Modern diagnosis of celiac disease

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Overview

- history of celiac disease
- immunopathogenesis
- clinical picture
- diagnostic criteria
  - serology
  - histopathology
- new methods
  - genetics
  - Immunohistochemistry
  - serology
- future perspectives

Background

- 1888 SJ Gee: Description of CD: On coeliac affection
- 1950 WK Dicke: Toxic effect of wheat
- 1959 M Shiner: Oral biopsy of intestinal mucosa
- 1969 ESPGHAN: Classic criteria
- 1989 ESPGHAN: Revised criteria
- 2005 NASPGHAN criteria
- possible new revisions

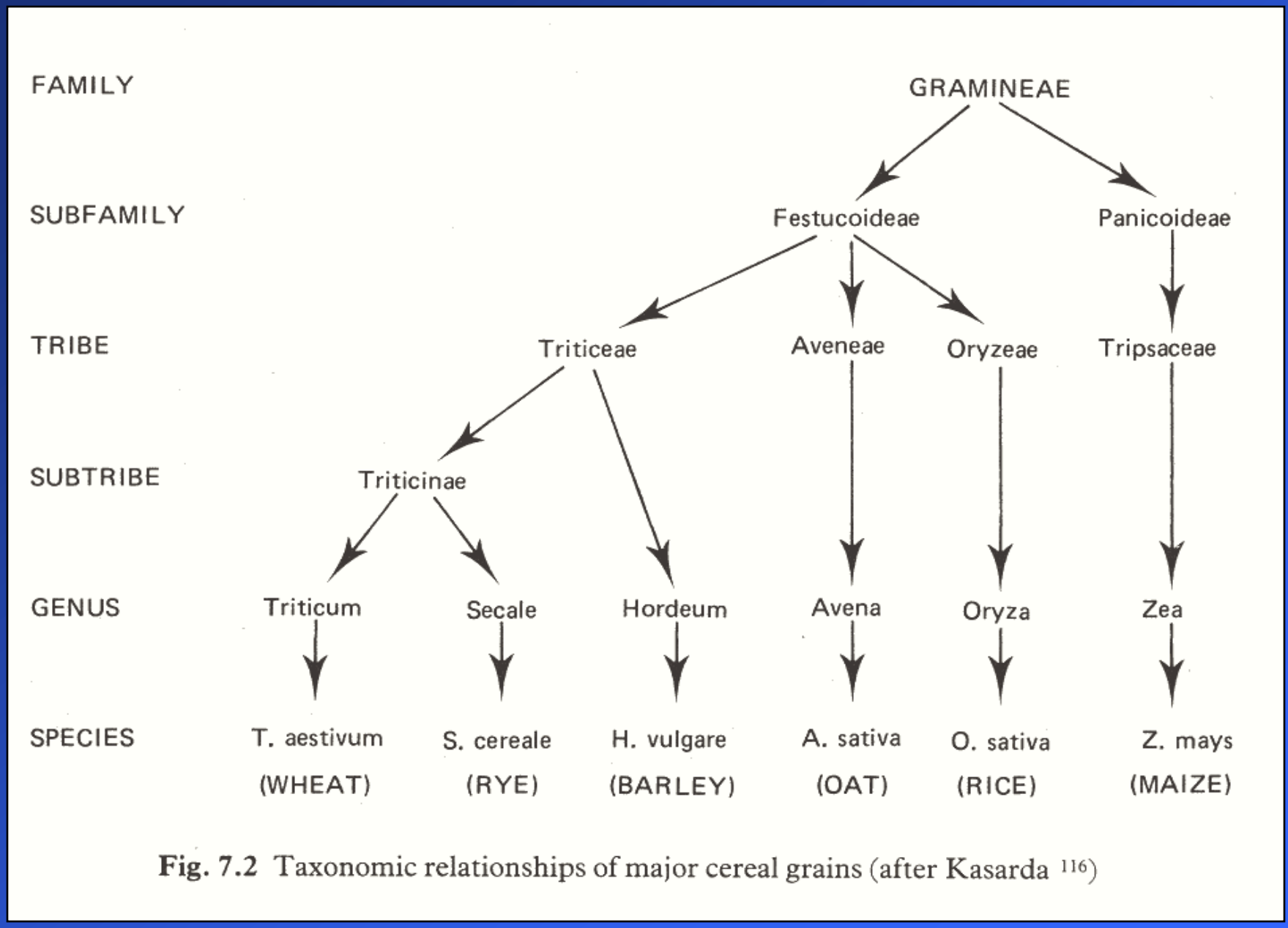
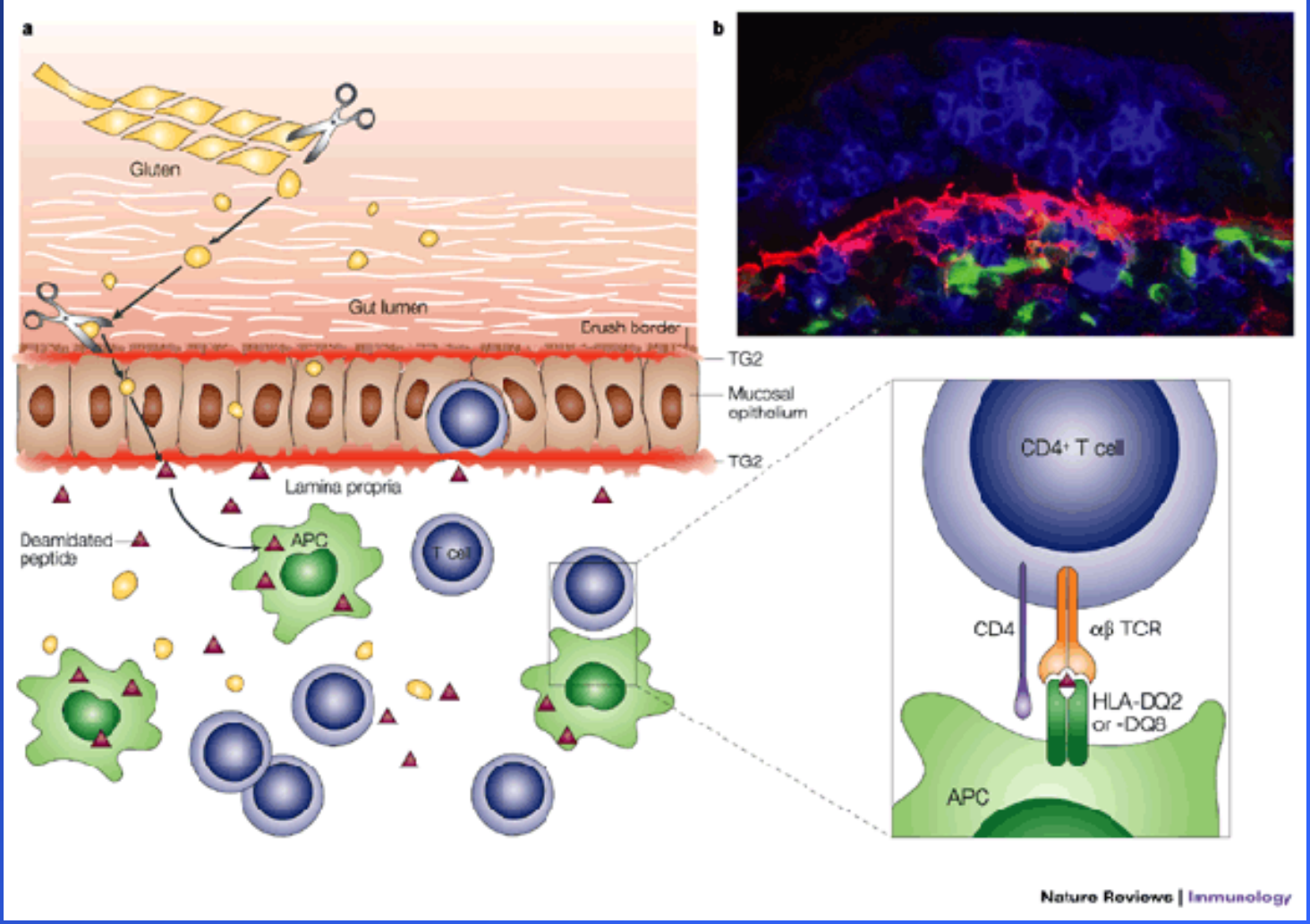
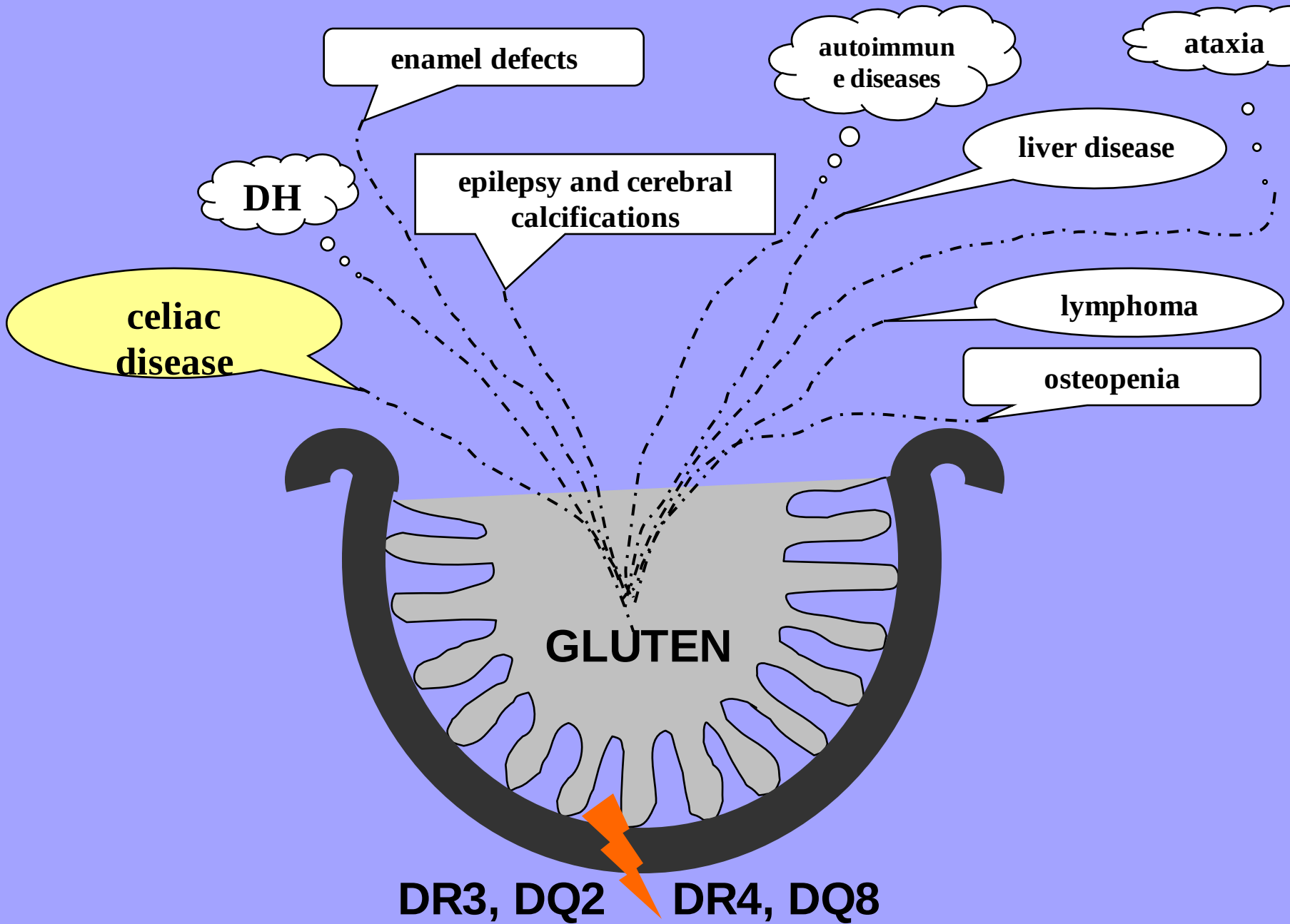


