Mucosal immunology and immunopathology (IBD, CD & NCGS)

•Ass. 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

Norwegian Centre of Excellence

UiO : University of Oslo FOCiS CENTERS of EXCELLENCE Oslo universitetssykehus

Organic - functional

- Common diseases common.

- Medical history
- Look / listen / feel.
- Which laboratory test?
- Supplementary examinations; Which? When?

Oslo universitetssykehus

Opposing views

The endoscopist

- **IBD**
- **Cancer**
- Reflux
- Celiac disease
- Ulcus
- Functional disorders

The patient

- **Functional disorders**
- **Reflux (50 % endoscopy neg)**
- Celiac disease
- Cancer
- IBD/Ulcus

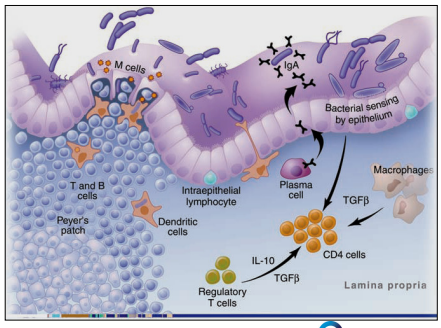
Oslo universitetssykehus

Simple investigation of GI disorders

- Clinical examination including patient age
- Clinical chemistry
- Coeliac disease?
  - Serology (and possibly endoscopy)
- IBD?
  - Stool calprotektin (and endoscopy)
- Cancer
  - Fecal blood and endoscopy

Oslo universitetssykehus

Immune homeostasis of mucosa



MacDonald and Monteleone, Science 2005

Oslo universitetssykehus

The 64 000 dollar questions

- Why do some but not all DQ2+ and DQ8+ individuals develop celiac disease?
- Why do some but not all individuals inflammatory bowel disease?
- Why not GI cancer in all?

- It is all about immunology and genetics – and maybe some good/bad luck!

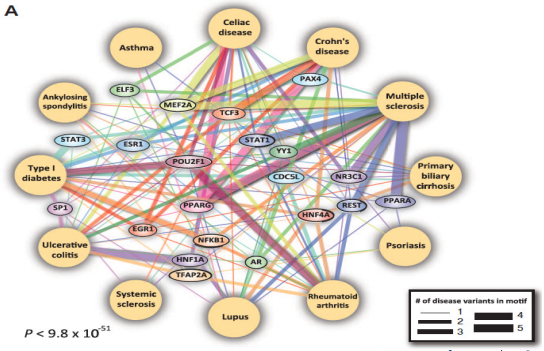
Oslo universitetssykehus

GWAS

- Genome wide association studies.
- Usually done on with SNP analysis (single nucleotide polymorphisms)
- Large sample sizes (thousands of patients and controls)
- SNPs are markers for all genes in human DNA
- Most of them regulatory!!!

Oslo universitetssykehus

Common disease networks



Maurano et al. Science 2012

GWAS and GI disorders

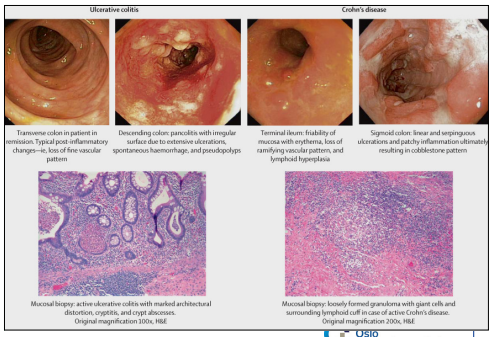
- Several in Inflammatory Bowel Disease
  - Almost 200 genes involved
  - Immune genes, barrier functions, autophagy
- Some in Celiac Disease
  - Almost 50 genes involved
  - Immune genes, T and B cell regulation
- None in functional disorders!!!

