

Anemia in celiac disease: Connecting blood to the bowel

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Celiac disease

Classical Definition

Disease of the small intestine characterized by an abnormal mucosa and associated with permanent intolerance to gluten in genetically susceptible individuals.

Celiac disease

Current Definition

A multi-system auto-immune disorder:

- Genetic predisposition (*HLA DQ2/DQ8*)
- Autoantigen (*tissue transglutaminase*)
- Exogenous trigger (*gluten*)

The Celiac Iceberg

Classical
clinical
manifestations

waterline

Diagnosed

Atypical
clinical
manifestations

Undiagnosed

- silent celiac disease
- latent celiac disease



“Atypical is typical”

Canadian Celiac Health Survey (2002)

Physician consulted before the diagnosis of celiac disease confirmed

Pediatric data (n=168)

24% consulted ≥ 2 family physicians

30% consulted ≥ 2 pediatricians

6% consulted ≥ 2 gastroenterologists

Adult data (n=2,681)

37% consulted ≥ 2 family physicians

14% consulted ≥ 2 gastroenterologists

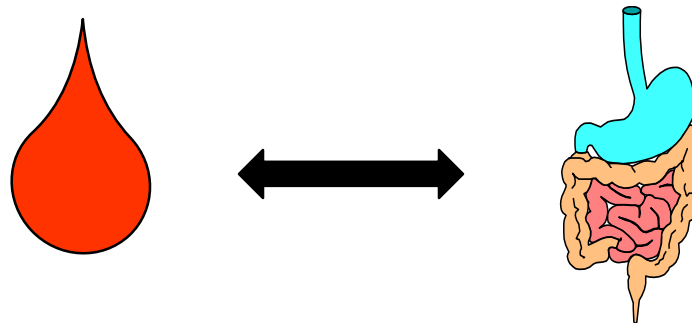
Mean delay in diagnosis in adults 11.7 years



Objectives

To learn about:

- Various hematological (blood) abnormalities in celiac disease
- **Nutritional anemias in celiac disease with emphasis on iron deficiency**



Hematological manifestations of celiac disease

- **Anemia** – *Common*
- **IgA deficiency** – *Common*
- **Hyposplenism** – *Common*
- **Thrombocytosis** – *Common*
- **Thrombocytopenia** – *Uncommon*
- **Leukopenia** – *Uncommon*
- **Thromboembolism** – *Uncommon*
- **Coagulopathy** – *Uncommon*
- **Lymphoma** – *Uncommon*

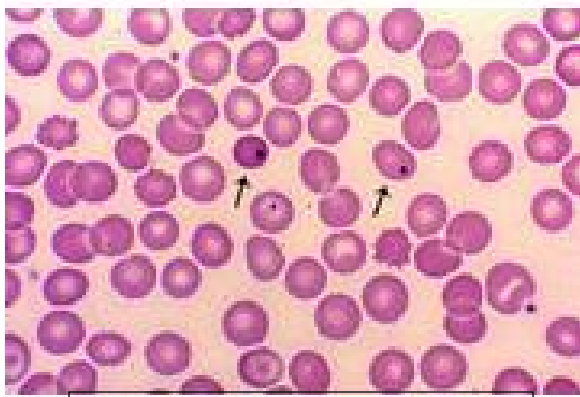
IgA deficiency

- 2%-3% of individuals with celiac disease are IgA-deficient
 - 10-16 fold increase in prevalence in those with CD
- Up to 8% of IgA-deficient individuals have celiac disease
 - 10 fold increased risk of CD
- Two important associations
 - Increased risk of other bowel problems (IBD, parasites)
 - Risk of anaphylactic transfusion reactions

Collins P et al. *Scan J Gastroenterol* 1992
Cataldo F et al. *Gut* 1998

Hyposplenism (splenic dysfunction)

- First described in 1923
- Reported in 20-70% of adults
 - Varies by evaluation method
- Rare in children
- More common with co-existent auto-immune disorder or complicated CD



Howell-Jolly bodies

Marsh GW et al. *Br J Haematol* 1970
Pettit JE et al. *Br Med J* 1972
Ferguson A et al. *Lancet* 1970

Hyposplenism

- Risks associated with hyposplenism unknown
- Infectious complications uncommon but can occur
- No definite recommendations regarding routine immunizations against encapsulated bacteria
- Those with signs of hyposplenism should be treated as being asplenic
- Controversy exists regarding reversibility with adherence to strict gluten-free diet

