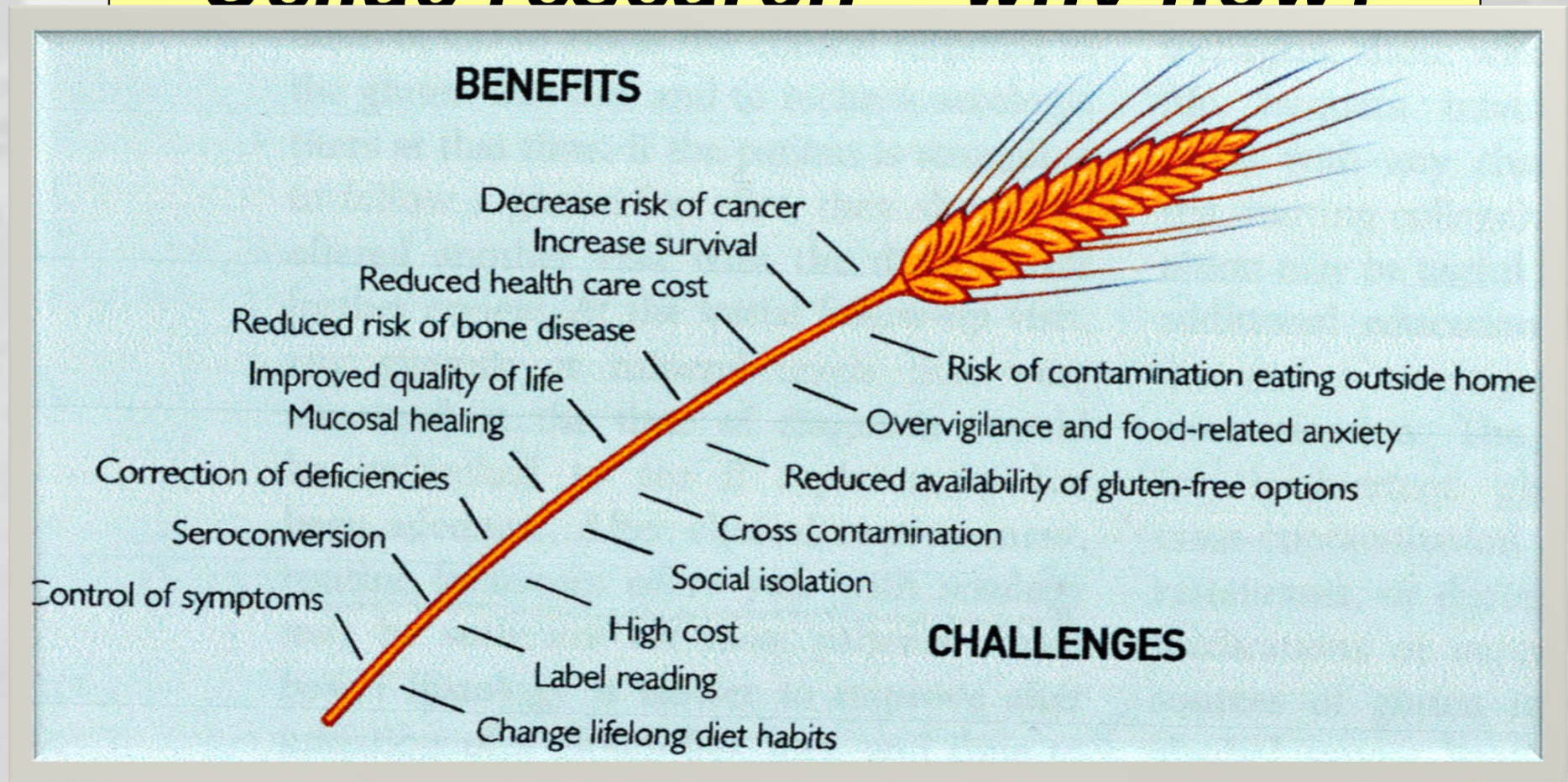




Celiac research – Why now?

Benny Kerzner MD

Celiac research – why now?



