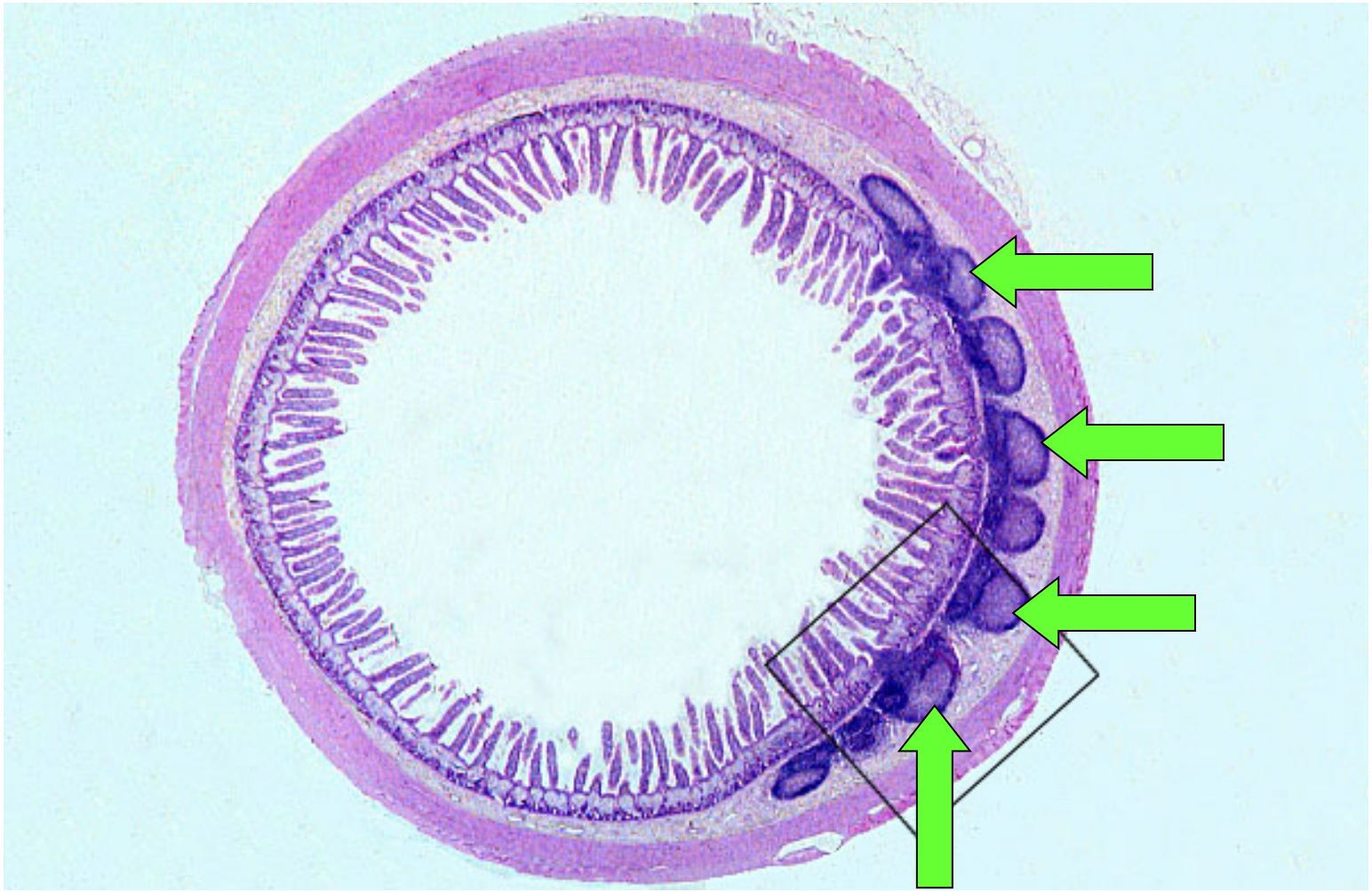
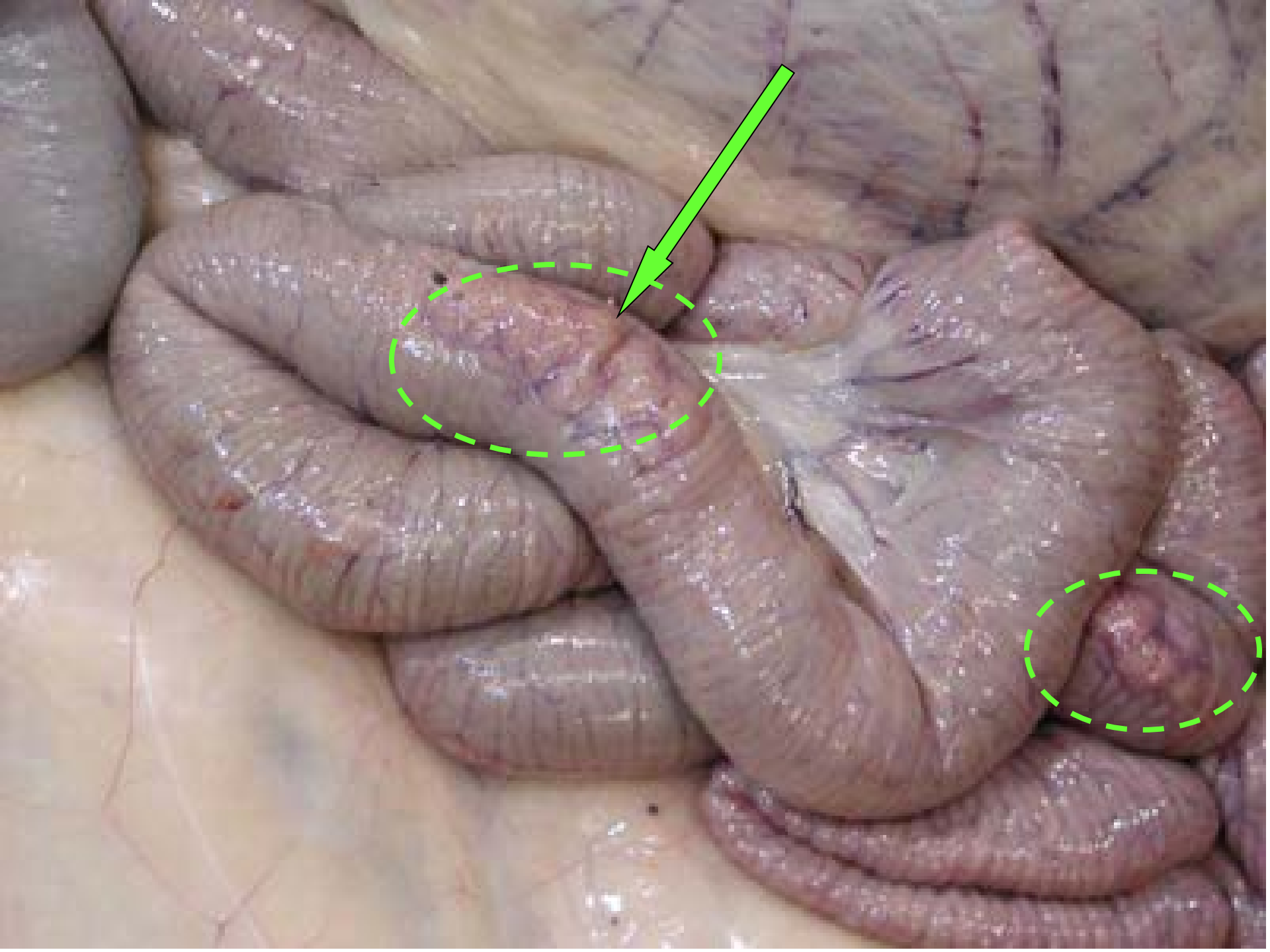
Microbiome and shaping of the Immune Response

