Coeliac disease

•Prof. Knut E. A. Lundin, MD, PhD
•Endoscopy Unit, Dept of Transplantation medicine
•Centre for Immune Regulation "www.med.uio.no/cir/english"
•Oslo University Hospital, Rikshospitalet
•Medical Faculty, University of Oslo

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Topics

- History of coeliac disease
- Epidemilogy of coeliac disease and the changing pattern of human diseases and welfare
- Current understanding of the disease
  - Immunology
  - Clinical
- The future of coeliac disease
- Non-celiac gluten sensitivity

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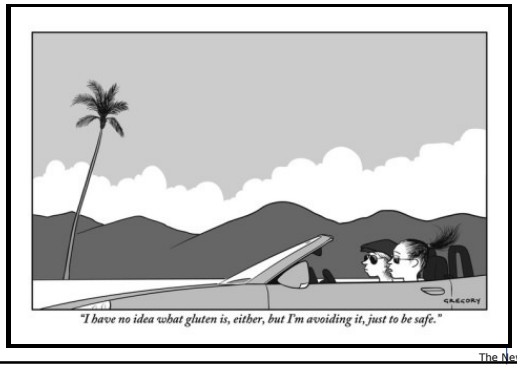
'I have no idea what gluten is either, but I am avoiding it just to be safe'



"I have no idea what gluten is, either, but I'm avoiding it, just to be safe."

The New Yorker

ORIGINAL ARTICLE

The Oslo definitions for coeliac disease and related terms

Jonas F Ludvigsson,[1,2] Daniel A Leffler,[3] Julio C Bai,[4] Federico Biagi,[5] Alessio Fasano,[6] Peter H R Green,[7] Marios Hadjivassiliou,[8] Katri Kaukinen,[9] Ciaran P Kelly,[3] Jonathan N Leonard,[10] Knut Erik Aslaksen Lundin,[11] Joseph A Murray,[12] David S Sanders,[13,14] Marjorie M Walker,[14] Fabiana Zingone,[15] Carolina Ciacci[16]

- Gluten intolerance
  - the broadest term for all aspects of adverse reactions to gluten
- Coeliac disease
  - a small intestinal enteropathy, usually also typical serology (IgA-tissue transglutaminase)
- Wheat allergy a rapid, allergic response
- Non-coeliac gluten sensitivity
  - clinically quite like coeliac disease, but without enteropathy or serology

Ludvigsson et al, Gut 2012

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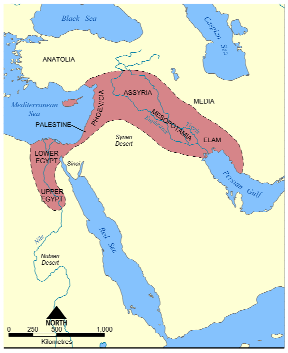
The Neolithic period

Fertile crescent



- Started about 9500 BC
- First signs of cultivation of grains

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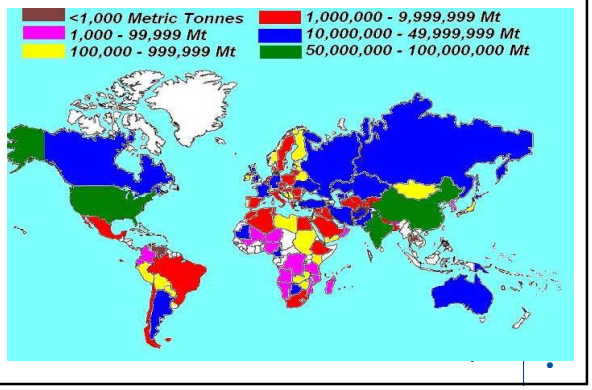
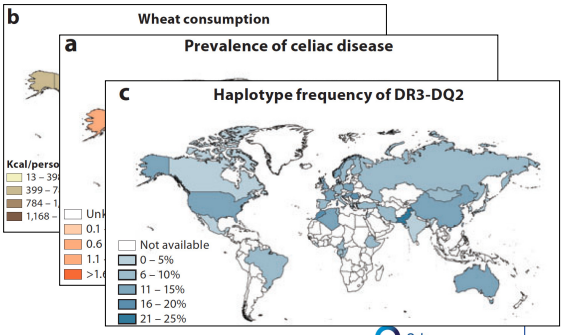
Wheat harvest