Ultima

3

helps

□ Bet

□ Du



□ Mo

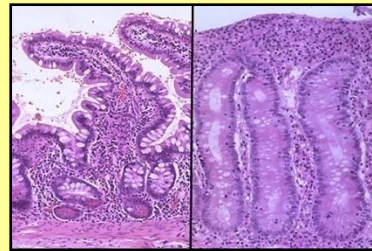
con

Durin



Defining the Intestinal Pathology

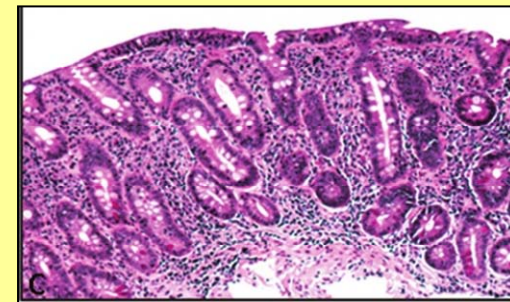
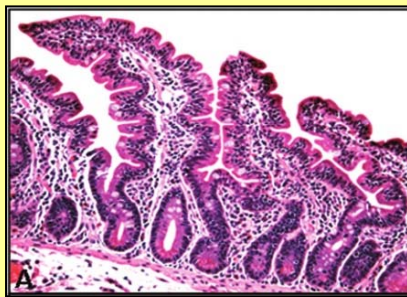
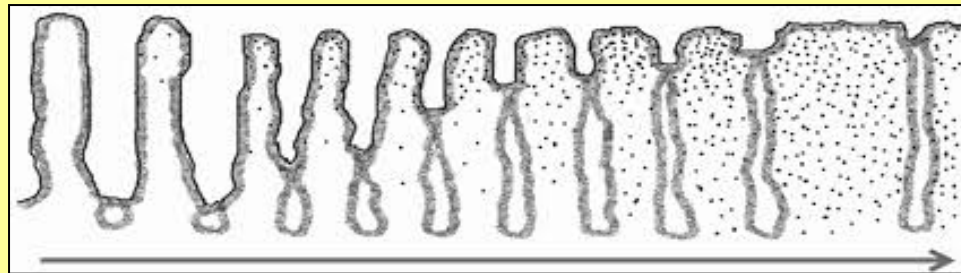
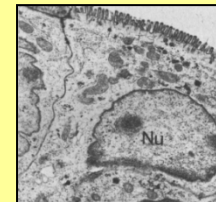
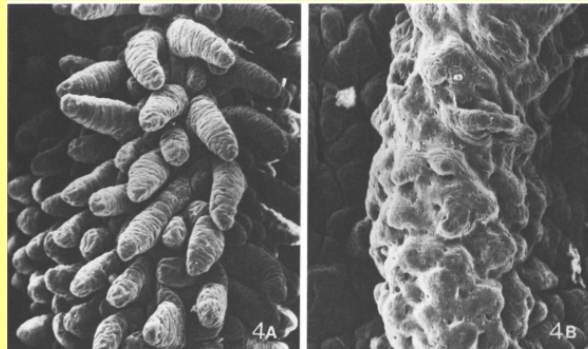
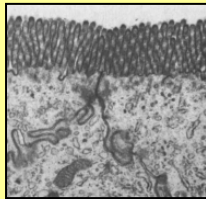
- 1950s Dr. Margot Shiner and Dr Crosby evolve the suction biopsy capsule

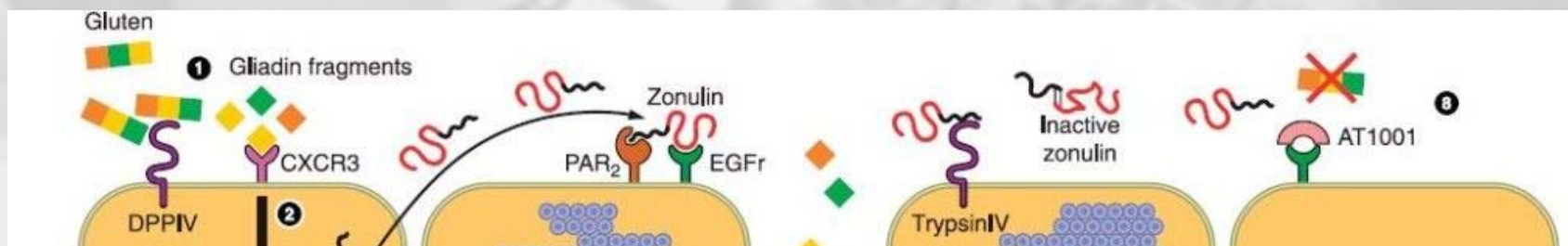


- Fifteen causes of mucosal atrophy
- Three biopsy ritual for defining celiac disease.
- Blood tests needed i.e. understanding of chemical progression.