O'Grady JG et al. *Gastroenterology* 1984

Di Sabatino A et al. *Clin Gastroenterol Hepatol* 2006

Platelets (Thrombocytes)

■ Thrombocytopenia (decreased platelets)

- Rare
- ? Autoimmune
- Gluten-free diet may help

■ Thrombocytosis (increased platelets)

- More common, seen in up to 60% of patients
- Iron deficiency, inflammatory mediators and hyposplenism may contribute
- Resolves with gluten-free diet

Kahn O et al. *J Clin Gastroenterol* 1996

Fisgin T et al. *Acta Haematol* 2004

Schafer AI. *N Engl J Med* 2004

Leukopenia/Neutropenia (low white blood cell count)

- Reported in a few children
- Possibly related to folate and/or copper deficiencies
- Copper supplements if deficiency present, in addition to gluten-free diet

To clot or not to clot

Coagulopathy

- Depletion of vitamin K dependant factors
 - 18% of patients with CD had prolonged PT/INR
 - More likely to have anemia and abnormal iron proteins
 - Bleeding can be the presenting symptom

Cavallaro et al. *Eur J Gastroenterol Hepatol* 2004

Thrombosis

- Mostly venous
- Hyperhomocysteinemia
- Increased TAFI (Thrombin-Activatable Fibrinolysis Inhibitor)
- Decreased protein C & S (vitamin K dependant)

Saibeni S et al. *Clin Gastroenterol Hepatol* 2005
Thorburn D et al. *Gut* 2003

Lymphoma

Non-Hodgkin lymphoma (NHL)

- Overall relative risk of NHL 2.1-6.6
- Enteropathy-type T-cell lymphoma (ETL)
 - Strong association with celiac disease
 - A rare lymphoma
 - Odds ratio as high as 19.2
- Intestinal B-cell lymphoma
- Extra-intestinal T-cell lymphomas

Catassi C et al. *JAMA* 2002

Askling J et al. *Gastroenterology* 2002

Green PH et al. *Am J Med* 2003

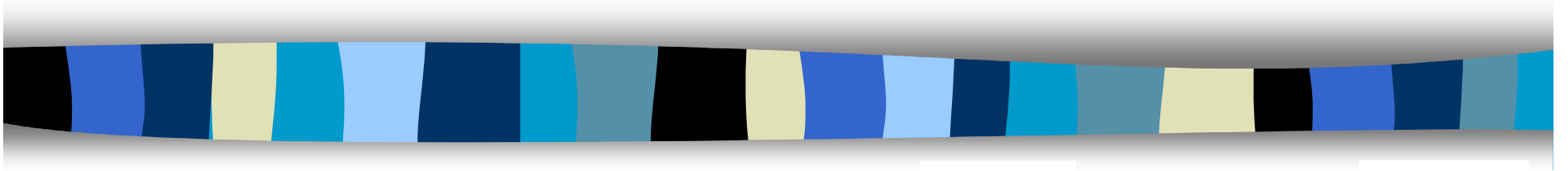
Smedby KE et al. *Gut* 2005

Lymphoma

Good News

Adherence to a strict gluten-free diet reduces the risk of developing lymphoma in celiac disease and dermatitis herpetiformis

Anemia in celiac disease



Canadian Celiac Health Survey:

Adult data (n=2,681)

Other diagnoses prior to the diagnosis
of celiac disease

	%
Anemia	40
Stress	31
Irritable bowel syndrome	29
Vitamin deficiency	16
Peptic ulcer	15

Canadian Celiac Health Survey:

Paediatric data (n=168)

Other diagnoses prior to the diagnosis of celiac disease

	%
Anemia	15
Irritable bowel syndrome	11
Gastroesophageal reflux	8
Stress	8
Stomach ulcer	4

