



# Celiac Disease

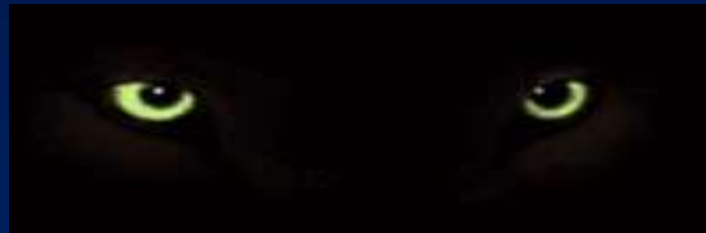
## Exploring the Iceberg

Ahmad WASSOUF M.D

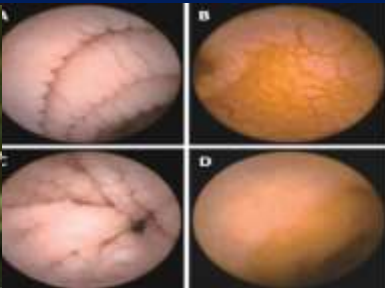
Assistant Professor of Gastroenterology

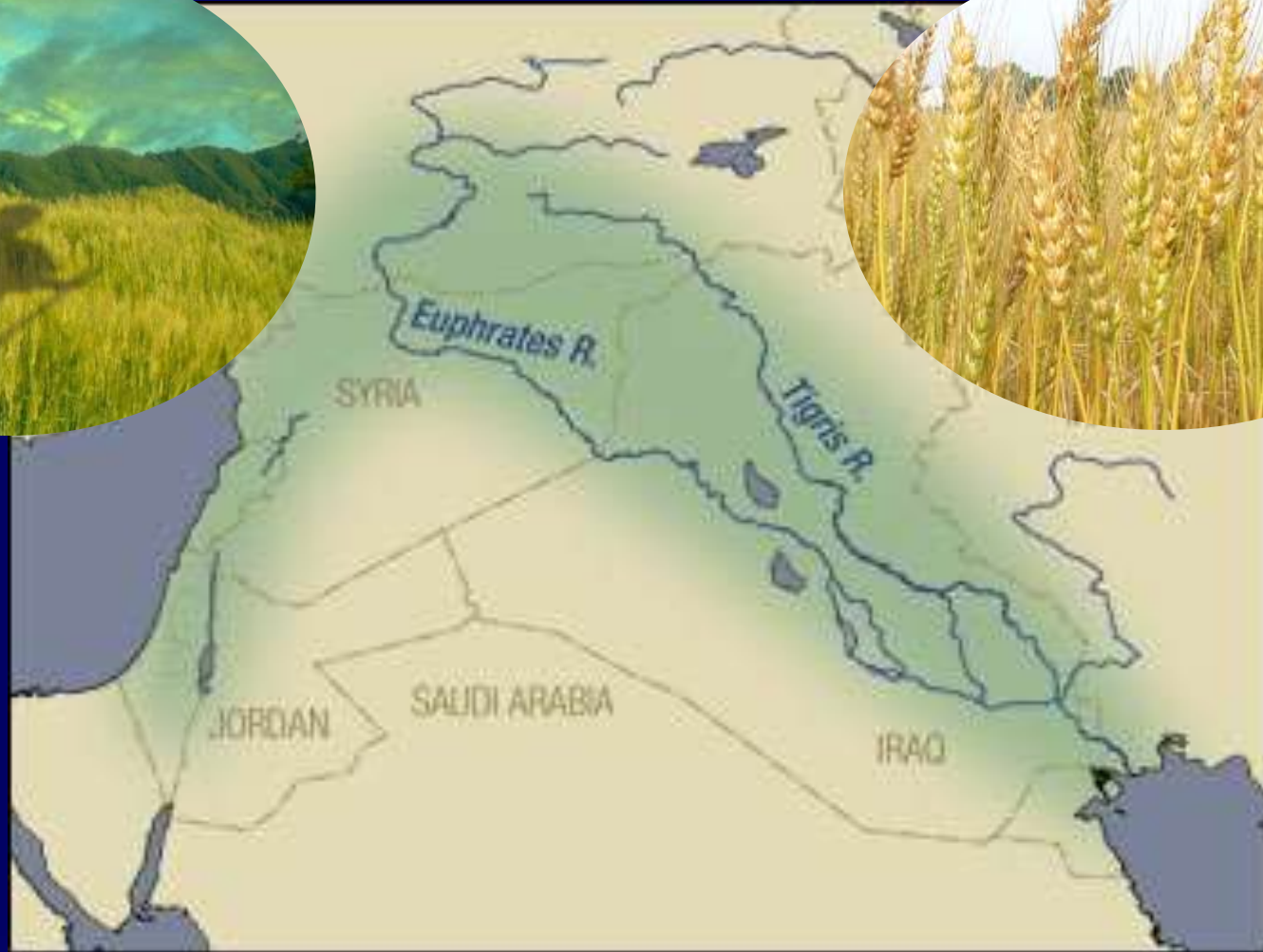
Almouassat University Hospital

Faculty of medicine –Damascus,Syria



2.—Photograph of the cases of celiac disease showing the general clinical features.





**Cereals domestication started 10,000 years ago  
in the Fertile Crescent**



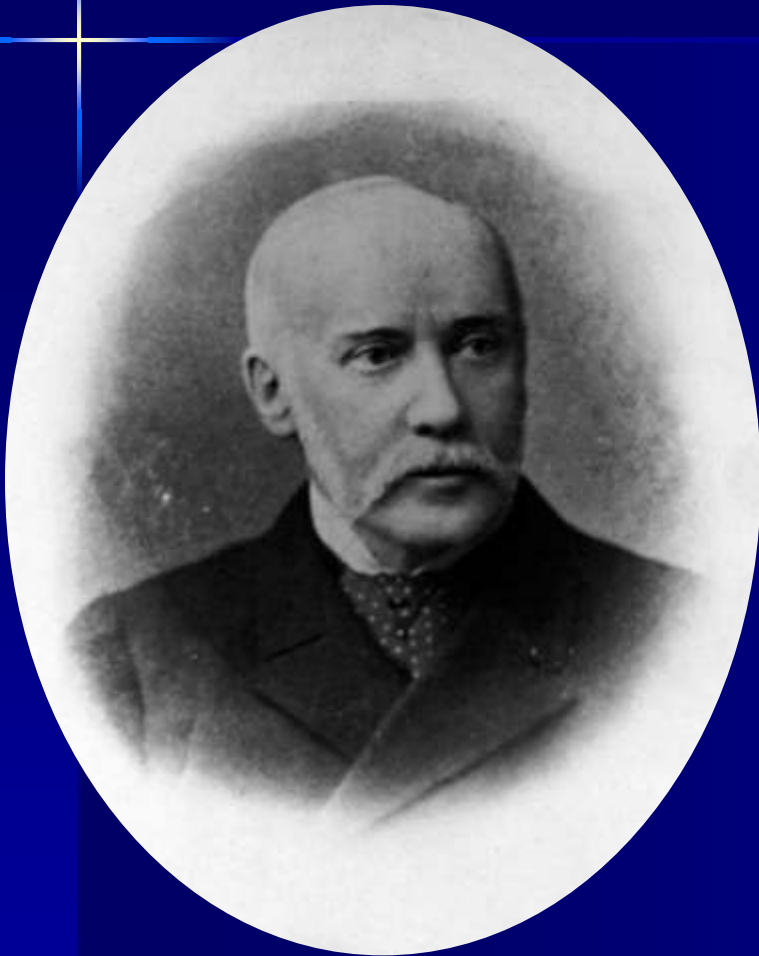
Agriculture slowly spread with a East-West gradient (1 Km/y)

# Aretaeus of Cappadocia



- Aretaeus from Cappadocia (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."

# Samuel Gee



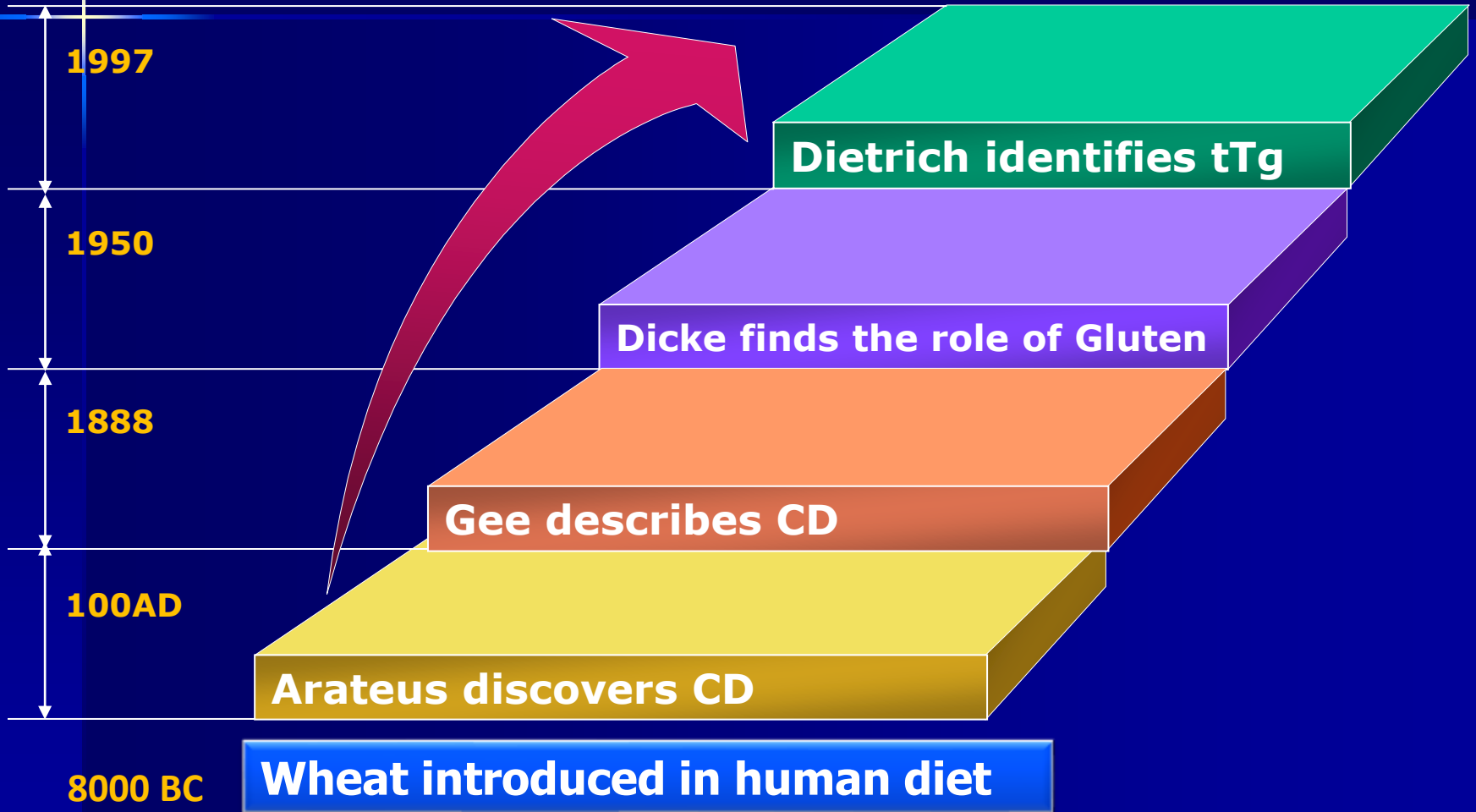
- The second classical description was in 1888 in a report entitled "**On the Coeliac Affection**" by Samuel Gee

# Willem K Dicke



- 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.

# A diagrammatic summary of the history of CD



# ***We'll talk about...***

- How we define celiac disease
- Who gets it and how?
- How common it is
- What are its clinical manifestations
- What conditions can accompany it
- Complications

# Definition

- Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.

It leads to gastrointestinal and non-gastrointestinal symptoms, but it may as well be asymptomatic

***Indeed, celiac disease occurs more often in people who have few or no symptoms!***

**Gluten**

**Flattened villi**  
↓  
**Malabsorption**

**Normal villi**  
↓  
**Absorption**



TAKE  
THAT  
VILLUSES

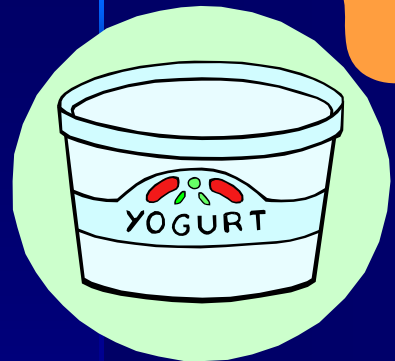
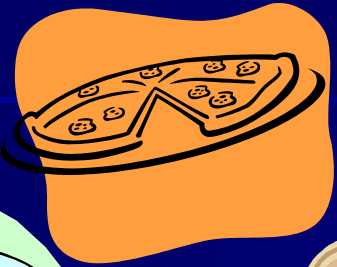
**GLUTEN**



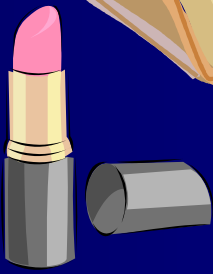
# Where is gluten found?



