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University Medical Center Rotterdam



# **BACTERIA AND MUCOSAL INFLAMMATION OF THE GUT: LESSONS FROM *HELICOBACTER PYLORI***

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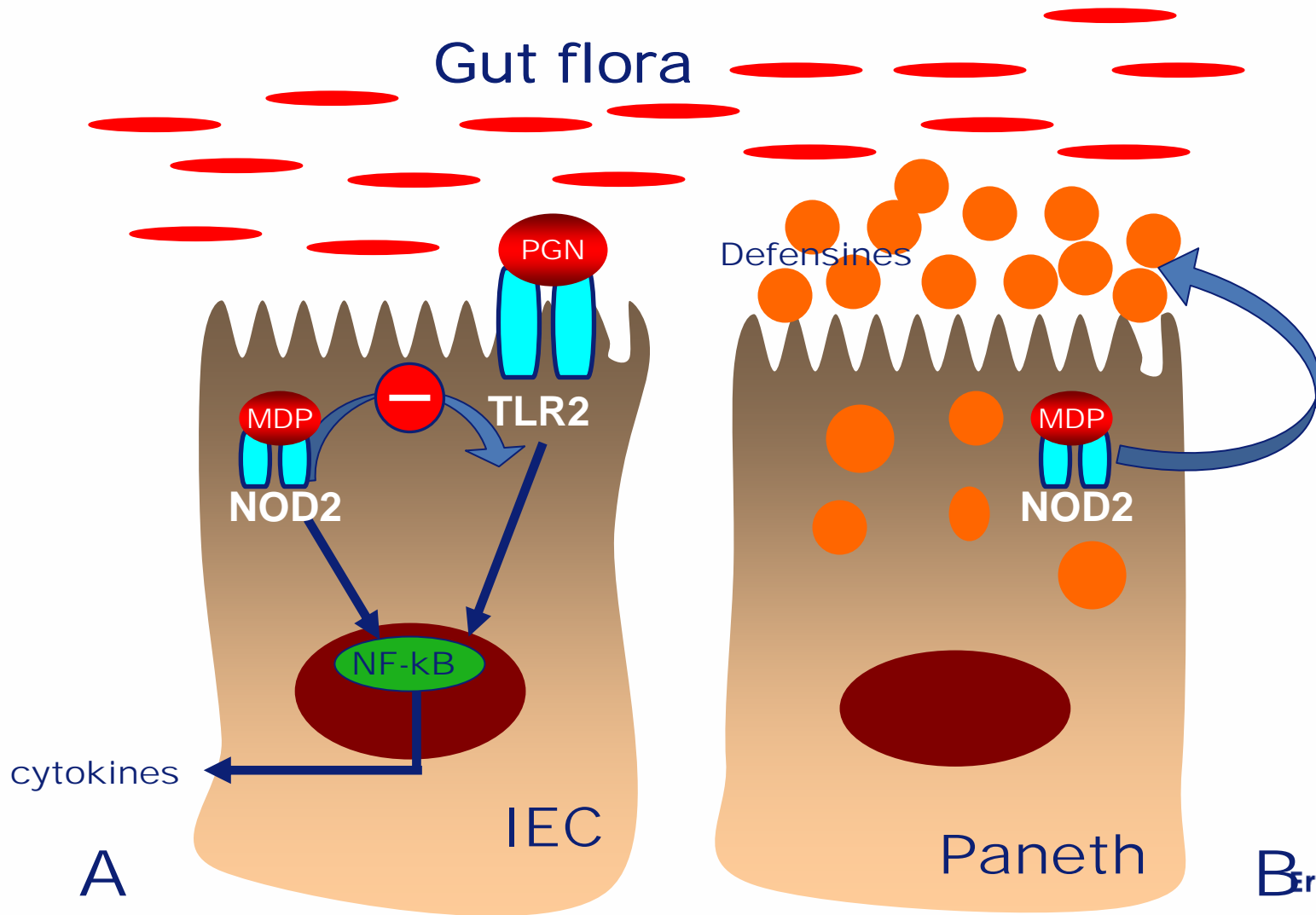
Rotterdam, the Netherlands

# The human gut flora and disease

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- The human gut is colonized by an abundance of bacteria
- This flora is in constant interaction with the epithelial lining usually leading to an intricate balance between tolerance and immunological response
- There is ample evidence that the gut microbiota play a role in health and disease, including chronic inflammatory disorders of the GI tract