Oslo universitetssykehus

Inflammatory bowel disease IBD

Oslo universitetssykehus

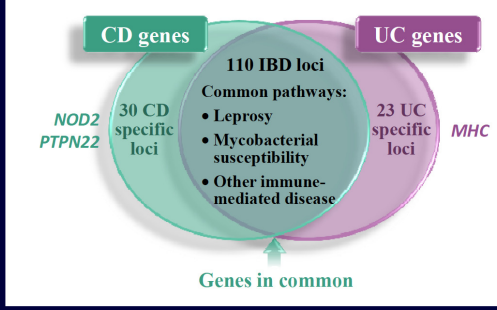
IBD – endoscopy and histology



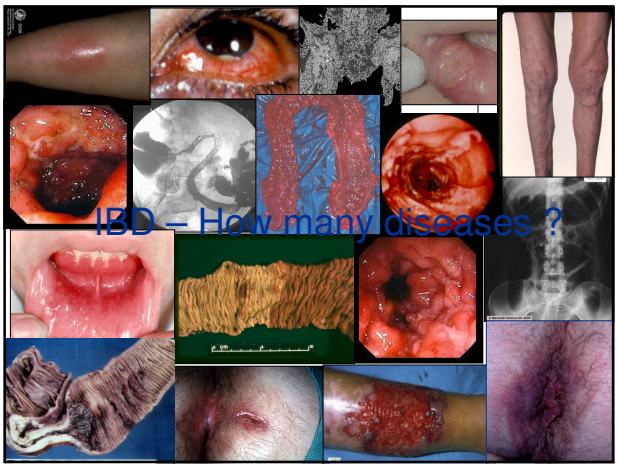
Baumgart and Sandborn Lancet 2007

Oslo universitetssykehus

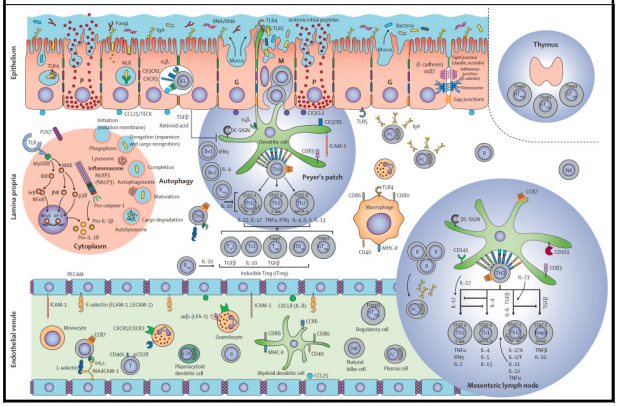
Genetics of IBD: 173 confirmed loci



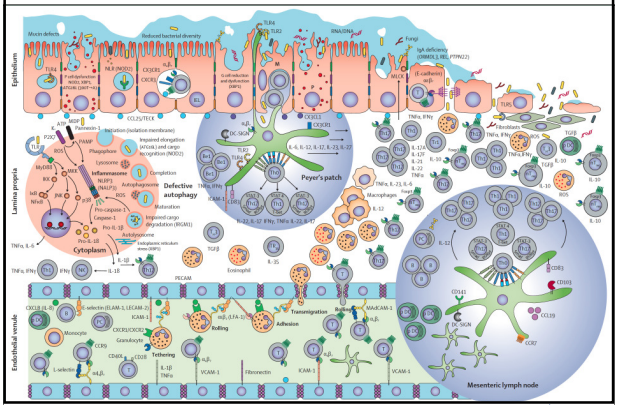
Cho J et al. *Nature*. 2012;491:119.



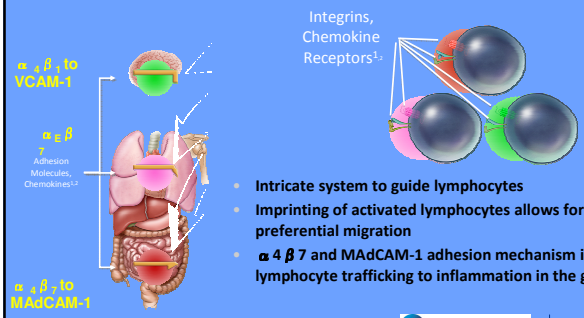
Baumgart and Sandborn, The Lancet 2012



Baumgart and Sandborn, The Lancet 2012



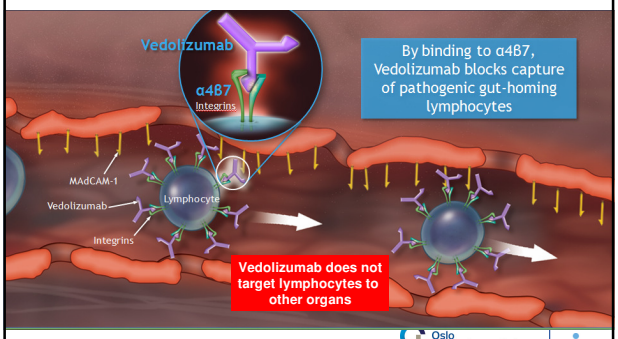
Lymphocytes Are Migratory Cells That Traffic to Specific Tissues



