diet
- Serology provides supportive evidence

ESPHGAN Guidelines 1991
UEDW Guidelines 2001

Serologic Tests In CD Diagnosis

- Anti endomysial antibodies (EMA)
  - **Indirect immunofluorescence**
  - **Excellent specificity and good sensitivity**
  - **Expensive (monkey esophagus needed)**
  - **Subjective**
- Anti whole Gliadin antibodies (AGA)
  - **Cheap**
  - **Easy**
  - **Fair sensitivity and poor specificity**

New deaminated Gliadin peptide antibodies

- Tissue transglutaminase antibodies (TTG)
  - **Good sensitivity and specificity**
  - **Easy to test**

Limitations of Serology

- IgA deficiency (3-5% of celiacs are IgA deficient and 10 % of IgA deficient patients have CD)
- Less sensitive for partial villous atrophy

Rostami, 1999

- Effect of prior gluten free diet

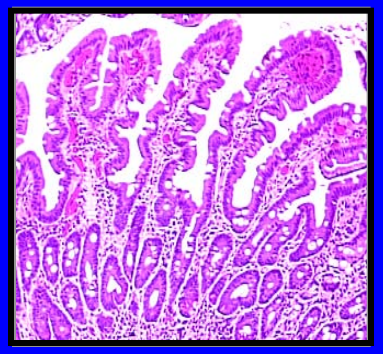
Histopathology of Celiac Disease

How good are biopsies?

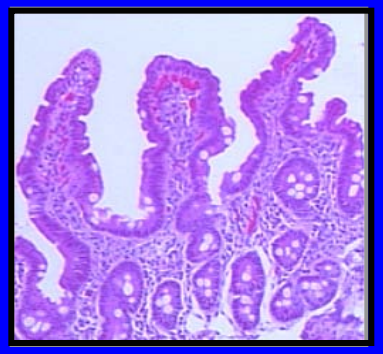
Normal Intestine

Celiac Disease

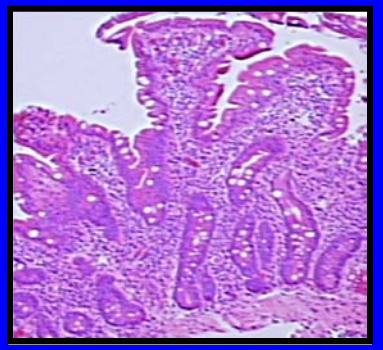
Histological Features Vary



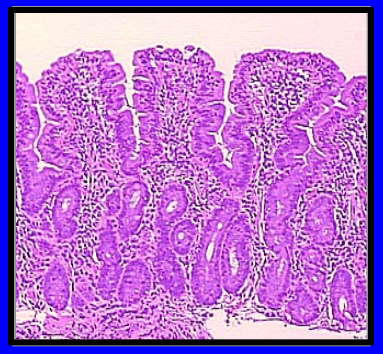
Normal 0



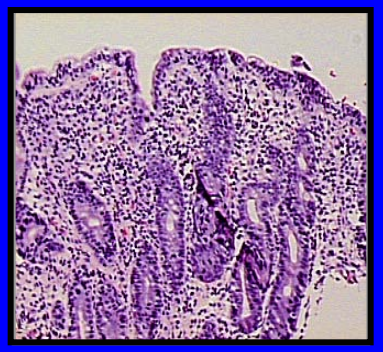
Infiltrative 1



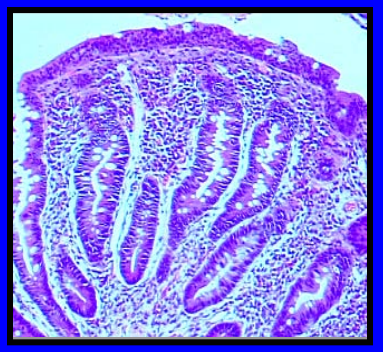
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

Horvath K. Recent Advances in Pediatrics, 2002.

False Positive Biopsies

- Poorly oriented " flattened biopsies"
- NSAIDS
- Self-limited enteritis in 7 adults Goldstein, Am J Clin Path 2004
- Tropical sprue (travel history)
- Combined variable immunoglobulin deficiency
- Autoimmune enteropathy Akram et al. CGH 2007
- Non granulomatous enterocolitis