**Answer:**

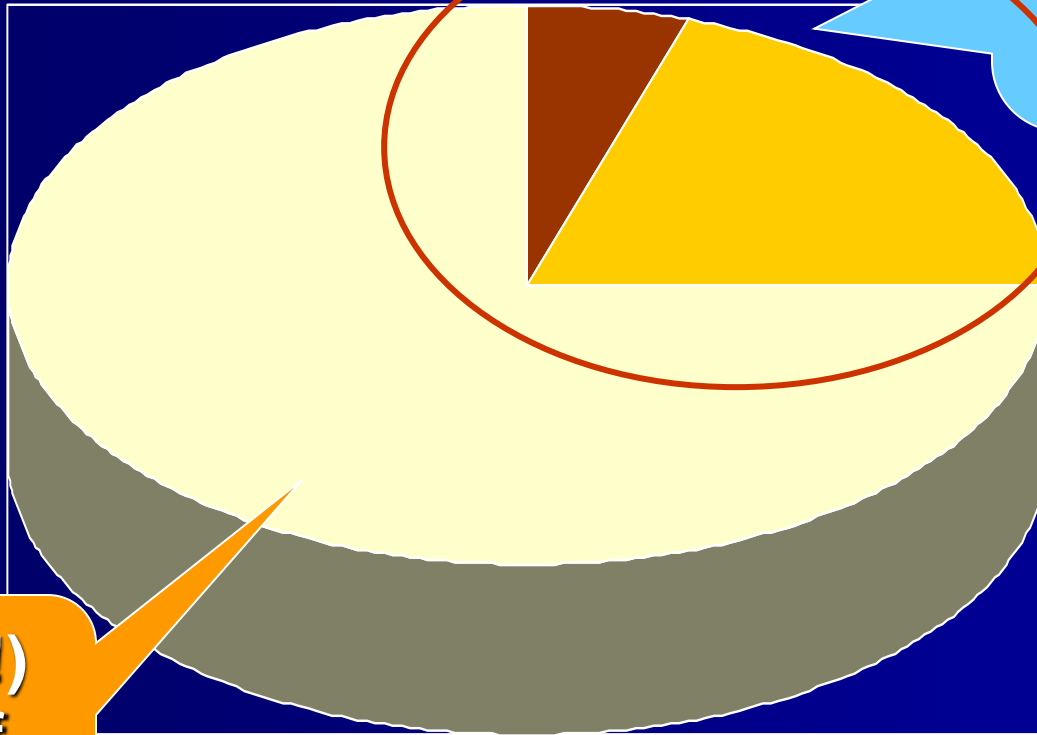


**Everywhere**



# And what exactly is it?

Gluten is made up by **Gliadin** and **Glutenin**



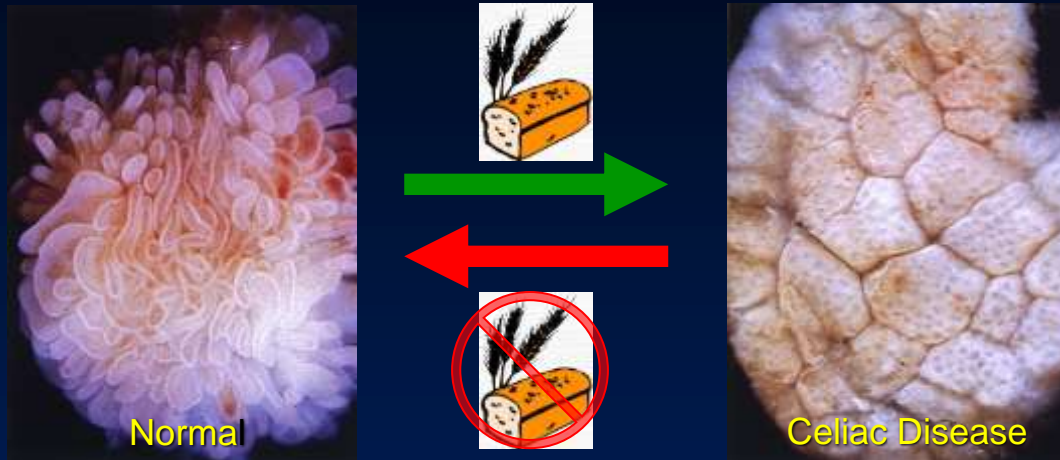
A (huge!) grain of

Some well-identified pieces (called "peptides") of gliadin are resistant to digestion in the gut and are toxic for celiac patients

# ***We'll talk about...***

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# Celiac Disease: Definition



- autoimmune-mediated enteropathy

# Gluten is the Popular Name for Proteins that are Present in Certain Dietary Grains

## Grain

## Scientific Name - Prolamins



**WHEAT**

**GLUTEN**

Consists of a mixture of  
**GLIADINS & GLUTENINS**



**BARLEY**

**HORDEINS**



**RYE**

**SECALINS**

# Who gets celiac disease?

Gluten



*Nothing....*

HLA is not  
DQ2, DQ8



# Who gets Celiac Disease?

Gluten

Other necessary  
Risk Factors

Infant  
feeding  
Infections...

***Celiac Disease***

HLA is either  
DQ2 or DQ8



# ***We'll talk about...***

- How we define celiac disease
- Who gets it and how?
- How common it is
- What are its clinical manifestations
- What conditions can accompany it
- Complications

# How common is celiac disease?

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		1:184
Netherlands		1:198
Poland		1:250
Spain		1:70
Slovenia		1:550
Sweden		1:190
United Kingdom	1:300	1:112
USA	1:10,000	1:133

**Currently accepted worldwide  
Prevalence (in Caucasians):  
1%**

**Projected number of celiacs in North America: about 3,000,000**

**Actual number of known celiacs: about 50,000**

**For each known celiac there are 53 undiagnosed patients.**

# Celiac Disease: It's common, and commonly misdiagnosed

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## Celiac disease: It's common, and commonly misdiagnosed

Updated 11/1/2006 9:04 PM ET

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By **Mary Brophy Marcus**, Special for USA TODAY



[Enlarge](#)

By John Zich, USA TODAY

The Libreris: Aldo, left, Pietro, Claudio and Lucio, in front row, all have celiac disease. Mom Rosalia, Angela, Ignazio, Rosalba and father Luciano do not.

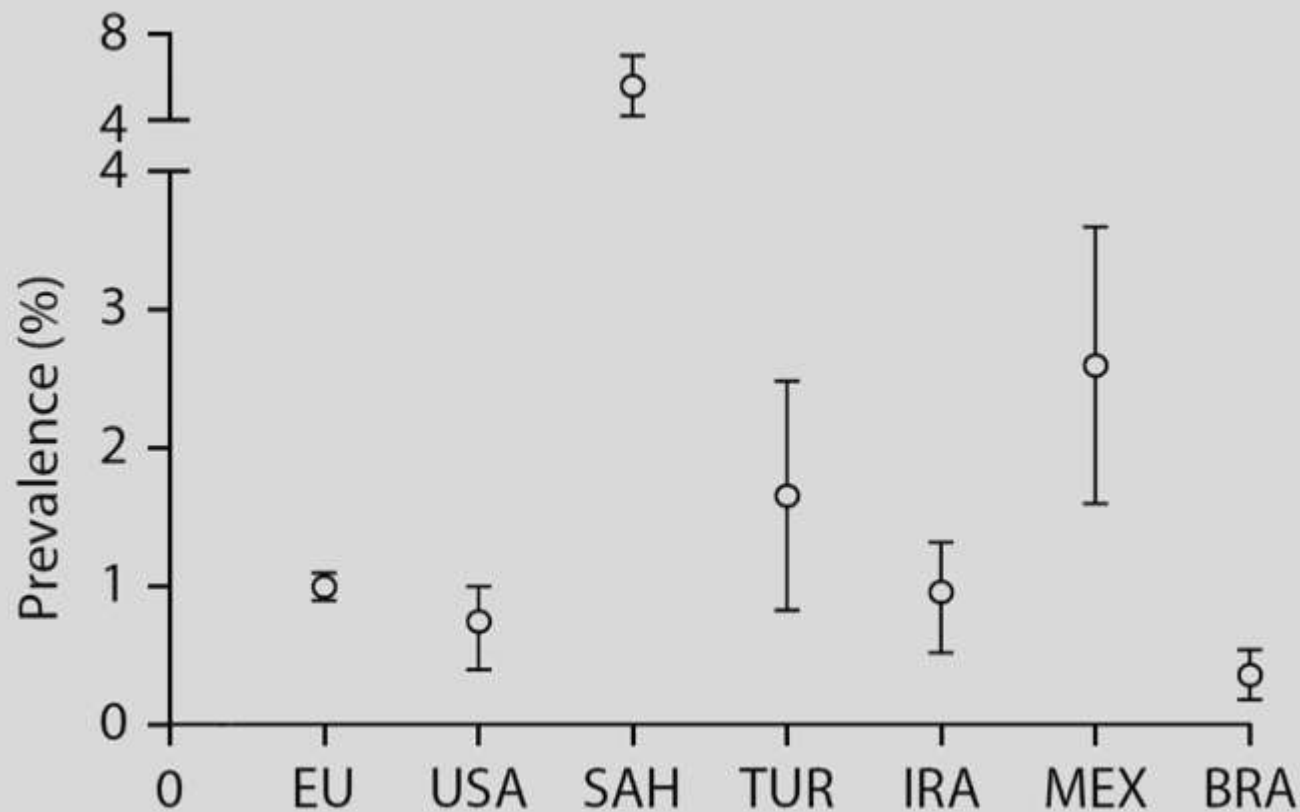
Lucia Libreri, 16, stopped growing when she was 8. Four years later after a battery of tests and visits with medical experts, her parents, Rosalia and Luciano, finally found a doctor who pinned down her problem: celiac disease, a condition scientists say is much more widespread in the USA than previously believed.

This summer, the National Institutes of Health launched the Celiac Disease Awareness Campaign to educate physicians and the public about the prevalence of the disease, the myriad of symptoms it can cause and the tests that can detect it.

People with celiac disease can't digest gluten, a protein found in wheat, rye, and barley — grains commonly used in bread, pasta, cookies and beer. Oats don't contain gluten, but U.S. oats are considered contaminated due to crop rotation and milling.

Less than a decade ago, it was thought celiac disease affected one in every 10,000 Americans, says Michelle Pietzak, clinical assistant professor of pediatrics at the University of Southern California Keck School of Medicine in Los Angeles and founder of website [glutenfreemd.com](#).

# Prevalence of Celiac Disease



# Celiac Disease in Syria

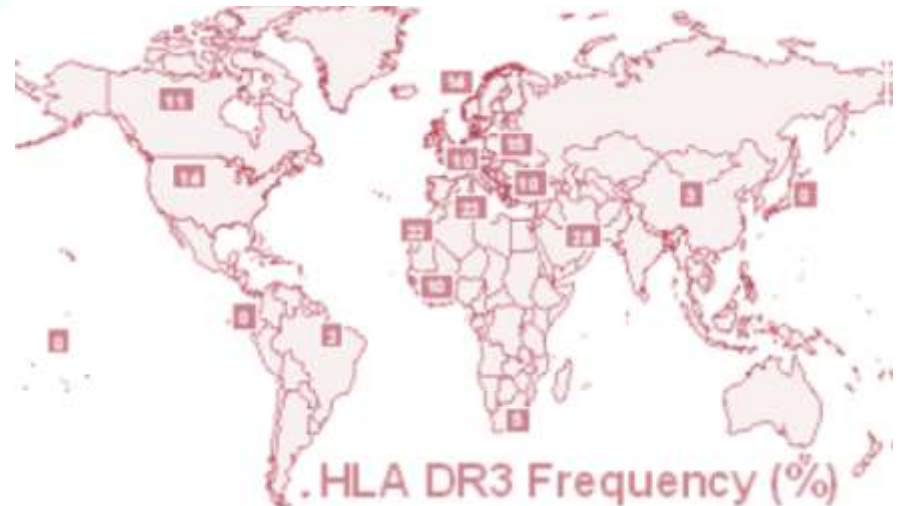


# We have...



## The Grains

## The Genes



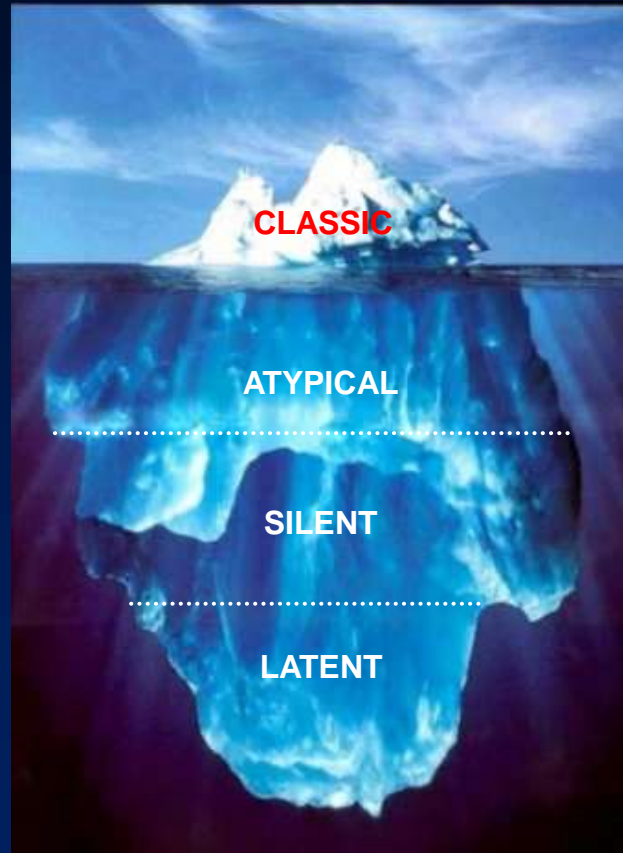
# The prevalence of coeliac disease (CD) in healthy blood donors in syria

At least 1.5%

# THE CELIAC ICEBERG



# THE CELIAC ICEBERG



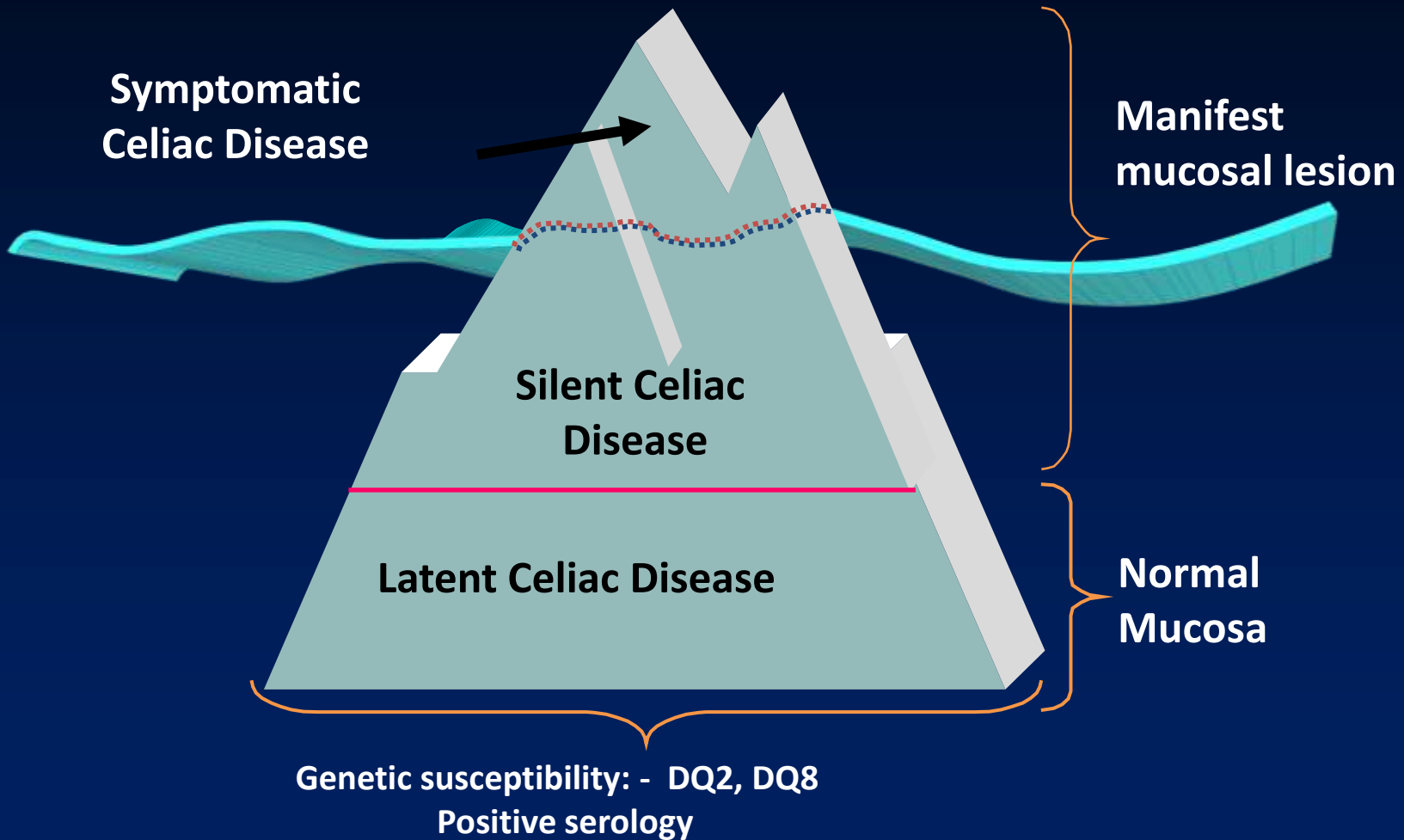
# The Spectrum of Celiac Disease

Type	GI manifestations	Ab,s	Biopsy
1- Classic	GI manifestations	present	dg biopsy
2- Atypical	Non GI manifestations	present	dg biopsy
3- Silent	Asymptomatic	present	dg biopsy
4- Potential	May be symptomatic	present	non-dg biopsy
5- Latent	Asymptomatic	present	normal biopsy