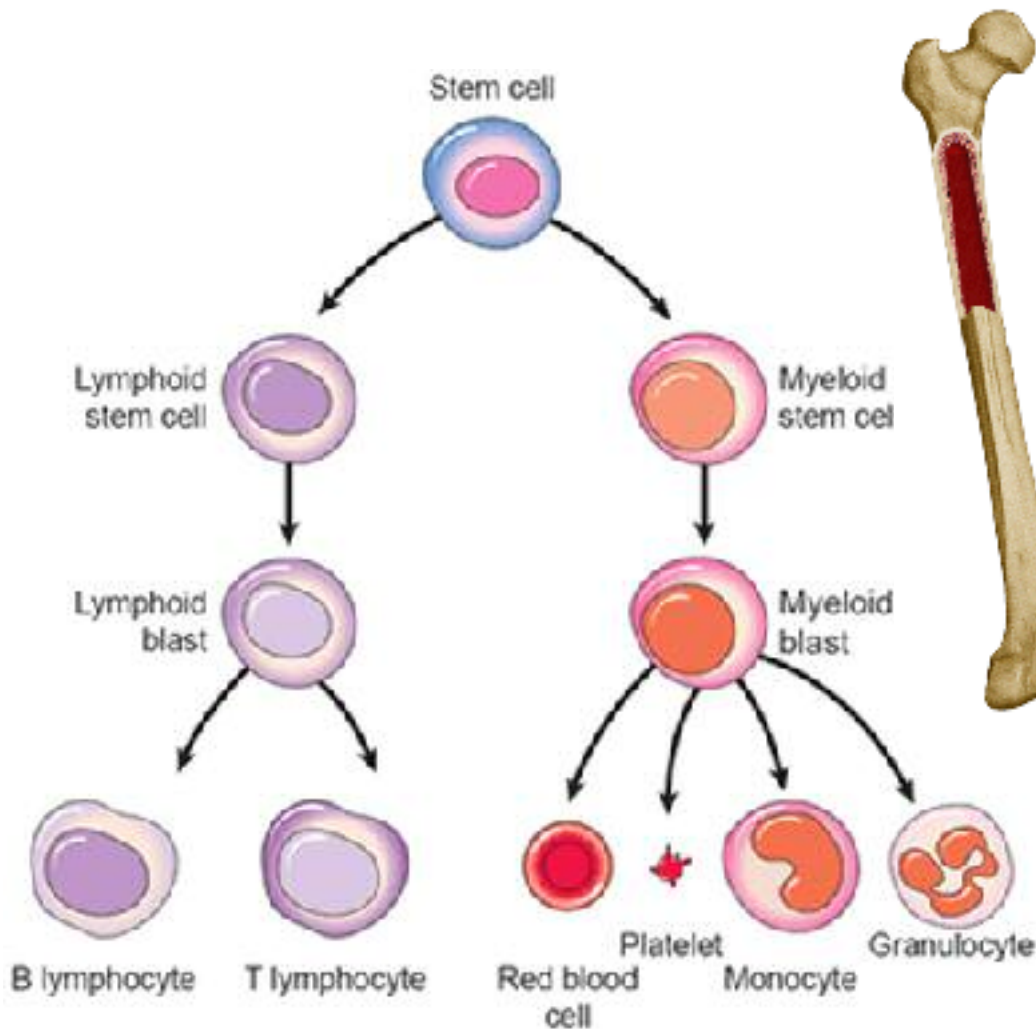
Anemia

- A frequent finding
- May be the presenting feature
- Found in 12% to 69% of newly diagnosed
- Also common in dermatitis herpetiformis