# NOD2 in the balance between gut flora and mucosa

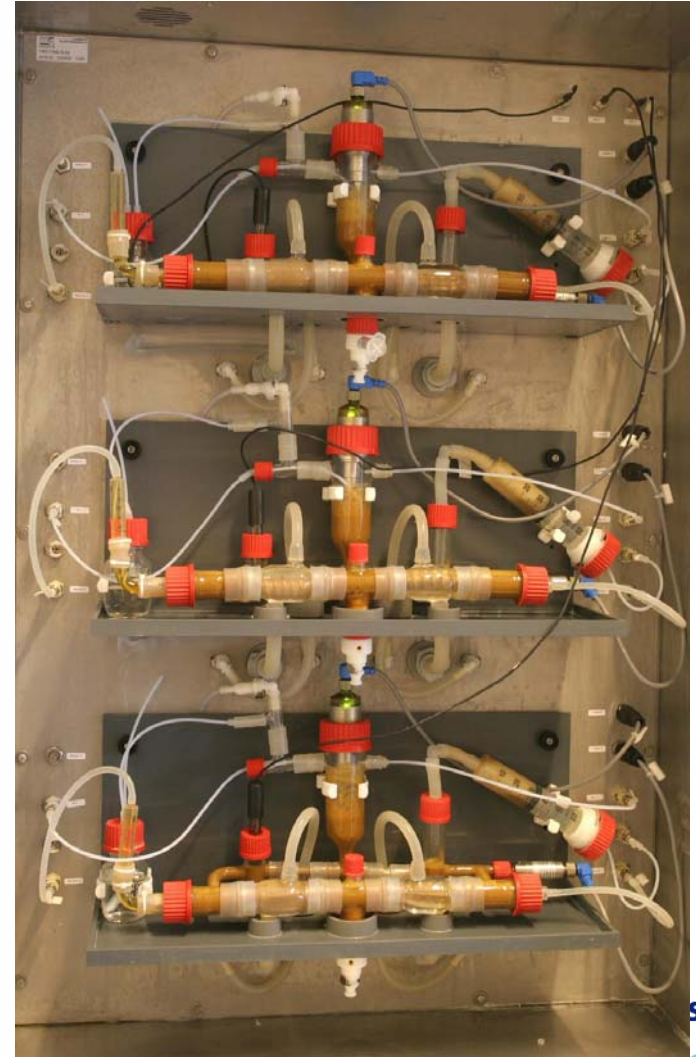
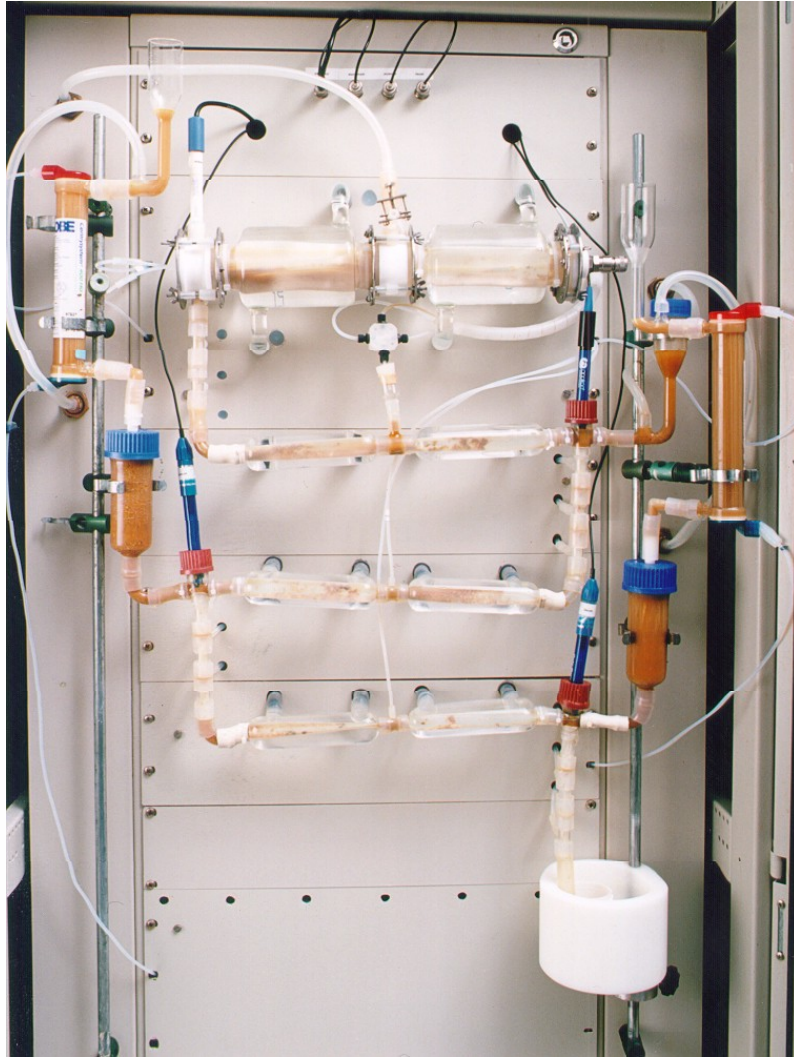


# Limitations in the study of human gut flora and disease

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- Microbiota of the human gut contains over 500 species
- Only 40% of them can be cultured, the study of others require techniques such as denaturing gradient gel electrophoresis (DGGE), fluorescent *in situ* hybridization (FISH), or DNA-arrays (DNA-chips)
- Bacterial populations adherent to the mucosa may differ from those in the faecal stream
- Populations are difficult to obtain
- Disease activity may have an effect on composition and metabolic activity of the gut flora