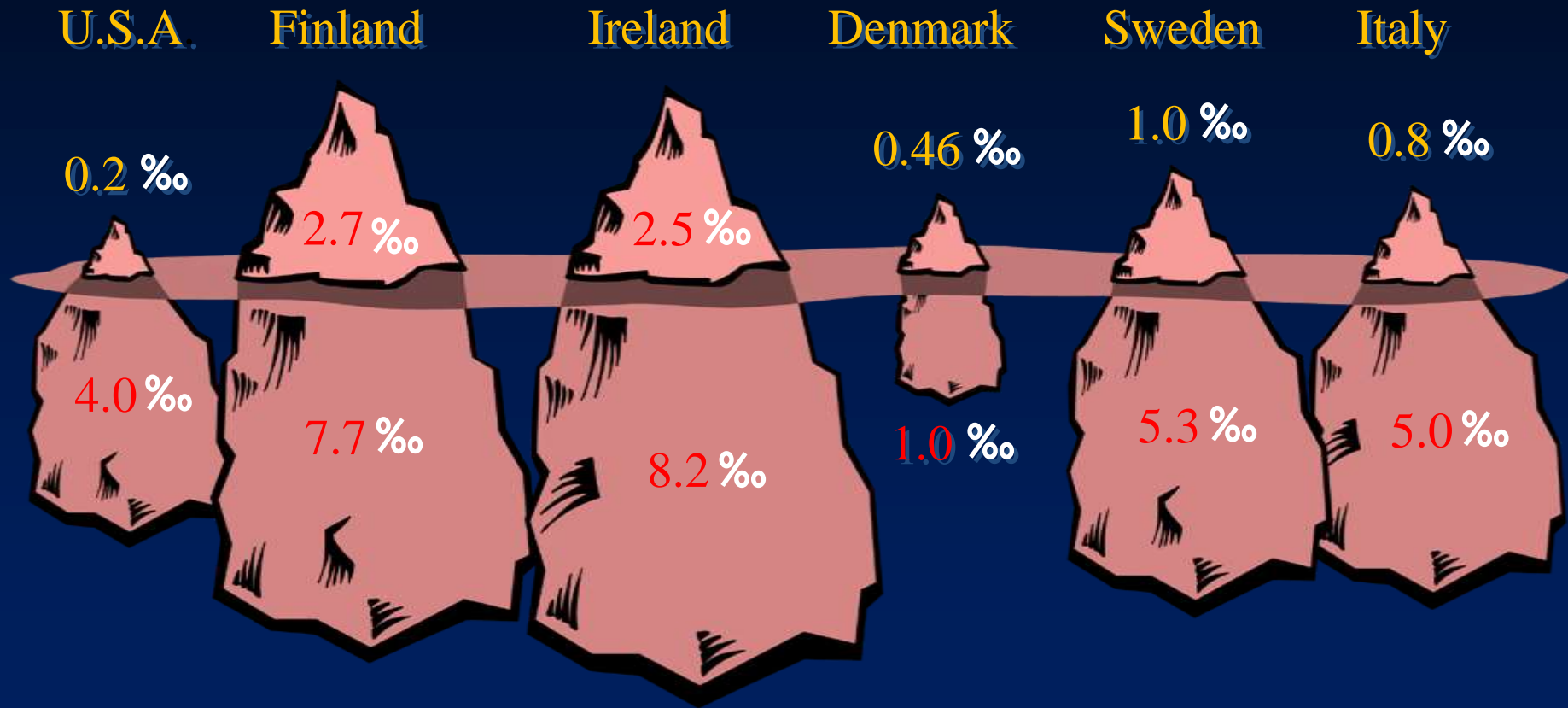


Farrell RJ et al. Am J Gastroenterol 2001 ; 96 3237 - 3246

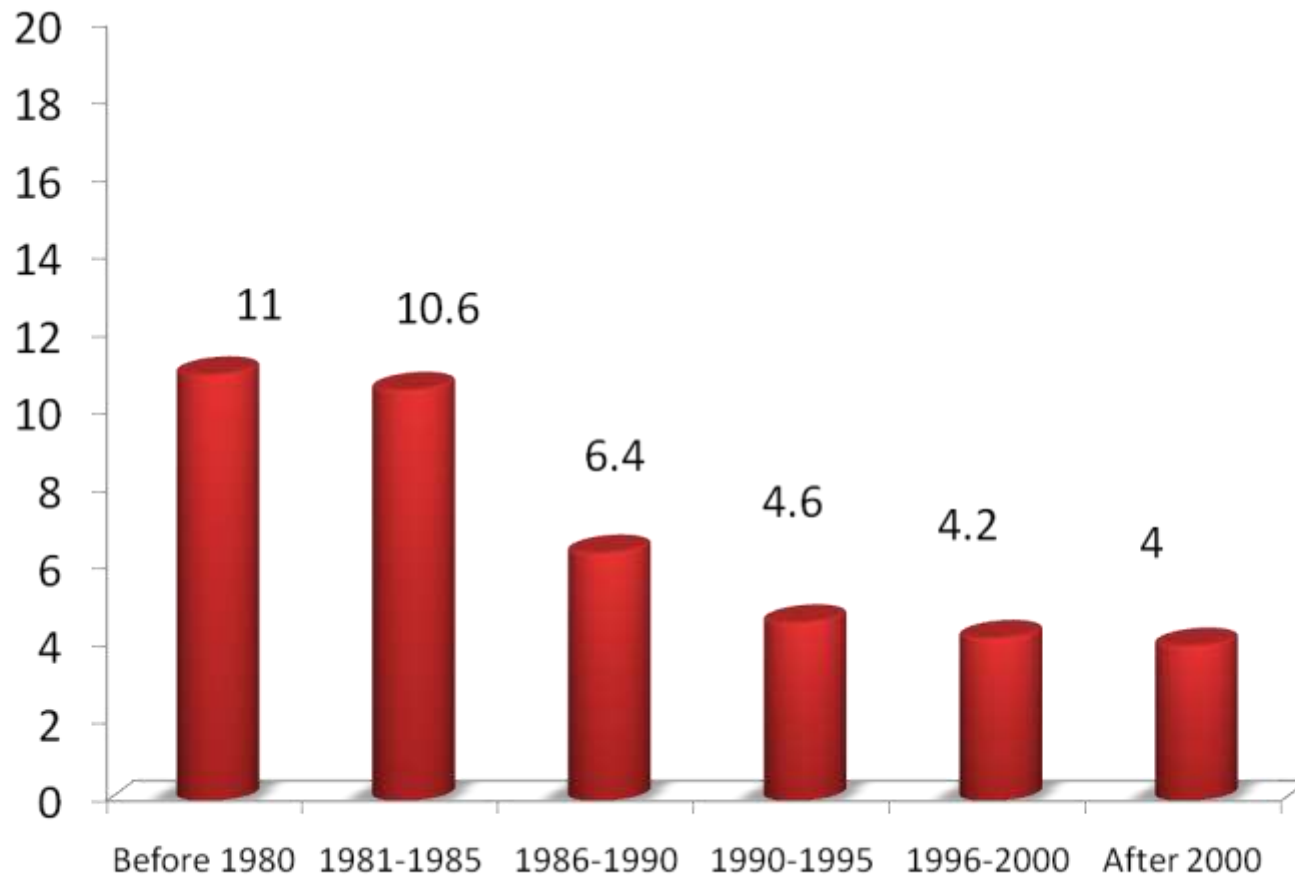
# The Celiac Iceberg



# Celiac Iceberg



# Delay in diagnosis

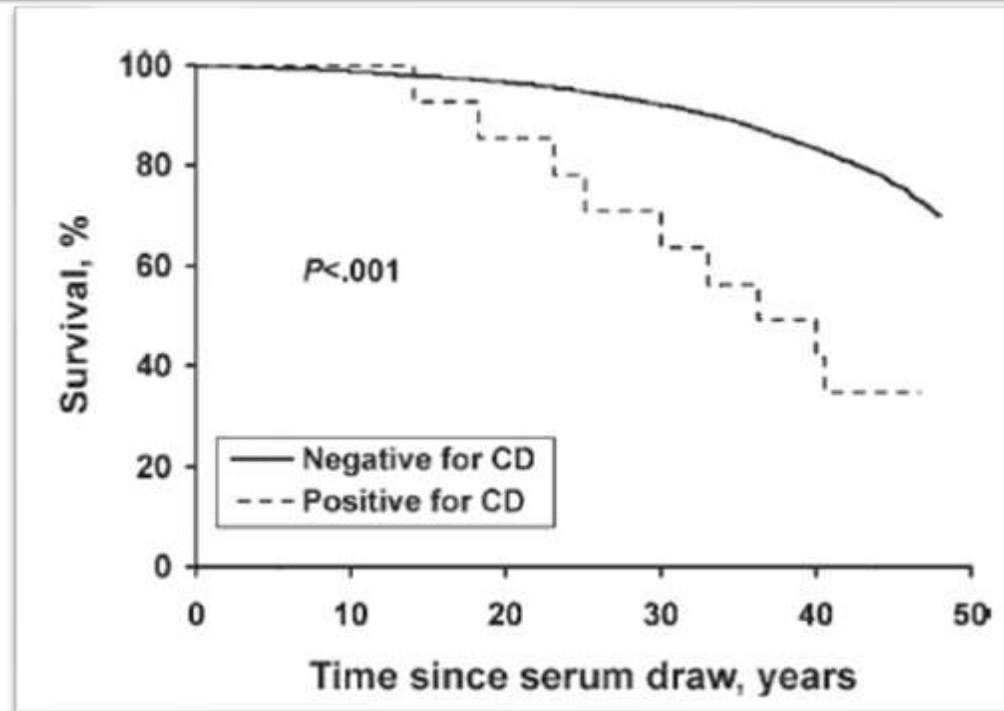


# Importance of celiac disease

- The Prevalence is high.
- The Diagnosis is often delayed.
- Delayed diagnosis associated with increased mortality



# Increased Prevalence and Mortality in Undiagnosed Celiac Disease



- Undiagnosed CD was associated with a nearly 4-fold increased risk of death.

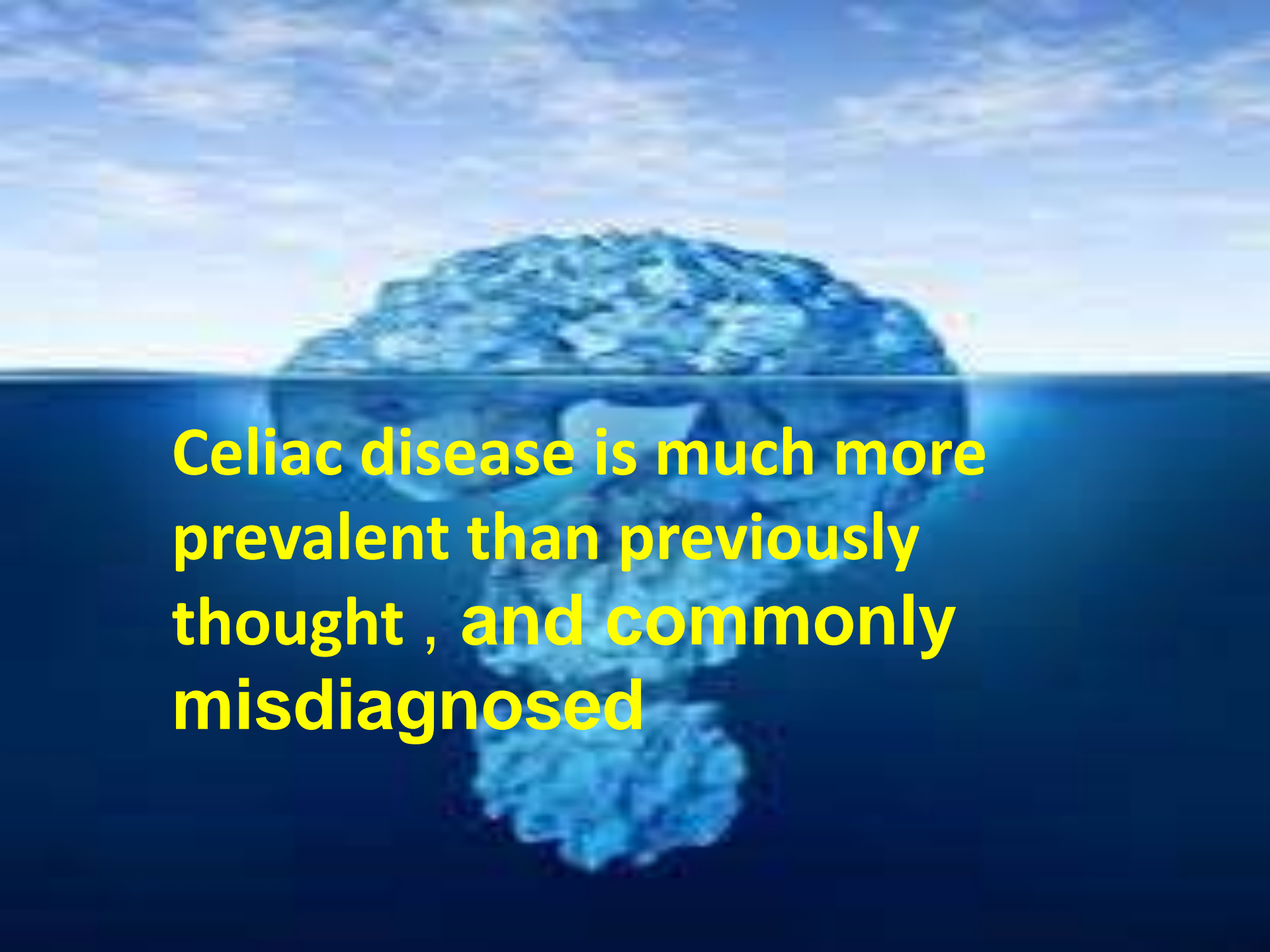
# Increased incidence of Autoimmune Diseases

- Autoimmune diseases occur 3–10 times as frequently as in the general population