Hoffbrand AV et al. *Clin Gastroenterol* 1974

Bottaro G et al. *Am J Gastroenterol* 1999

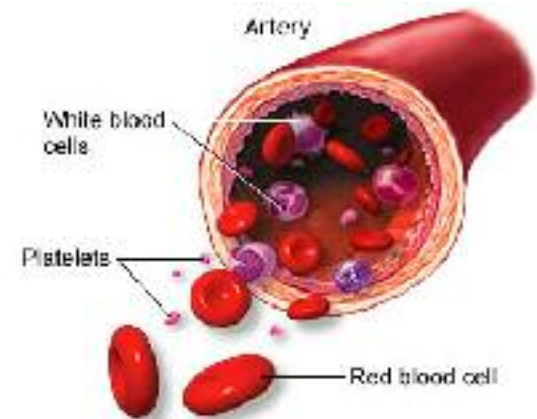
Lo W et al. *Dig Dis Sci* 2003



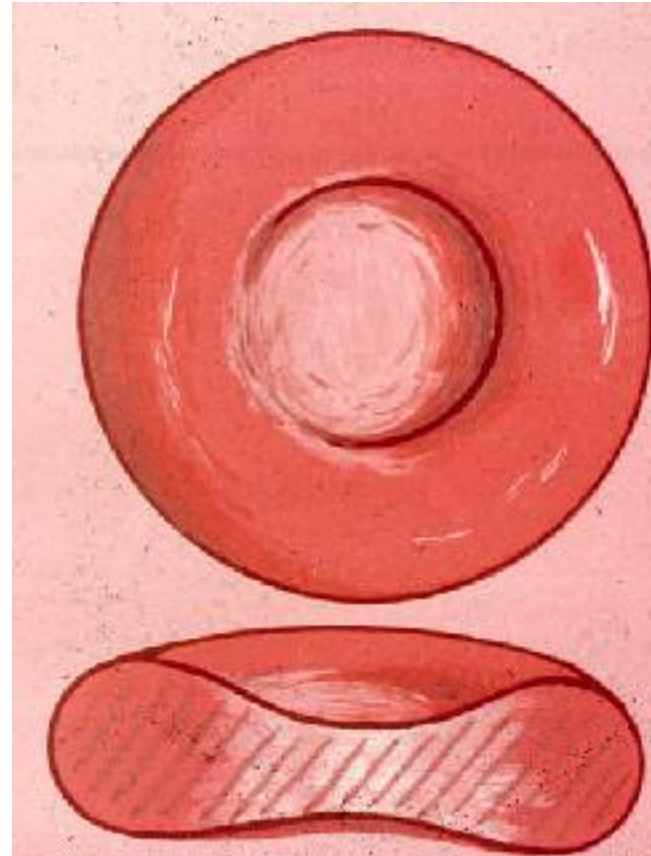
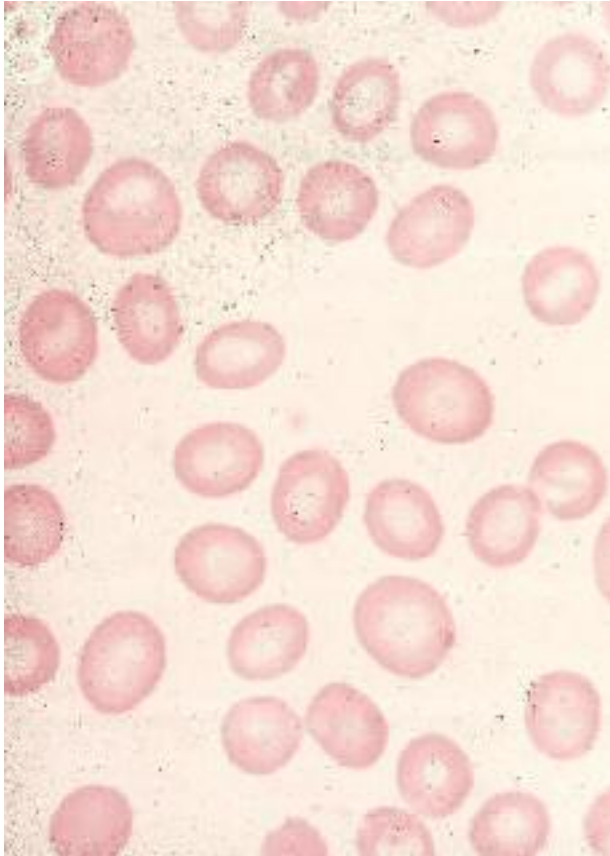
{bone marrow}