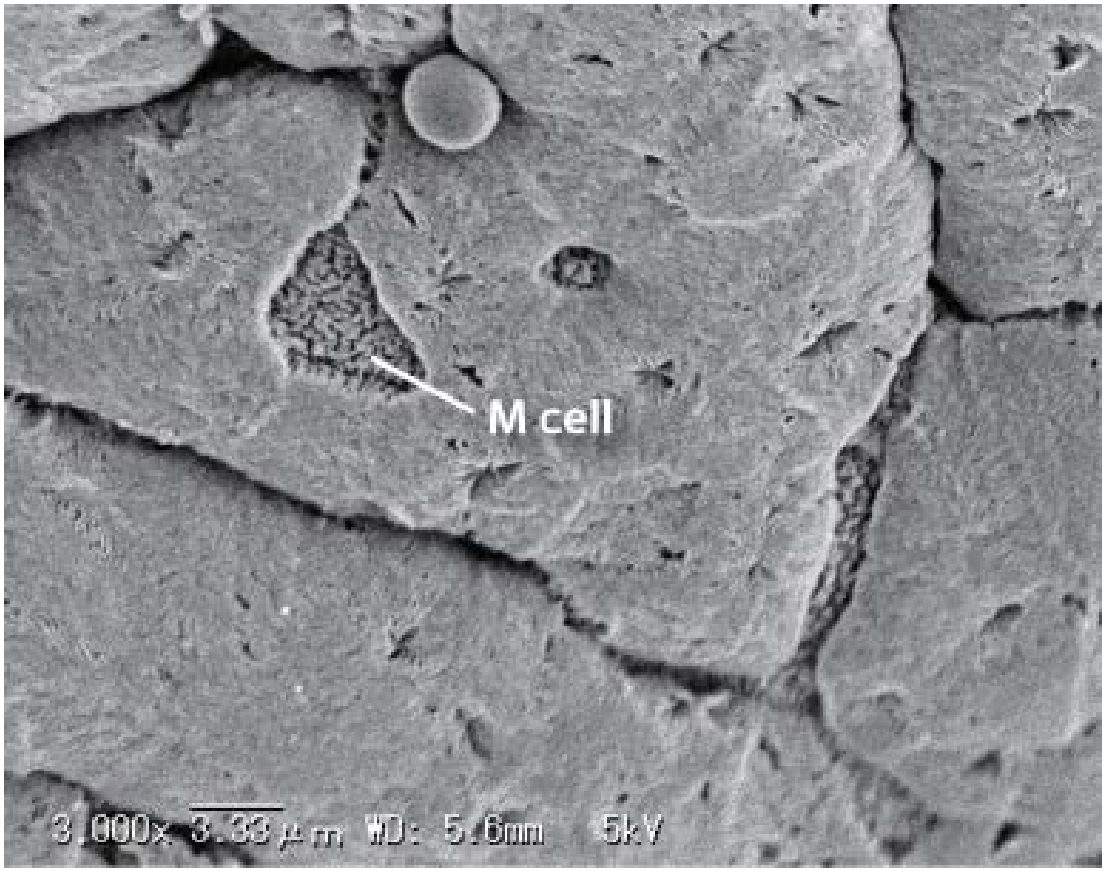
Jan 31, 2017

Identify the lymphoid organ indicated by the green arrows.





M cell (microfold cell) in the surface of the Peyer's patch is the cell specialized to uptake Ag from the gut