Bai D, et al. 2005. *Scand. J. Gastroenterol.* 40:183–87

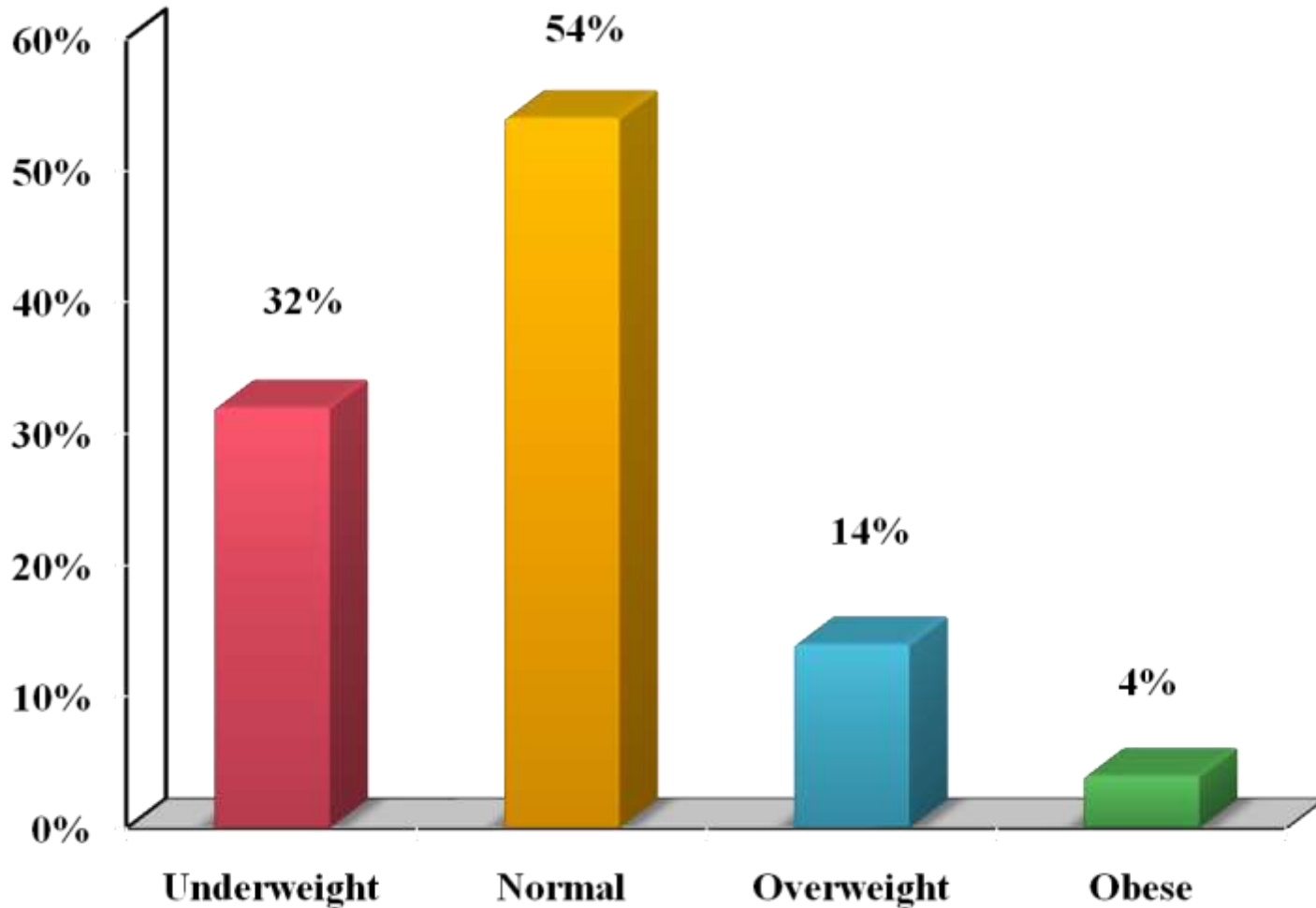
Guidetti SC et al. 2001. *Gut* 49:502–5

Ventura A et al. 1999. *Gastroenterology* 117:297–303

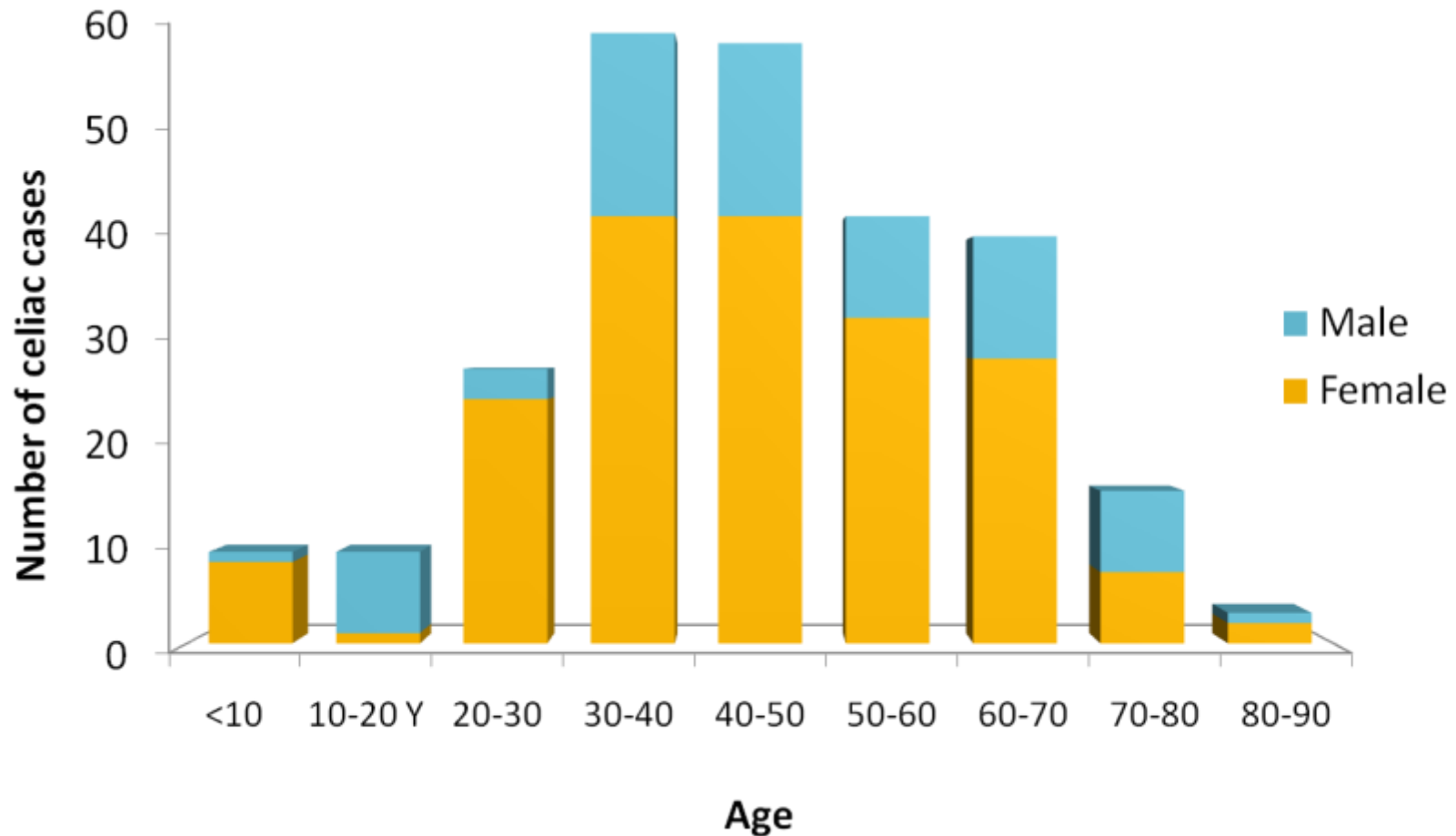
A blue-tinted image of a brain floating in water, with the text overlaid on the lower half. The brain is positioned in the center, with its top half above the water line and its bottom half submerged. The water is a deep blue, and the sky above is a lighter blue with some white clouds. The text is in a bold, yellow font.

**Celiac disease is much more prevalent than previously thought , and commonly misdiagnosed**

# BMI at time of diagnosis



# Age and sex at the time of diagnosis



An iceberg floating in a dark blue ocean under a cloudy sky. The tip of the iceberg is visible above the water, while the much larger, submerged part is visible below. The text "Celiac Disease affects all age groups" is overlaid in yellow on the submerged part of the iceberg.

**Celiac Disease affects all age groups**

# *We'll talk about...*

- How we define celiac disease
- Who gets it and how?
- How common it is
- Pathophysiology of Celiac Disease
- What are its clinical manifestations
- What conditions can accompany it
- Complications

# Pathophysiology Sequelae

## Malabsorption

- Malabsorption of nutrients, especially **iron, folate, calcium, and vitamin D**

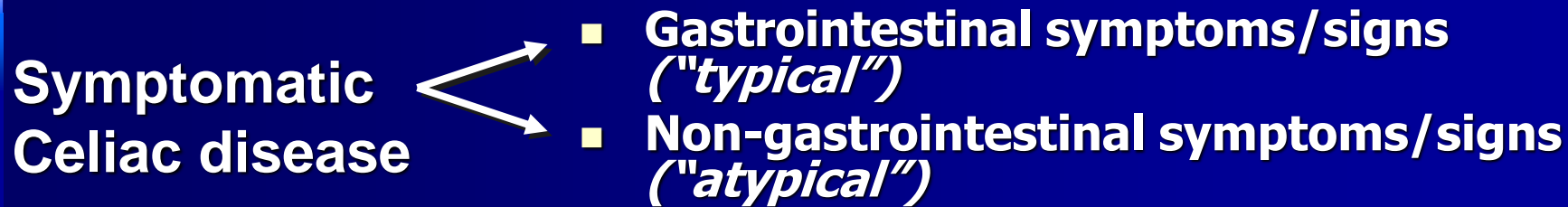
## Increased intestinal permeability

- Permit entry of other toxins which might induce **autoimmune diseases**

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# Clinical Manifestations



*Celiac Disease may also be associated with other conditions, and mostly with:*

- Autoimmune disorders
- Some syndromes

# 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

# Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

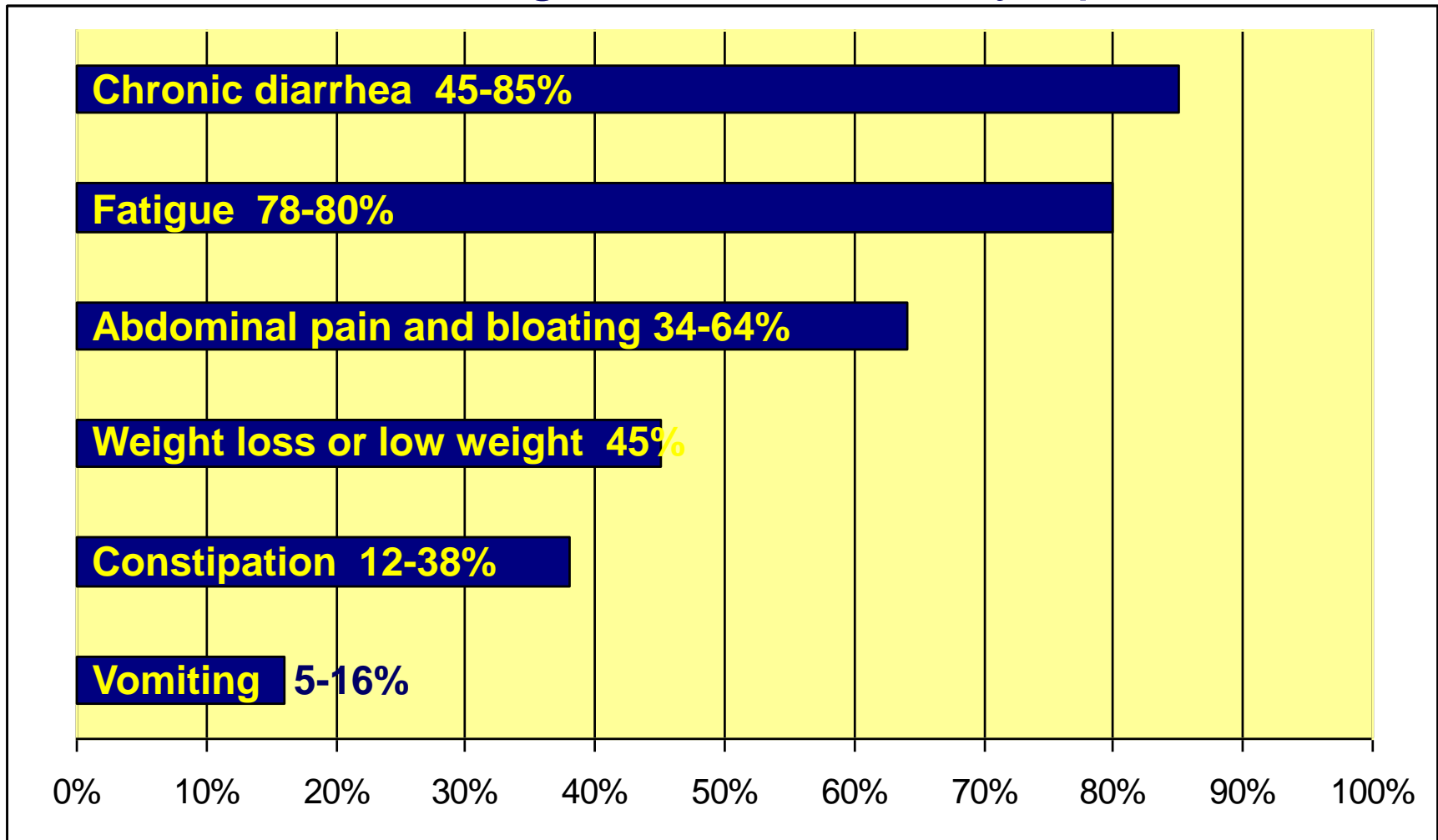
- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