# Laboratory models for the study of the composition of gut contents



# Metabolic activity in proximal colon of IBD patients and controls as determined in the TIM-model

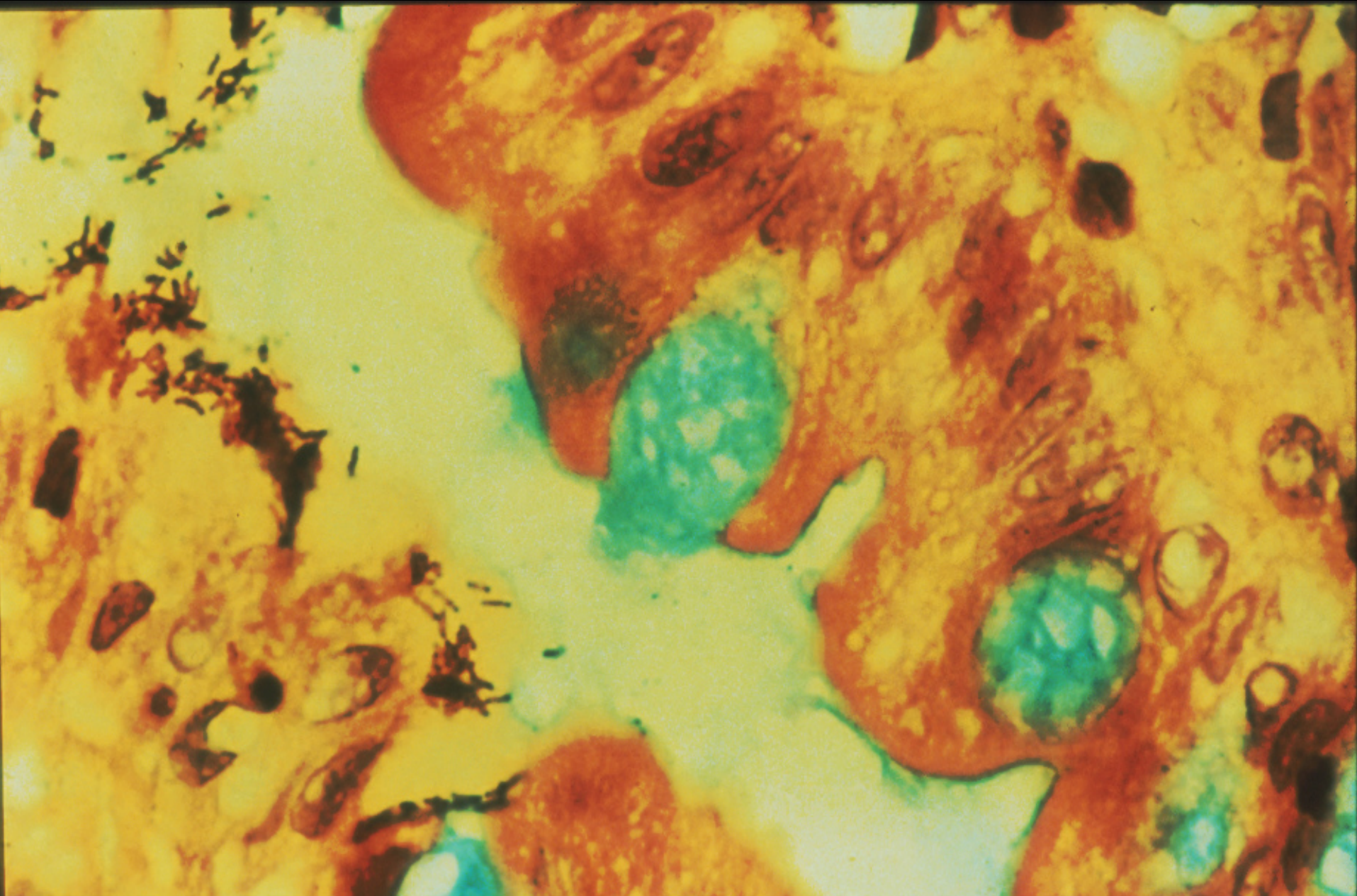
	Crohn's disease	Ulcerative colitis	Healthy controls
SCFA ( $\mu\text{mol/g}$ )	$103 \pm 33^*$	$96 \pm 48^*$	$38 \pm 13$
BCFA ( $\mu\text{mol/g}$ )	$6.0 \pm 1.6$	$5.6 \pm 4.0$	$3.1 \pm 0.6$
Lactate ( $\mu\text{mol/g}$ )	$66 \pm 56^*$	$21 \pm 13$	$13.1 \pm 6.8$
pH	$6.2 \pm 0.5$	$6.4 \pm 0.5$	$6.3 \pm 0.3$

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\*  $p < 0.05$  in comparison with controls

van Nuenen et al. Dig Dis Sci 2004



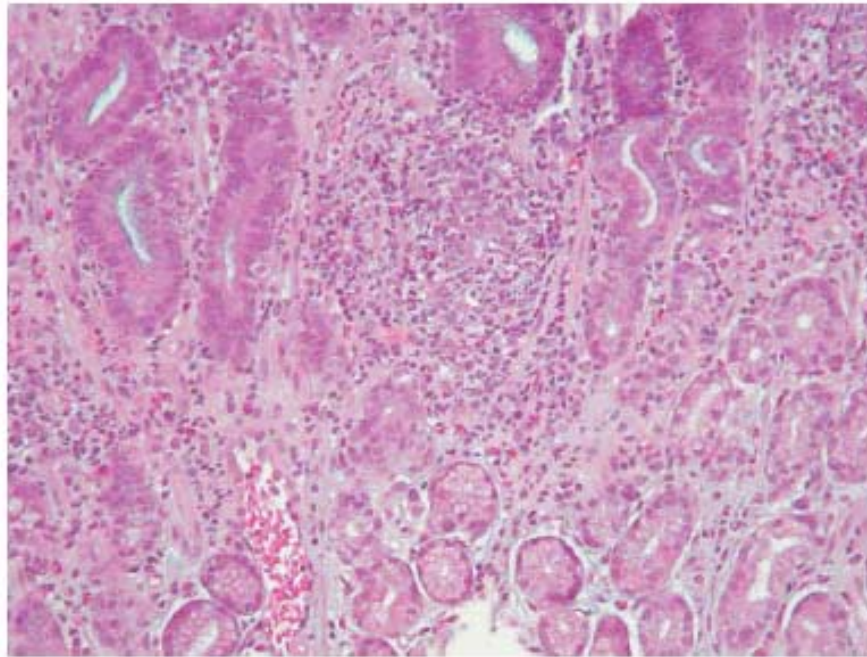
# *Helicobacter* gastritis as a model for inflammation-associated cancer development

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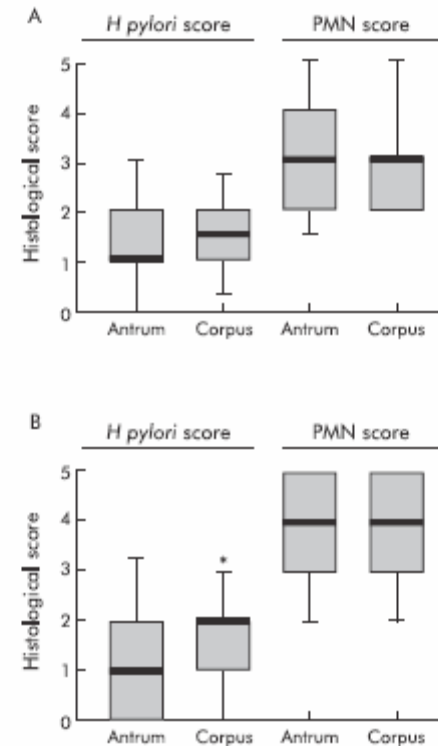
## Pro

- Colonization with *H. pylori*
  - is very common
  - is easily diagnosed
  - is (in adults) a stable condition
  - is always associated with chronic gastritis
  - is easily sampled
  - can be manipulated

# A human challenge model for *H. pylori* infection



**Figure 2** Two weeks post therapy. Typical *Helicobacter pylori* associated acute and chronic inflammation was observed two weeks after acquiring infection.