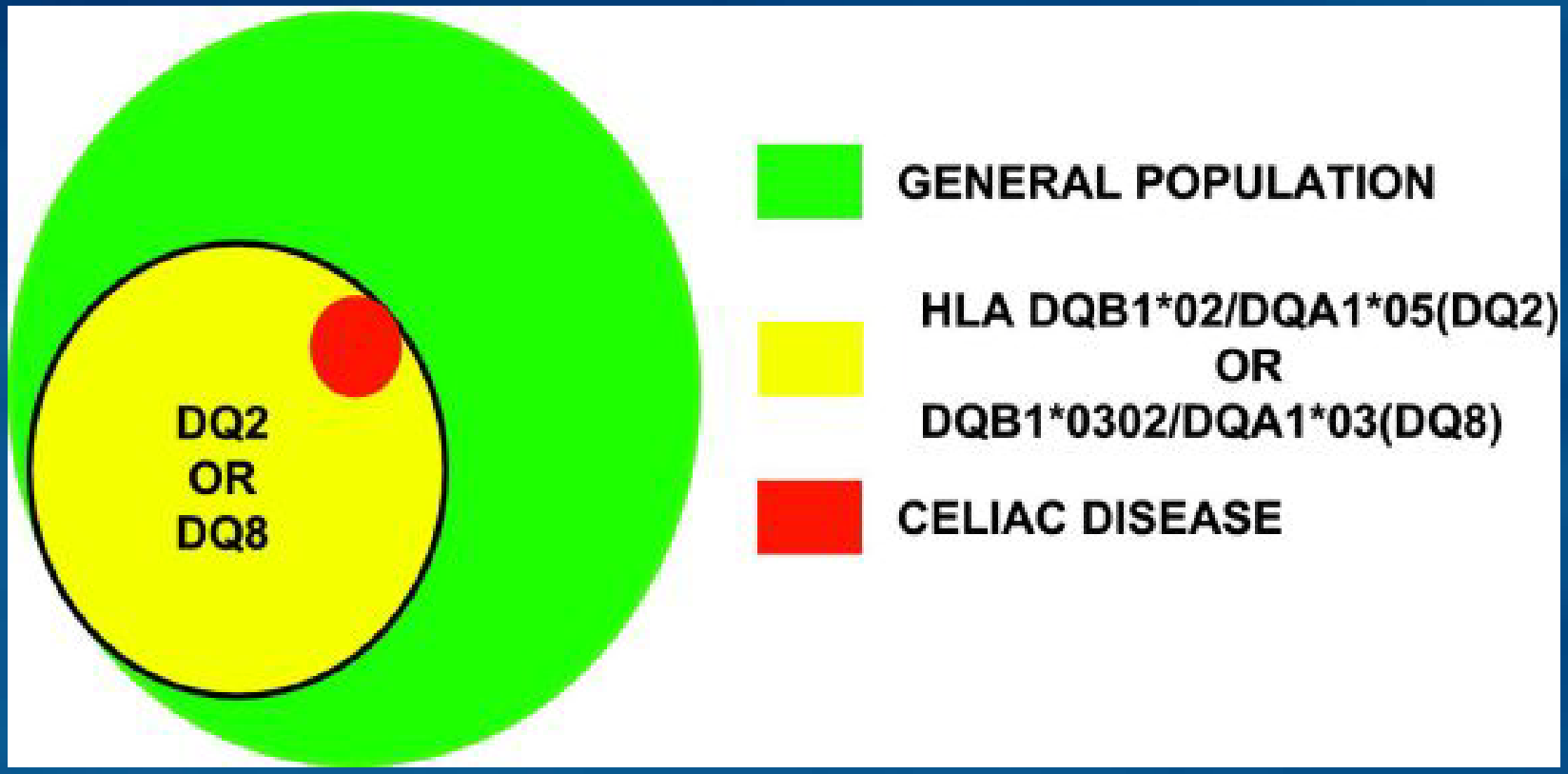
What About Patients on GFD Diet?

- Often unhappy patient
- Serology and biopsies can normalize
- HLA type might help
- Challenge
- Some patients will not eat gluten
- Why argue with success if diet is nutritionally adequate?

Genetic Testing for Celiac disease

- Used DNA methods to HLA type
- Detects pairs of genes
- Good to rule out if absent
- Not specific
- Direct to patient testing

Celiac Disease And HLA Risk



When to Use HLA?

- People on a gluten free diet (including refractory)
- Seronegative positive biopsy patients
- Those at genetic risk who are seronegative
  - Down's Syndrome
  - Turner's syndrome
  - William's syndrome
  - Asymptomatic family members
  - Type one diabetes

Usual prevalence of DQ2

High prevalence of DQ2/8

The Case for Screening

- ~ 1% of general population
- Long pre-symptomatic phase
- Diverse symptoms/groups affected
- Increased risk of malignancy
- Easily applied detection test
- Treatable
- Big unknown is natural history

The Silence of the Intestines: Increased Prevalence and Mortality of Undiagnosed Celiac Disease

Alberto Rubio-Tapia, Brian D. Lahr, Alan R. Zinsmeister, Robert A. Kyle, L. Joseph Melton, Tricia L. Brantner, Carol T. Van Dyke, Tara K. Phelps, Edward L. Kaplan, Joseph A. Murray