# Celiac Disease: the clinical chameleon



# Clinical Presentation

“Classic” – gastrointestinal symptoms





London, 1938

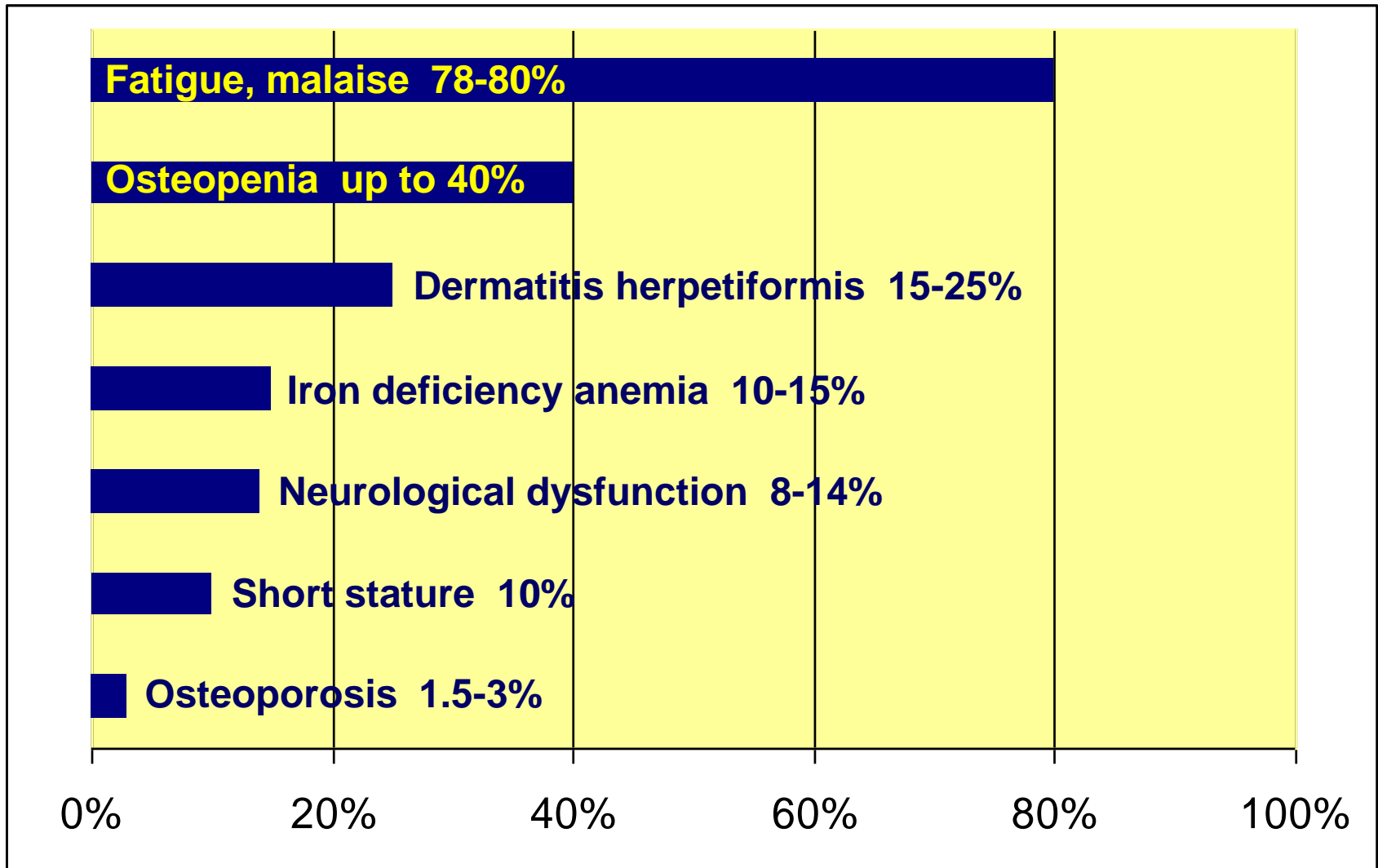
o. 2.—Photograph of five cases of coeliac disease showing the general clinical features

# Typical Celiac Disease



# Clinical Presentation (continued)

“Atypical” – non-GI symptoms



# **It's not just DH!**

## **Other skin disorders possibly associated with celiac disease**

- Urticaria
- Hereditary angioneurotic edema
- Cutaneous vasculitis
- Erythema nodosum
- Psoriasis
- Vitiligo
- Dermatomyositis
- Alopecia aerata...

# Dermatitis Herpetiformis



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

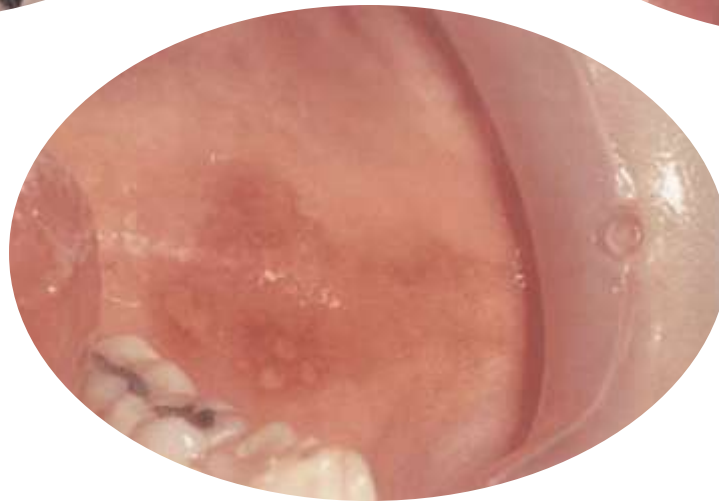
Garioch JJ, et al. *Br J Dermatol.* 1994;131:822-6.  
Fry L. *Baillieres Clin Gastroenterol.* 1995;9:371-93.  
Reunala T, et al. *Br J Dermatol.* 1997;136:315-8.

# Dental Enamel Defects

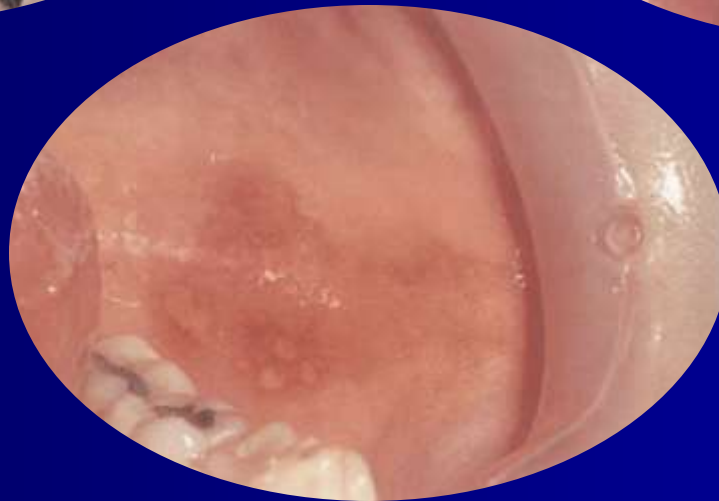


*Involve the permanent teeth and  
can be the only presenting sign of Celiac Disease*

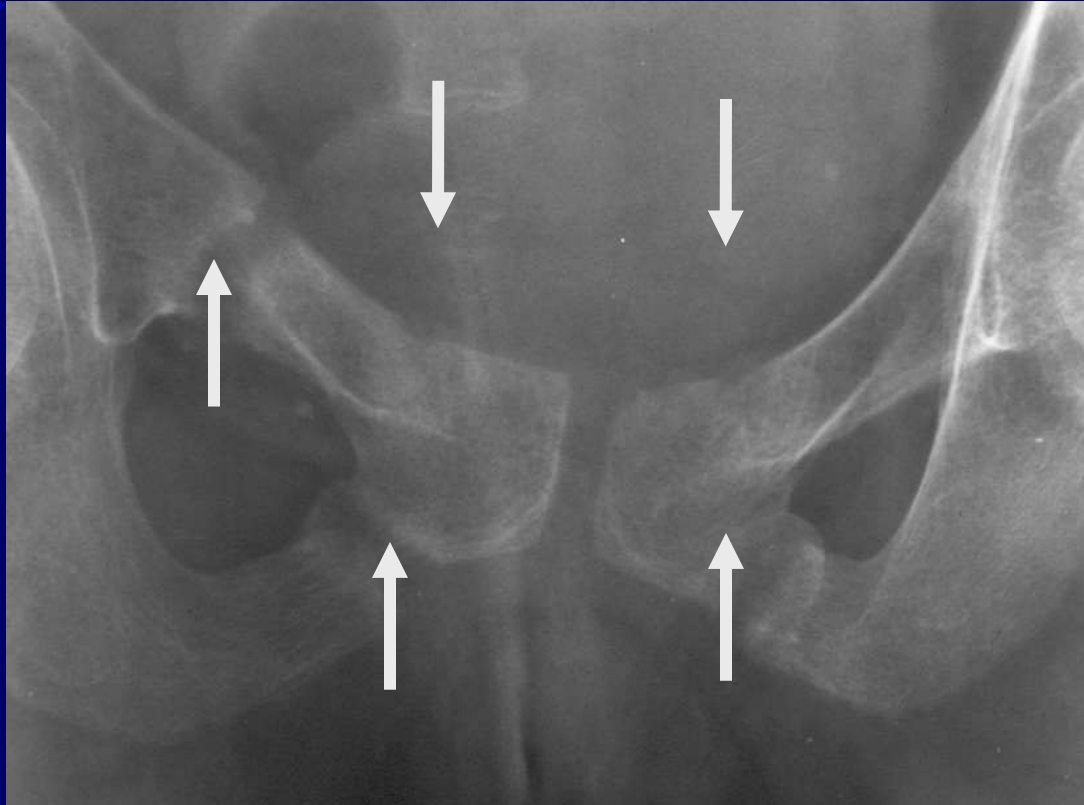
# Recurrent Aphthous Stomatitis



# Recurrent Aphthous Stomatitis



# Low bone density (Osteoporosis)



***Normal Peak Bone Mass can be achieved at puberty  
by celiac children on a GFD, but only if the diet is  
strict!***

# Short Stature/Delayed Puberty

Can anyone guess how many children who are short have celiac disease as cause of their reduced height?

- ~**10%** of short children and teens are celiacs
- Delayed onset of menstrual periods:
  - Not uncommon in teen girls with untreated Celiac Disease
- Underachievement in education.
- Poor school marks

Pynnonen PA et al. Psychosomatics 2004;45:325-35

Scand J Gastroenterology, 2005; 40: 1407/1412

# Anemia

- Considered the most common non-GI manifestation in older teenagers and adults
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- In children with newly diagnosed Celiac Disease:
  - Anemia is very common
  - However, in children presenting with anemia only, celiac disease is not very frequent

# Liver disease: A study on 14,000 CD patients and 67,000 controls

Highly statistically ( $p < 0.001$ ) increased risk for the following conditions in celiac disease (occurring before and after diagnosis) is shown for:

- Acute and chronic hepatitis
- Primary sclerosing cholangitis
- Fatty liver
- Liver failure
- Liver cirrhosis or fibrosis
- Primary biliary cholangitis

# Arthritis and Neurological Problems

## ■ Arthritis in adults

- Fairly common, including those on gluten-free diets

## ■ Juvenile chronic arthritis

- Up to **3%** have Celiac Disease

## ■ Neurological problems in teenagers and adults

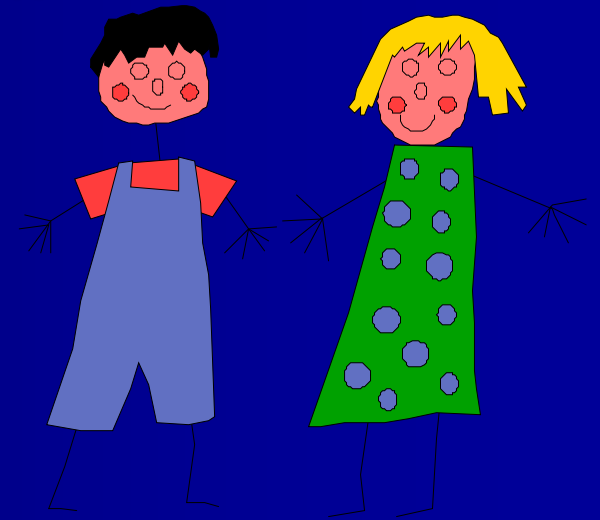
- Cerebellar ataxia (abnormal gait)
- Peripheral neuropathies
- Epilepsy with cranial calcifications

# The list keeps growing

- Idiopathic dilated cardiomyopathy
- Pancreatitis (ESPGHAN 2007)
- Cardiac valves involvement (ESPGHAN 2007)

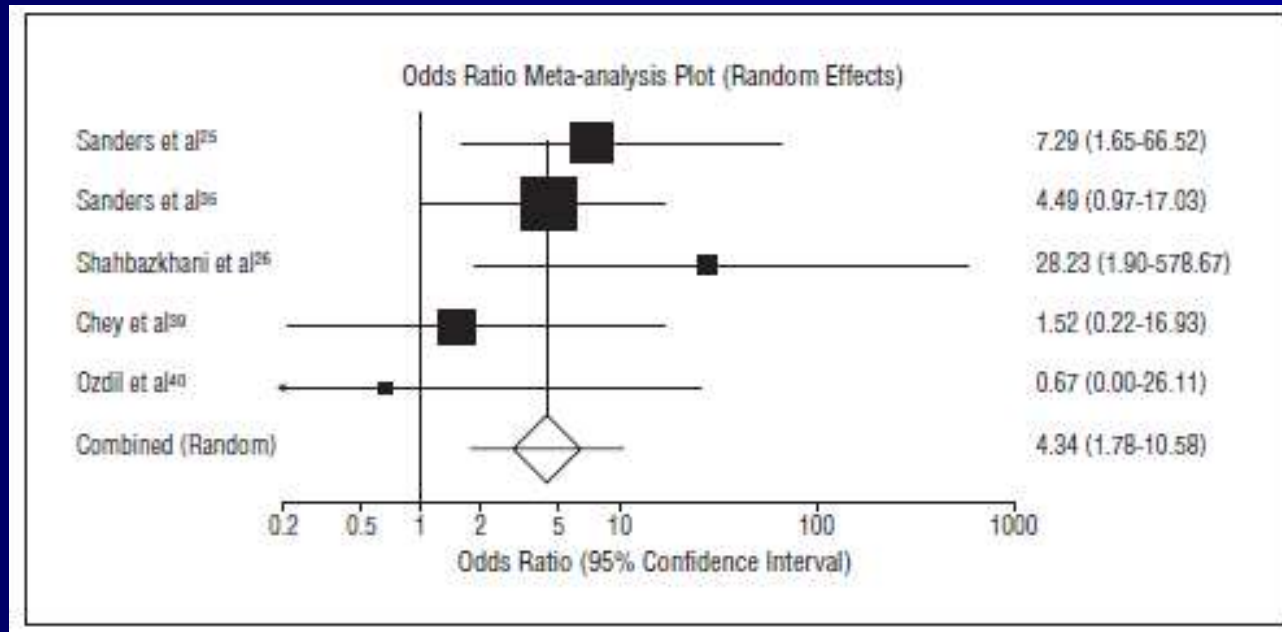
# Poor school performance

- Underachievement in education.
- Poor school marks



# Yield of Diagnostic Tests for Celiac Disease in Individuals With Symptoms Suggestive of Irritable Bowel Syndrome

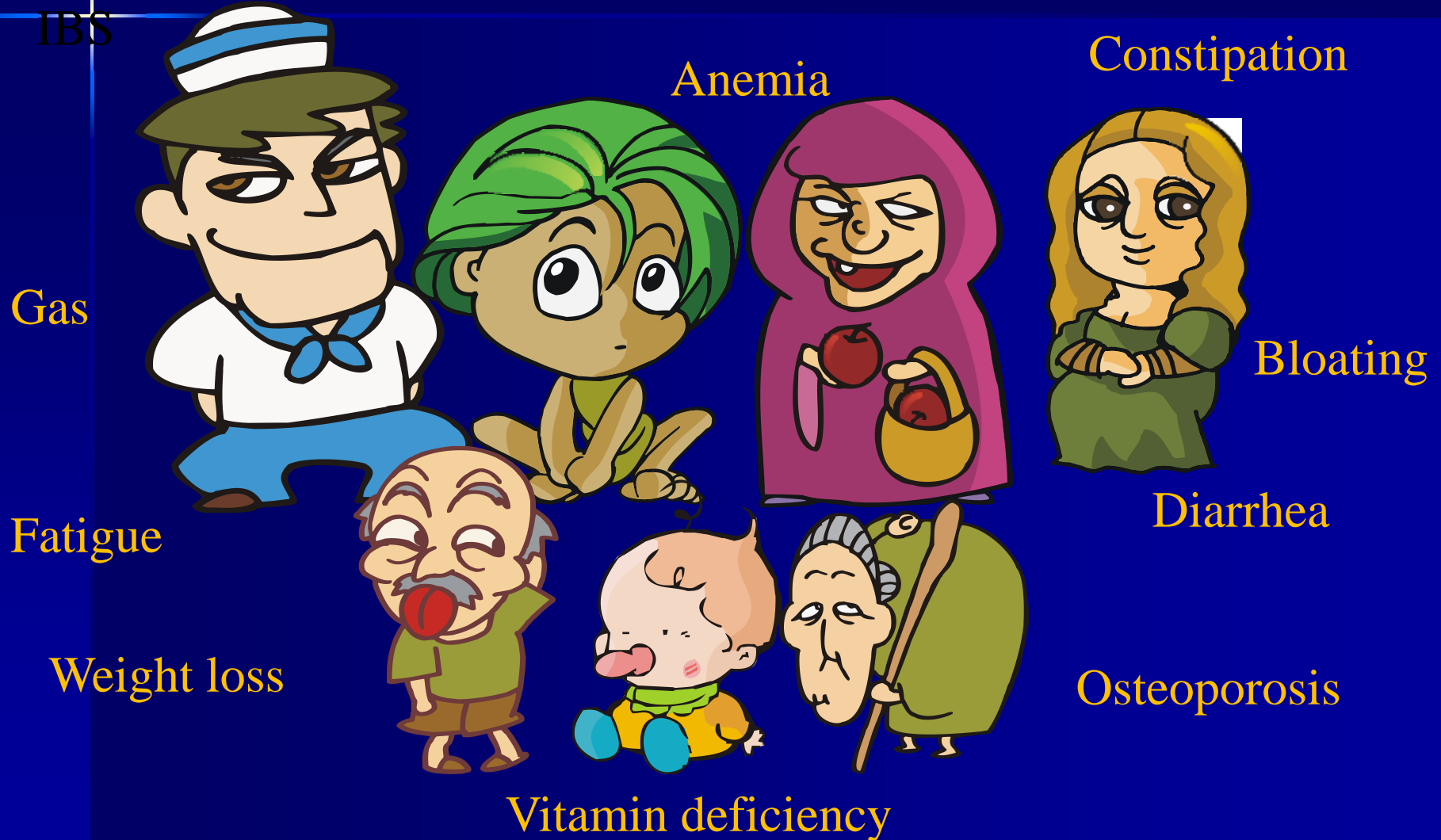
- Prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS was more than 4-fold that in controls without IBS.