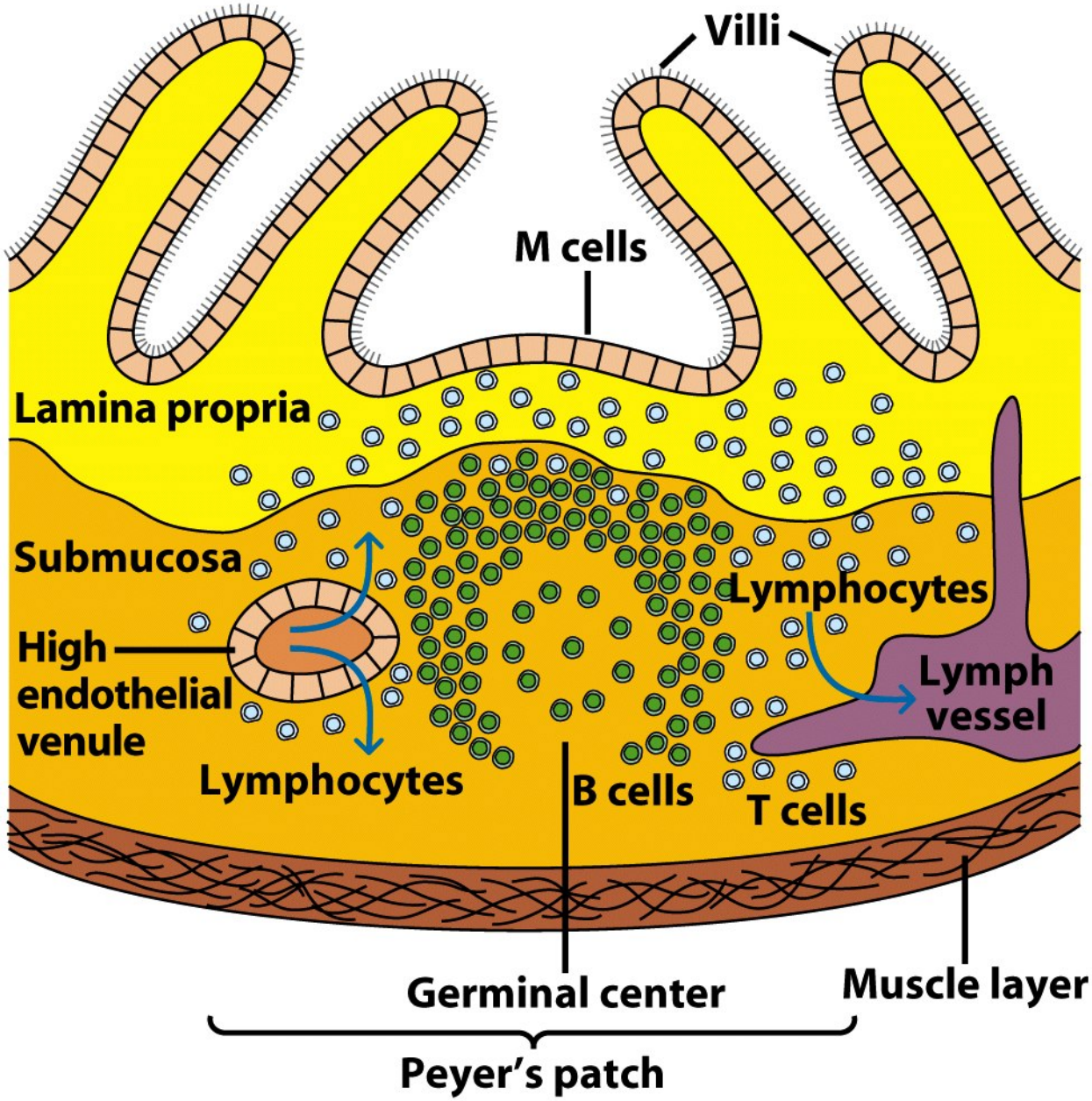


Figure 2-18
Kuby IMMUNOLOGY, Sixth Edition

M cells do not have microvilli, but have a flat smooth surface. They have a deep pocket under them containing B cells, T cells and APC's, including DCs. They endocytose Ags from the gut and transport them across the cell to deliver them to the area of the immune cells. Leads to activation of B cells– become plasma cells and release Abs into the gut.