- Intricate system to guide lymphocytes
- Imprinting of activated lymphocytes allows for preferential migration
- α4β7 and MAdCAM-1 adhesion mechanism in lymphocyte trafficking to inflammation in the gut

Oslo universitetssykehus

Vedolizumab blocks gut homing lymphocytes that would contribute to inflammation



Oslo universitetssykehus

IBD

- Lot of progress in understanding
  - But what is "the point of no return"?
- Several new therapeutic options
  - The old workhorses 5-ASA, steroids and immunsupression
  - Anti-TNF (infliximab, adalimumab, golimumab)
  - Anti-adhesion (vedolizumab)
  - But several that did not reach the market (anti-IL-17, anti-IFNγ, anti-CD3)
  - Only 50(-70) % of severe cases respond to treatment

Oslo universitetssykehus

Coeliac disease and gluten related disorders

ORIGINAL ARTICLE

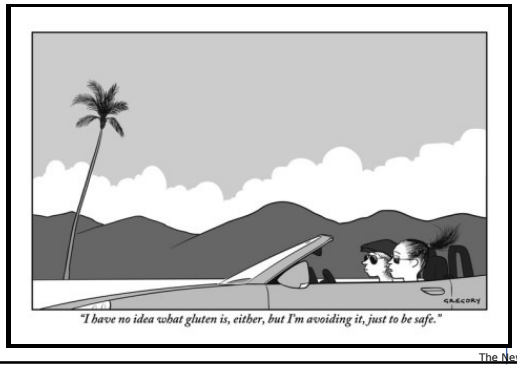
The Oslo definitions for coeliac disease and related terms

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

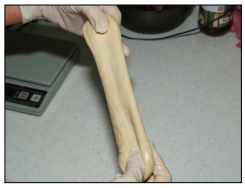
'I have no idea what gluten is either, but I am avoiding it just to be safe'

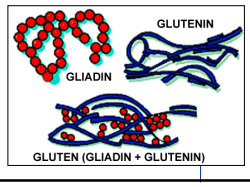


The New Yorker

Gluten – definitions

- Gluten as in
  - Gluten free food
  - The glue-ish mass after washing of flour
  - The gliadin and glutenin proteins in wheat, hordeins of barley and secalin of rye





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

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.

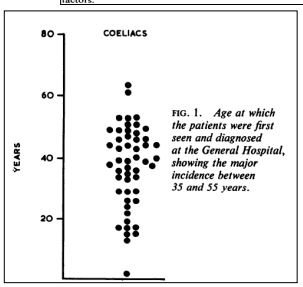


FIG. 1. *Age at which the patients were first seen and diagnosed at the General Hospital, showing the major incidence between 35 and 55 years.*

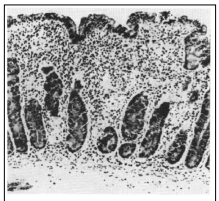
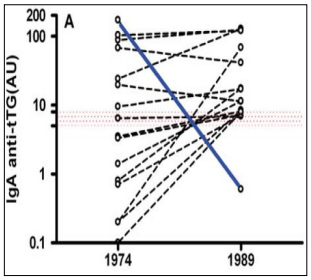


FIG. 3. *Typical histological appearance of 'flat' biopsy showing the absence of normal villi; abnormal surface epithelial cells.*

The CLUE cohort – adults develop coeliac disease!

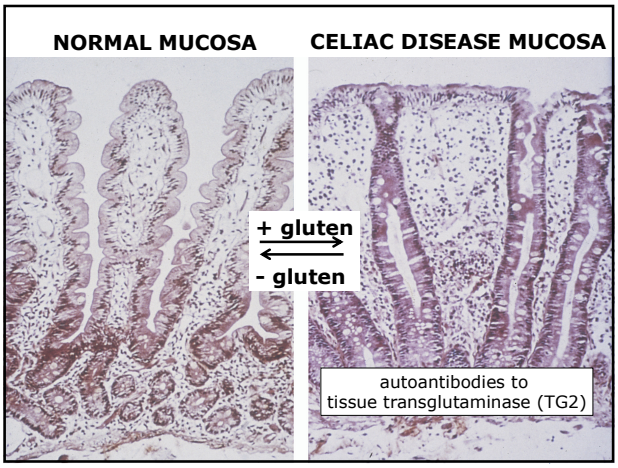


- 3511 adults followed from 1974 to 1989 (no intervention)
- 1974: Seven with coeliac disease
- 1989: Additional nine with coeliac disease