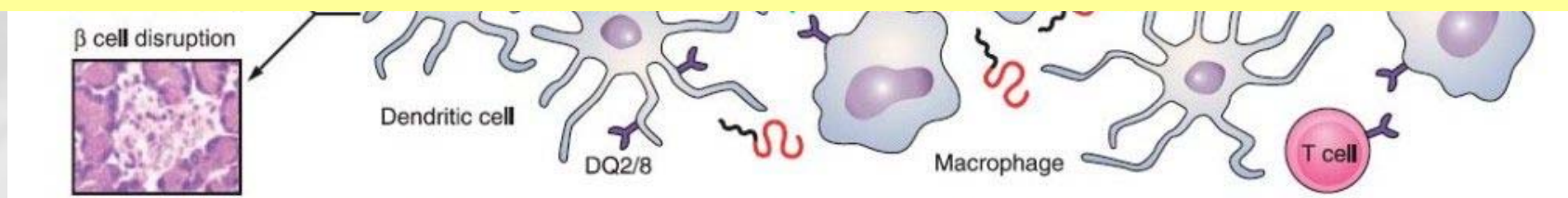


Progression of Villous Injury

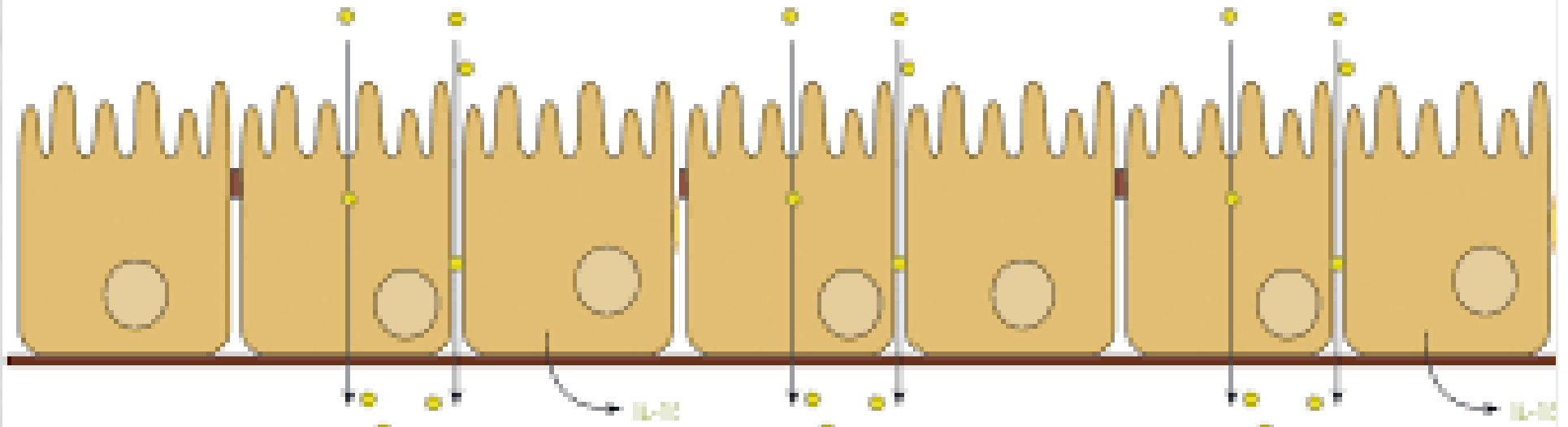




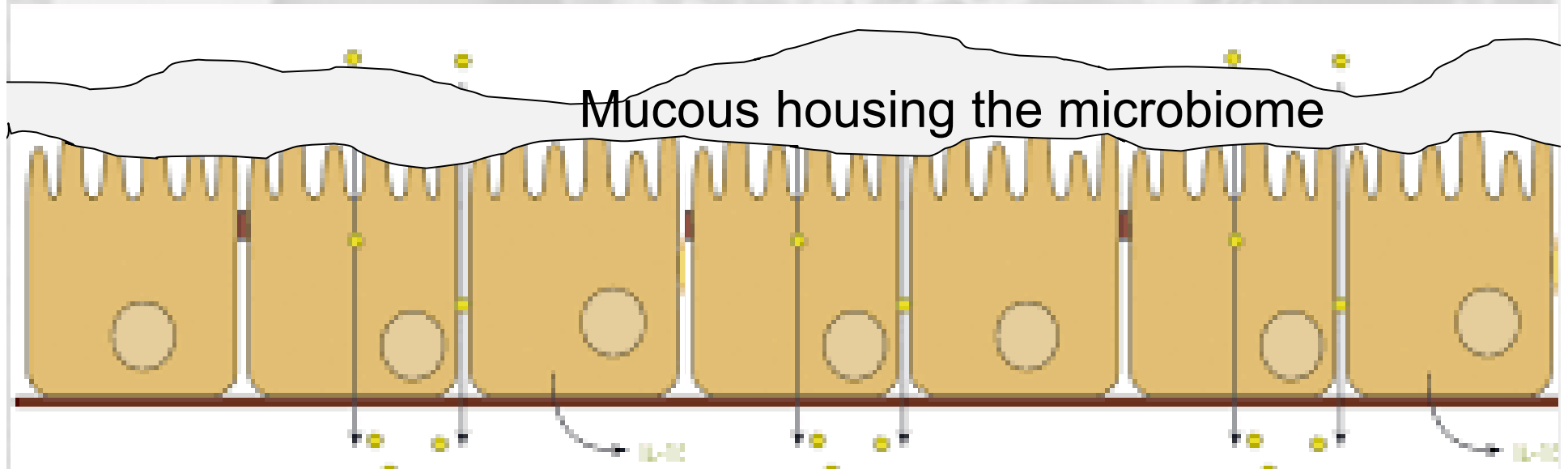
- Gliadin derived peptides cause **zonulin** release
- Cause small intestine **tight junction disassembly**
- **Antigens enter** the lamina propria including gliadin
- **Presented** by HLA –DQ molecules to dendritic cells
- **Abrogation of oral tolerance** (Th1/TH17 response) and **marked immune response** to Gliadin.
- Gliadin loaded **dendritic cells go to lymph nodes** to **summon CD4, CD8 gamma delta and alpha beta T cells** which **cause inflammation**