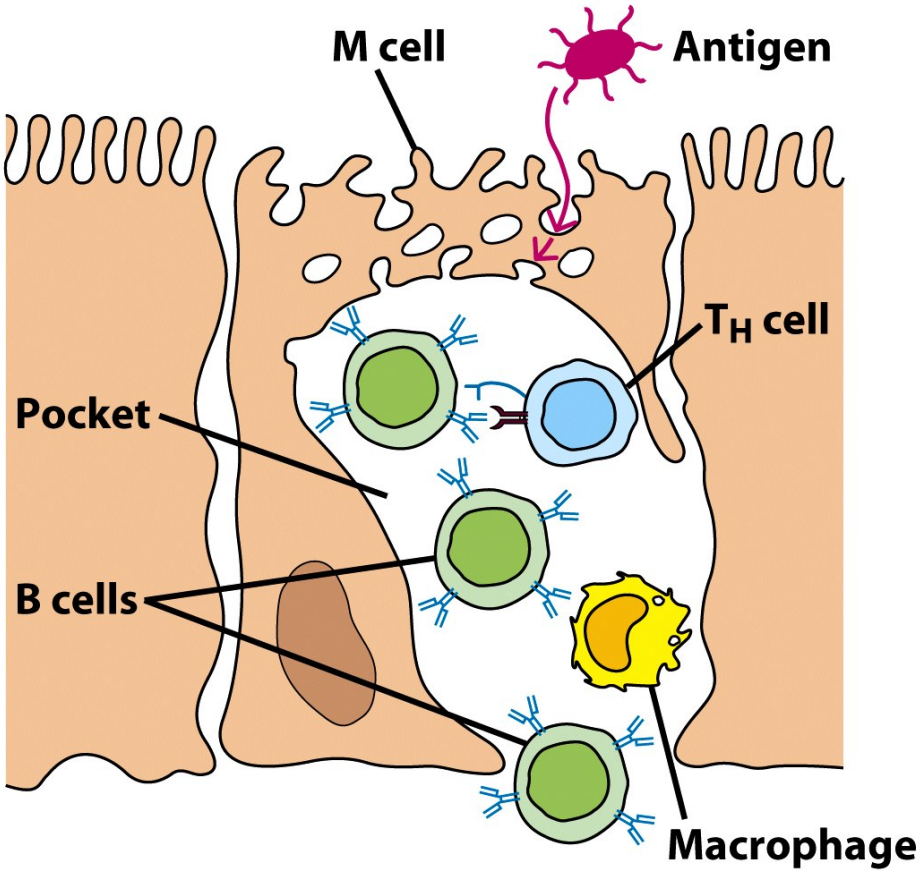


Figure 2-19a
Kuby IMMUNOLOGY, Sixth Edition