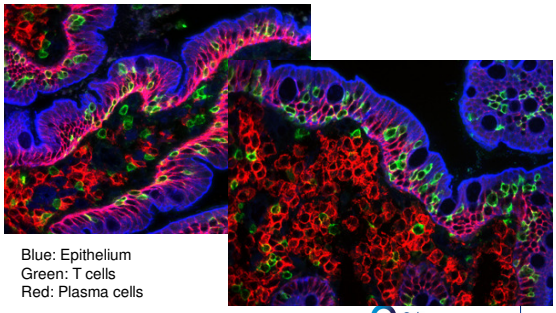
Catassi et al. Ann Med 2010

Coeliac disease worldwide

- Chronic diarrhoea in India
- 1:40 in Saharawi population in Sahara
- 1:200 – 1:50 in most Western European countries, increasing
- 1:100 in US, increasing, vast majority without diagnosis
- Unknown among most Far Asian, African and native Americans populations. China???



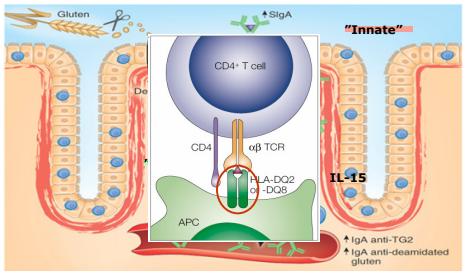
The celiac lesion



Blue: Epithelium
Green: T cells
Red: Plasma cells

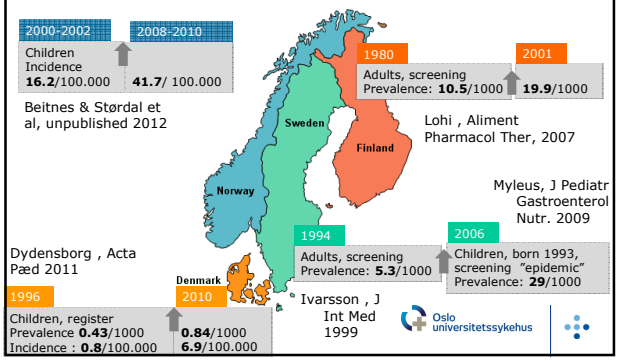
Courtesy of dr. Beitnes, CIR

The Immune reaction in CD

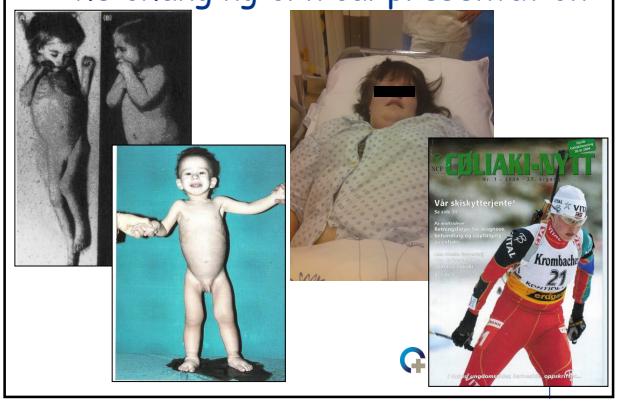


Sollid/Lundin, Mucosal Immunology 2009, modified

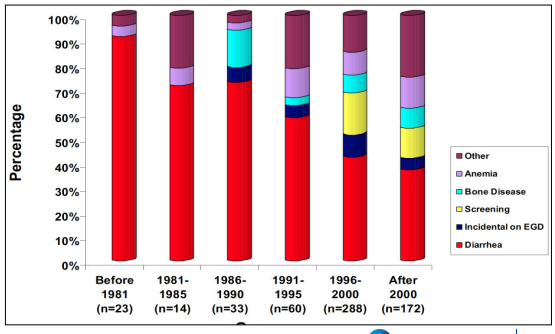
CD increases in Scandinavia



The changing clinical presentation



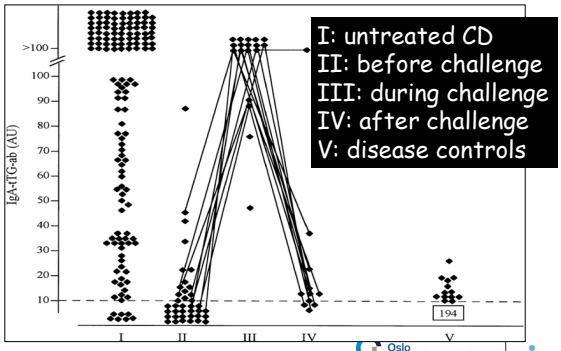
Changing clinical presentation



Rampertab et al. Am J Medicine 2006

Oslo universitetssykehus

IgA-Transglutaminase (TG2)