Wheat consumption – CD - HLA



Abadie et al. Ann Rev Immunol 2012

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Coeliac disease worldwide

- Most frequent cause of chronic diarrhoea in India
- 1:40 prevalence in Saharawi population in Sahara
- 1:200 – 1:50 in most Western European countries, increasing
- Unknown among most Asian, African and native Americans populations. China???

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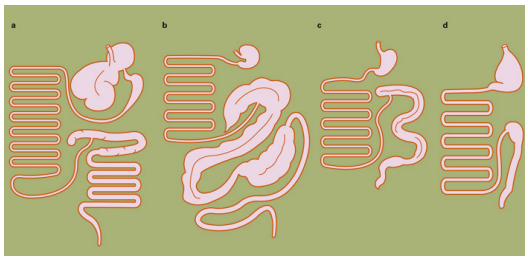
Mammalian digestive system



Ruminating herbivores (sheep) | Non-ruminating herbivores (horse) | Omnivores (humans) | Carnivores (dog)

Valeur and Berstad 2008

tidsskriftet.no

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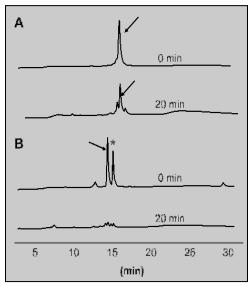
Digestive resistance

- Perfusion of gliadin peptides in rat intestine:
- A: 33 amino acid long
- B: 12 amino acid long



Shan et al. Science 2002

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The basic problem

- Humans moderately adapted to eating cereals
- All mammalians digest gluten poorly
  - Unlike most other proteins
- The plot thickens…..

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Willem K. Dicke defined celiac disease a lifelong and gluten induced disease

- Dutch pediatrician
- On track of gluten since 1934, concluded during and after WWII
- Challenge experiments
- Wheat, rye and barley (and oats) responsible

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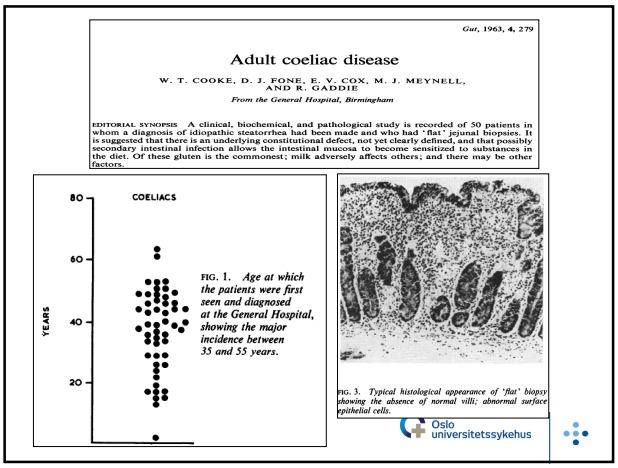

Gut, 1963, 4, 279

Adult coeliac disease

W. T. COOKE, D. J. FONE, E. V. COX, M. J. MEYNELL, AND R. GADDIE

From the General Hospital, Birmingham

EDITORIAL SYNOPSIS A clinical, biochemical, and pathological study is recorded of 50 patients in whom a diagnosis of idiopathic steatorrhea had been made and who had 'flat' jejunal biopsies. It is suggested that there is an underlying constitutional defect, not yet clearly defined, and that possibly secondary intestinal infection allows the intestinal mucosa to become sensitized to substances in the diet. Of these gluten is the commonest; milk adversely affects others; and there may be other factors.