An iceberg floating in the ocean. The tip of the iceberg is visible above the water, while the much larger, submerged part is hidden below the surface. The sky is blue with a bright sun, and the water is a deep blue. The text is overlaid on the submerged part of the iceberg.

**The Non-Gastrointestinal  
Symptoms are the  
predominant Symptoms**

# The Many Faces of Celiac Disease





# The Great Imitator

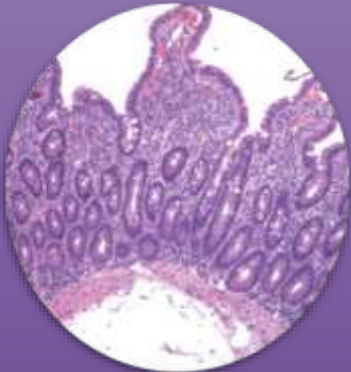
# Diagnosis of Celiac Disease



# Diagnosis of Celiac Disease



Serological Tests



Intestinal Biopsies

“The most important diagnostic test in CD is the suspicion of the disease.”

NIH consensus 2004

# Conclusion

- On ne trouve que ce que l'on cherche...



# Serologic Tests

Test	Sensitivity	Specificity
IgA endomysial antibody (indirect IF)	85-98%	97-100%
IgA tissue transglutaminase	90-98%	94-97%
Deamidated gliadin peptide	94%	99%

# Serological Tests

- ~~Antigliadin antibodies (AGA)~~
- Antiendomysial antibodies (EMA)

- Anti tissue transglutaminase antibodies (TTG)
- Deamidated gliadin peptide antibodies (DGP)
- HLA typing

# Antigliadin Antibodies - AGA

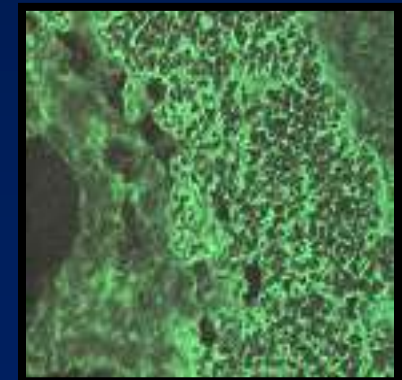
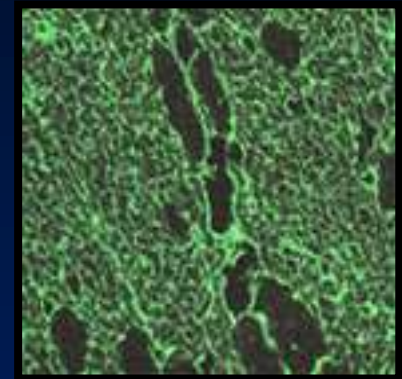
- Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
- Advantages
  - relatively cheap & easy to perform
- Disadvantages
  - **poor sensitivity and specificity**

# Endomysial Antibody - EMA

- IgA based antibody against reticulin connective tissue around smooth muscle fibers
- Advantages
  - high sensitivity and specificity

## Disadvantages

- false negative in young children
- operator dependent
- expensive & time consuming
- false negative in IgA deficiency



# Tissue Transglutaminase - TTG

- IgA based antibody against tissue transglutaminase (Celiac Disease autoantigen)
- Advantages
  - High sensitivity and specificity (human TTG)
  - Non operator dependent (ELISA/RIA)
  - Relatively cheap

## Disadvantages

- False negative in young children
- False negative in IgA deficiency
- Possibly less specific than EMA

# Deamidated Gliadin Peptide Ab

- Uses synthetic gliadin peptides that mimic tTG gliadin sequences to capture serum IgA or IgG against DGP
- Useful in IgA deficiency

# Deamidated Gliadin Peptide Antibodies as a Routine Test for Celiac Disease: A Prospective Analysis

- Our prospective study shows that the **combined search for IgA tTGA and IgG DGP-AGA provides the best diagnostic accuracy** for CD, allowing the identification of all CD cases with a very high specificity.

# HLA Tests

HLA alleles associated with Celiac Disease

- DQ2 found in 95% of celiac patients
- DQ8 found in remaining patients
- DQ2 found in ~30% of general population

Value of HLA testing

- High negative predictive value
  - **Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence**

# Endoscopic Diagnosis

# What is the role of endoscopy in the evaluation of patients with possible celiac disease?

**Primarily:** confirm Dx by obtaining Bx of proximal small intestine

- In pts w/ positive serologic test results
- High clinical suspicion of celiac disease in absence positive serologic test results

Have pathologist w/ expertise in GI diseases examine Bx slides (esp if Dx uncertain)

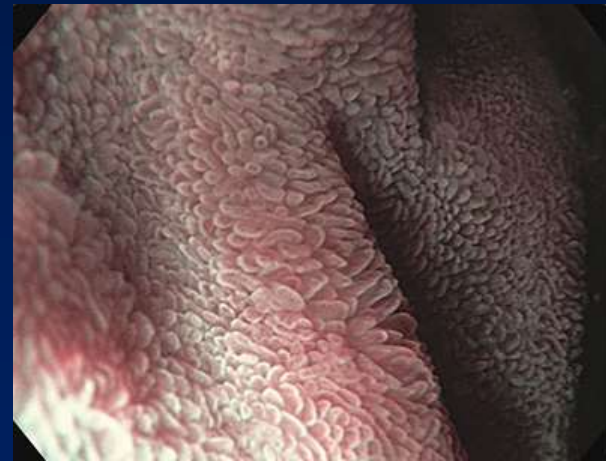
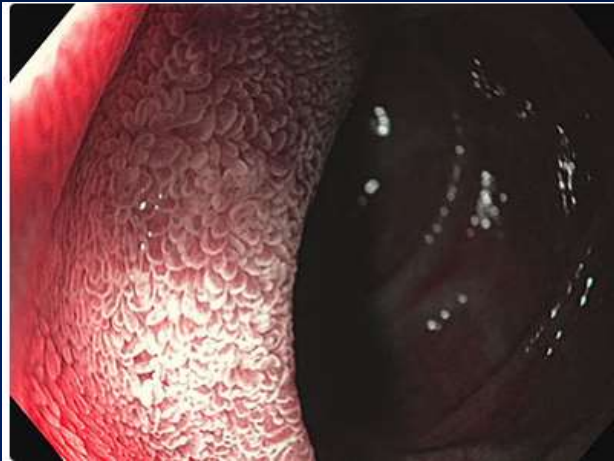
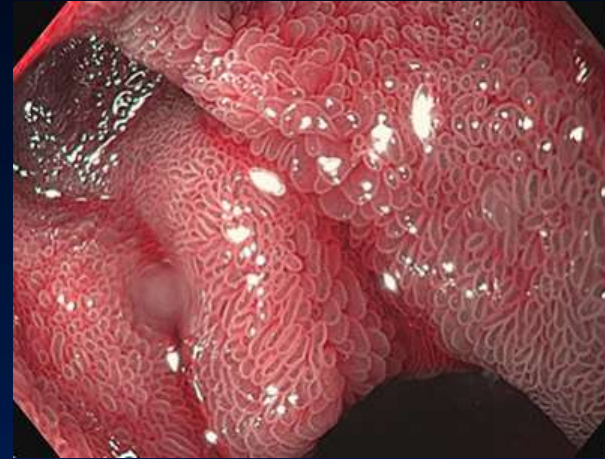
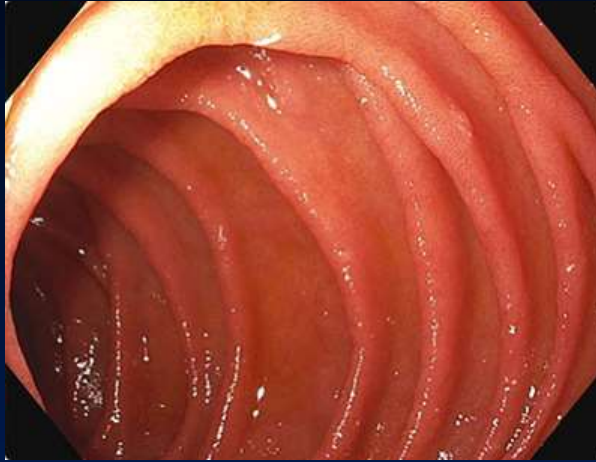


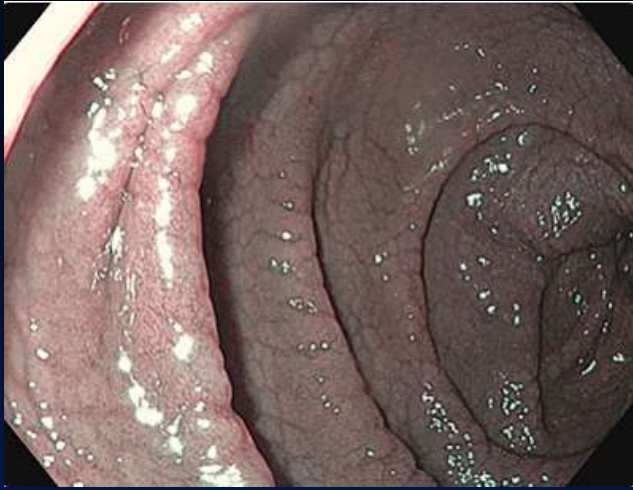
Scalloping or notching of folds, fissuring or cracking of flat intervening mucosa between folds also seen. Features help target Bx sites; absence does not r/o Dx.

# Gross Endoscopic Views

- There are several well-described **endoscopic features** of CD,
  - mucosal fold loss,
  - mosaic pattern,( in children)
  - scalloping,
  - nodularity,
  - fissuring, and prominent submucosal vascularity
- **Sensitivity** of endoscopic markers varies (59%–94%),
- **specificity** is high (92%–100%). The pattern of endoscopic markers may **differ between adults and children.**
- **Water Immersion** : instilling 100–200 mL water into the duodenum after deflation, takes only 30 seconds to perform, has high sensitivity and specificity for detecting total villous atrophy, and may help target duodenal biopsies because of the patchy nature of CD

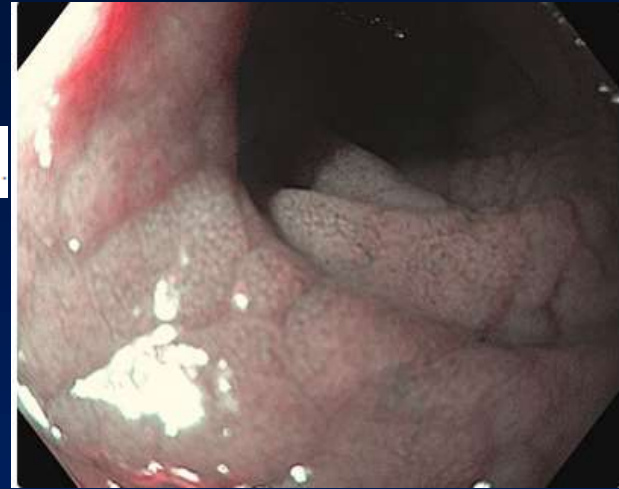
# REGULAR FOLDS AND VILLI



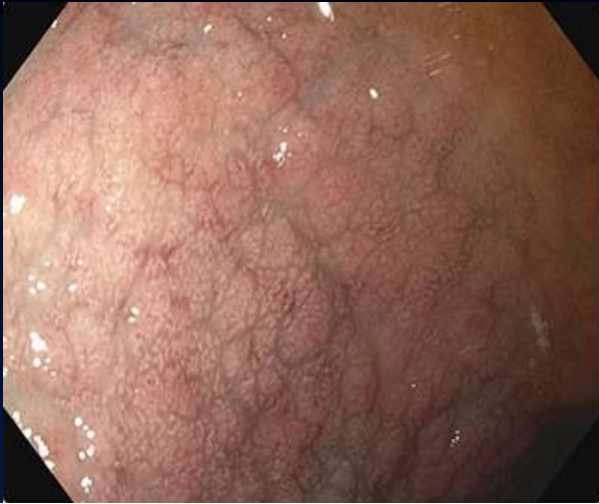


MARSH- 3

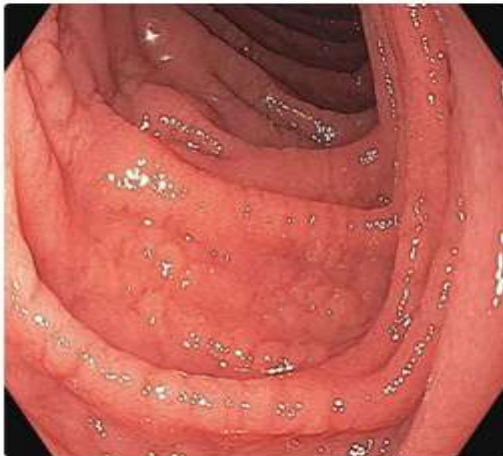
folds with visible fissures and nodular appearance.



A closer look at the folds reveals absence of villi.