Fig. 7.2 Taxonomic relationships of major cereal grains (after Kasarda [116])

Cooke WT and Holmes GKT: Coeliac disease, 1984

Celiac disease and immunology

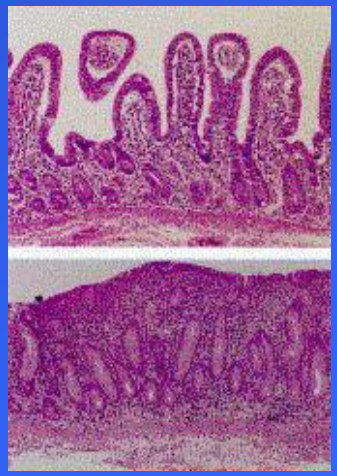



enamel defects
autoimmune diseases
ataxia
DH
epilepsy and cerebral calcifications
liver disease
celiac disease
lymphoma
osteopenia
GLUTEN
DR3, DQ2
DR4, DQ8

Diagnosis of CD

- history
- physical examination

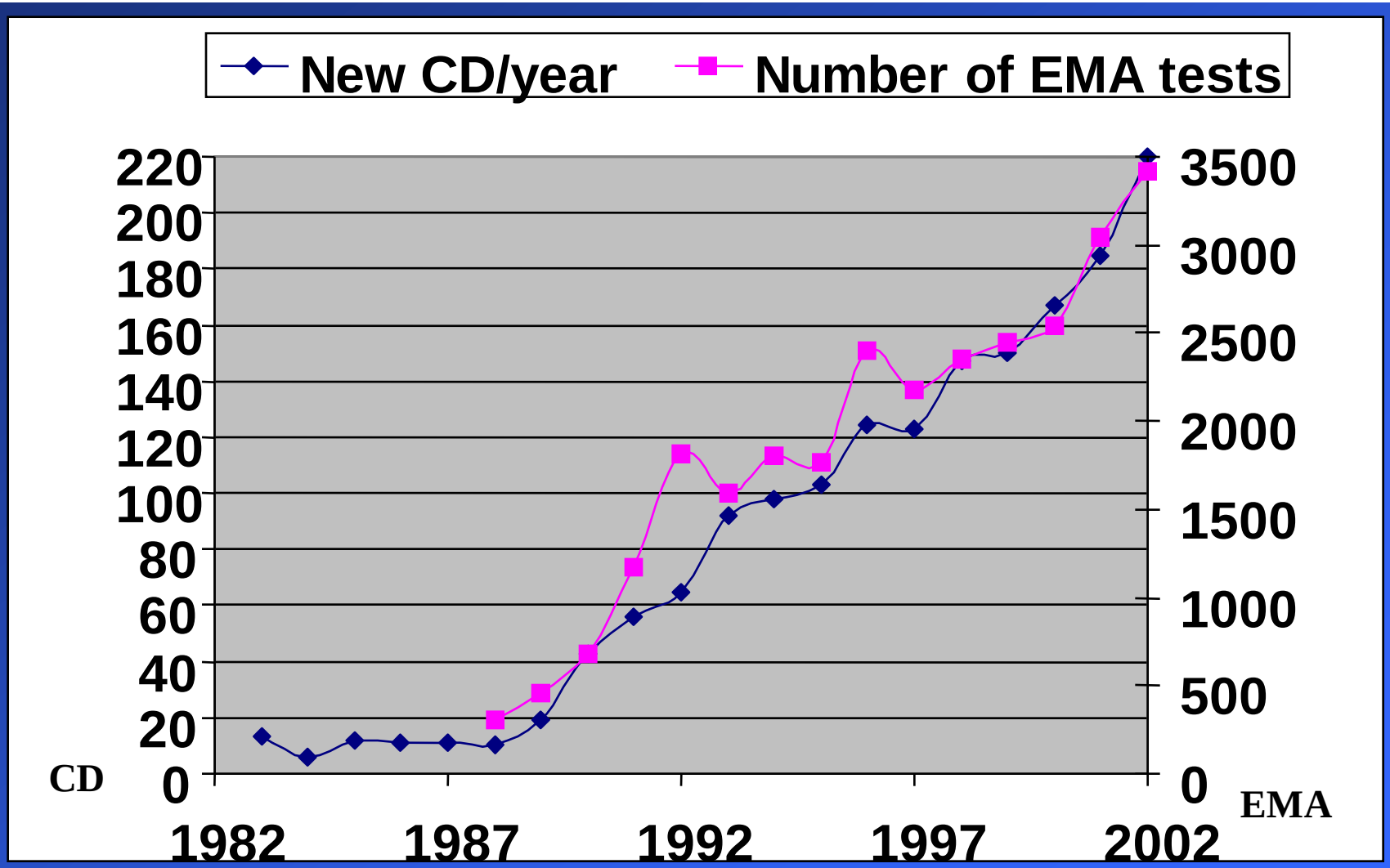
- serology
- intestinal biopsy
  - histology
  - immunohistochemistry



Diagnosis of CD

If you suspect it - you will detect it.

Serologic markers



Diagnosis of CD

- Current golden standard
  - intestinal biopsy
    - tissue diagnosis of CD
- Diagnostic criteria
  - "classic criteria" ESPGHAN
    - 3 biopsies
  - "revised criteria" ESPGHAN
    - 1 biopsy
    - serological markers
      - AGA, EMA, t-TG

Weijers HA, et al. Diagnostic criteria in coeliac disease. Acta Paediatr Scand 1970.
Walker Smith JA, et al. Revised criteria for diagnosis of coeliac disease. Arch Dis Child 1990.

Classic criteria ESPGHAN

- intestinal biopsy – GOLDEN STANDARD
- life-long gluten intolerance
- abnormal mucosa when eating gluten
- normal mucosa after GFD
- deterioration after gluten reintroduction
  - gluten challenge
- 3 biopsies

Weijers et al. Acta Paediatr Scand 1970;59:461-3.