FIG. 1. *Age at which the patients were first seen and diagnosed at the General Hospital, showing the major incidence between 35 and 55 years.*

FIG. 3. *Typical histological appearance of 'flat' biopsy showing the absence of normal villi; abnormal surface epithelial cells.*

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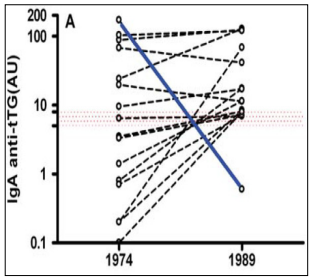
The CLUE cohort – adults develop coeliac disease!



- 3511 adults followed from 1974 to 1989 (no intervention)
- 1974: Seven with coeliac disease
- 1989: Additional nine with coeliac disease

Catassi et al. Ann Med 2010

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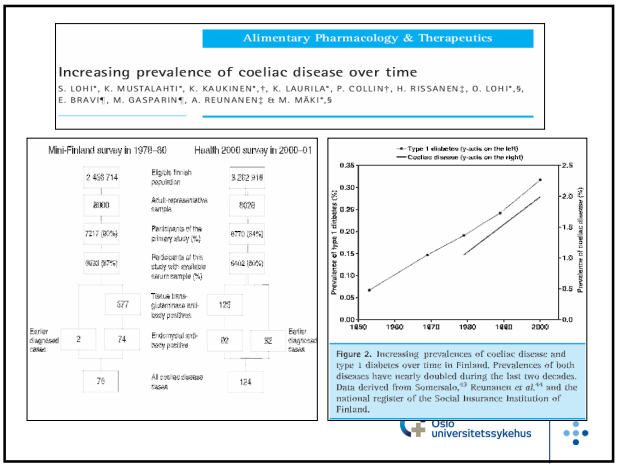

Alimentary Pharmacology & Therapeutics

Increasing prevalence of coeliac disease over time

S. LOHI*, K. MUSTALAHTI*, K. KAUKINEN*,†, K. LAURILA*, P. COLLIN†, H. RISSANEN‡, O. LOHI*,§, E. BRAVI¶, M. GASPARIN¶, A. REUNANEN‡ & M. MÄKI*,§

Figure 2. Increasing prevalences of coeliac disease and type 1 diabetes over time in Finland. Prevalences of both diseases have nearly doubled during the last two decades. Data derived from Somersalo,[52] Reunanen et al.[53] and the national register of the Social Insurance Institution of Finland.

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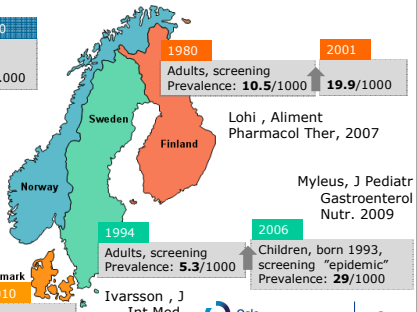
CD increases in Scandinavia



2000-2002 Children Incidence **16.2**/100.000 → 2008-2010 **41.7**/ 100.000

Beitnes & Størdal et al, unpublished 2012

1980 Adults, screening Prevalence: **10.5**/1000 → 2001 **19.9**/1000

Lohi , Aliment Pharmacol Ther, 2007

Myleus, J Pediatr Gastroenterol Nutr. 2009

1994 Adults, screening Prevalence: **5.3**/1000

2006 Children, born 1993, screening "epidemic" Prevalence: **29**/1000

Dydensborg , Acta Pæd 2011

1996 Children, register Prevalence **0.43**/1000 Incidence : **0.8**/100.000 → 2010 **0.84**/1000 **6.9**/100.000

Ivarsson , J Int Med 1999

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CD awareness Norway

CD week September 2012
– Internet based test; www.ncf.no

		Numbers
IgA TG2 testing Fürst lab	2010	34691
	2011	43495
	2012	55535

1977: Seldom 0.1-1/1000

2012: TV-news for children

Grafikk: Lene Sæter

Cøliaki – hva er det?