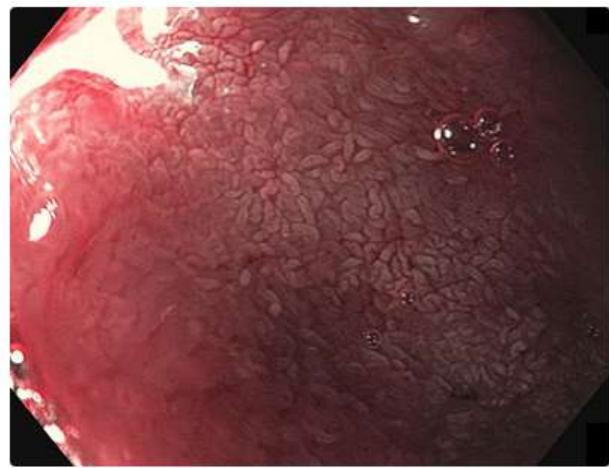
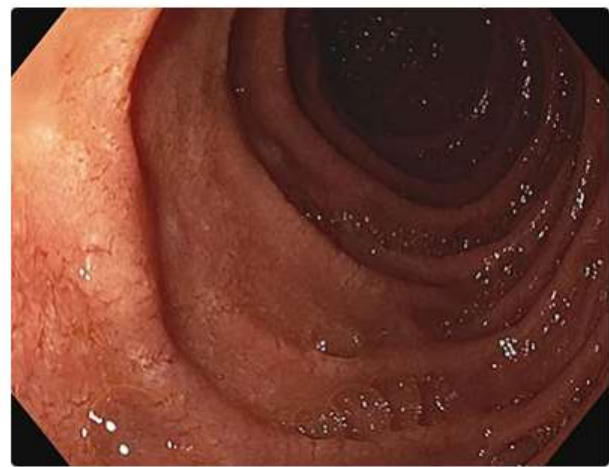


loss of folds with a granular appearance of the mucosa. NBI and near focus reveals loss of villi



Left image presents a granular appearance of the folds including visible fissures. The right image generated using NBI and near focus reveals loss of villi.

# IMPROVEMENT AFTER DIETARY RESTRICTIONS



## Other Endoscopic Techniques

### ➤ Video capsule endoscopy (VCE) ,indicated in :

- who are unable to undergo upper endoscopy,
- Have normal histology but positive celiac serologies.
- Evaluating refractory or atypical features
- The sensitivity of VCE in CD is 89% with specificity of 95%

### ➤ Double-balloon endoscopy (DBE) or push enteroscopy

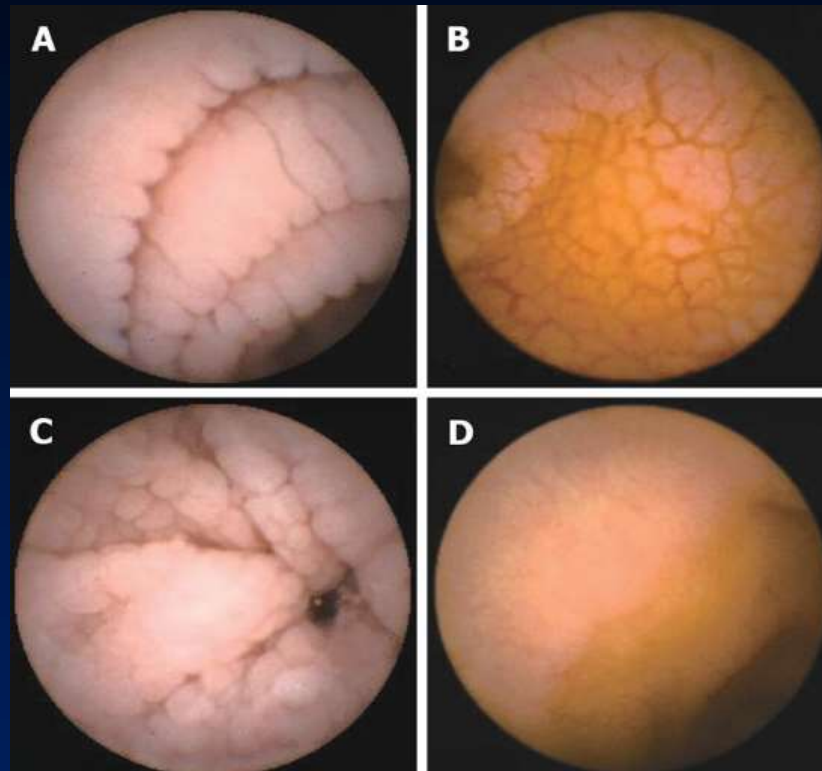
- In Patchy, disease limited to the jejunum, evaluation for complications of the disease. Antegrade DBE may uncover ulcerative jejunitis or enteropathy-associated T-cell lymphoma (EATL) and refractory celiac disease

### ➤ Chromoendoscopy



World J Gastroenterol. Jul 14, 2008; 14(26): 4146-4151

# Role of capsule endoscopy



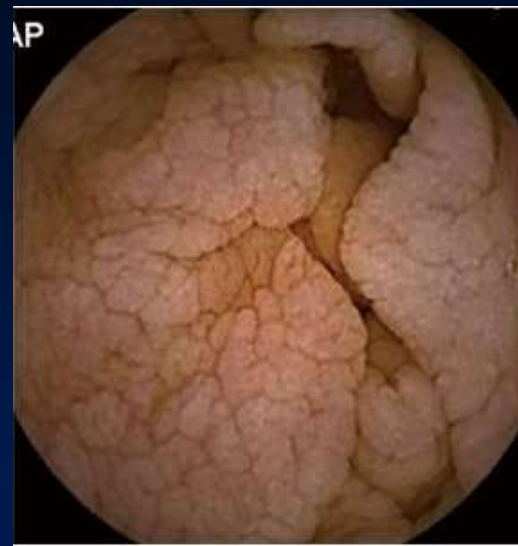
Endoscopic markers of celiac disease at capsule endoscopy: scalloping (A), mosaic pattern (B), micronodularity (C), and reduction of folds (D).

World J Gastroenterol. Jul 14, 2008; 14(26): 4146-4151

## Role of capsule endoscopy



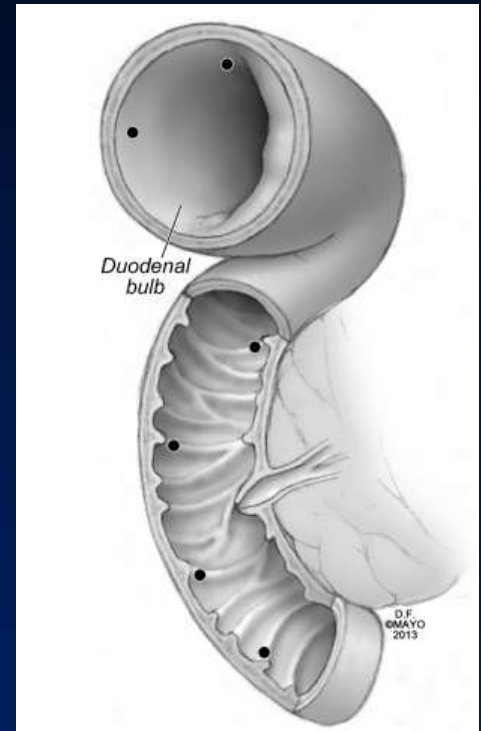
ulcerative jejunitis.

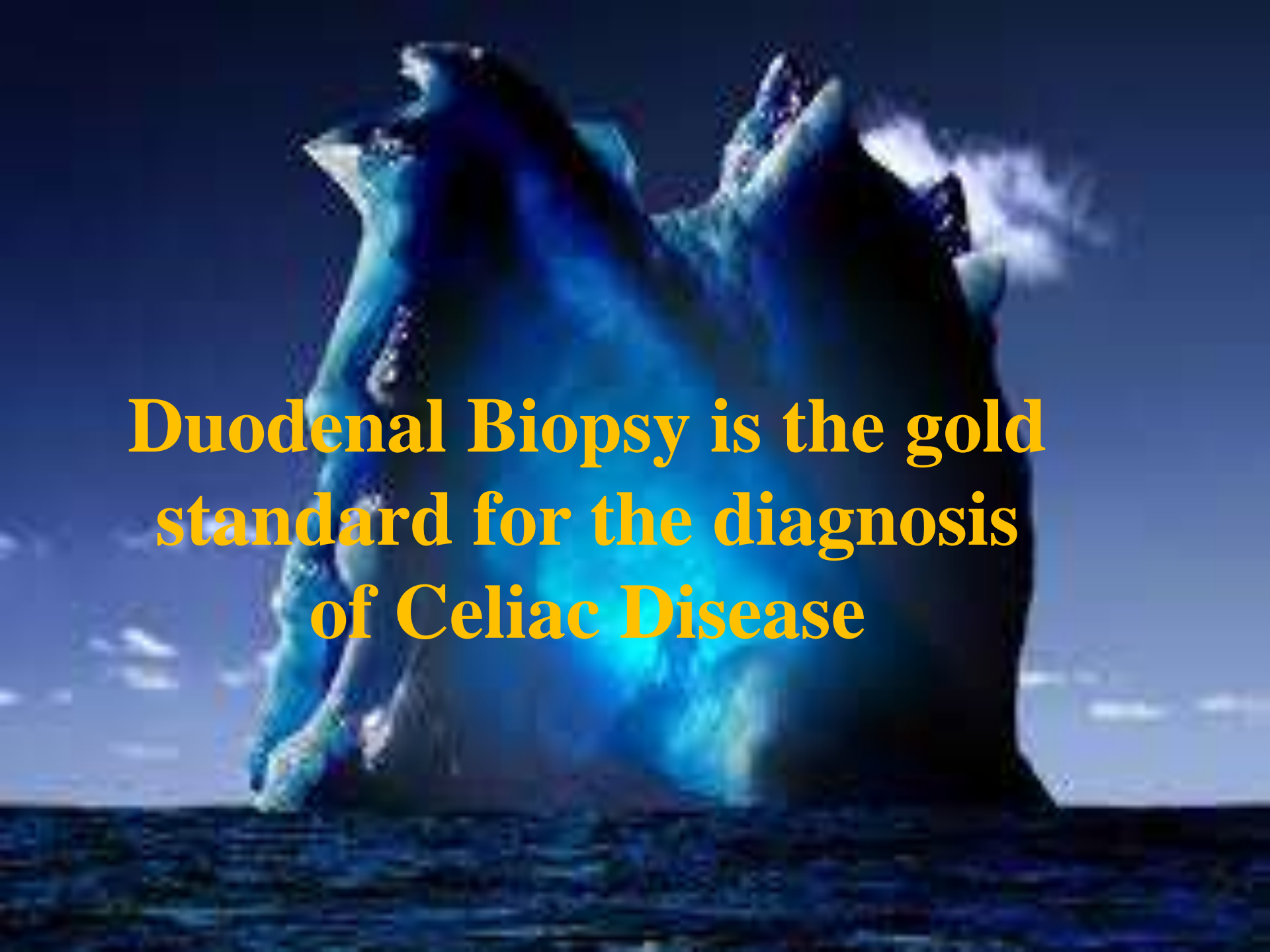


celiac disease by capsule endoscopy

# What Biopsies Should Be Taken to Evaluate for Celiac Disease?

- Take 4 biopsies from the post-bulbar duodenum and 1–2 biopsies from the 9 o'clock and/or 12 o'clock position of the bulb
- High sensitivity (100%)
  - Normal mucosa does not exclude celiac disease



A large, dark, textured rock formation or iceberg in the ocean under a cloudy sky. The rock is the central focus, with a rough, layered appearance. The sky is filled with soft, white clouds, and the water in the foreground is dark and calm.

**Duodenal Biopsy is the gold  
standard for the diagnosis  
of Celiac Disease**

# ***We'll talk about...***

- How we define celiac disease
- Who gets it and how?
- How common it is
- What are its clinical manifestations
- What conditions can accompany it
- Complications

# “Mines” of Celiac Disease Were Found Among:

## Relatives

short stature, anaemia, fatigue,  
hypertransaminasemia

## Patients with

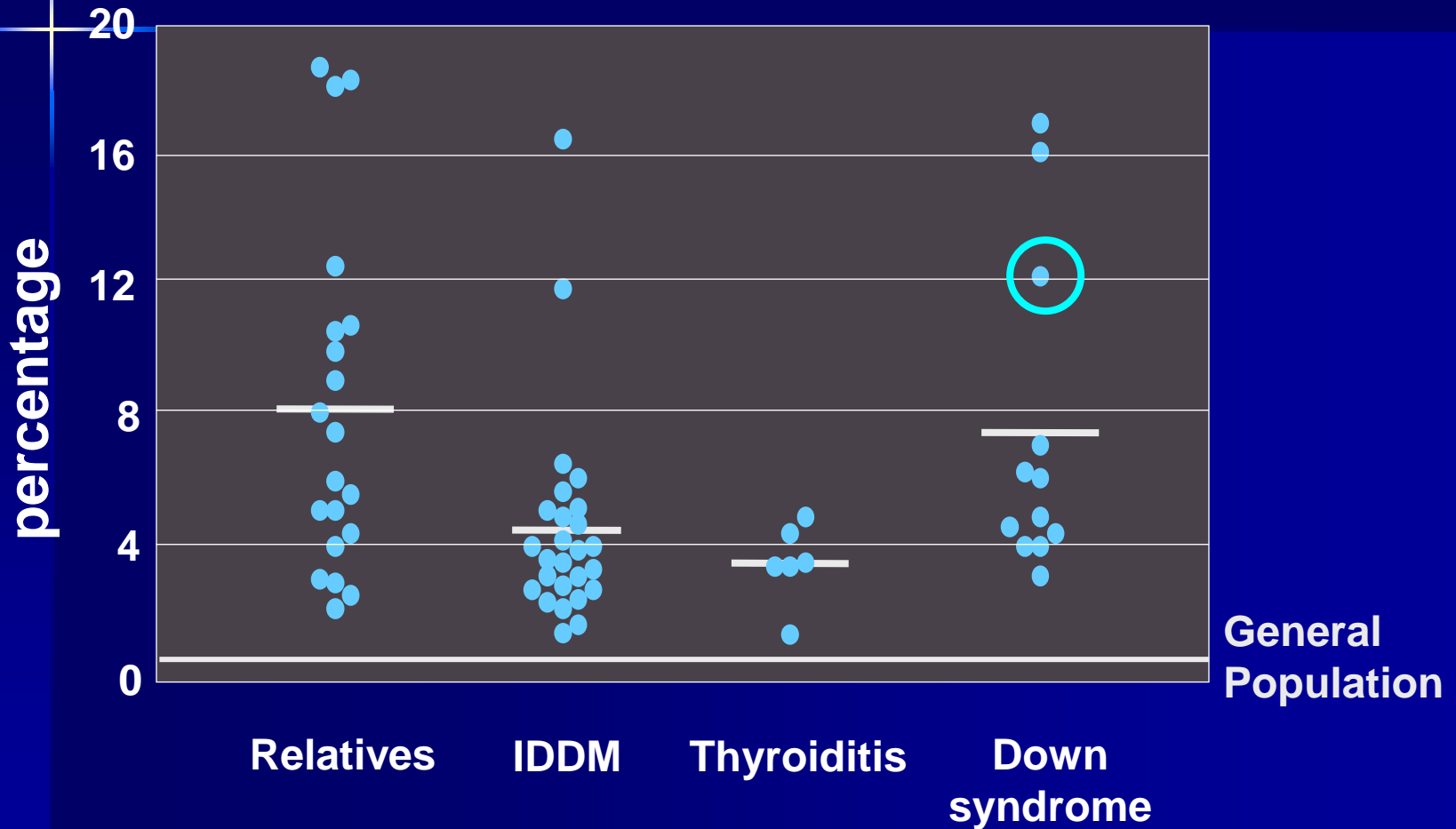
autoimmune disorders, Down s, IgA deficiency,  
neuropathies, osteoporosis, infertility