Mayo Clinic Rochester

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Subjects: 50-year Old Sera

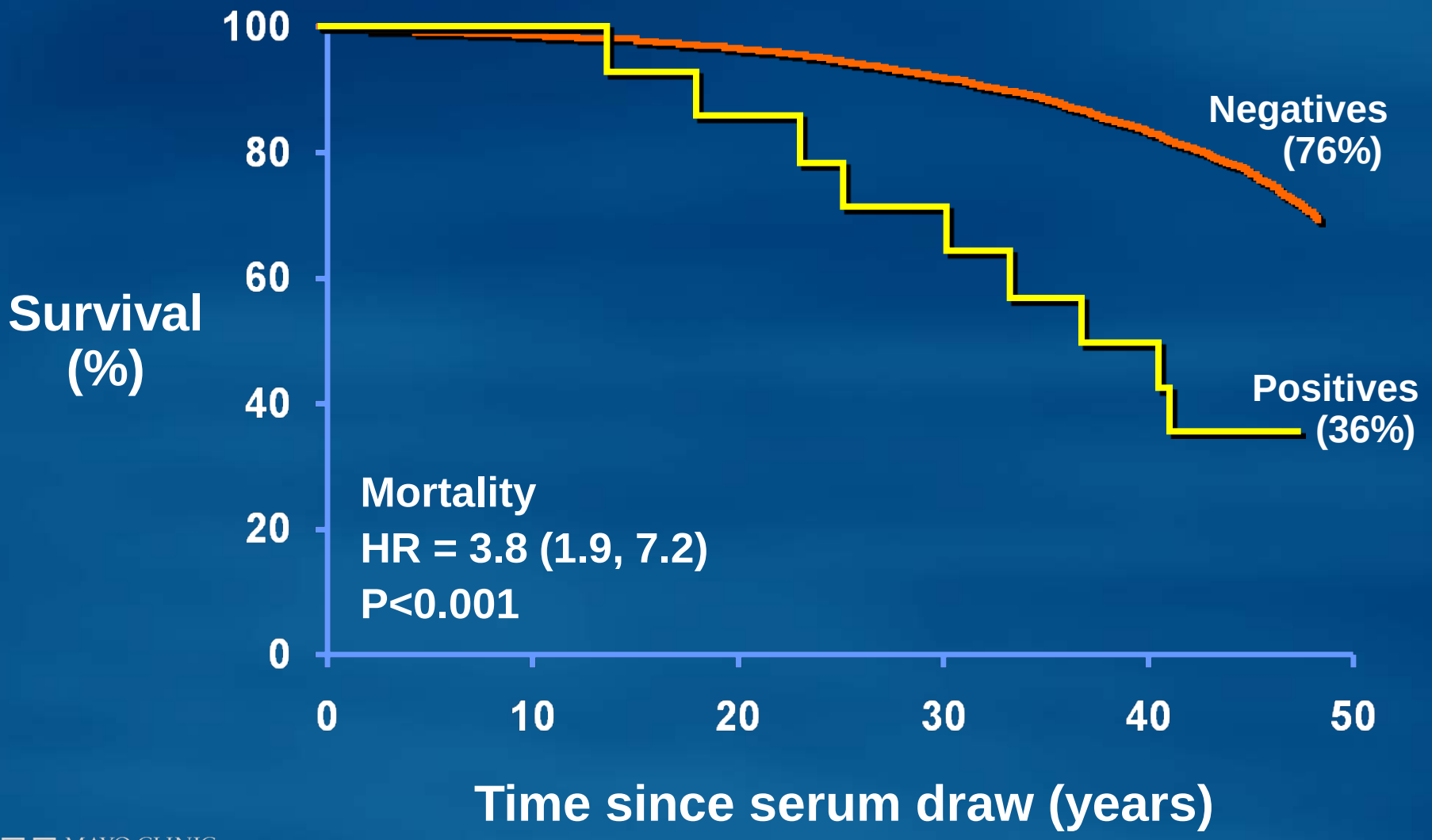
- **The sera was collected from 1948-1954 in 8916 healthy persons***

(Warren Airforce Base Cohort - WAFB)

Age **(mean ± SD)**	**20.5 ± 2.8**
Gender	
MALE	99%
Race	
WHITE	89.1%
African American	**10.5%**
Others	**0.4%**

* Denny FW, et al. Prevention…streptococcic infection. JAMA 1950

Survival


100
80
60
40
20
0
Survival (%)
Negatives (76%)
Positives (36%)
Mortality
HR = 3.8 (1.9, 7.2)
P<0.001
0
10
20
30
40
50
Time since serum draw (years)

Management Plan

- Explain the disease
- Strongly advocate a gluten free diet
- Refer to expert dietitian!
- Check bone density
- Identify and treat deficiencies
- Calcium and vitamin D replacement
- Support group

Summary

- Celiac Disease is common ~1%
- It can present in many ways or remain covert
- Frequent in the endoscopy suite
- Detected by serology (tTg-IgA)
- Confirmed by biopsy
- Treatment is dietary ……

Crowds panic as flooding threatens Ireland...