Appropriate entry is encouraged

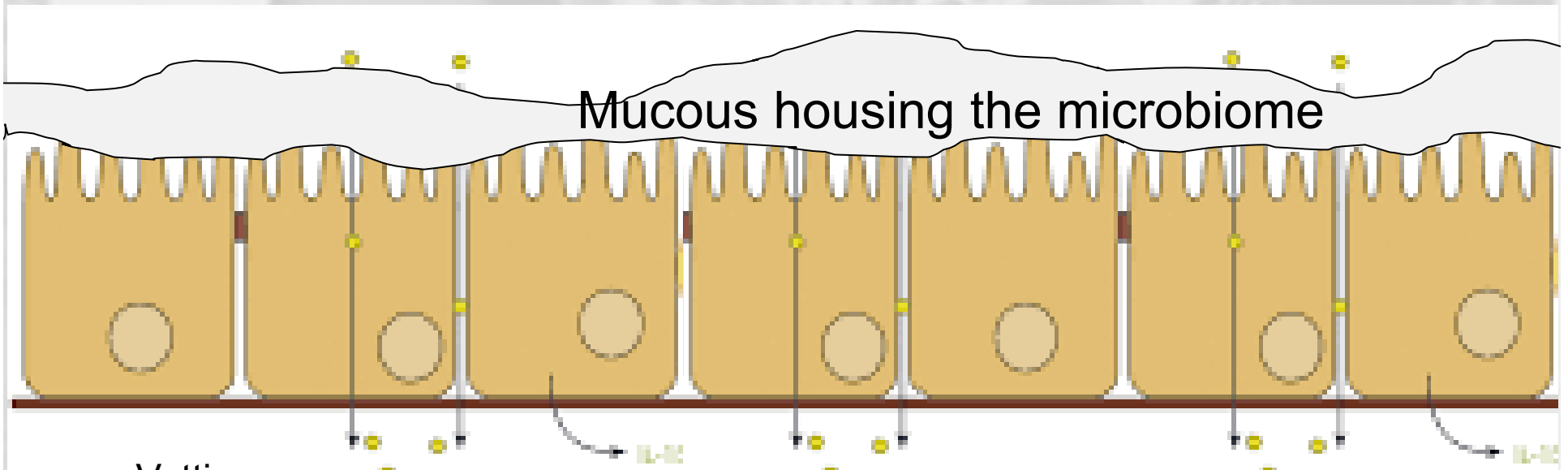


Protective layer of mucus contains the microbiome



National Guard Innate immune system

Mucous housing the microbiome



Vetting

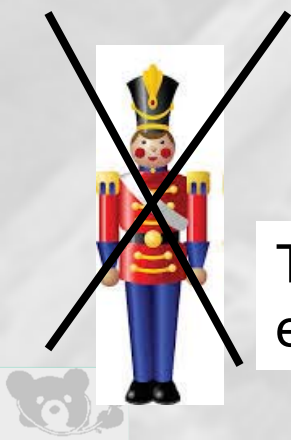
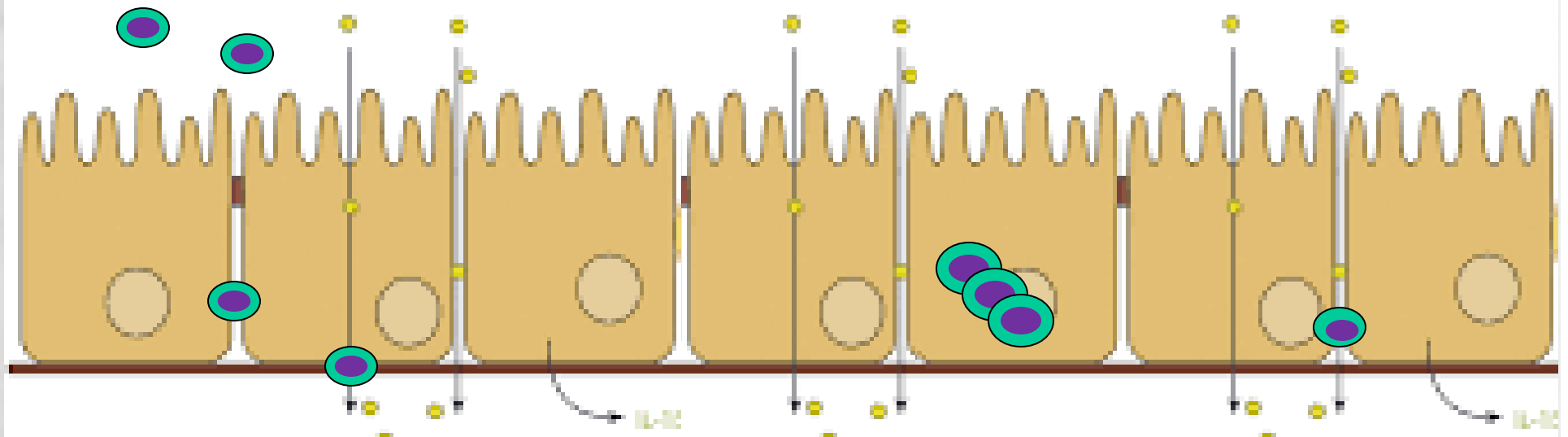


Conveyer

Delivering

National guard – Innate immune system

Handling Gliadin when it crosses the wall.