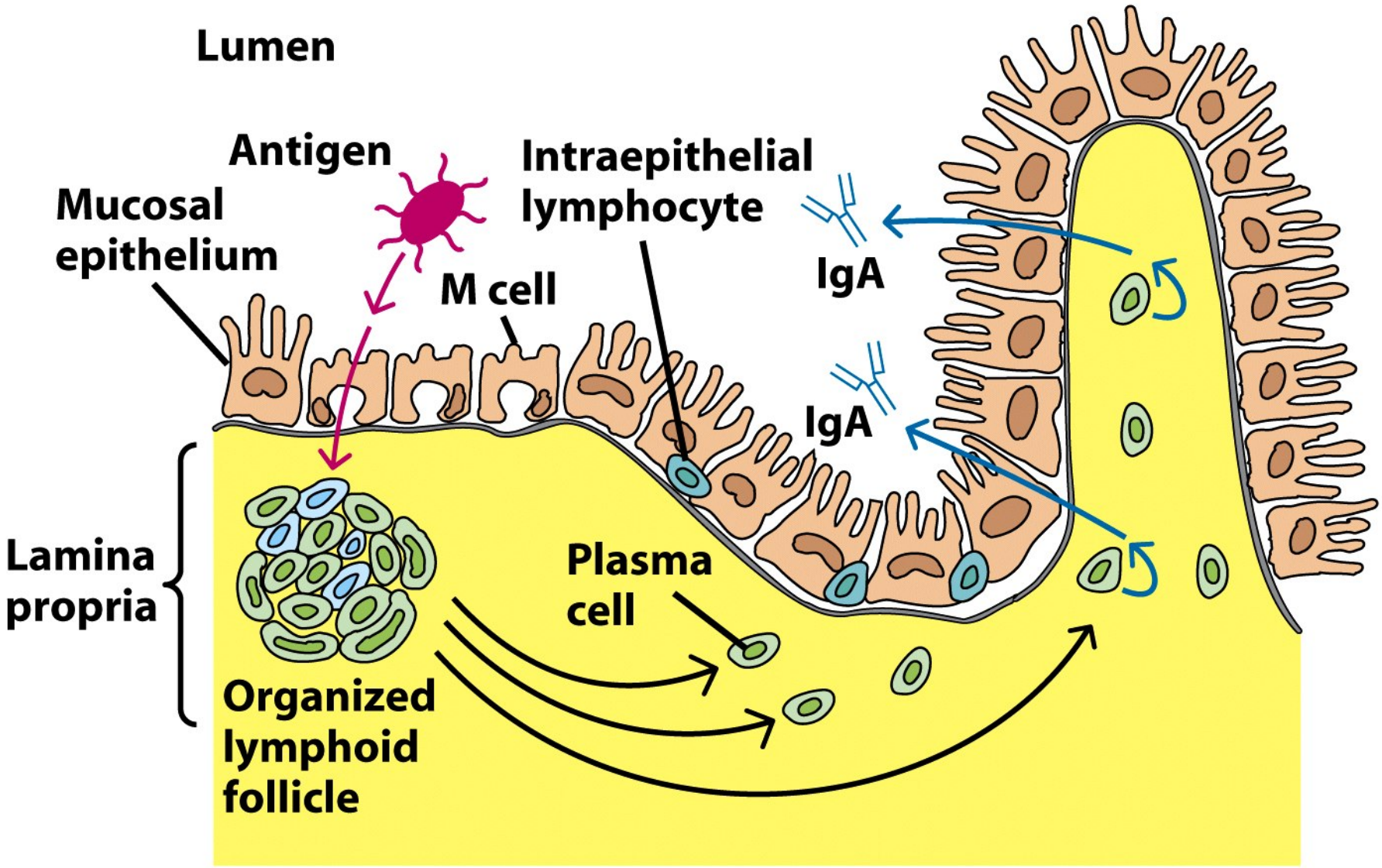
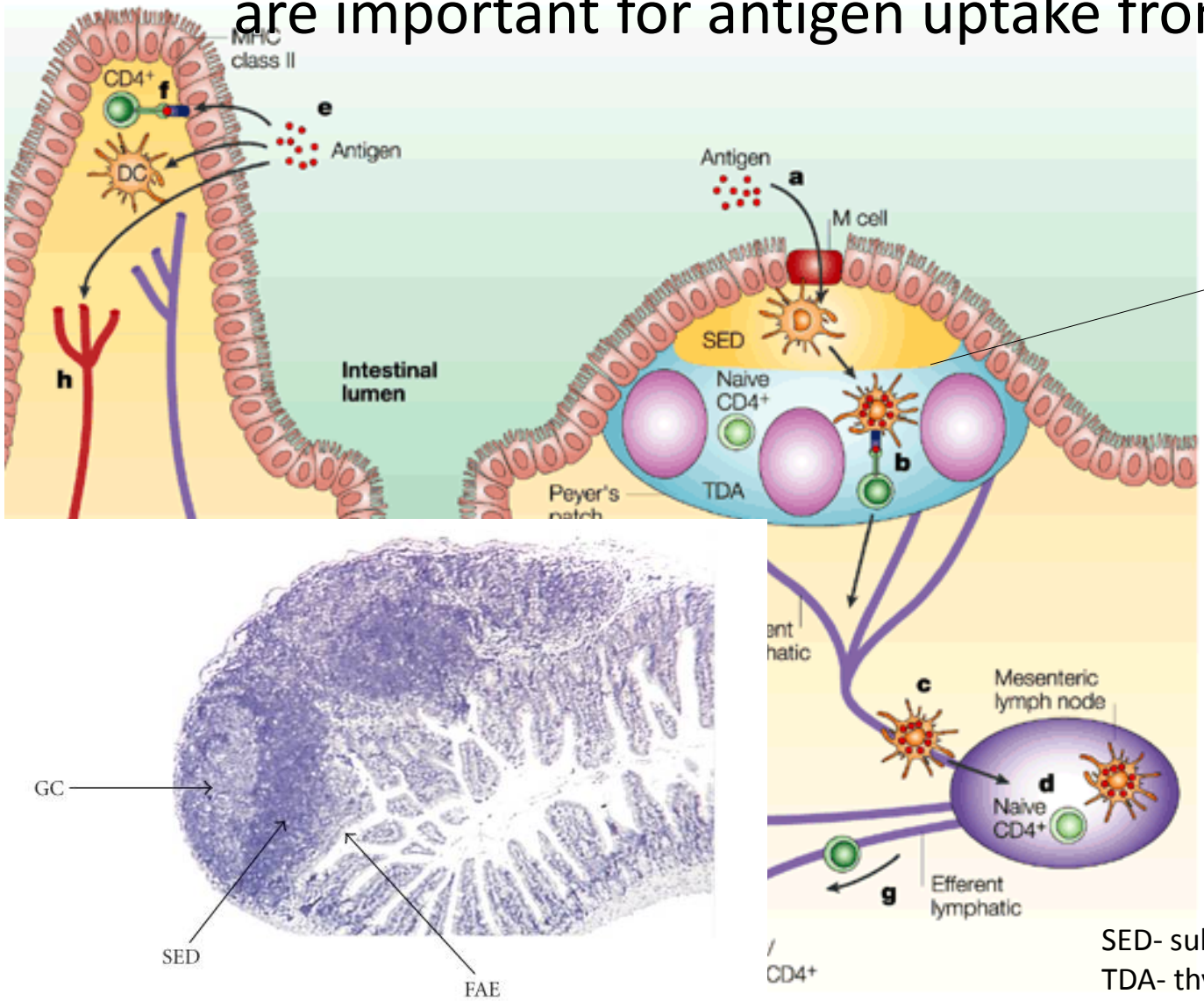