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The rise in CD parallells many other diseases

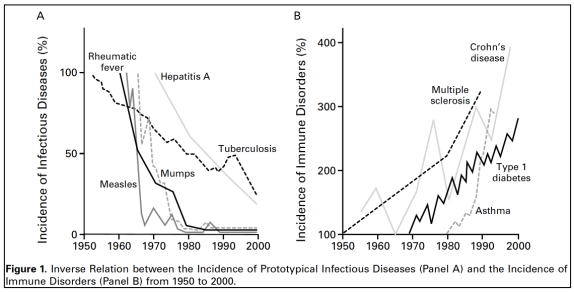

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Bach JF. New Eng J Med 2002

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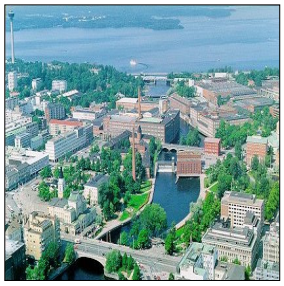
Our new health threat

Knut E. A. Lundin

Increasing prevalence of coeliac disease

- ”Everybody” knows someone with CD
- Active search will find the coeliacs
  - Tampere in Finland:
  - 250 000 inhabitants
  - 0,75 % with CD diagnosis



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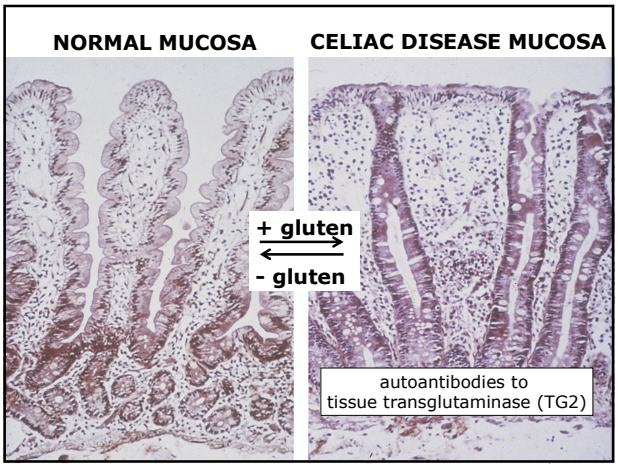
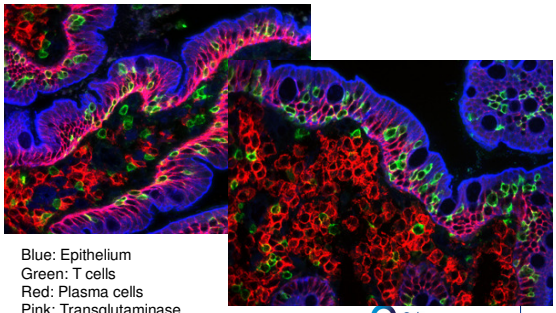


The celiac lesion



Blue: Epithelium
Green: T cells
Red: Plasma cells
Pink: Transglutaminase

Courtesy of dr. Beitnes, CIR

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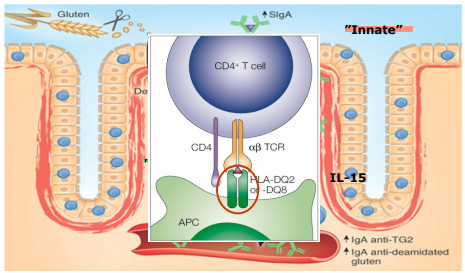
The Immune reaction in CD



Sollid/Lundin, Mucosal Immunology 2009, modified

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Celiac disease pathogenesis

- Digestion of gluten is incomplete
- Fragments of gluten becomes modified and can bind to two HLA molecules present in 40-50 % in Europeans
- 1-2 % of Europeans develop an immune response to gluten presented by these HLA molecules

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The 64 000 dollar questions

- Why do not all DQ2+ and DQ8+ individuals develop celiac disease?
- Why do some DQ2+ and DQ8+ individuals develop celiac disease?
- It is all about immunology and genetics!