Tolerance is eliminated



tTG
modifies
gliadin



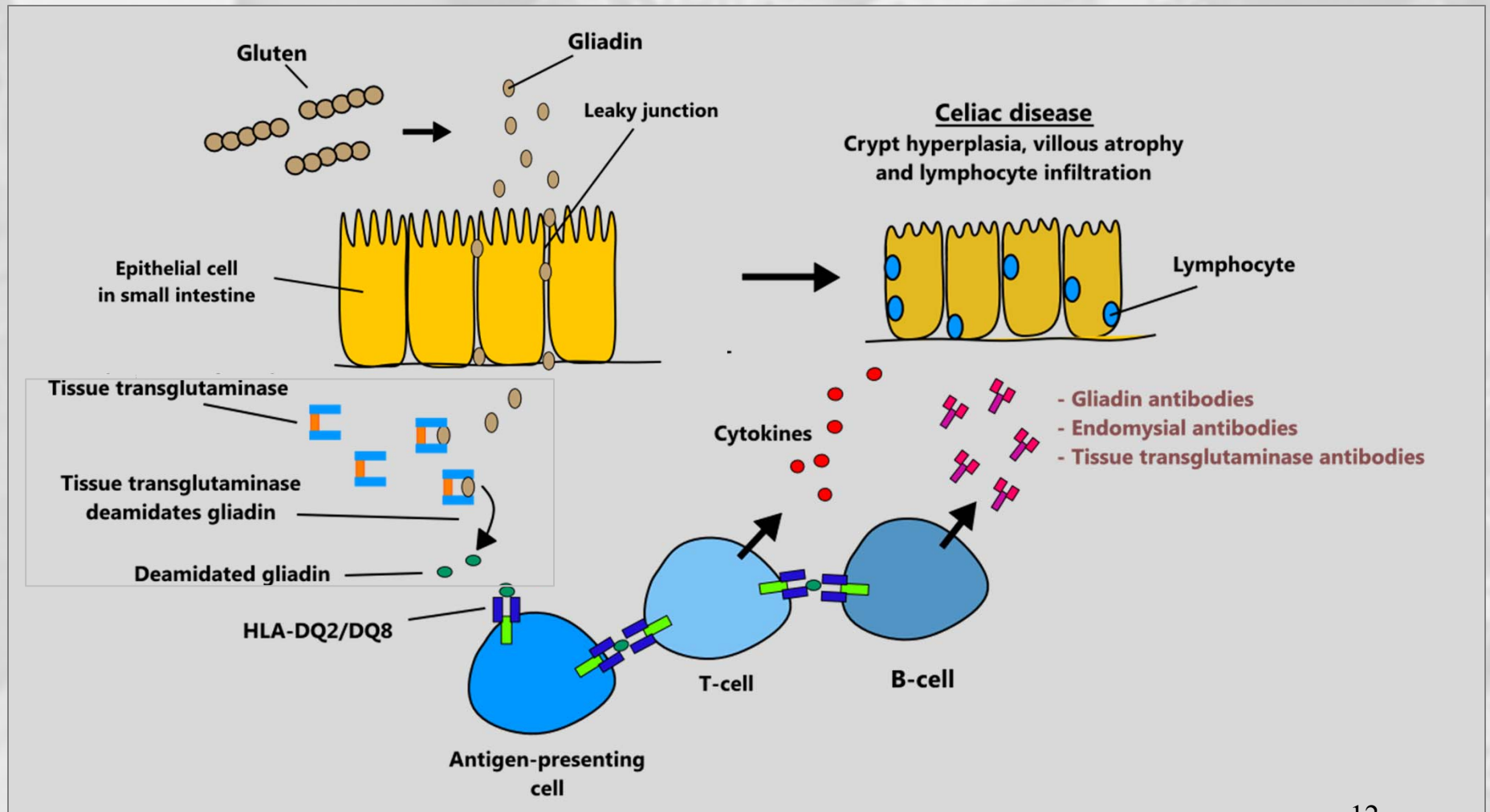
Genes
DQ2 and
DQ8 allow
transfer to
messenger



Calling in the military (The adaptive immune response)



Pathogenesis once more



Once serology became available....