**Figure 6** Box plots showing *Helicobacter pylori* density and polymorphonuclear (PMN) cell infiltrate scores for (A) study A, with biopsies at 14 days, and (B) study B, with biopsies at 30 days. The bold line represents the median value (50th percentile); shaded areas mark the 25th and 75th percentile points; and the two small horizontal lines show the 10th and 90th percentiles.

# *Helicobacter* gastritis as a model for inflammation-associated cancer development

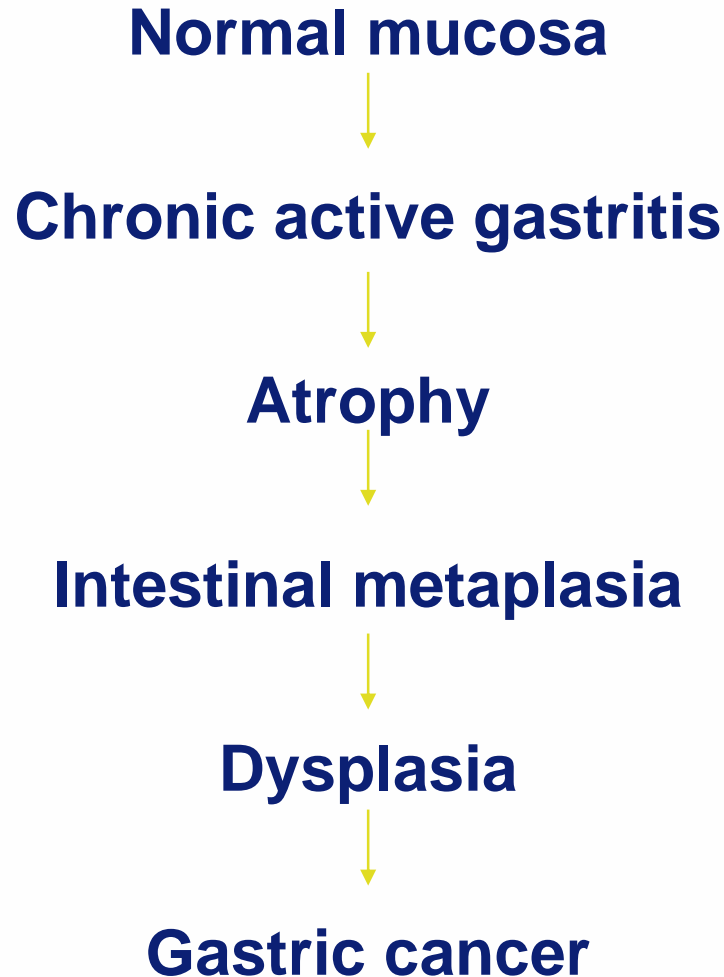
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## Con

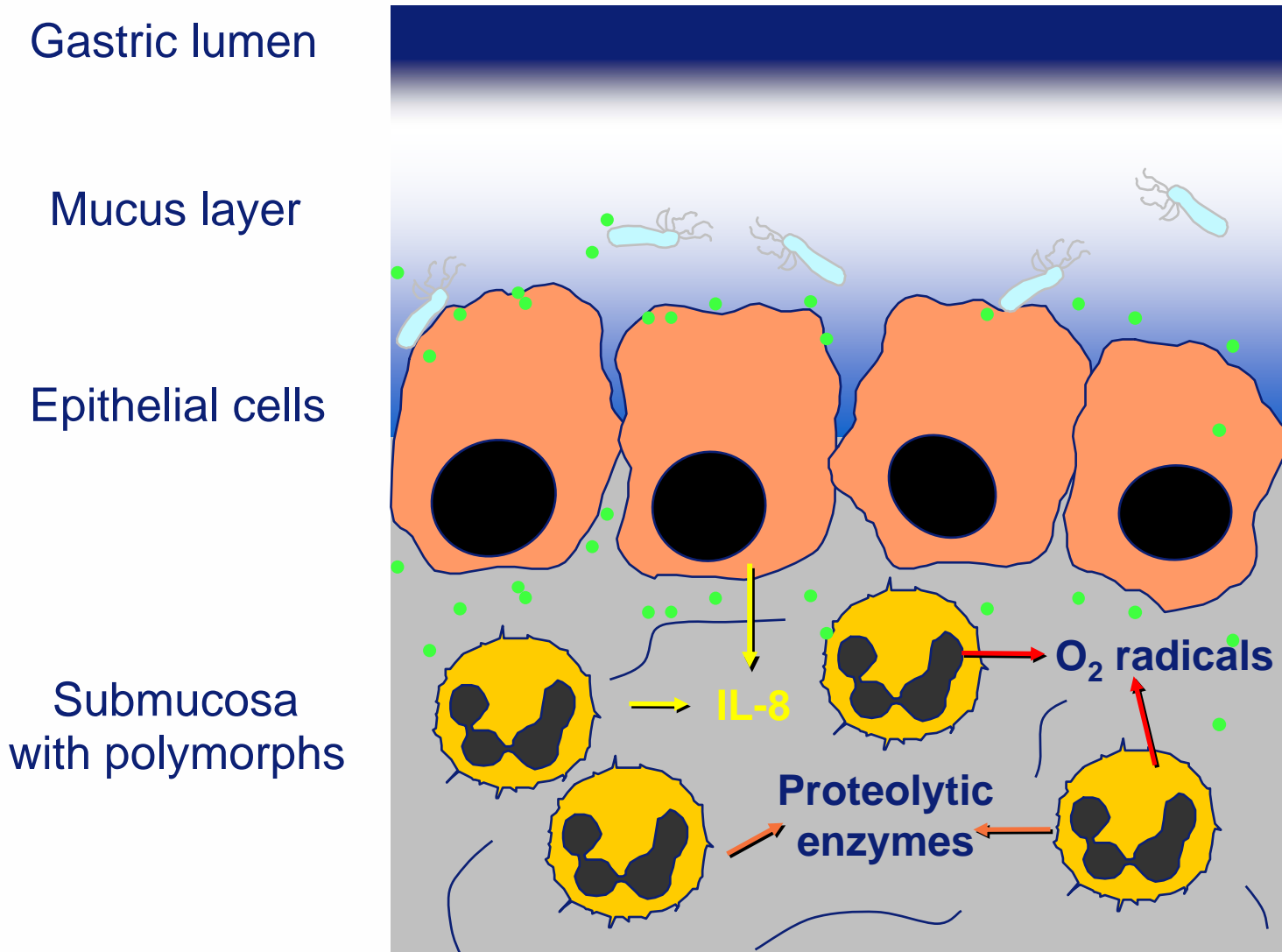
- Premalignant conditions of gastric cancer
  - are incompletely understood
  - may be unevenly distributed in the stomach
  - are only weakly associated with cancer development
  - are subject to observer bias