## Associated diseases

blood donors, students, general population

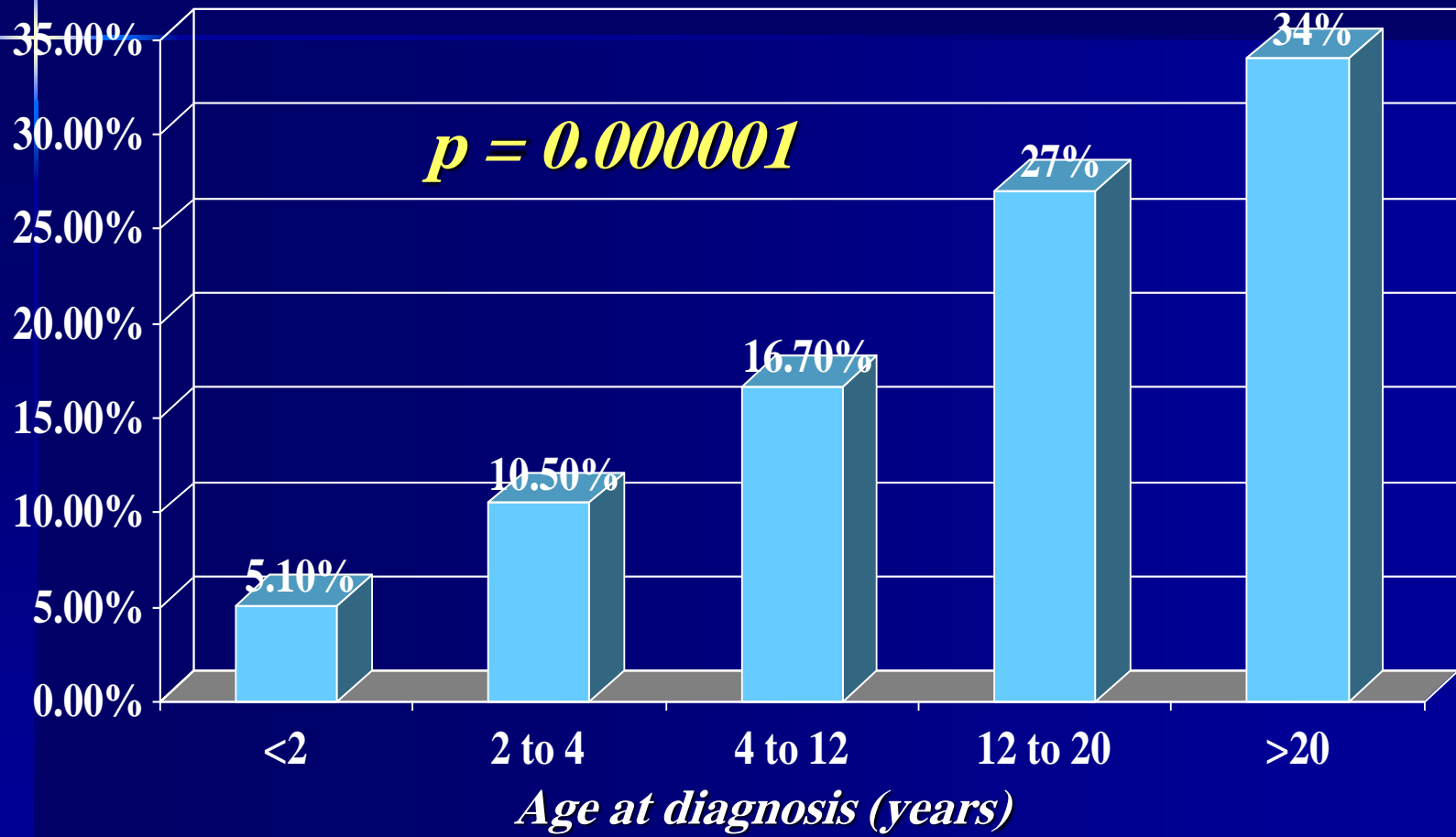
“Healthy”  
groups

# Associated Conditions



# Celiac Disease and Autoimmunity

*The Prevalence Of Autoimmune Disorders Increases As Diagnosis Is Delayed*



# ***We'll talk about...***

- How we define celiac disease
- Who gets it and how?
- How common it is
- What are its clinical manifestations
- What conditions can accompany it
- Complications

# Malignancies Associated with CD

Malignancies	Overall Relative Risk (RR)
All Cancers	2 - 3
EATL (Enteropathy associated T cell Lymphoma)	30 - 40
	78 if no GFD
	No increase if GFD > 5 years
Small intestine adenocarcinoma	83
Mouth, pharynx, esophagus	23
NHL	2.6

# Major Complications of Celiac Disease

- Refractory celiac disease and related disorders
- Intestinal lymphoma



Reduced life expectancy  
**(if not on the diet!)**

*Prompt diagnosis is crucial to minimize, if not prevent, serious complications*



القرن ٢١

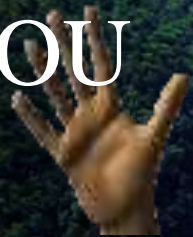
القرن ٢٠

مرض مناعي ذاتي  
تظاهرات جهازية  
جميع الأعمار

مرض هضمي  
تظاهرات هضمية  
يصيب الأطفال

الداء الزلاقي بين قرنين

THANK  
YOU



# "Mines" of Celiac Disease Were Found Among:

## Relatives

short stature, anaemia, fatigue,  
hypertransaminasemia

## Patients with

autoimmune disorders, Down s, IgA deficiency,  
neuropathies, osteoporosis, infertility

## Associated diseases

blood donors, students, general population

"Healthy"  
groups

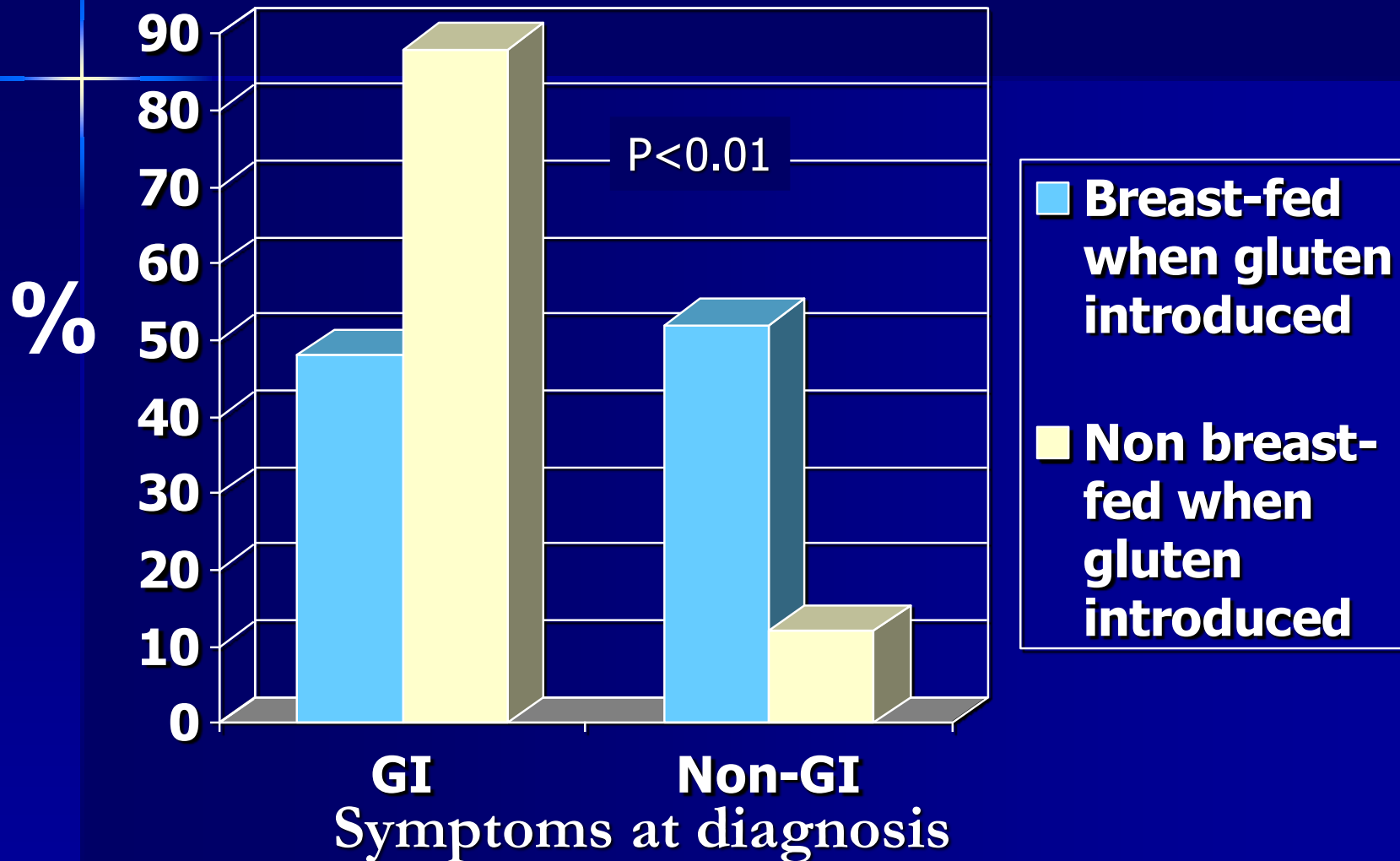
A large, white iceberg with a jagged, irregular shape floats in the dark blue ocean. The sky is a clear, bright blue. The iceberg's surface shows some texture and shadows, suggesting its massive scale. The water in the foreground is dark blue with small ripples.

**celiac disease can be prevented!**

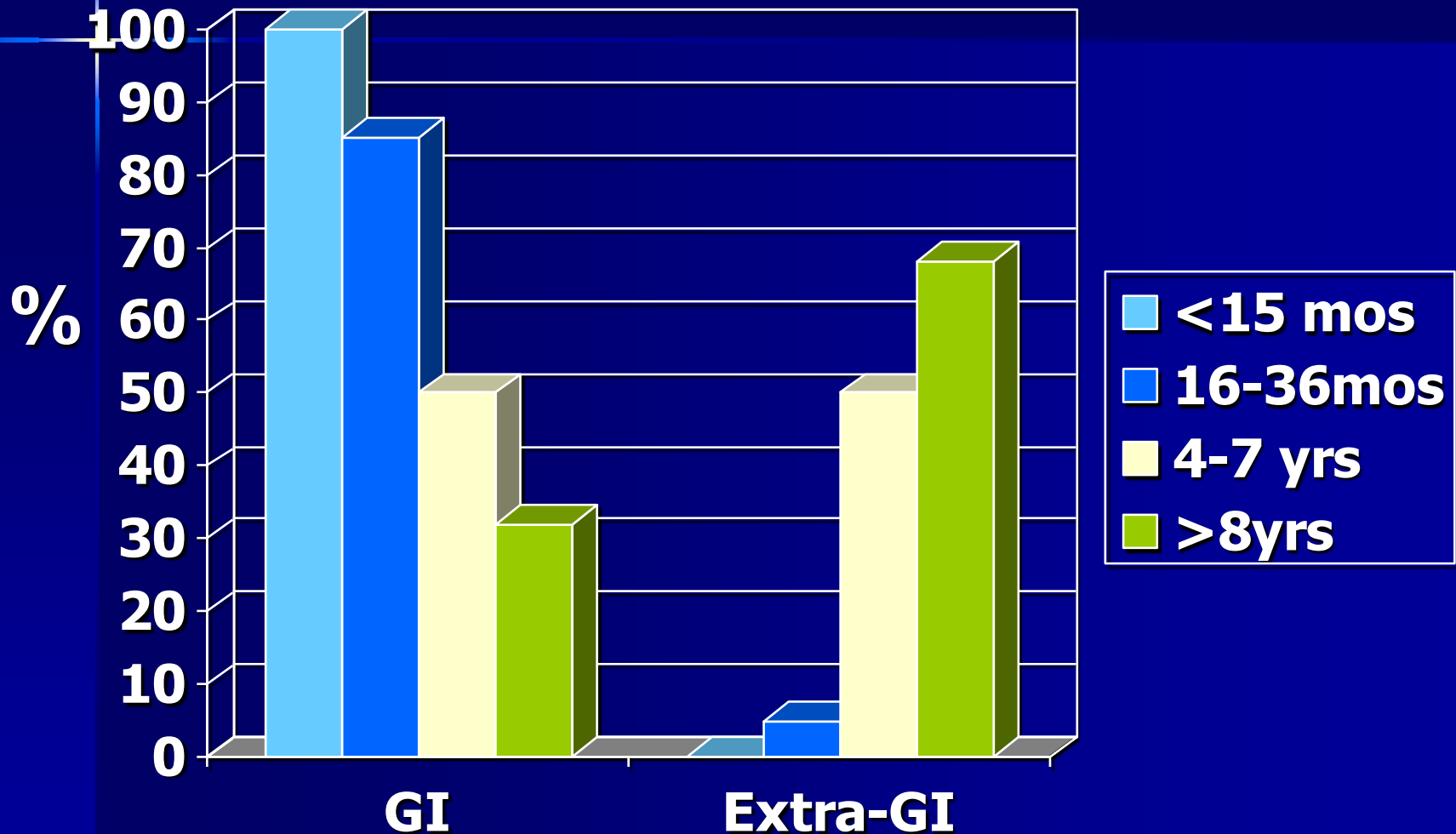
# In summary, the role of environmental factors in celiac disease

- Breast feeding reduces the risk of celiac disease and/or at least delays its onset.
- Infants non breast-fed at the time of gluten introduction seem to be more likely to develop typical (GI) celiac disease.
- To reduce risk of celiac disease, gluten should be introduced in small amounts.
- Intestinal infections – especially by Rotavirus – increase the risk of developing celiac disease

# Breast feeding at time of gluten introduction influences the presenting symptoms of celiac disease



# Changing pattern of celiac disease according to age at presentation



Guandalini S., UCCDP – n=92 pts

# Differentiating...

## Celiac vs. Wheat Allergy vs. Gluten sensitivity

Investigation	Coeliac disease* (adaptive immune response)	Wheat allergy† (allergic immune response)	Non-coeliac gluten sensitivity‡ (Innate immune response)
Coeliac serology (endomysial and tissue transglutaminase antibodies)	Positive	Negative	Negative
Duodenal biopsies	Villous atrophy	Normal	Normal or near normal with raised intraepithelial lymphocytes
IgE serology or skin prick test to wheat	Negative	Positive	Negative

Aziz I, Hadjivassiliou M, Sanders D. Does gluten sensitivity in the absence of coeliac disease exist? *BMJ*. 2012;345:7907.

**My bloating got better  
when I started a GFD...**

Does that mean I have celiac disease?