Diagnostic tools

- histology
  - aspiration capsule biopsy
  - endoscopic biopsy

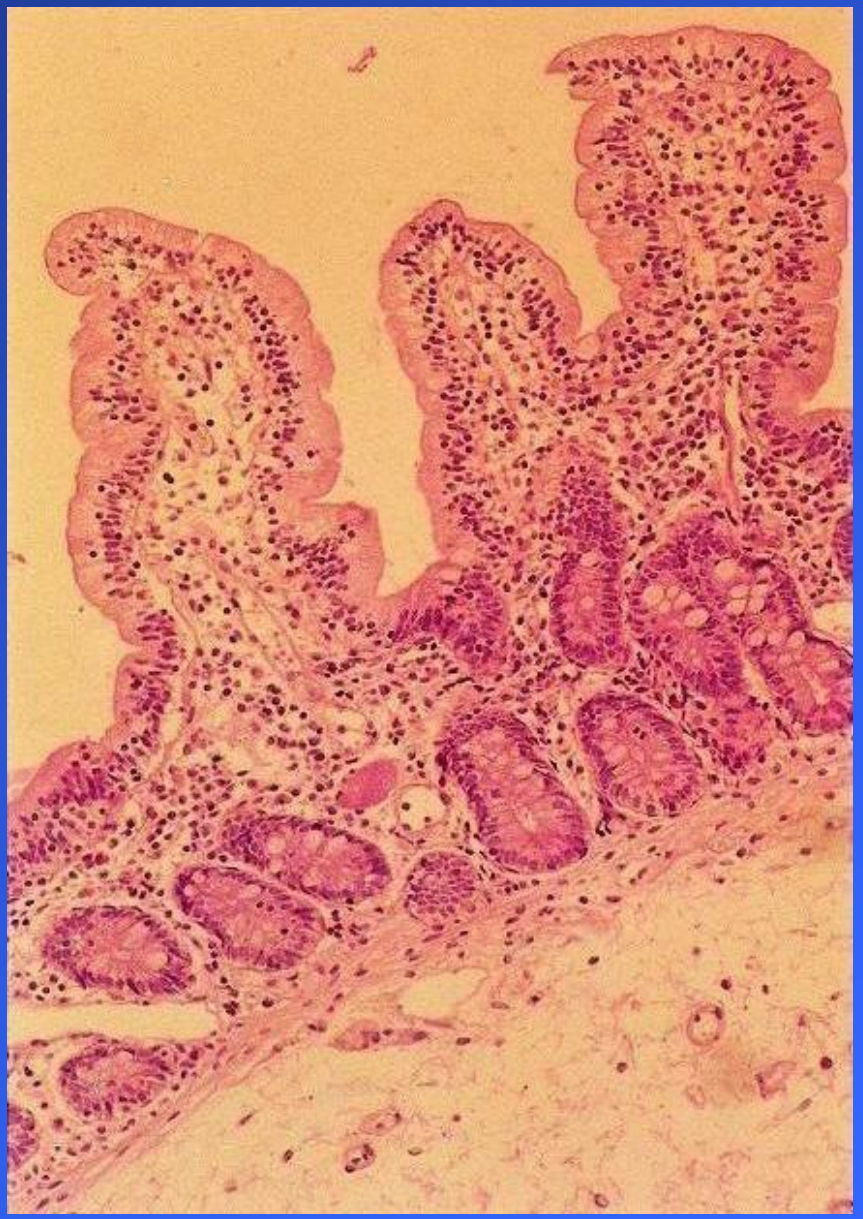
Diagnostic tools

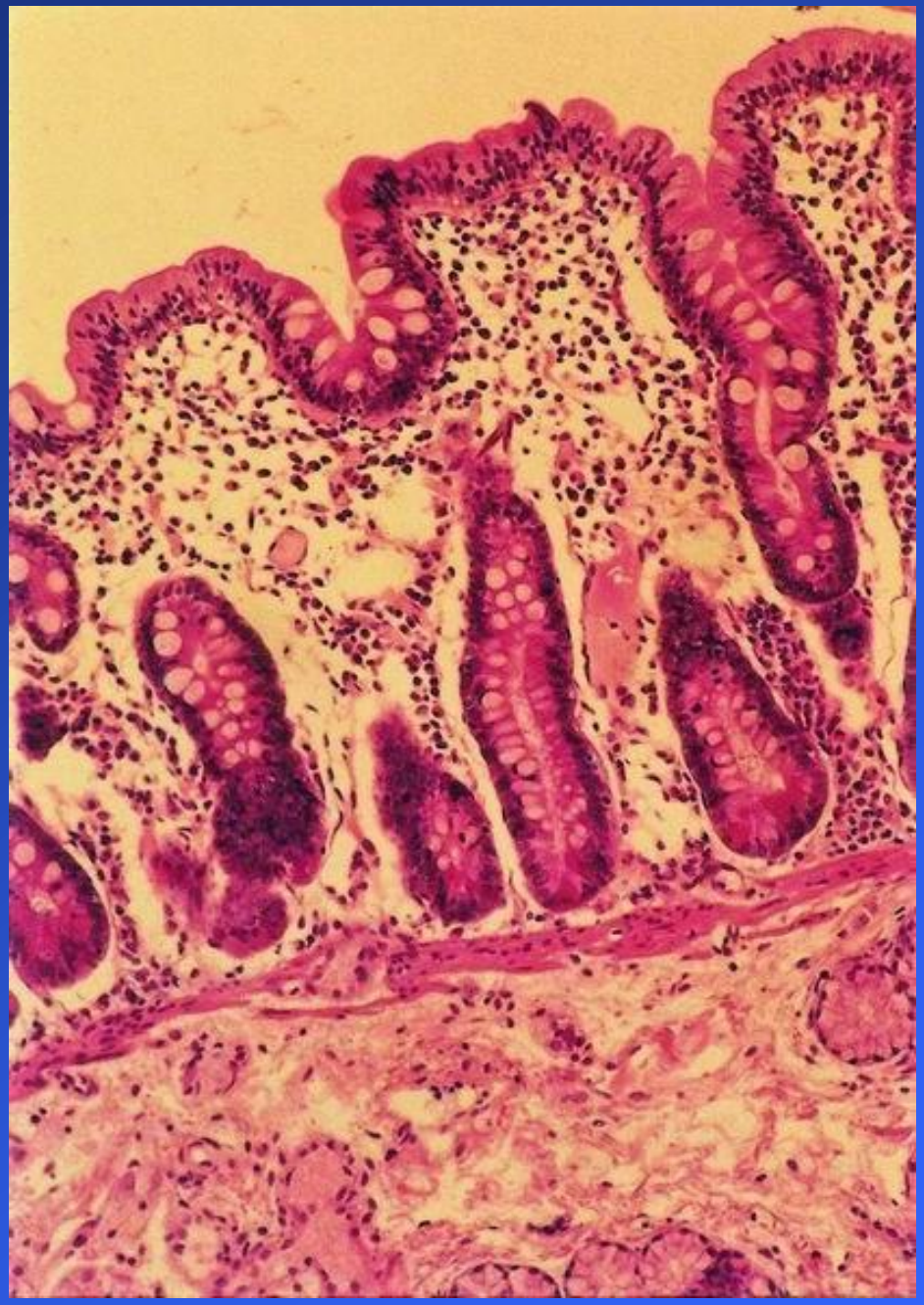
- histology
  - aspiration capsule biopsy
  - endoscopic biopsy

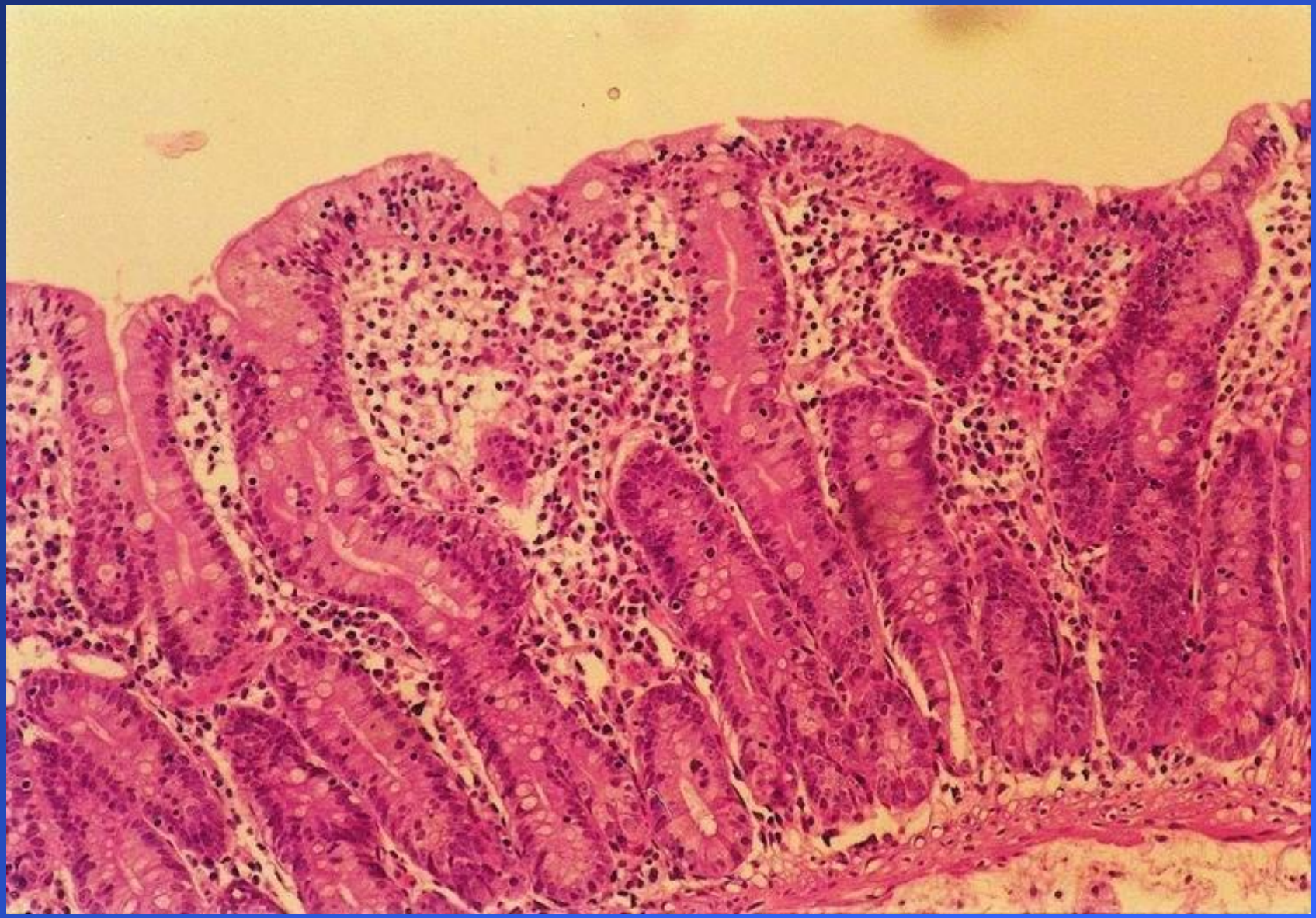
Intestinal biopsy

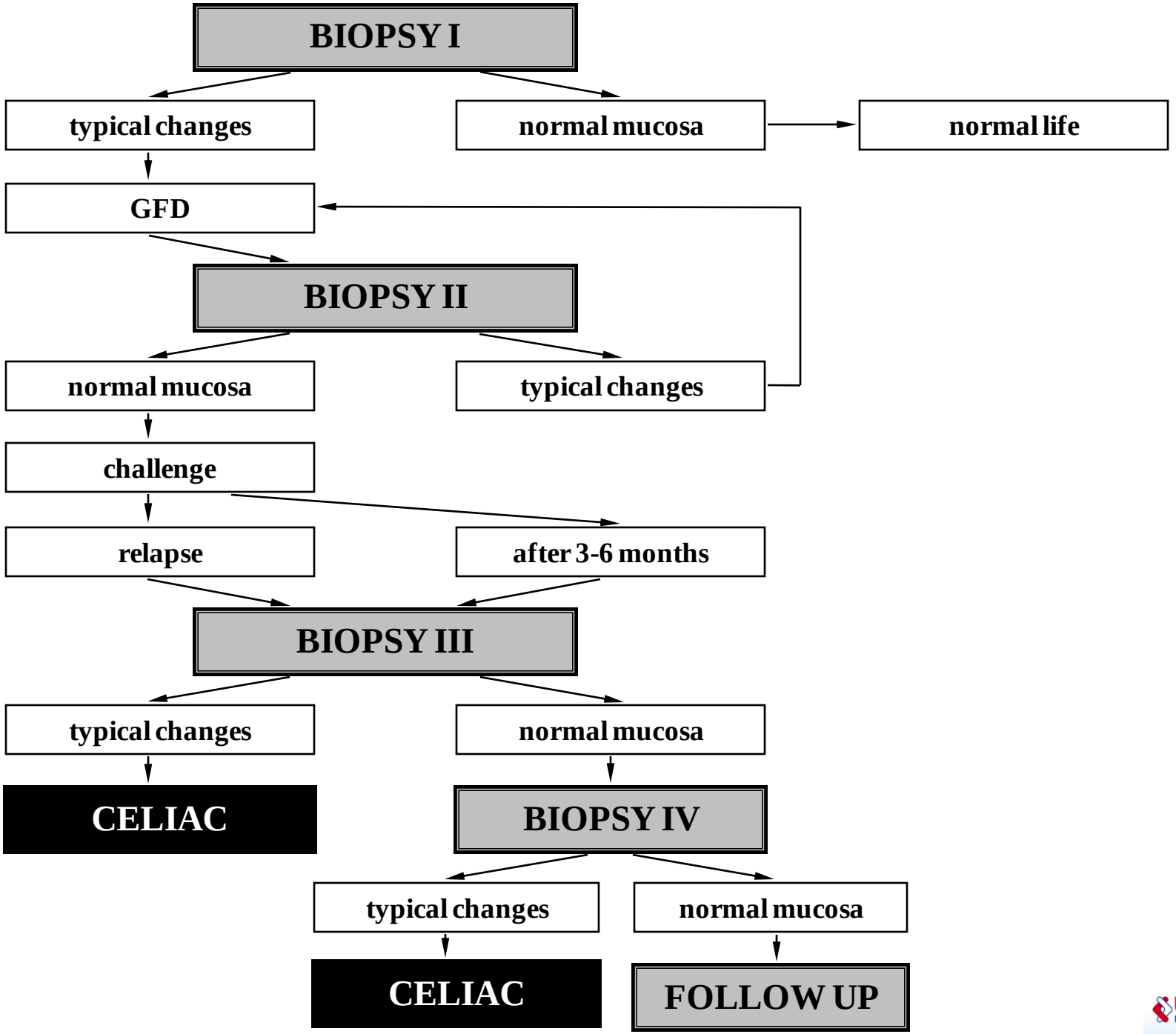
- Histologic changes
  - mucosal atrophy
    - Marsh classification
      - type 0: preinfiltrative phase
      - type 1: infiltrative phase
      - type 2: infiltrative-hyperplastic phase
      - type 3 (a, b, c): destructive phase
      - type 4: atrophic-hypoplastc phase
    - villous atrophy, crypt hyperplasia, IEL count

Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992.
Oberhuber G, et al. The histopathology of coeliac disease: time for a standardised report scheme for pathologist. Eur J Gastroenterol Hepatol 1999.