# Multi-step development of intestinal type gastric cancer

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# Colonization with *Helicobacter pylori* and the development of chronic gastritis



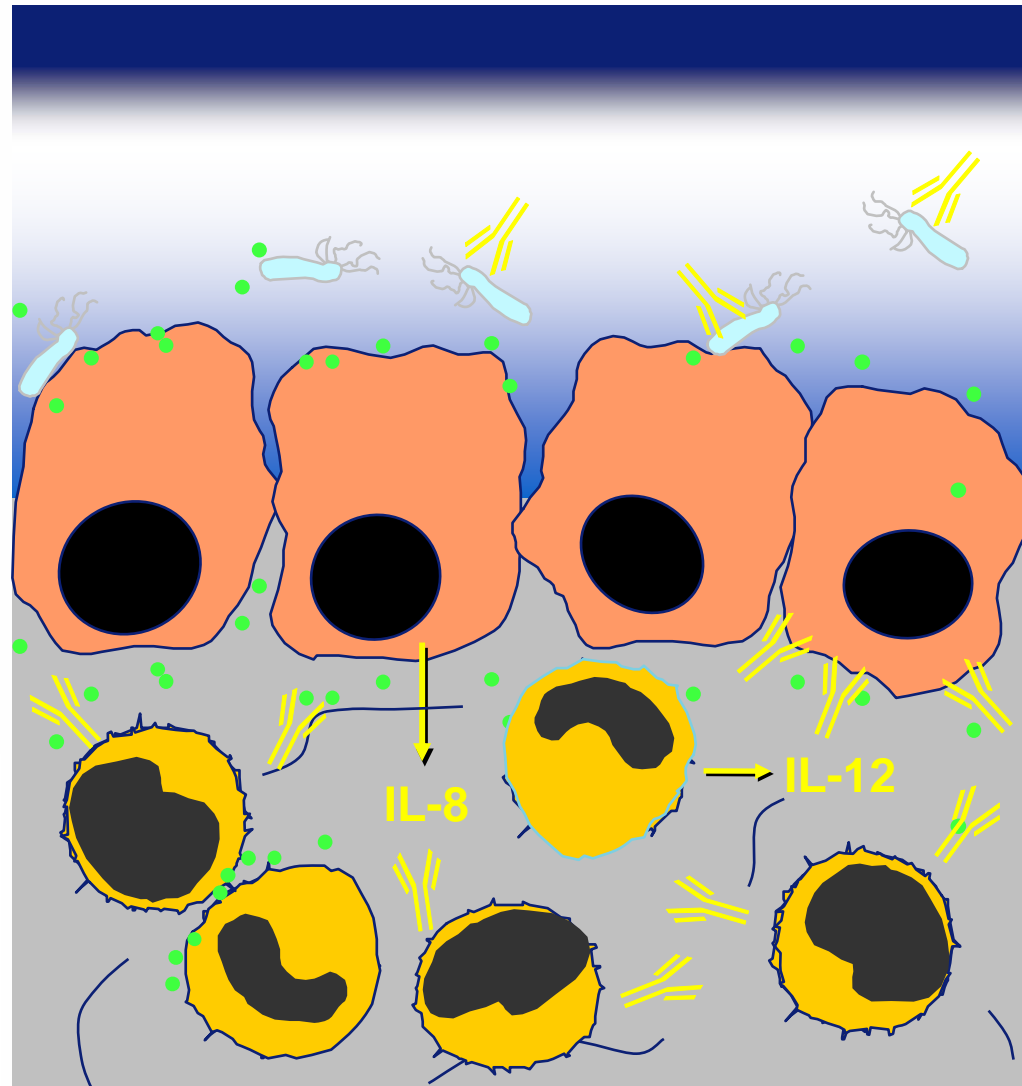
# Colonization with *Helicobacter pylori* and the development of chronic gastritis

Gastric lumen

Mucus layer

Epithelial cells

Submucosa  
with  
monocytes  
and  
lymphocytes



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# Association between *H. pylori* and non-cardia gastric cancer by histologic type: analysis of 7 nested case-control studies

Histologic type	<u>Cases</u>		<u>Controls</u>		Matched OR	95% CI
	Total	%	Total	%		
	<i>H. pylori</i> +		<i>H. pylori</i> -			
Intestinal	241	90.5	700	65.4	4.45	2.74-7.24
Diffuse	114	90.4	353	69.1	3.39	1.70-6.76