Red cells-28 days

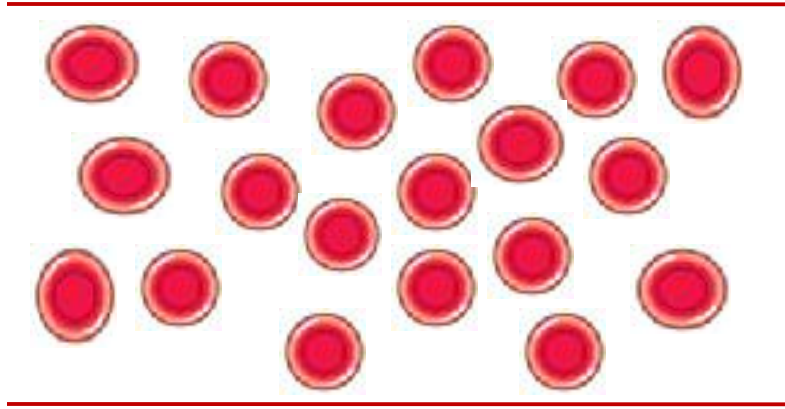
{blood vessel}



Production of red blood cells

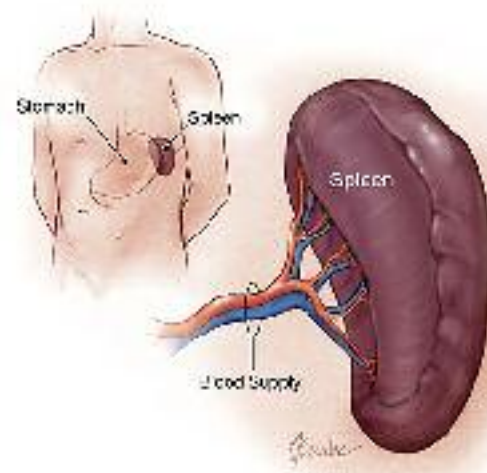


Normal red blood cells



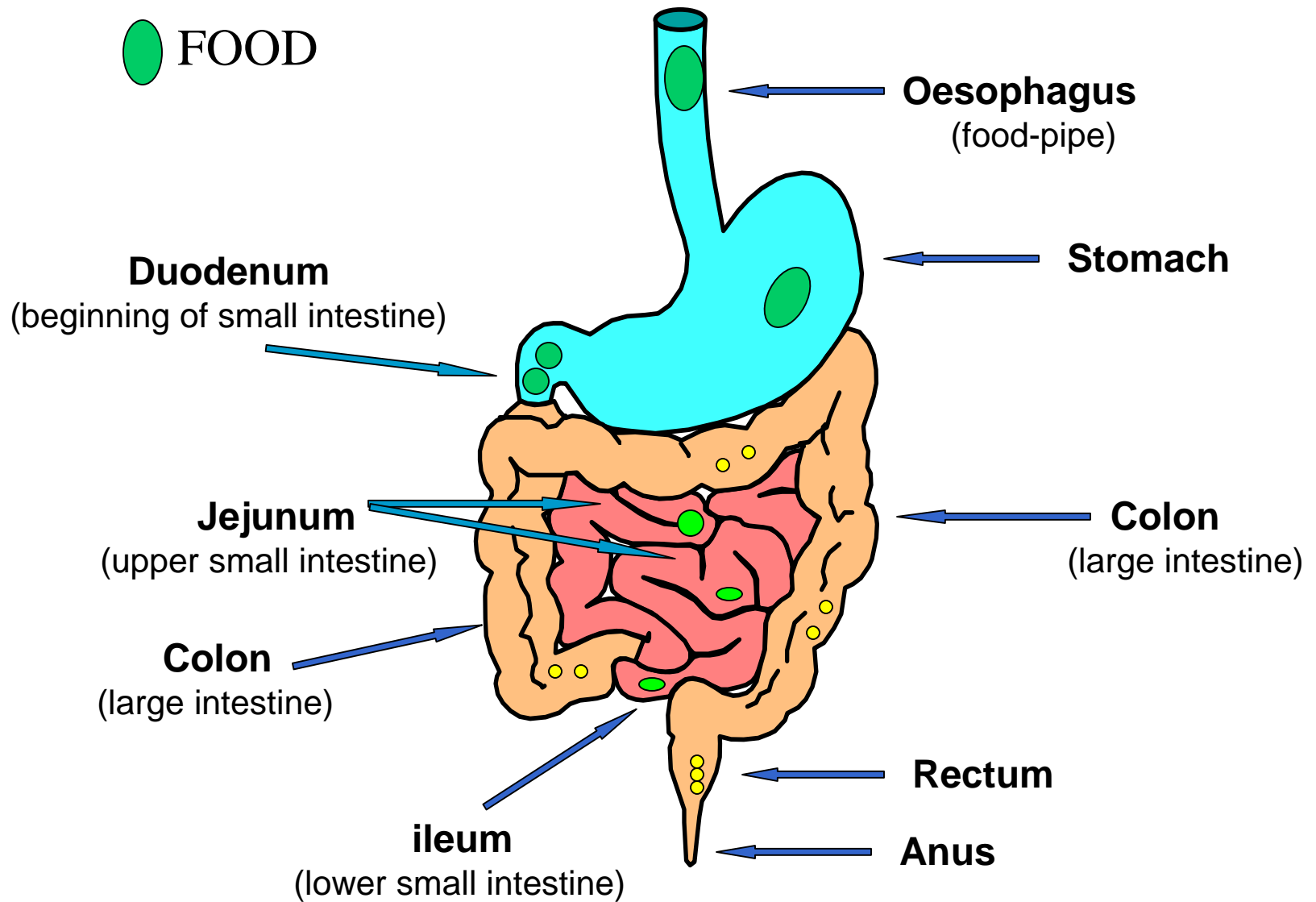
{blood vessel}

Red cell life-120 days



{spleen}

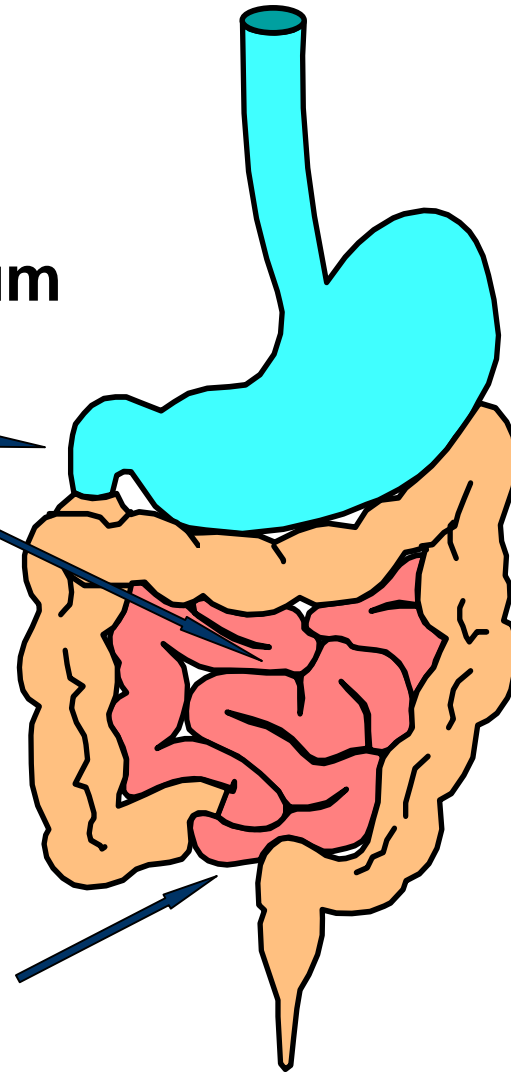
Life of red blood cells



The Gastrointestinal Tract

Duodenum & upper jejunum
(iron, folate)

Distal ileum
(vitamin B₁₂)



Site of absorption of iron, folate and vitamin B₁₂

Causes of Anemia

- Decreased production of red cells