Sulkanen et al. *Gastroenterology* 1998

Oslo universitetssykehus

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
- But
  - false pos / false neg serology is not infrequent
  - Biopsy sampling / interpretation / cut-off may be problematic

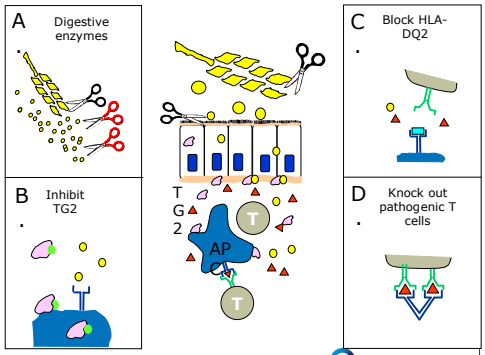
Oslo universitetssykehus

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 (gluten free diet)
- 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

Oslo universitetssykehus

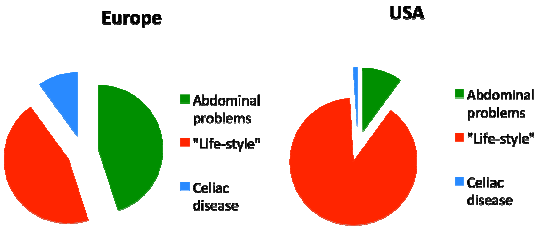
Potential therapetic targets



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

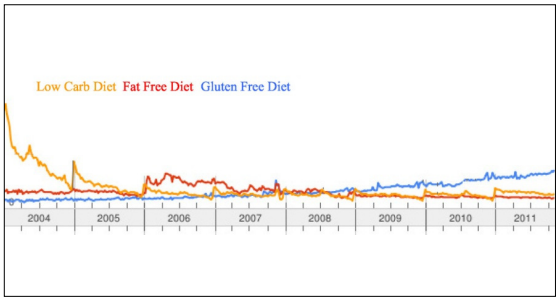
Oslo universitetssykehus

Gluten-free market Europe vs US



US consumption of gluten free food USD 5-10 000 000 000

US trends 2004-2011



Sapone et al. 2012

Pressure from celebrities

Djokovic

Lady Gaga

Kim Kardashian

Tried gluten free food/diet in 2013?

	Percentage
All	17 %
Females	21 %
Men	14 %
15-24 years	32 %
25-45 years	17 %
46 + years	14 %

General public - Norway

	2006	2012
I try to get a more fit body	55 %	77 %
I avoid food with a lot of sugar and fat	64 %	81%
I am not so concerned about my body	24 %	10 %
I do not consider much what I eat	20 %	14 %

Volunteers for a GFD?

- Gluten free not always tasty!

- But can be!

Price for one (1) bread: USD 15
3-500 customers every day

Opposing views

- NCGS is due to a specific reaction to gluten or "something else" in wheat, rye and barley
- NCGS is due to a reaction to FODMAP

The FODMAP concept

- Fermentable Oligo-, Di-, Monosaccharides And Polyols (FODMAP)
- Colonic fermentation of poorly digestible carbohydrates
  - «Invented» by Gibson and Shepherd in Australia

Oslo work on NCGS

- Celiac disease is rare among NCGS "individuals" reqruited from general population
  - 130 responded, 35 were DQ2+, 3 had CD
    - endoscopy and a "HLA-DQ2-gliadin peptide tetramer test"
      - Brottveit et al Am J Gastro 2011
- No signs of psychosomatic disorder
  - Brottveit et al Scand J Gastro 2012
- Increased levels of IEL in NCGS and activation of IFN-γ after challenge with bread
  - Brottveit et al Am J Gastro 2013

The placebo problem

- Traditional placebo
  - Capsules with flour or decoy capsules
  - Poor performance
    - Lundin and Alaedini 2012
- Most studies not well described
- Pioneer work from Gibson group
  - Quinoa based müsli bars spiked with gluten
  - Complete meals

Concluding remarks

- Glutenfree diet and living
  - Has reached considerable proportions
  - NCGS lacks strict diagnostic criteria
    - Placebo-controlled blinded or open challenge?
    - Avaliability of proper placebo?
    - Treshold for diagnosis?
    - Biomarkers of limited value (but being over-used)
- No signs of "hard end points" for NCGS
- Huge public pressure