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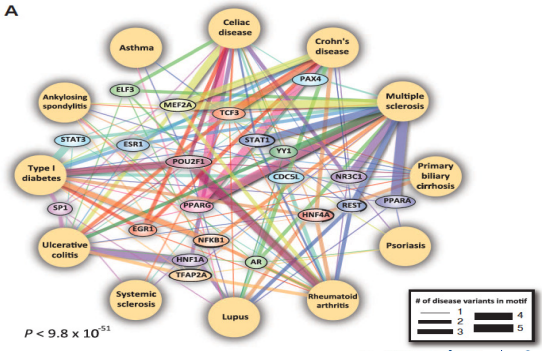
Common disease networks



Maurano et al. Science 2012

How to diagnose?

- Consider celiac disease!!!
- Clinical signs
- Serology will pick up most celiacs.
  - Anti-gluten IgA or IgG (obsolete)
  - Anti-TG2 IgA/anti-DGP IgA or IgG
- HLA typing
  - DQ2/8:
  - good negative predictive value,
  - no positive predictive value
- Small intestinal biopsy (endoscopy)

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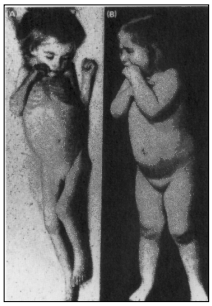
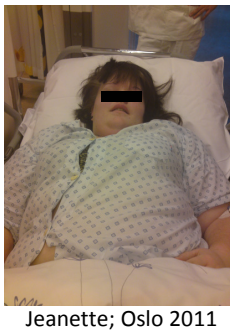
The changing clinical presentation



Judith; Birmingham 1950



Jeanette; Oslo 2011

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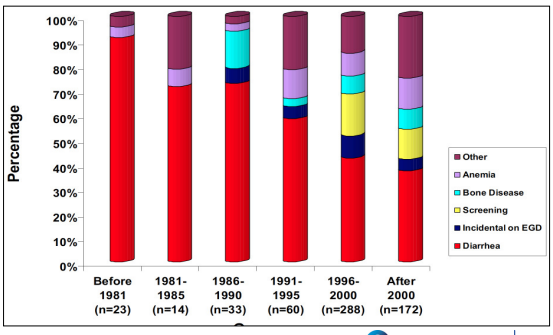
Changing clinical presentation



Rampertab et al. Am J Medicine 2006

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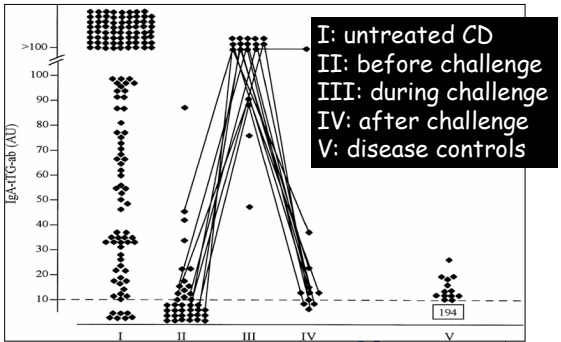
IgA-Transglutaminase (TG2)



Sulkanen et al. *Gastroenterology* 1998

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Update on Serologic Testing in Celiac Disease

Daniel A. Leffler, MS, MD[1] and Detlef Schuppan, MD, PhD[1]

Table 1. Summary of test characteristics of celiac serologies

Test	Sensitivity (reported range) (%)	Specificity (reported range) (%)	Positive predictive value(%),pretest probability of 5%	Negative predictive value (%), pretest probability of 5%
IgA AGA	85 (57–100)	90 (47–94)	18	99
IgG AGA	85 (42–100)	80 (50–94)	31	99
EMA	95 (86–100)	99 (97–100)	83	99
IgA anti-tTG[a]	98 (78–100)	98 (90–100)	72	99
IgG anti-tTG[b]	70 (45–95)	95 (94–100)	42	99
IgA anti-DGP	88 (74–100)	95 (90–99)	44	99
IgG anti-DGP	80 (63–95)	98 (90–99)	68	99
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)	51	99

AGA, anti-gliadin antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibody; tTG, tissue transglutaminase
[a]Anti-human-tTG-based assays only; older tests based on guinea pig antibodies have lower sensitivity and specificity. [b]Sensitivity is significantly higher, about 90–95%, in IgA-deficient populations but lower in the overall celiac population.
Adapted from refs. 5–7, 18, 24, 26, 29, 31, 34, 36, and 37.