- Increased destruction of red cells
- Loss of blood from body

Anemia in celiac disease – Causes

- Decreased absorption
 - Iron
 - Folate
 - Vitamin B₁₂
 - Copper
- Gastrointestinal blood loss
- Anemia of inflammation/chronic disease

Anemia: Iron deficiency

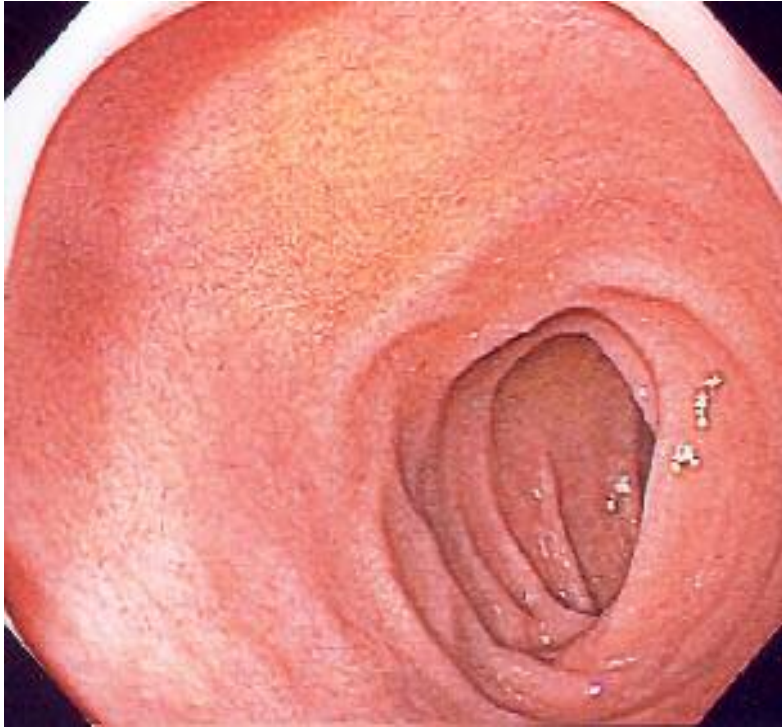
- Commonest variety
- Up to 9% of patients presenting with iron deficiency have celiac disease
- 20% of patients with refractory iron deficiency anemia have celiac disease
- Causes:
 - Mainly impaired absorption
 - Occult blood loss (variable)