Revised criteria ESPGHAN

- intestinal biopsy – GOLDEN STANDARD
- abnormal mucosa when eating gluten
- clinical improvement after GFD
  - normalisation of serologic markers
- challenge no longer needed
- 1 biopsy
- exceptions
  - uncertain initial diagnosis
  - children under age of 2

Walker Smith et al. Arch Dis Child 1990; 65: 909-11.

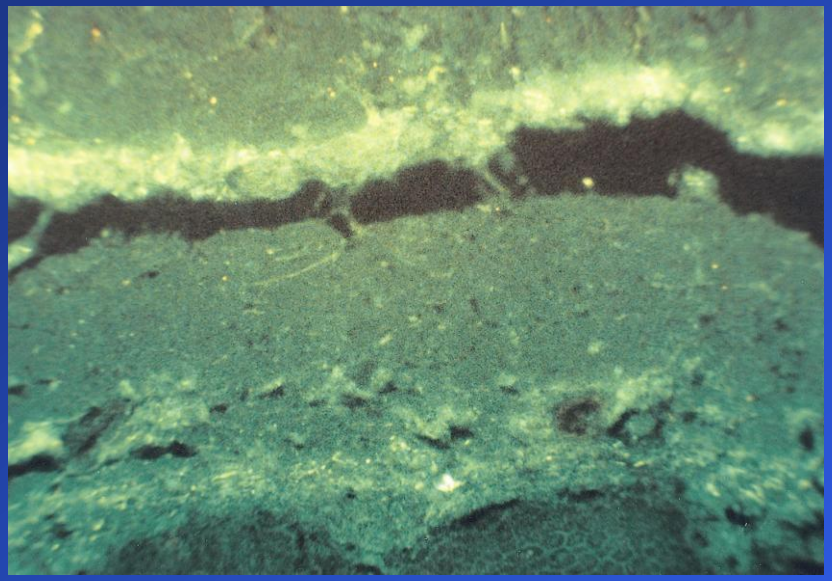
Serologic markers

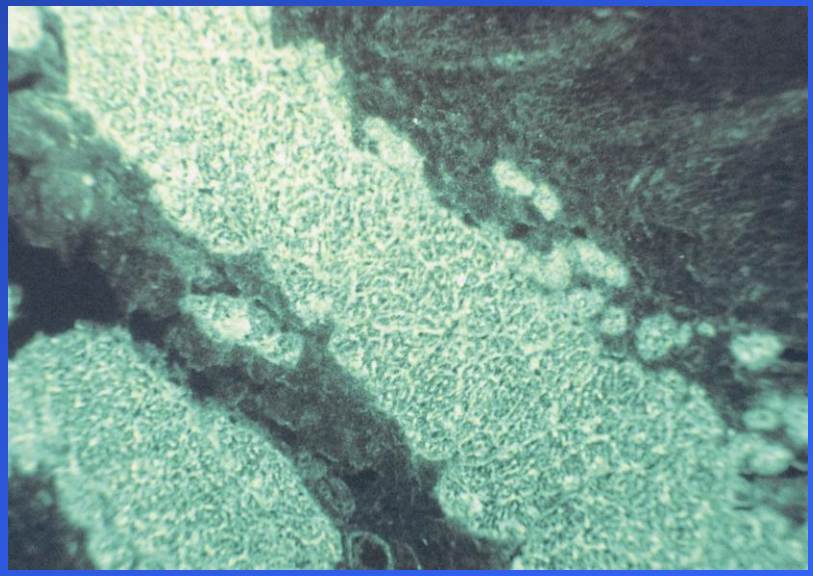
- Serologic markers
  - AGA IgA and IgG
    - ELISA, commercial kits
  - EMA IgA
    - indirect immunofluorescence, commercial kits
    - substrate: monkey esophagus (umbillical cord)
  - t-TG IgA (IgG)
    - ELISA, commercial kits
    - substrate: human recombinant t-TG
  - deamidated gliadin IgA, IgG
    - ELISA, commercial kits
  - other Ab (ARA, JAB, antiglutenin)
  - importance of total IgA determination

Children		Patients	Controls	IgA reticulin antibodies (ARA)		IgA endomysial antibodies (EMA)	
				Sensitivity	*Specificity*	*Sensitivity*	*Specificity %*
Bottaro	1997	50	25	74	100	96	96
Hällström	1989	14	24	100	100	100	100
Kolho	1997	53	114	96	92	94	100
Lerner	1994	34	41	65	100	97	98
Mäki	1984	29	245	97	98		
Sacchetti	1996	32	42	94	100	97	100
Volta	1991	29	20	52	100	90	100
Adults							
Ferreira	1992	21	160	90	99	100	99
Hällström	1989	35	145	91	100	91	100
Mäki	1991	13	109	92	95	92	95
Sategna-Guidetti	1997	104	94			95	100
Valdimarsson	1996	19	125			74	100
Volta	1991	41	20	44	100	85	100

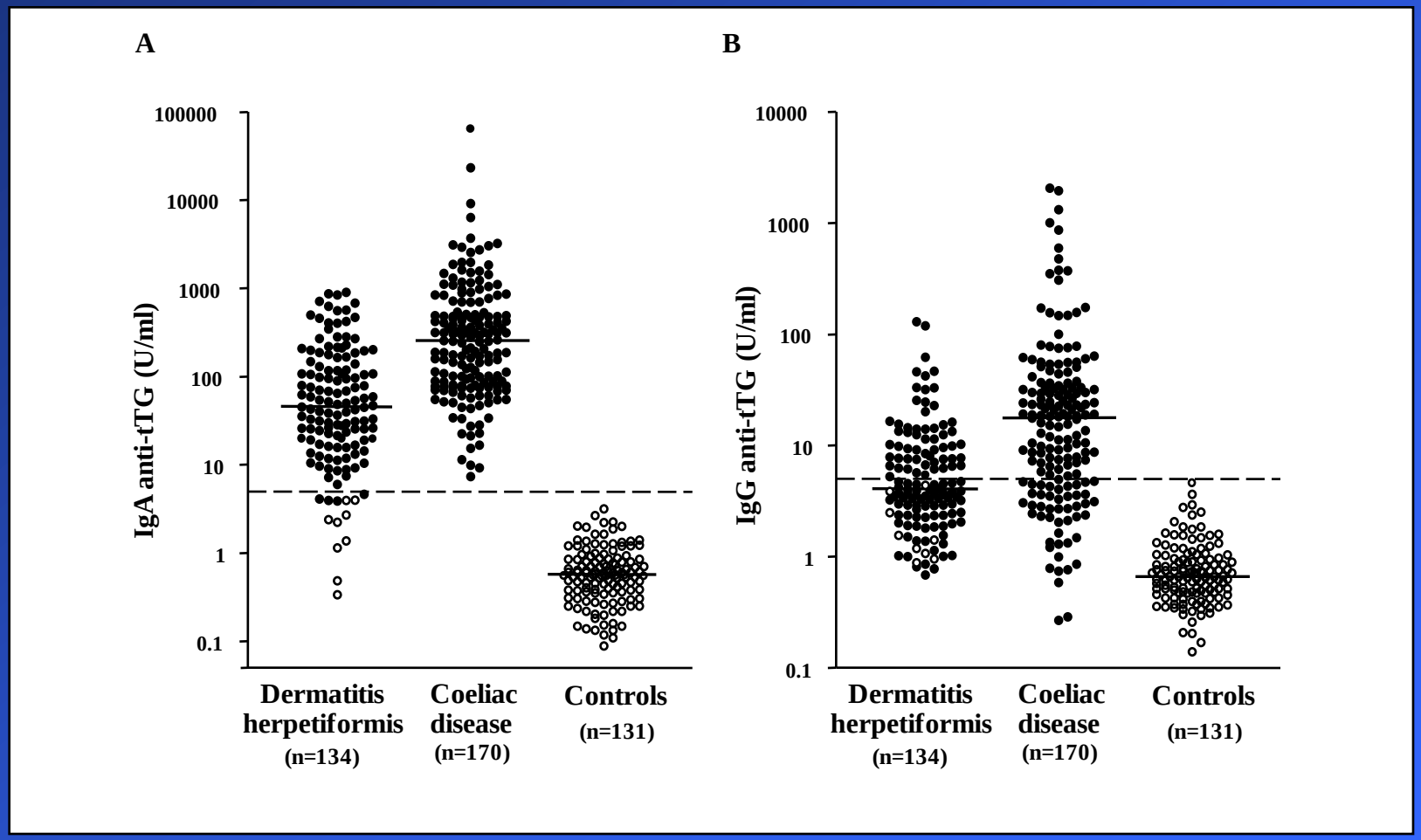
Children		Patients	Controls	IgA gliadin antibodies		IgG gliadin antibodies	
				Sensitivity	*Specificity*	*Sensitivity*	*Specificit %*
Asher	1990	36	92	97	92		
Bottaro	1997	50	25	92	68	50	36
Lerner	1994	34	41	52	94	88	92
Stahlberg	1986	31	278	90	86	94	67
Adults							
Bodé	1994	13	87	46	98	62	97
Ferreira	1992	21	160	90	85	76	88
Kilander	1983	36	54	67	94	78	94
Maki	1991	13	109	31	87	46	89
McMillan	1991	28	68	100	100	57	87
Sategna-Guidetti	1995	100	109	55	100	78	82
Vogelsang	1995	49	53	82	83	73	74