*Gut* 2001;49:347-353

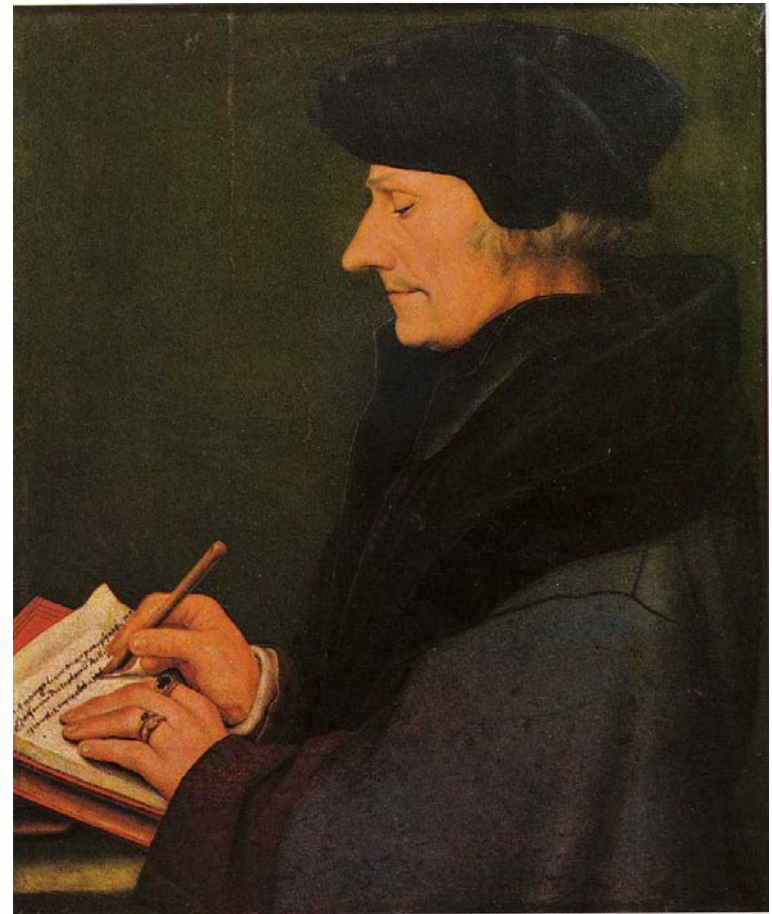
# Bacteria and mucosal inflammation; lessons from *Helicobacter pylori*

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1/ The level of mucosal inflammation in response to bacterial colonization is influenced by

- Bacterial factors
- Host response

2/ The level of inflammation may affect bacterial characteristics

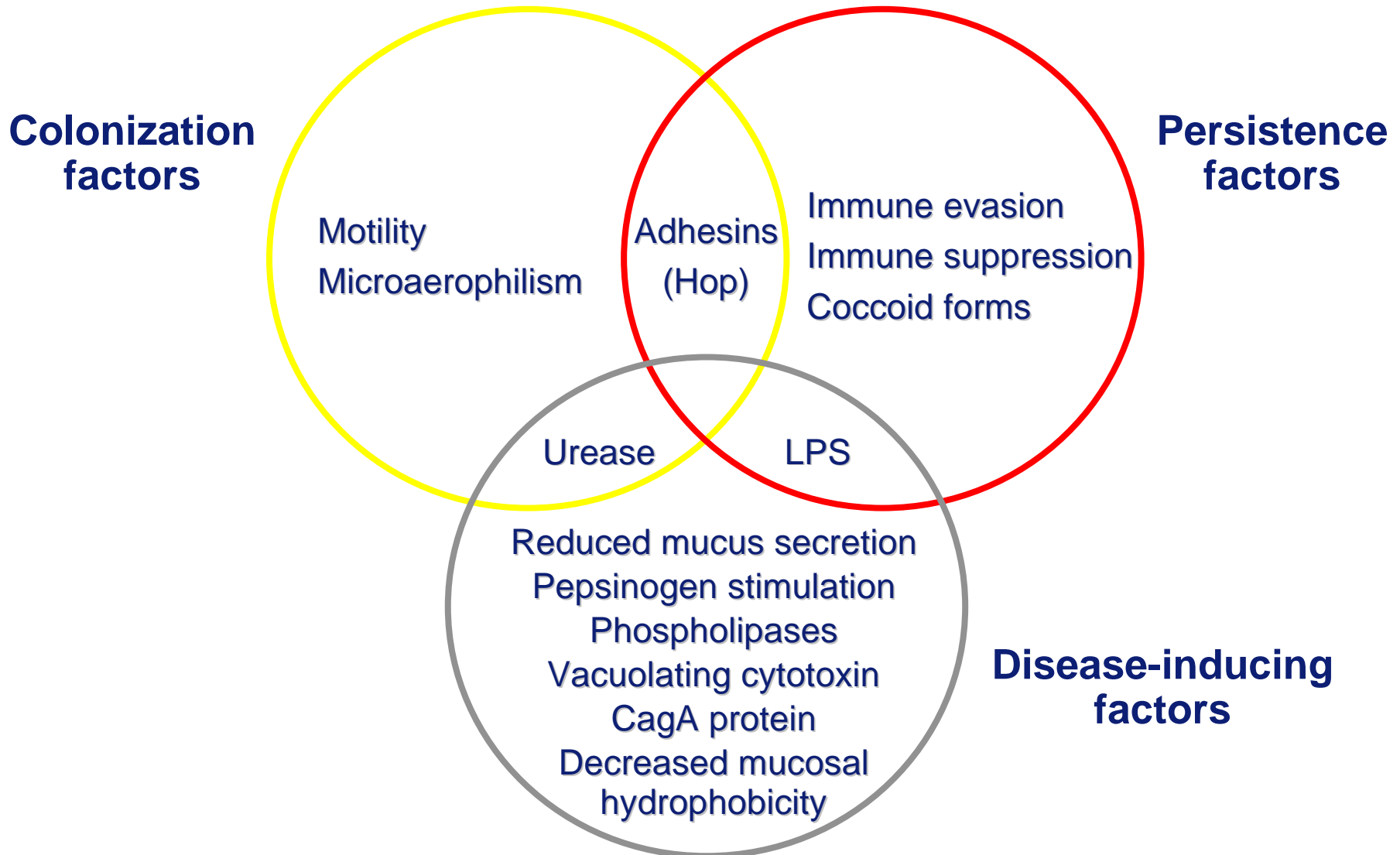


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The logo for Erasmus MC, featuring a stylized, handwritten signature of the name "Erasmus" in blue.