Carroccio A et al *Dig Dis Sci* 1998

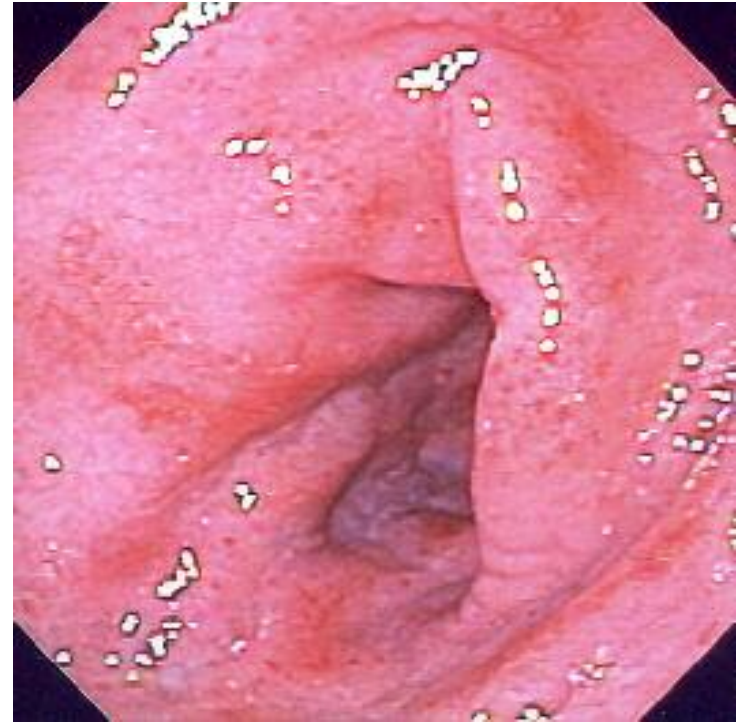
Bottaro G et al. *Am J Gastroenterol* 1999

Economou M et al. *J Pediatr Hematol Oncol* 2004

Duodenum



Normal



Celiac disease

Photo by: M. Rashid

Anemia: Folate deficiency

- Many untreated patients have folate deficiency
- Anemia may or may not occur
- Concomitant iron deficiency may be present making the diagnosis puzzling
- Diagnostic clue:-- elevated homocysteine levels
- Folate supplements along with a gluten-free diet is recommended