Serologic markers - EMA

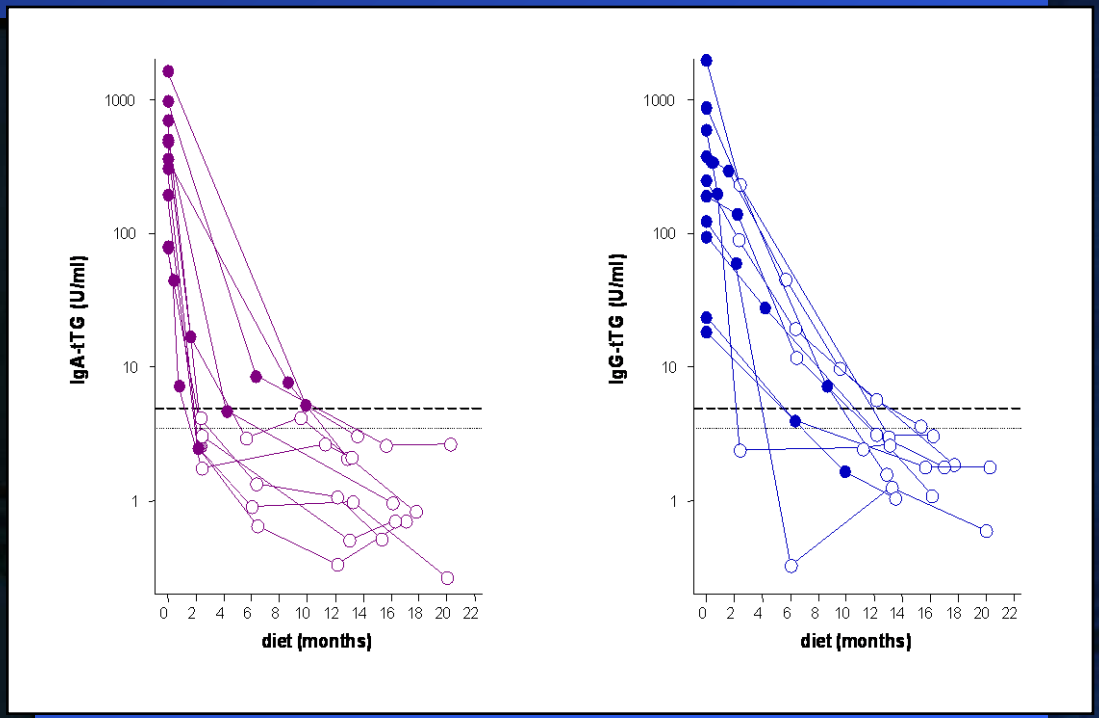




Serologic markers – t-TG

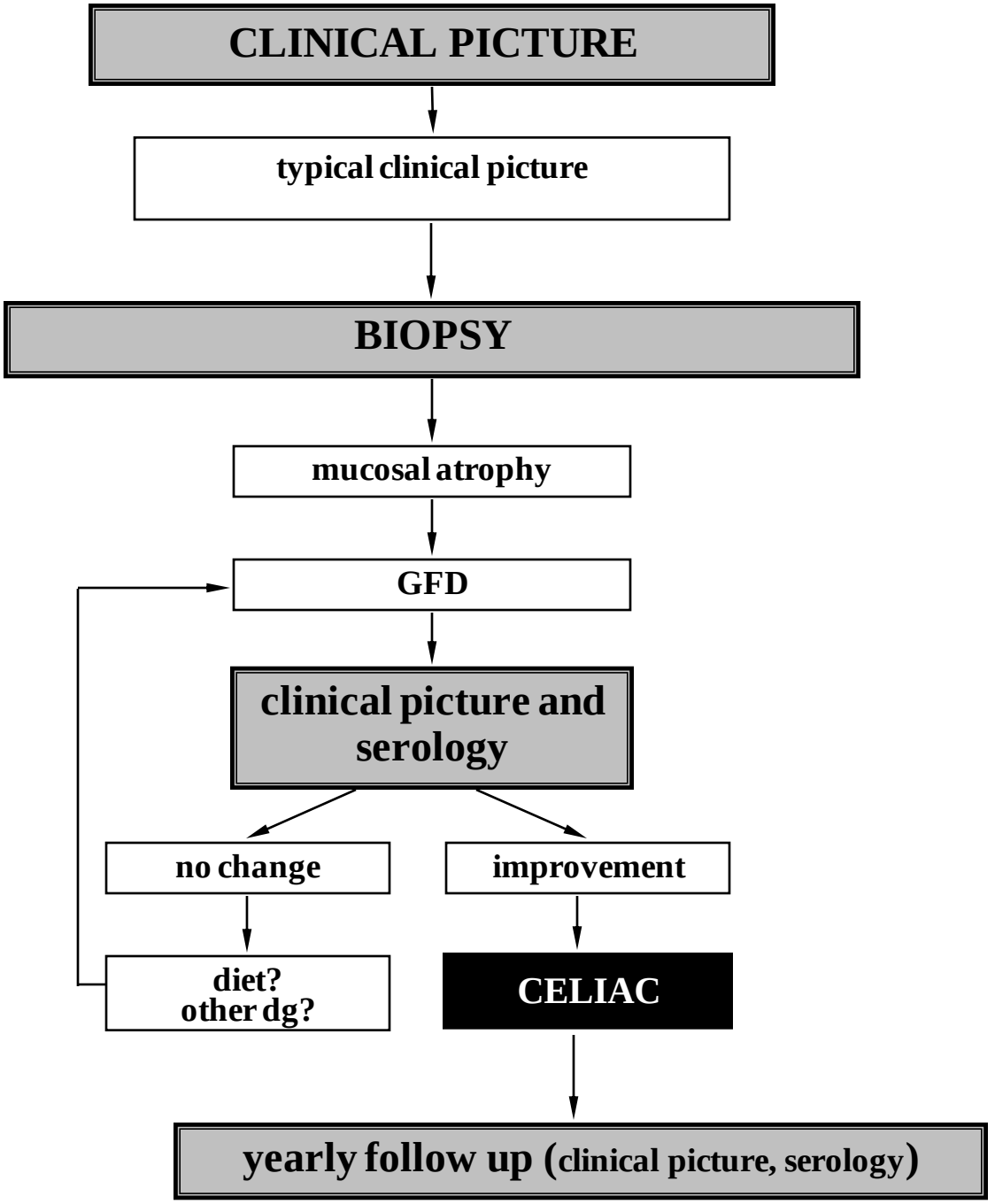


Serologic markers – t-TG



Untreated

On diet for 6 months

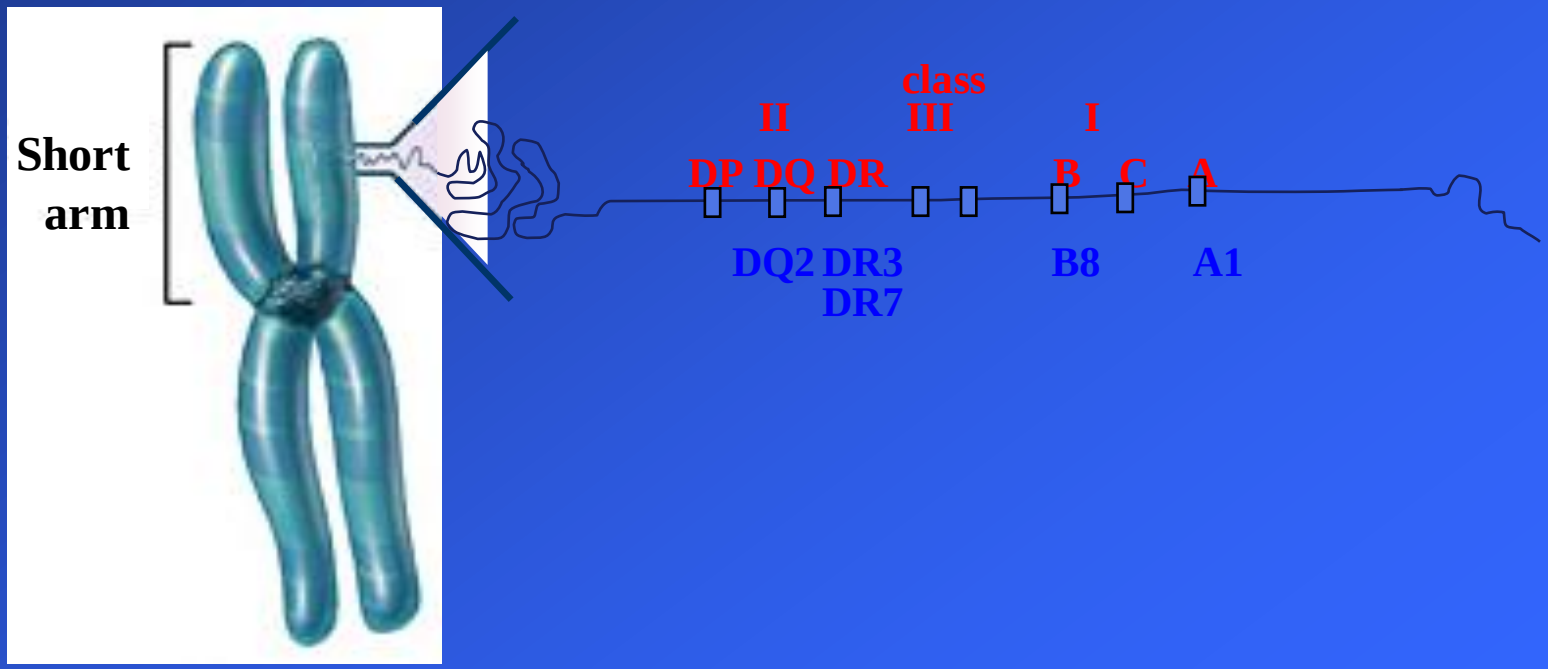


Other (newer) methods

- genetic testing
- histology
- serology

CD and genetics

- Celiac disease: OMIM 142800
- Medline: cca. 1600 hits
  - celiac disease and genetics