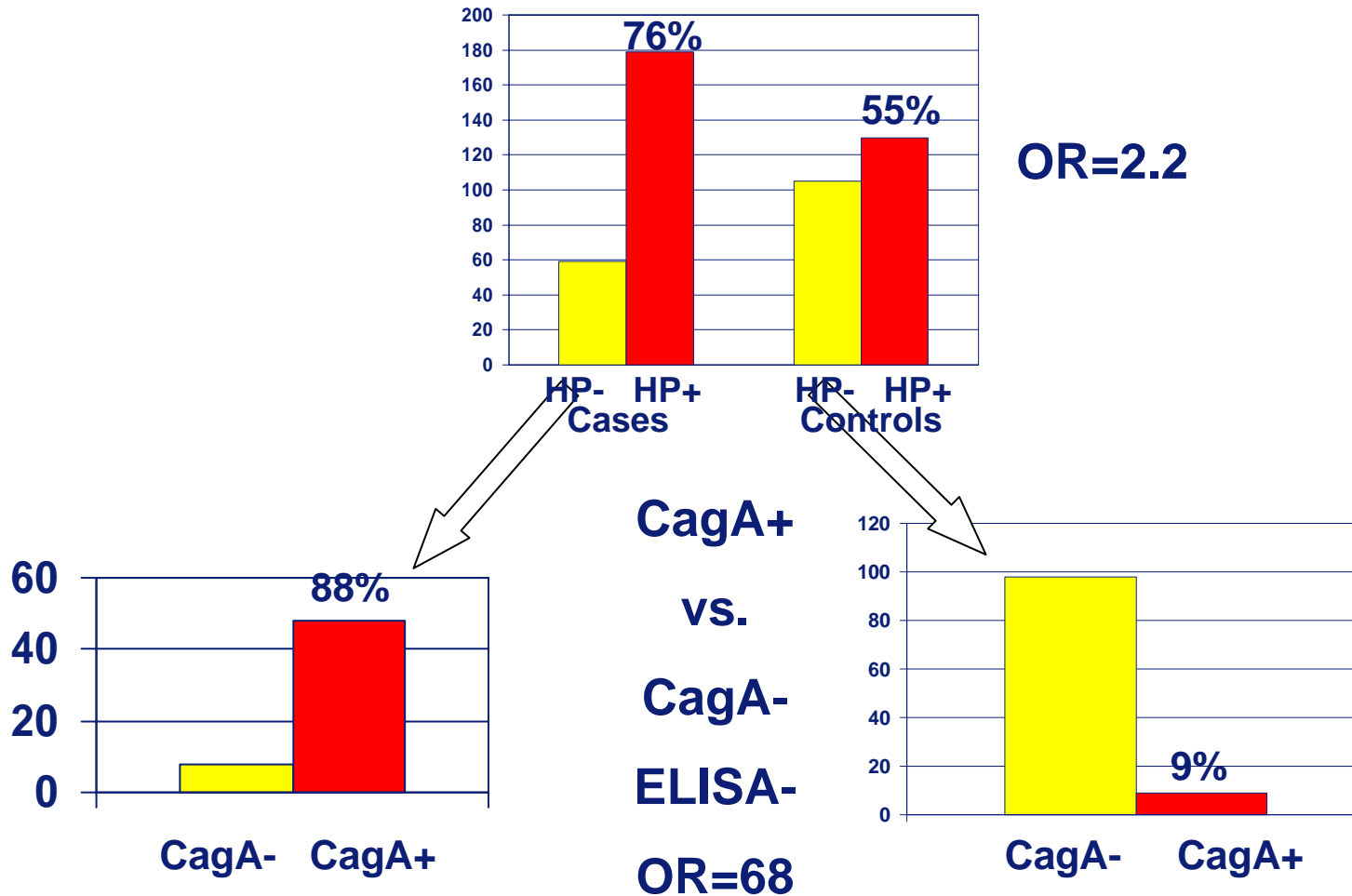
# Bacterial factors contributing to epithelial damage

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# Population-based case-control study of gastric cancer in Sweden

- 298 gastric cancer patients, 244 population-based controls



# Relation between vacA s and m region genotypes and gastric cancer

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		Odds ratio (95% CI)
<b>VacA s region</b>	s2	1 (referent)
	s1	17 (7.8 to 38)
<b>VacA m region</b>	m2	1 (referent)
	m1	6.7 (3.6 to 12)

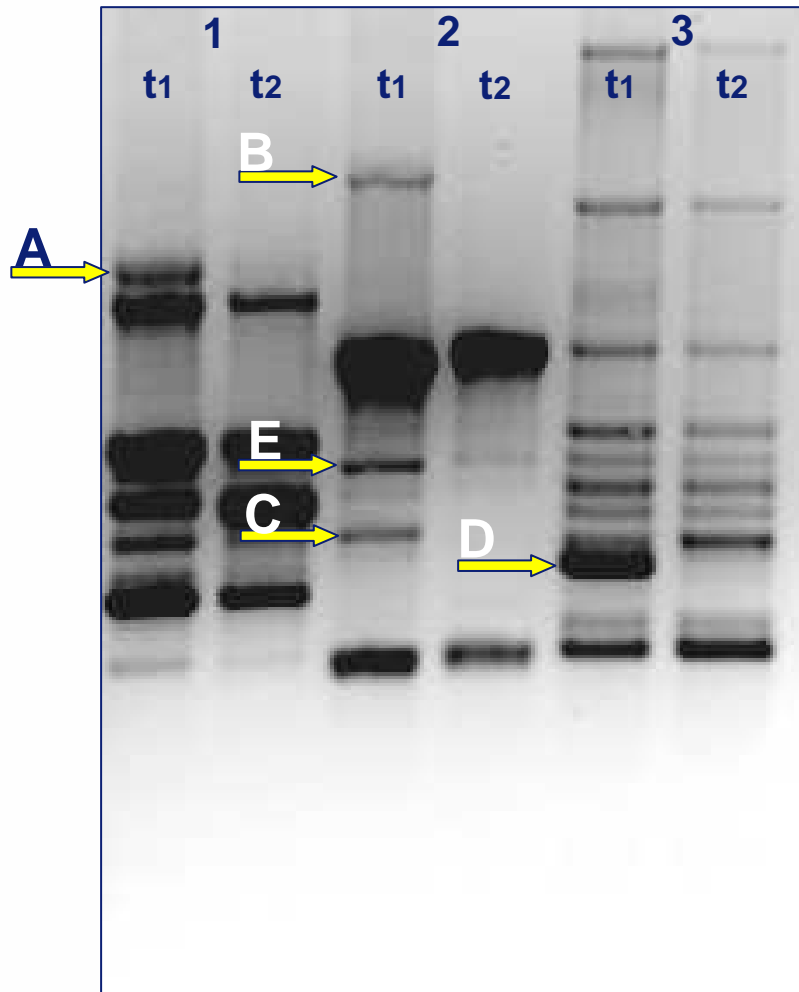
## Other polymorphic virulence genes possibly linked to increased carcinogenicity

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- *BabA2* (Gerhard *et al*, 1999)
- *iceA1* (Kidd, 2001 and Koehler, 2003)
- *oipA* (Yamaoka *et al*, 2000) – IL-8 induction
- Gene coding for HP-MP1 (Suganuma, 2001)
- *JHP947* (Santos *et al*, 2003)

# Clonal variation and persistence in *Helicobacter pylori*

primer d11344



Hypotheses:

- Clonal variation results of:
  - Gradual evolution over time
  - Rapid evolution during initial colonization
  - Polyclonal transmission with evolution of new strain

» The host gets the bacterium he deserves?