Leffler and Schuppan Am J Gastro 2010,
See also Anderson et al. BMC Gastroenterol 2013

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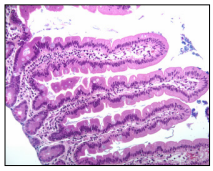
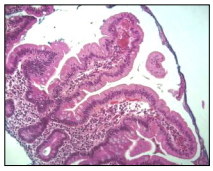
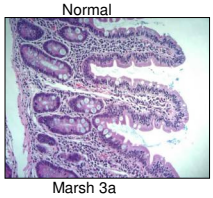
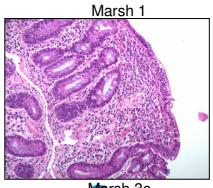
Small intestinal morphology


Normal


Marsh 1


Marsh 3a


Marsh 3c

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Diagnosis in Europe

- <u>Children:</u>
  - Clinical signs
  - Serology (IgA-TG2 or -DGP)
  - Repeat serology
  - HLA-DQ2 and DQ8
  - If IgA-TG2 > 10 x cut-off and correct HLA = CD!
  - If not: Biopsy
- <u>Adults:</u>
  - Clinical signs
  - Serology (IgA-TG2 or -DGP) supportive
  - Biopsy showing villous atrophy (Marsh 3A or more) diagnostic

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Diagnostic challenge

- Aim: Diagnose CD correctly, echonomically, definite
  - Leading to lifelong treatment (that precludes later re-diagnosis)
  - Leading to improvement of symptoms (that can be vague and "atypical")
- In many cases simple
- <u>But</u>
  - false pos / false neg serology is not infrequent
  - Biopsy sampling / interpretation / cut-off may be problematic

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Management and follow-up

- World Gastro Org guidelines
  - Bai et al. J Clin Gastro 2013
- American College Gastroenterol guidelines
  - Rubio-Tapia et al. Am J Gastroenterol 2013
- Guidelines often not followed
  - Herman et al. Clin Gastro Hepatol 2012
  - Gibson et al. Clin Gastro Hepatol 2012

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Management and follow-up

- Diagnosis based on combination of
  - clinical signs, serology (IgA-TG2, IgA-DGP, IgG-DGP), duodenal biopsy (1-2 from bulb, 4 from duodenum)
  - HLA? (very good neg predictive value)
- Refer to Clinical dietician
- Follow up by gastroenterologist once (?)
  - Clinical signs, serology, biopsy not needed (?)
  - Bone densitometry, clinical chem (Fe, folic acid, B_{12})
- Later follow-up by GP

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Gluten free diet

- "No" wheat (incl spelt), rye, barley
- Maximum level of gluten intake uncertain
  - 50 – 100 mg/day compared to 10-15 000 mg/day in regular Western diet? Or less? 0 mg?
- New WHO guidelines
  - Glutenfree products to contain less than 20 ppm (parts pr million)
- Wheat starch, oats and beer continous debate
- No association between symptoms after gluten intake and immunobiology or pathology!

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What about the "hard endpoints"?