Chromosome 6

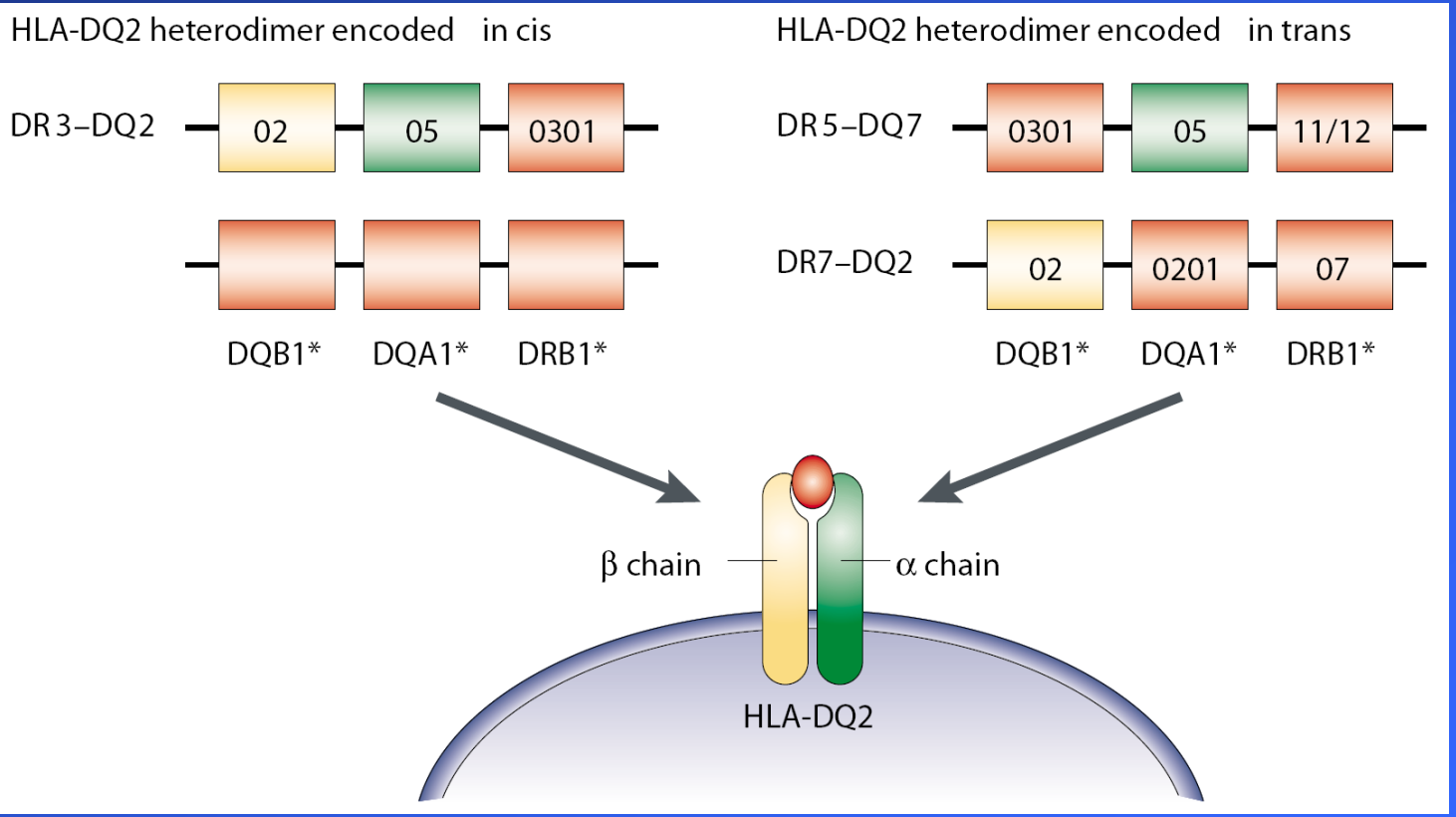
CD and genetics

- Genetic predisposition for CD
  - twin analysis
  - family occurence – 10%
  - poligenic disease
    - most important factor HLA locus
      - chromosome 6p21.3
      - ~90% patients HLA-DQ2
      - ~10% patients HLA-DQ8

Karell K, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. Hum Immunol 2003.
Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. Clin Gastroenterol Hepatol 2005.

CD and genetics

- Genetic predisposition for CD
  - HLA locus (chromosome 6p21.3)

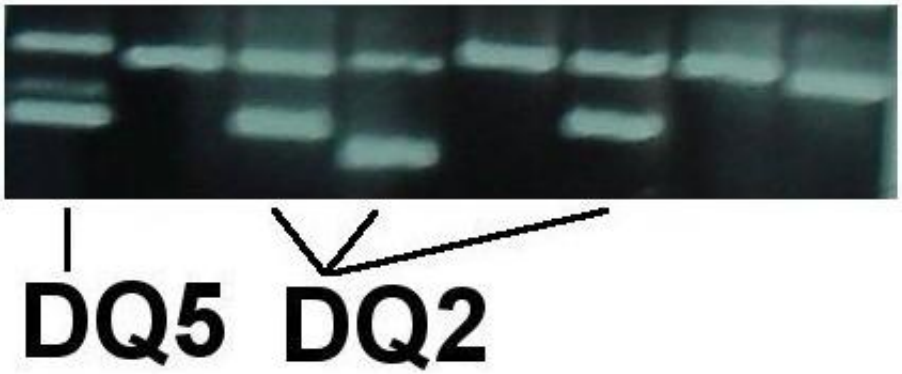


Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. Clin Gastroenterol Hepatol 2005.

Genetic testing

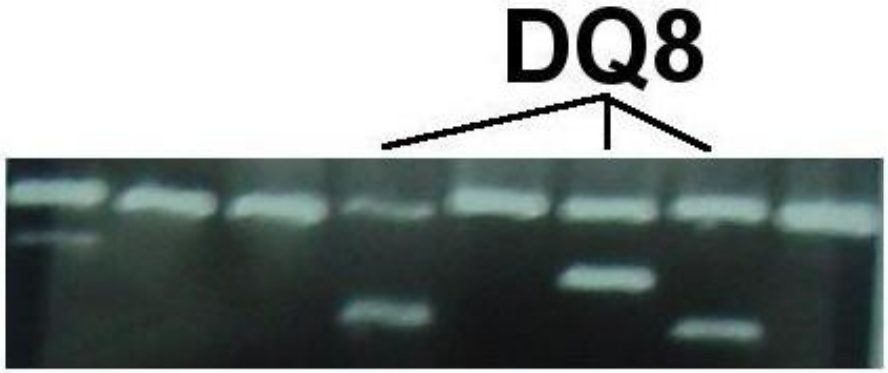
HLA-DQ2, DQ4

HLA-DQ2, DQ5

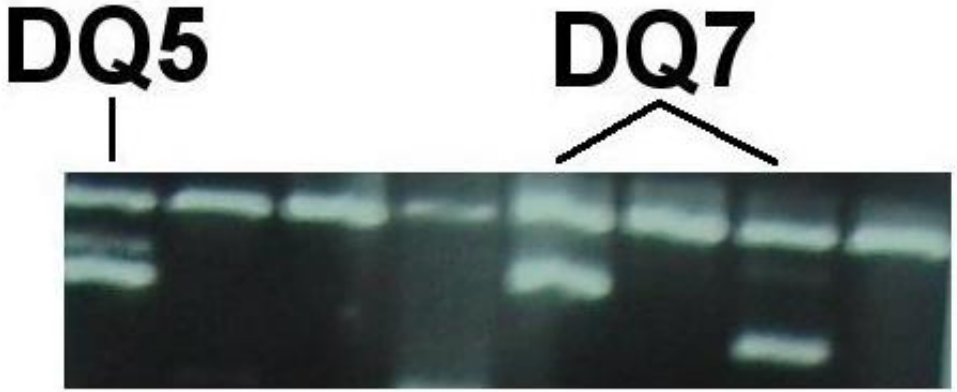


Genetic testing

HLA-DQ8, DQ8

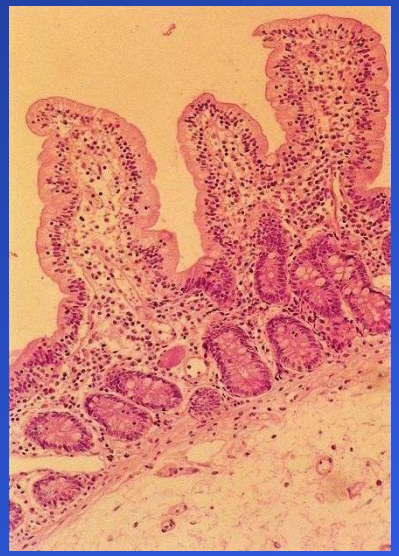


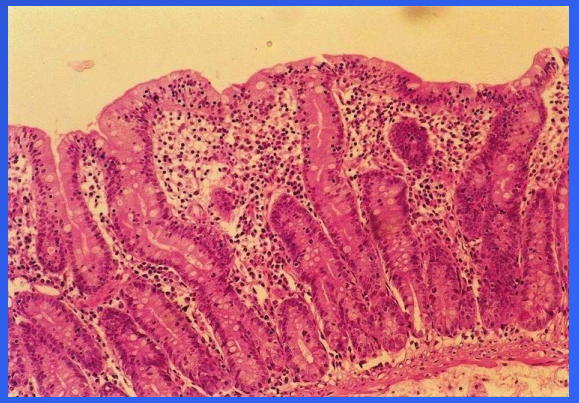
HLA-DQ5, DQ7



Histology

- Histology
  - mucosal atrophy

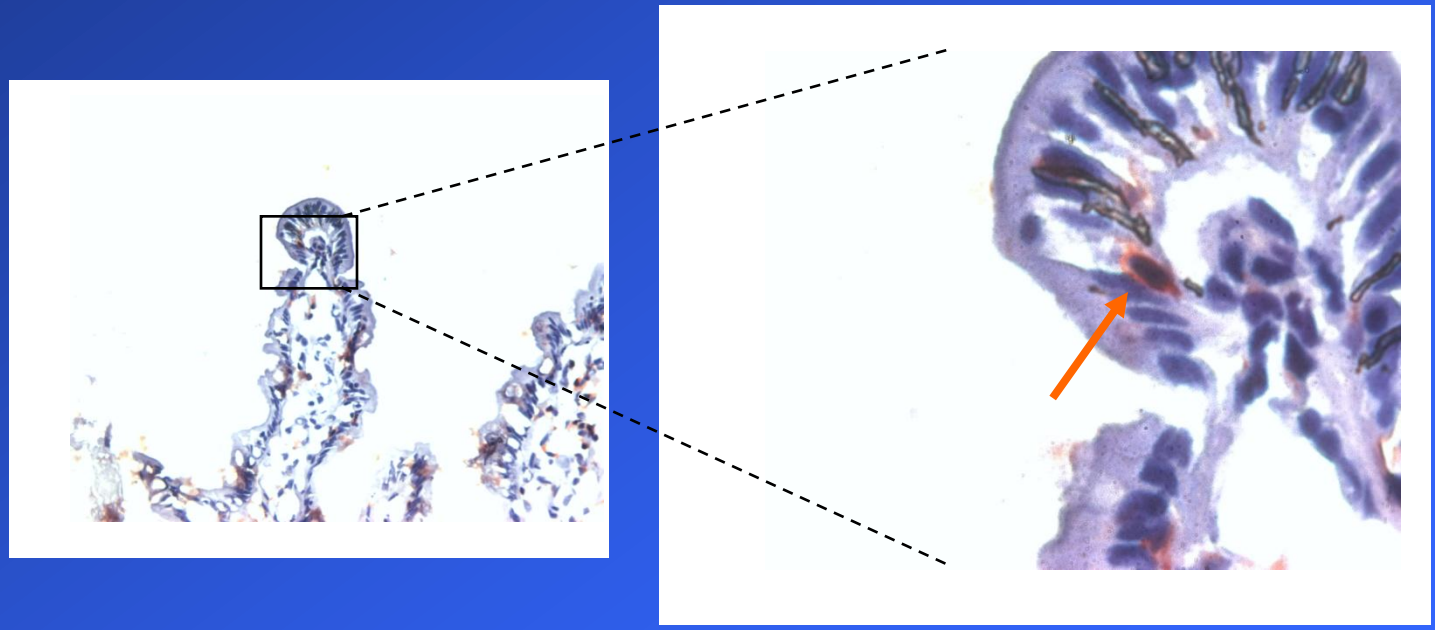


Histology

- IEL subpopulations
  - CD3
  - alpha/beta IEL
  - gamma/delta IEL
- Enterocyte apoptosis
  - TUNEL-terminal uridine nick end labeling
- IgA t-TG Ab tissue deposits