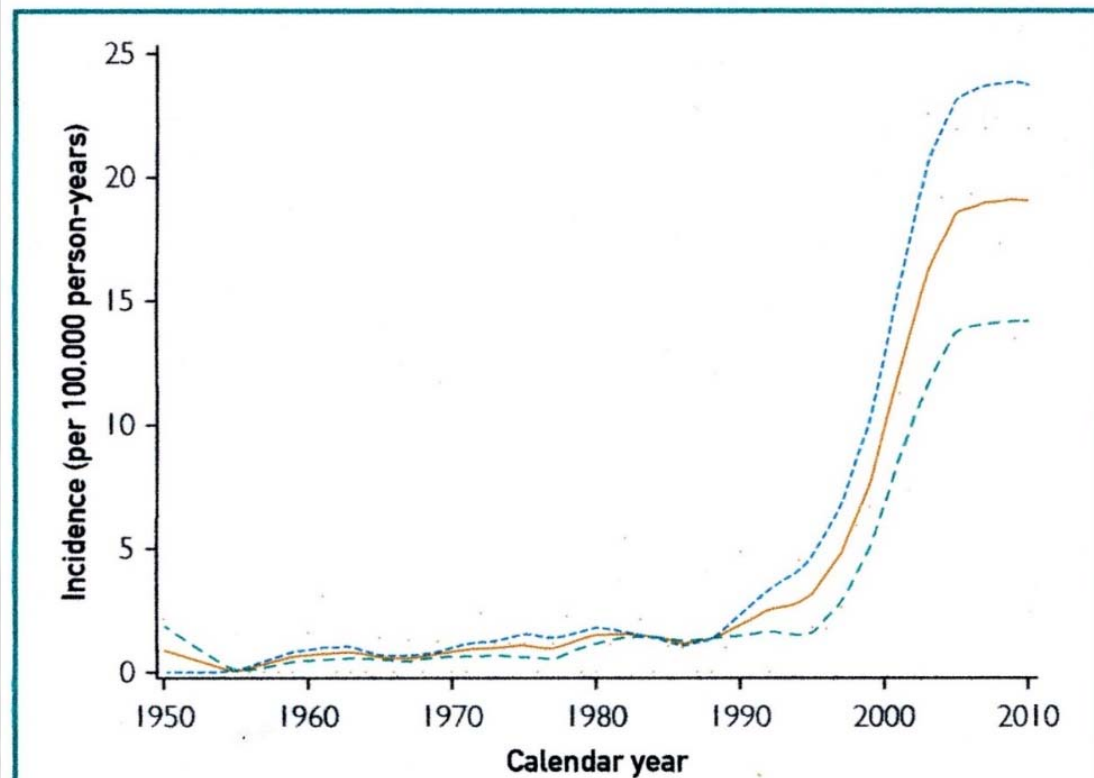


FIGURE 1. Incidence of clinical diagnosis of celiac disease in Olmsted County, Minnesota, 1950-2010. There is increasing incidence in both women (blue line) and men (green line) in the past 30 years. The red line represents overall incidence.



The background of the slide is a grayscale photograph of a large pile of discarded waste, including crumpled paper, plastic containers, and other debris. A bright yellow rectangular box is centered on the slide, containing the text.