- Other non-malignant diseases
- Malignant disease
- Mortality

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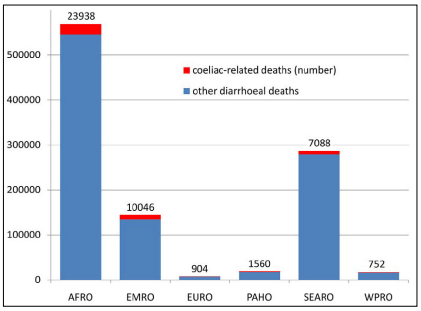
Diarrhoeal deaths < 5 years age



AFRO: African region
EMRO: Eastern Mediterranian
EURO: European
PAHO: Pan-American
SEARO: South-east Asian
WPRO: Western Pacific

Byass et al PLoS One 2011

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Swedish registry studies

- Causes of death:
  - 10 032 coeliacs
  - Hospitalized
  - Follow-up 1965-1994
  - 2 fold increased death for coeliacs
  - Cancer and immune diseases.
  - 1,4 fold increased death risk if CD was only diagnosis
    - Peters et al 2003
- Cancer types:
  - 12 000 coeliacs
  - Hospitalized
  - Adults (but not children) had 1,3 x cancer risk
  - Declining risk
    - After diagnosis
    - With time
  - Protection by gluten free diet
    - Askling et al. 2002

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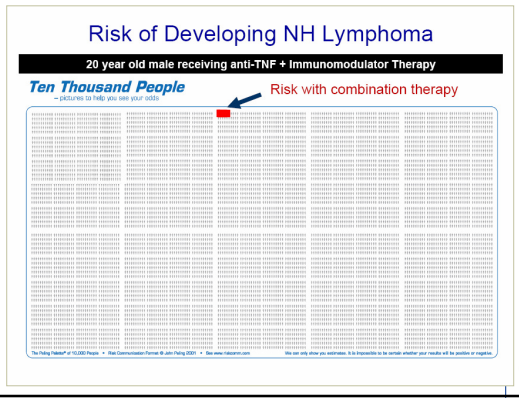
Risk assesment –lessons from IBD



Risk estimate

- Coeliac disease does impose a personal risk
- Risk less than previously thought
- Risk declining with time (similar to the changing clinical pattern)
- Personal risk evaluation currently difficult

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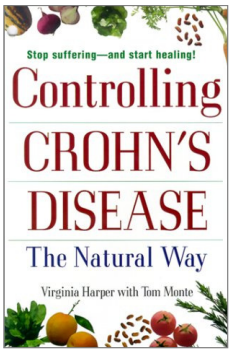
Coeliac disease and IBD



- Patients with Crohn and UC:
  - Find a diet to get rid of drugs!
- Patients with Coeliac disease:
  - Find a drug to get rid of the diet!
- East is east and west is west and never shall the twain meet?

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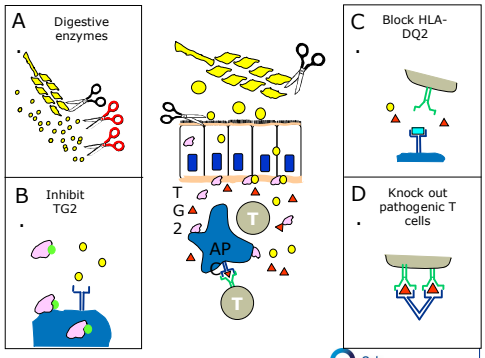
Potential therapetic targets



But a new drug takes 10 years and USD 1 000 000 000 to develop!

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Enzyme therapy

- An enzyme pill with a regular meal?
- No currently available product
- Enzyme from Dutch company on its way to market – no evidence

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Peptide vaccination

- Peptide based immunotherapy possible?
- Resembles hyposensitization for allergy
- Phase 1 done, Phase 1b ongoing
  - (ImmusanT)
- Long way to go.....

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Conclusions

- Coeliac disease is a life-long disorder with unique properties
  - Rather well defined clinically and immunologically
  - Strong genetic association
  - A cure is present
- The disease is on its rise
- Major challenges for the patients and the health care system
  - Case finding and risk stratification

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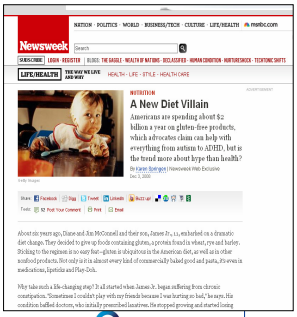
GFD as world-wide trend