Histology

- Histology
  - IEL count
    - immunohistochemical methods



Histology

- Histology
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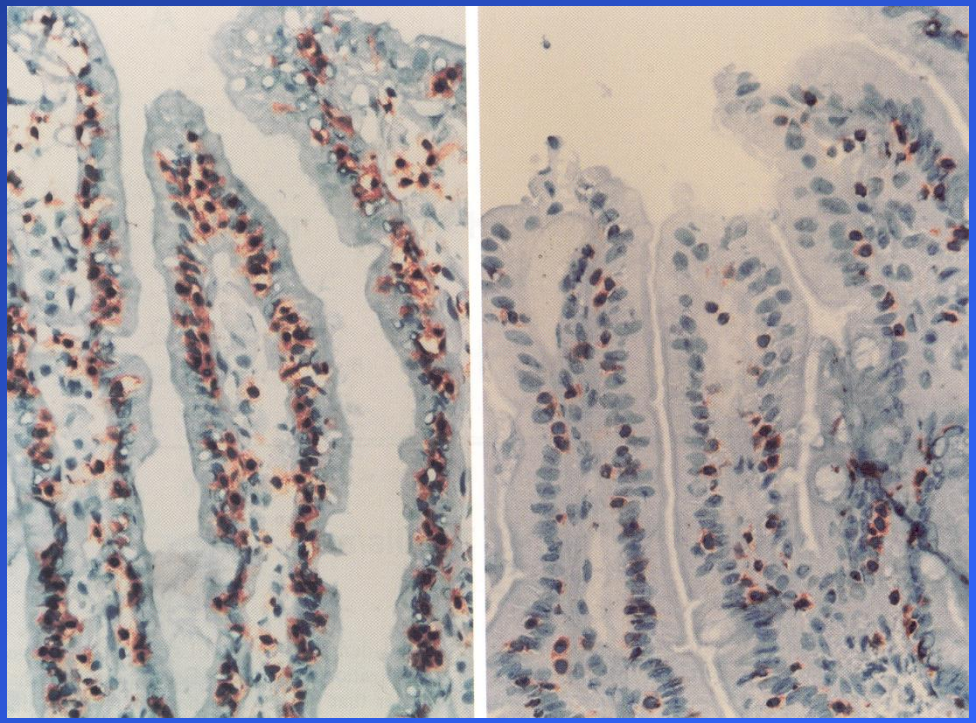
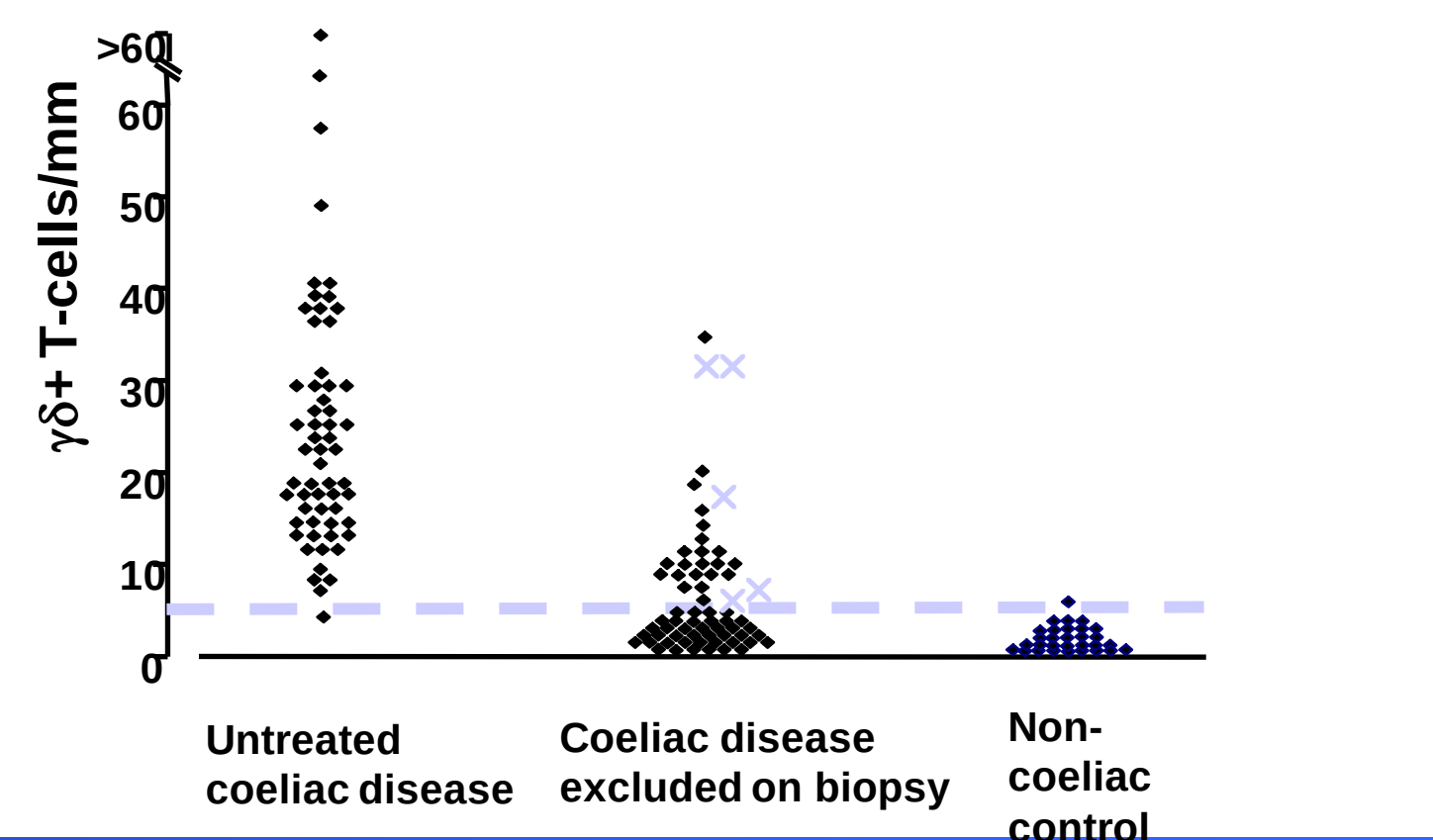


Kaukinen et al. Dig Dis Sci 2001;46:879

Histology

- Histology
  - IEL count



Kaukinen et al. Scand. J Gastroenterol, 1998

Histology

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- Enterocyte apoptosis
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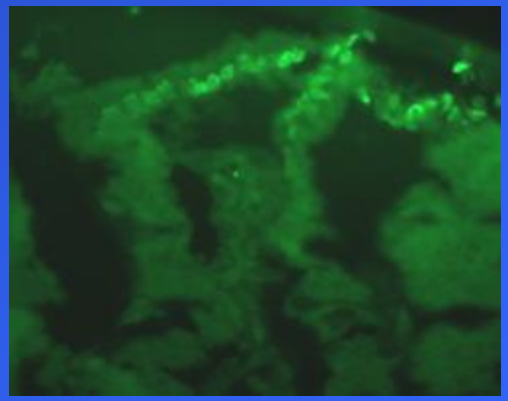
- IgA t-TG Ab tissue deposits



Histology

- IEL subpopulations
  - CD3
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- Enterocyte apoptosis
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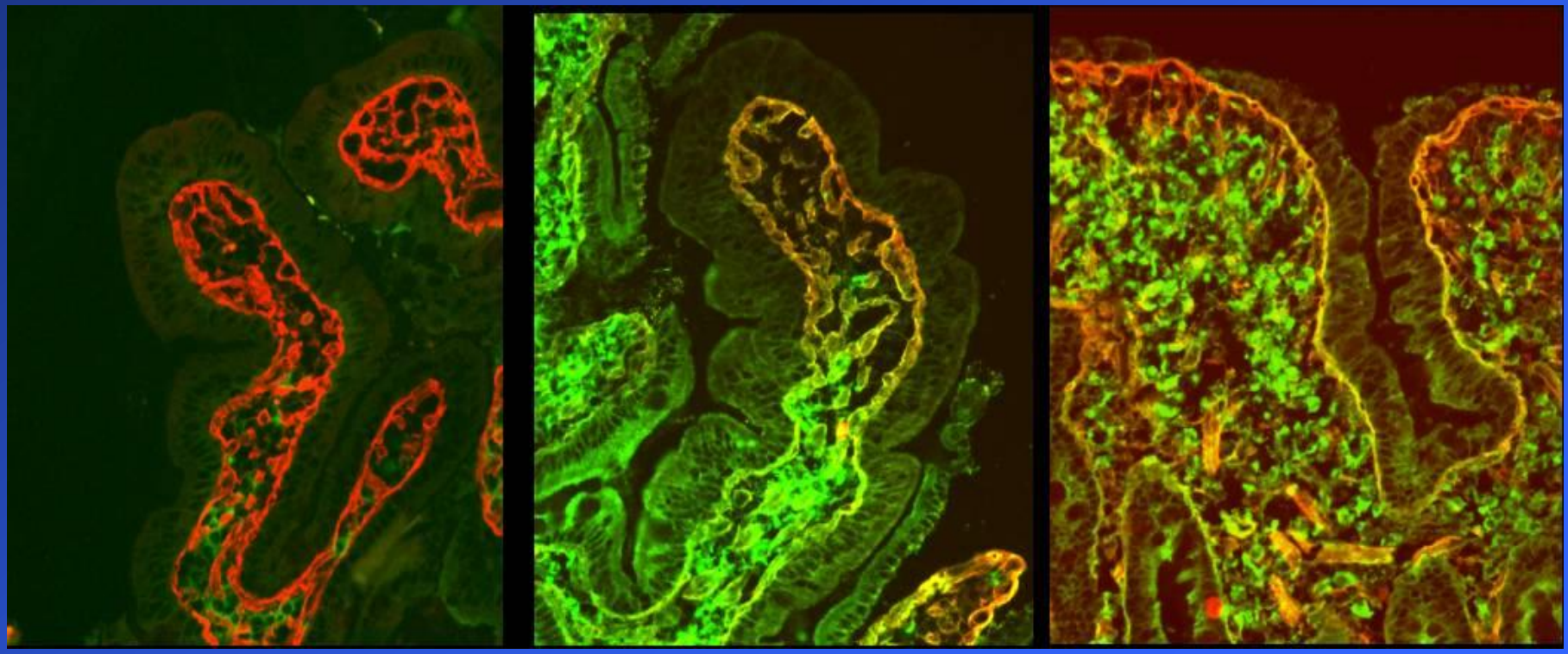
- IgA t-TG Ab tissue deposits