Implications for treatment



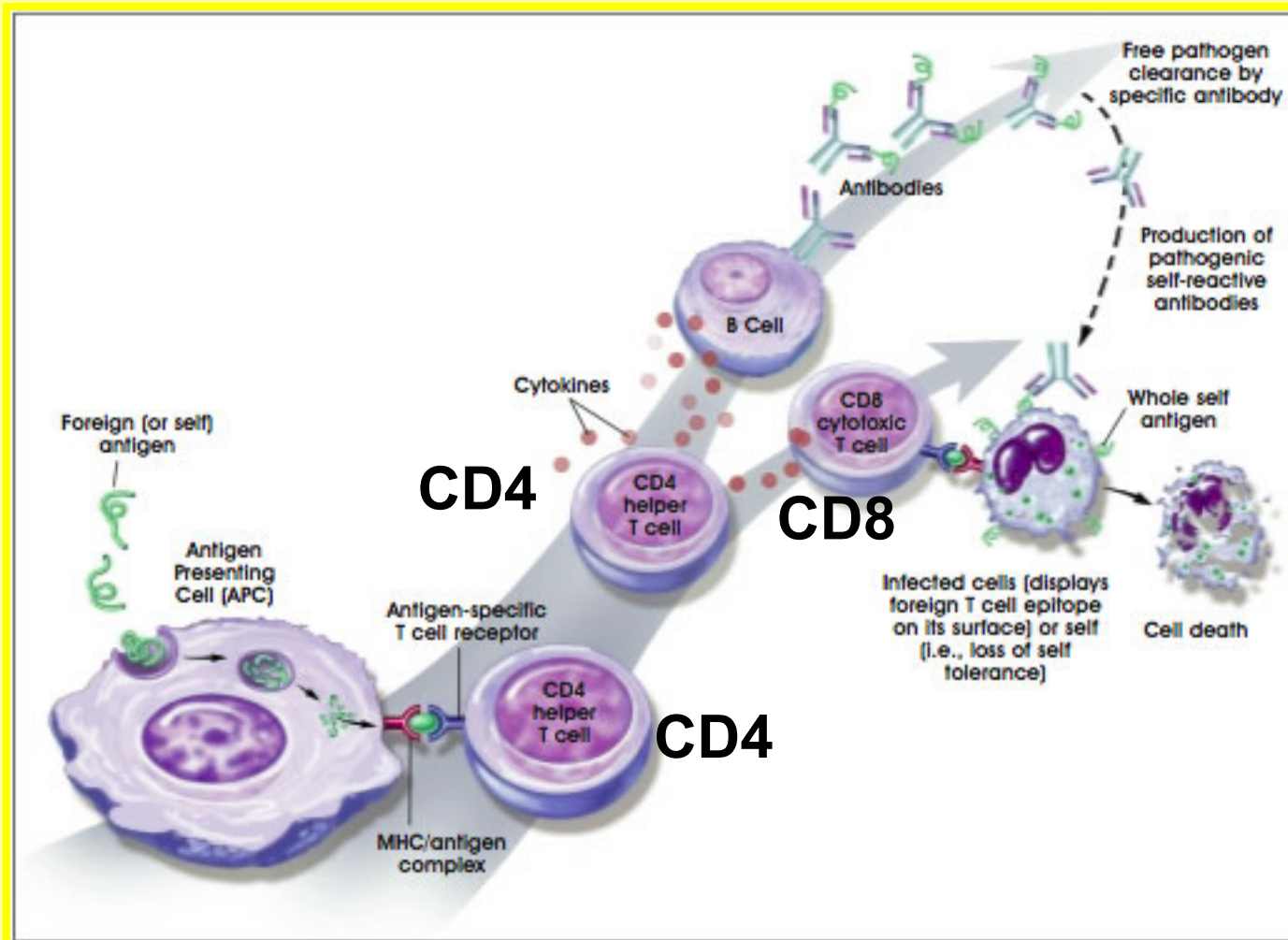
Evolving IBD therapy

Seventies → Nineties

- sulphasalazine
- steroids
- antibiotics
- mesalamine
- budesonide
- antibiotics
- nicotine
- fish oil
- 6 MP
- methotrexate
- nutrition
- probiotics



The immune sequence in IBD



Evolving IBD therapy

Past →

- sulphasalazine
- steroids
- antibiotics

Nineties →

- mesalamine
- budesonide
- antibiotics
- nicotine
- fish oil
- 6 MP
- MTX
- nutrition
- probiotics

Future

- receptor antagonism
- Remicade (biosimilars)
- blocking antibodies
- Humira
- cytokine therapy
- Entyvio
- free radical salvage
- Sterlara
- adhesion molecule
- Xeljanz (tofacitinib)
- antagonism



Drug development Pipeline

- ***Break down gluten using enzymes***
- ***Interrupt the immediate or delayed effect of gluten on the cells lining the intestine***
- ***Induce immune tolerance***
- ***Prevent the enzyme tTG from modifying gluten***
- ***Interrupt the immune reactions***



What it takes



\$\$\$\$\$\$