- Australia
  - 20 million inhabit
  - 1 million people on GFD
  - Market growth 15-20 %/year
- US market
  - USD 2 600 000 000
  - Market growth 23 %
- Non-coeliacs on GFD strictly adherent to diet
- But symptoms not always controlled (Biesiekiersky, unpublished)
- ....(similar findings in Oslo)



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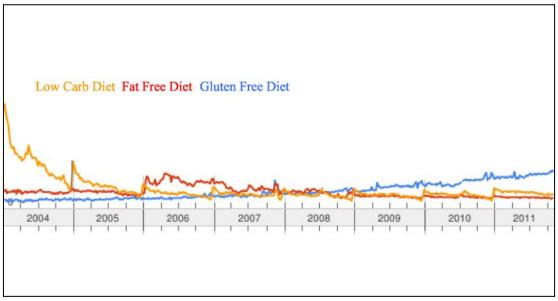
US trends 2004-2011



Sapone et al. 2012

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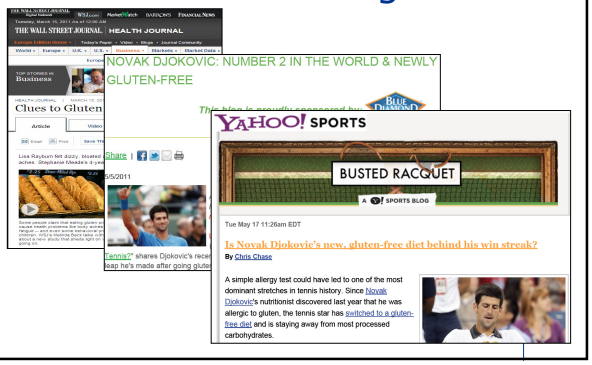
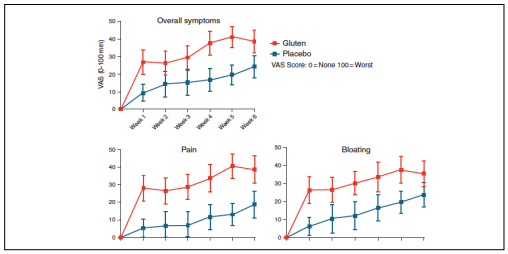
Djokovic + gluten = 2 330 000 Google hits



Gluten causes the symptoms



No clues to pathogenesis; immunology, or non-immunological, intestinal perception, or maybe even FODMAP effects?

Frequent lack of symptom control, very high nocebo effects in later challenge studies

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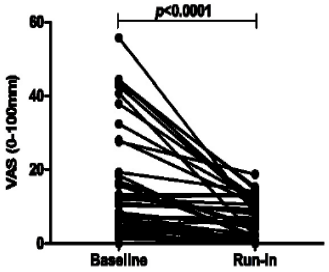
Is it maybe notgluten, after all?

- Individuals on GFD, self-reported
- Run-in using FODMAP reduction
- No signs of gluten response in blinded challenge
  - Bieriskerski et al. Gastroenterol, in press



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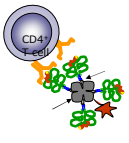
Challenge overview

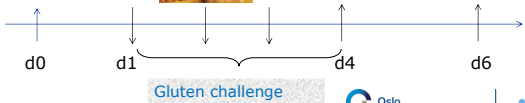
- 51 HLA-DQ2+ individuals, gluten free diet -16 with known CD, 35 without CD diagnosis
- 3 day oral gluten challenge, 4 slices sandwich bread/day.



-Venipuncture, tetramer test -Gastroscopy w biopsy

-Gastroscopy, w biopsy

-Venipuncture, tetramer test



Gluten challenge

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Conclusions

- NCGS appears to be increasing
- Celiac disease is infrequent among self-perceived NCGS patients
- No signs of somatization disorders in NCGS
- Decreased QoL in NCGS
- Signs of immune response in NCGS (IFN-γ/IEL)
- Is immune activation responsible – or maybe still the FODMAP hypothesis?

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Team work
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