Histology

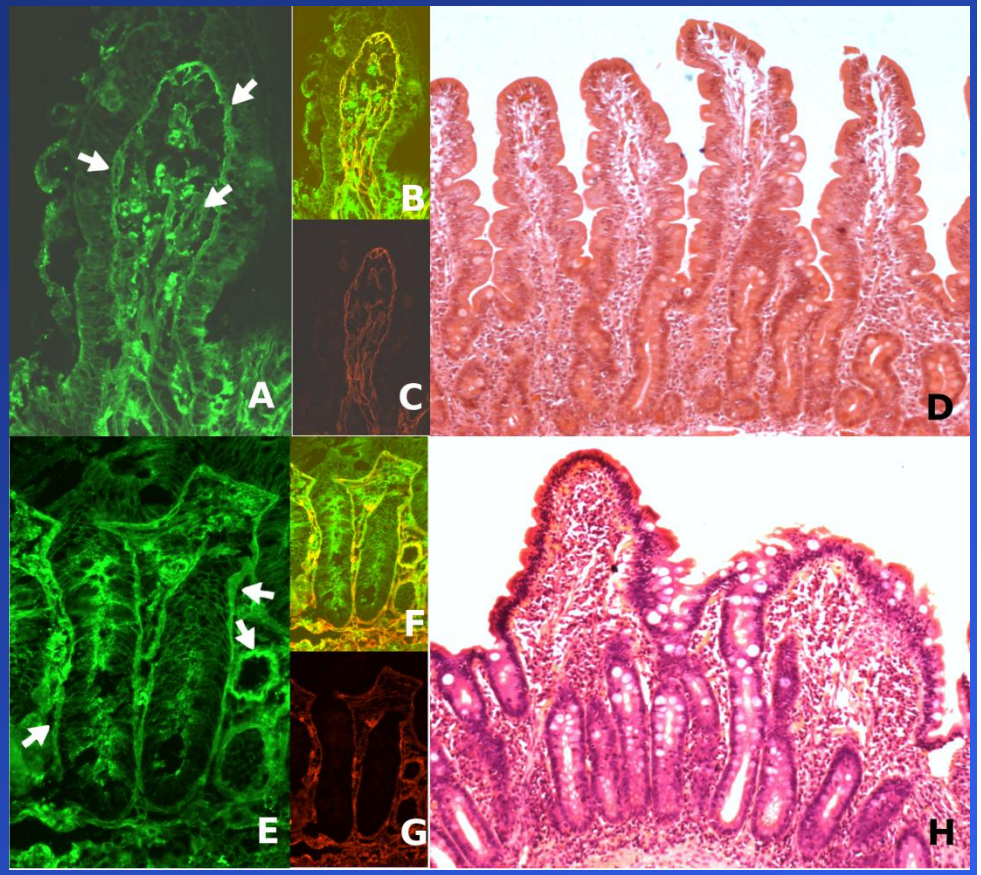
Normal | Early phase | Celiac flat lesion



IgA / Transglutaminase 2

Korponay-Szabo I, et al. Gut, 2004

Other (newer) methods

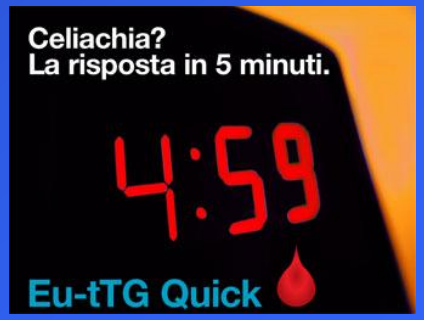


	Sens %	Specif %
Mucosal IgA-deposits	**93**	**93**
Serum autoantibodies	76	83
Mucosal villous tip IELs	88	71
Mucosal $\gamma\delta$ IELs	76	60
Mucosal IELs (Marsh 1)	59	57
HLA DQ2 or DQ8	100	66

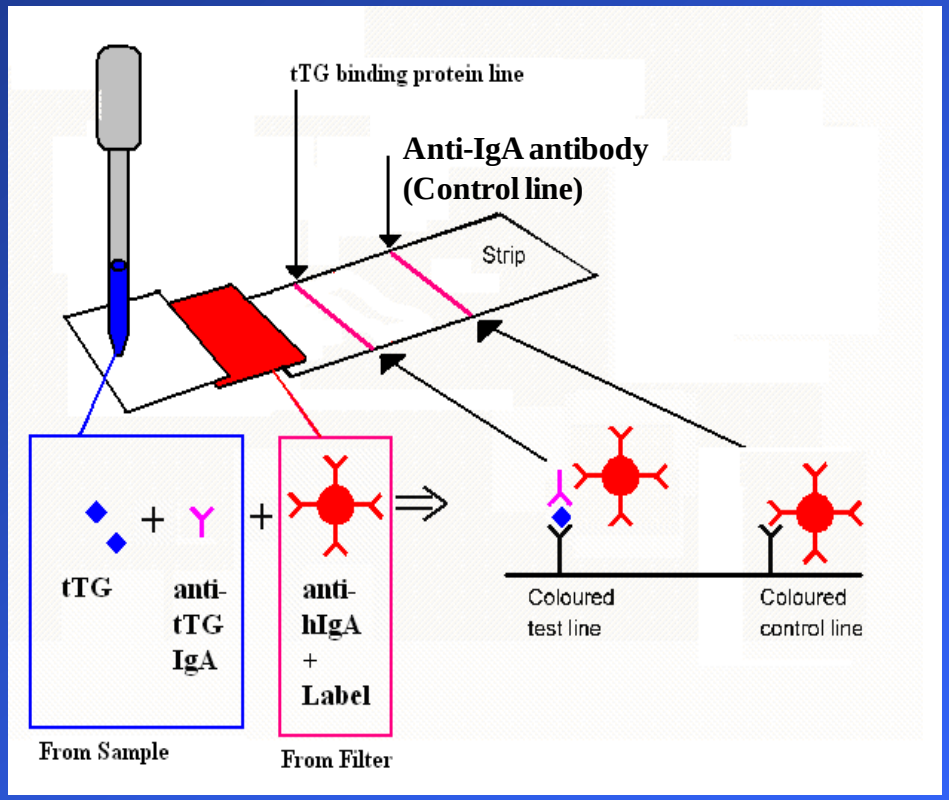
Salmi et al., Aliment Pharmacol Ther, 2006

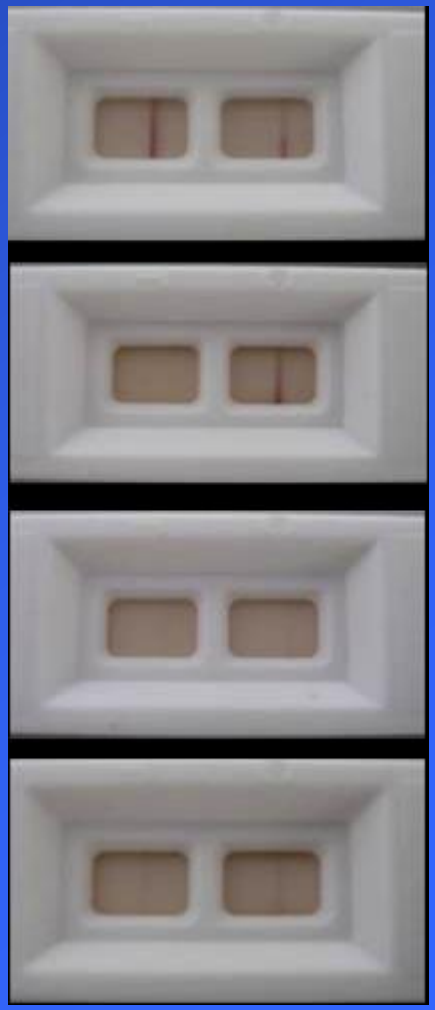
New diagnostic tests

- serological tests
  - tissue transglutaminase Ab (t-TG)
    - reliable, relatively inexpensive test
    - rapid finger-prick t-TG test



New diagnostic tests





New diagnostic tests

- serological tests
  - deamidated gliadin Ab (IgG, IgA)
    - high corellation with EMA and t-TG
  - glutenin Ab
  - new microsystems
    - simultaneus
      - multiple Ab test
      - IgA determination
      - HLA-DQ2/DQ8 status

CD medics
Coeliac Disease Management Monitoring and Diagnosis using Biosensors and an Integrated Chip System

SEVENTH FRAMEWORK PROGRAMME

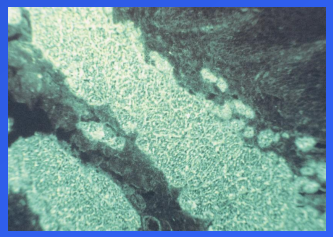
Prince HE. Evaluation of the INOVA diagnostics enzyme-linked immunosorbent assay kits for measuring serum immunoglobulin G (IgG) and IgA to deamidated gliadin peptides. Clin Vaccine Imunol 2006.
Aleanzi M, et al. Celiac disease: antibody recognition against native and selectively deamidated gliadin peptides. Clin Chem. 2001

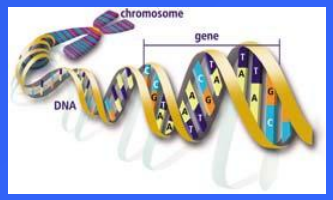
Conclusion

- ESPGHAN criteria
  - classic (at least 3 biopsies)
  - revised (1 biopsy)
  - future revisions (ESPGHAN working group)
- NASPGHAN criteria

Conclusion

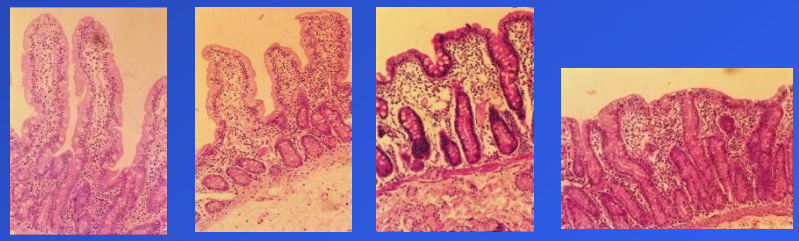
- clinical picture
  - typical celiac disease
  - atypical celiac disease
  - children
  - adults
- diagnostic tools
  - serological tests
    - EMA, t-TG, (watch for total IgA)
  - genetic tests
    - HLA DQ2/DQ8





Conclusion

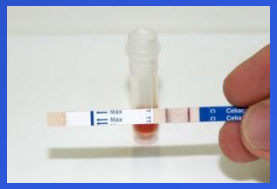
- diagnostic tools
  - histology

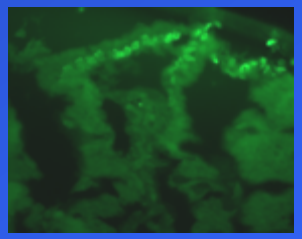


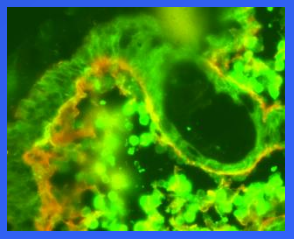
- clinical picture after introduction of GFD
  - reversibility of changes
    - clinical picture
    - serological tests
    - histological changes

Conclusion

- novel tests
  - serological tests
    - rapid t-TG test
    - other potentialy useful tests
      - deamidated gliadin
      - glutenin
  - histological tests
    - IEL
    - IgA t-TG deposits
    - apoptosis
  - nanotechnology
    - rapid multiparameter testing







Σας ευχαριστώ πολύ