Bode S et al. *Scand J Gastroenterol* 1996
Howard MR et al. *J Clin Pathol* 2002

Anemia: Vitamin B₁₂ deficiency

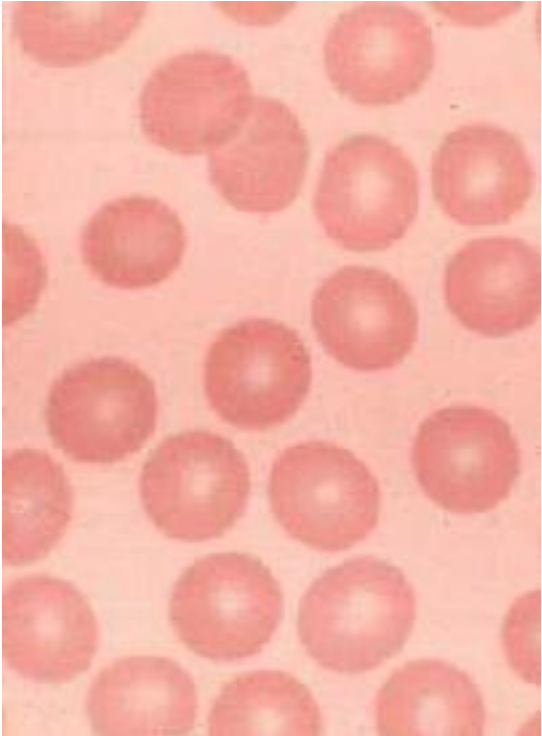
- Vitamin B₁₂ deficiency common (8% to 41%)
- Cause not known
 - Autoimmune gastritis?
 - Bacterial overgrowth?
 - Poor mixing with transfer factors in the intestine?
 - Subtle dysfunction of distal small intestine?
- Serum levels of vitamin B₁₂ unreliable
- Elevated levels of serum methylmalonic acid
- Parenteral B₁₂ supplements recommended

Bode S et al. *Scand J Gastroenterol* 1996

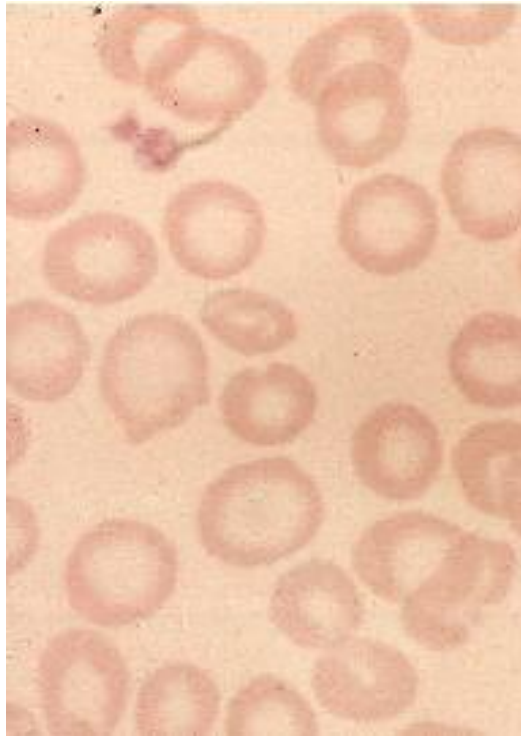
Dahele A et al. *Am J Gastroenterol* 2001

Dickey W. *Eur J Gastroenterol Hepatol* 2002

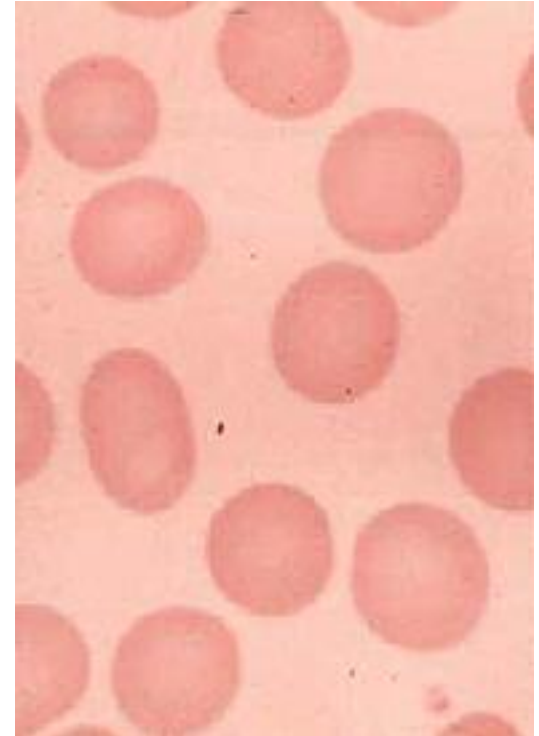
Red blood cells



Normal



Iron deficiency



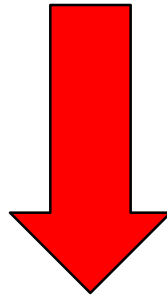
Folate/vitamin B₁₂
deficiency

Why is celiac disease missed in the investigation of iron deficiency anemia?

- Lack of awareness
- Scoping the “wrong end”
- Not doing duodenal biopsies during upper GI endoscopy

Take-home message

iron deficiency anemia



think of celiac disease