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# Multivariate analysis of host pro-inflammatory genotypes and gastric cancer risk

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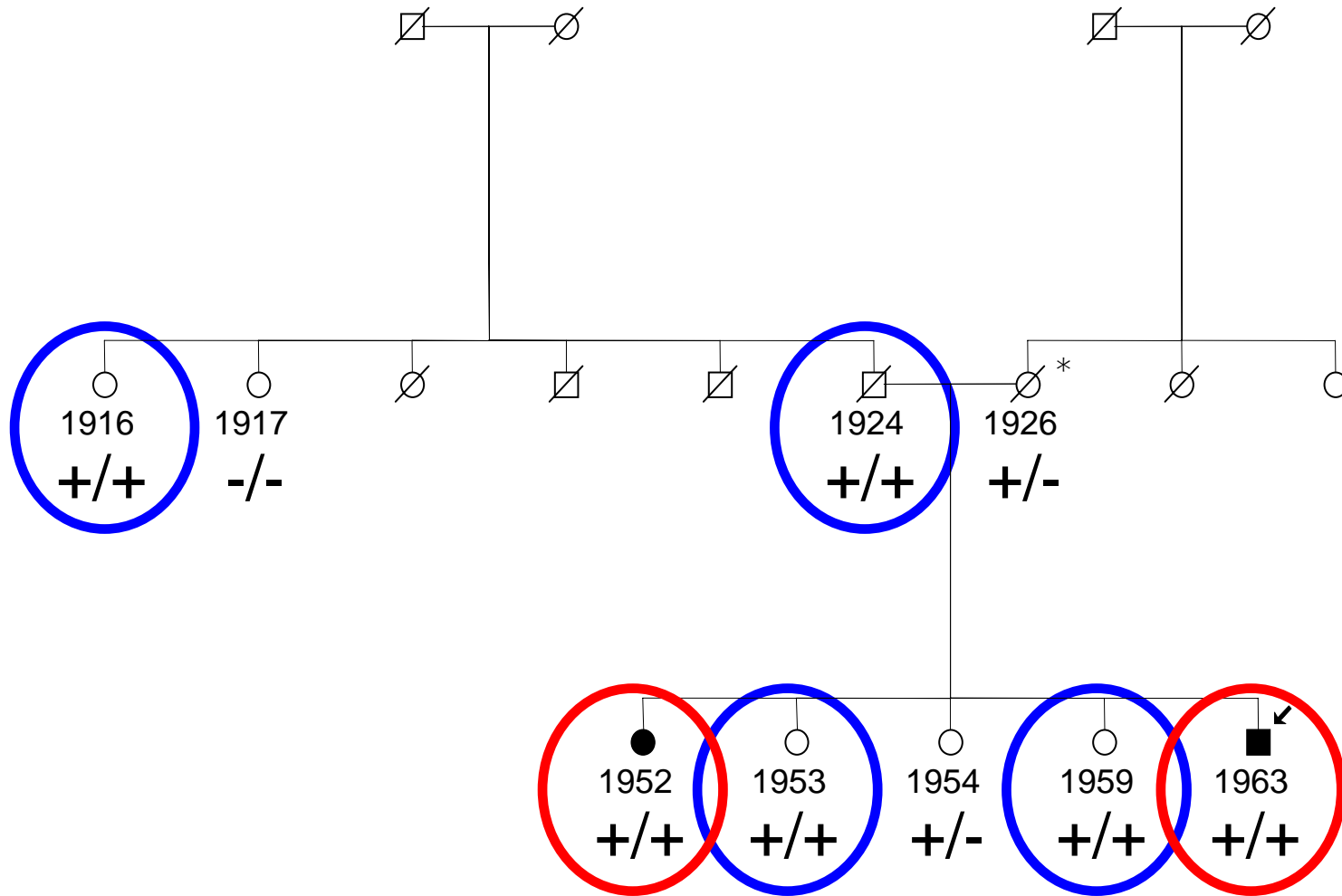
Genotype	Odds ratio (95% CI)
<i>IL-1B-511T+</i>	2.3 (1.4-3.8)
<i>IL-1RN*2*2</i>	3.6 (1.7-7.6)
<i>IL-10 ATA/ATA</i>	2.5 (1.1-5.7)
<i>TNF-A-308A+</i>	2.2 (1.4-3.7)

# Combining more than one proinflammatory polymorphisms further increases gastric cancer risk

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Polymorphisms	Cases	Controls	OR (95% CI)
0	22	75	1 (referent)
1	74	85	2.8 (1.6-5.1)
2	62	46	5.4 (2.7-10.6)
3	28	4	26.3 (7.1-97)
4	2	0	∞ (indefinite)

# NOD2-mutations and the risk for Crohn's disease



# Bacteria and gut mucosa; lessons from *H. pylori*; effects of bacteria – mucosa interaction may be two-sided

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- *H. pylori* colonization has been claimed to reduce the risk for diarrhea in children
- *H. pylori* gastritis has been negatively associated with GERD and its sequelae

# Conclusions

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- *H. pylori* gastritis serves as an excellent model for bacteria and mucosal inflammation of the gut
- This is due to a variety of epidemiological, histological and bacterial factors
- The risk for disease depends on bacterium and host
- Animal and human challenge models will further increase our knowledge on mucosa – gut flora interaction and outcome of disease

# Macrophage extending pseudopodium towards bacteria

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