Figure 2-19b
Kuby IMMUNOLOGY, Sixth Edition

M-cells (microfold cells) at the surface of Peyer's patches are important for antigen uptake from gut

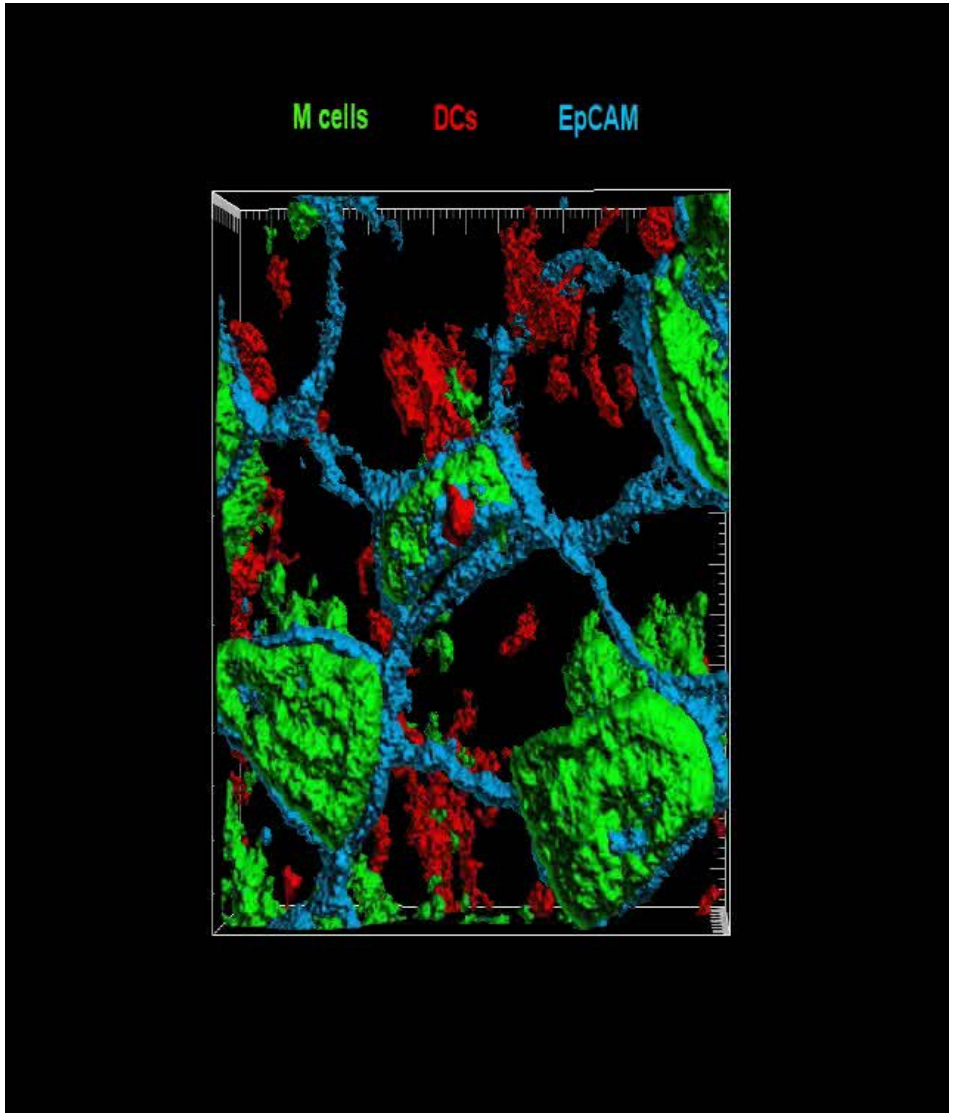


Dome: has dendritic cells

see Fig 1.20 p22 of Janeway

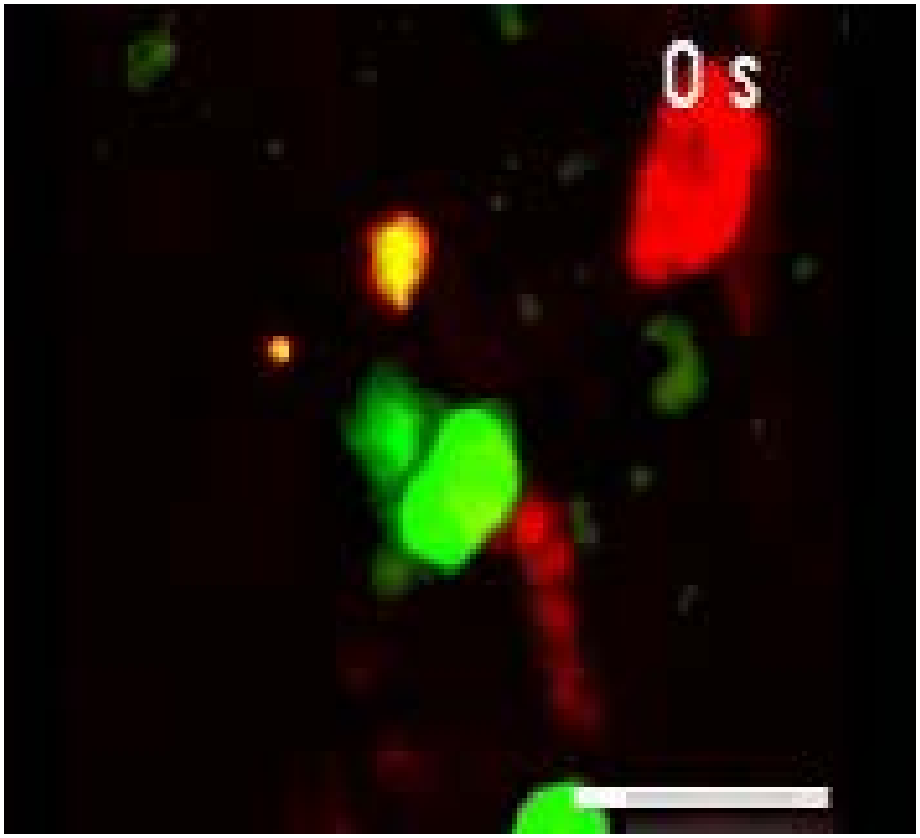
SED- subepith dome
TDA- thymus dependent area

PP DC’s extend processes through M cells to explore lumen



Lelouard et al, Gastroenterology (2012)
DC’s & M cells in Peyer’s patches

PP DC’s extended processes take up microspheres



M-cell= red
DC= green
Microsphere= yellow

~20 min

Lelouard et al, Gastroenterology (2012)
DC’s & M cells in Peyer’s patches

The GI Immune system

- Lamina propria, mesenteric LN, int ep cells
- Assist in immune cell migration and house cells
  - DC process Ags of lumen and tissues, I
  - Neutrophils & mϕ respond to tissue damage & translocated bacteria- orchestrate response
  - B-cell make Abs, IgA
  - When activated- immune cells produce pro-inflammatory cytokines (Il-6, IL-1B, TNFa) and anti-inflammatory mediators (Il-10, Il-4)
- Il 17 and Il-23 are pro-inflammatory mediators of mucosal immune function
- Chemokines- CCL6, CCL14, CCL15 chemotactic for T cells, Neutrophils & mϕ

Cook et al Immunol & Cell Biol 94: 158, 2016

Read:

Peyer's Patch Dendritic Cells Sample antigens by Extending Dendrites through M Cell-Specific Transcellular Pores

Lelouard, Fallet, Bovis, Meresse and Gorvel
Gastroenterology 2011

Role of Gut microbiome

- Prokaryotic bacteria, viruses, yeast and helminthes
- Population affects host immune system and physiology

Bacteria

Described species: 4 000

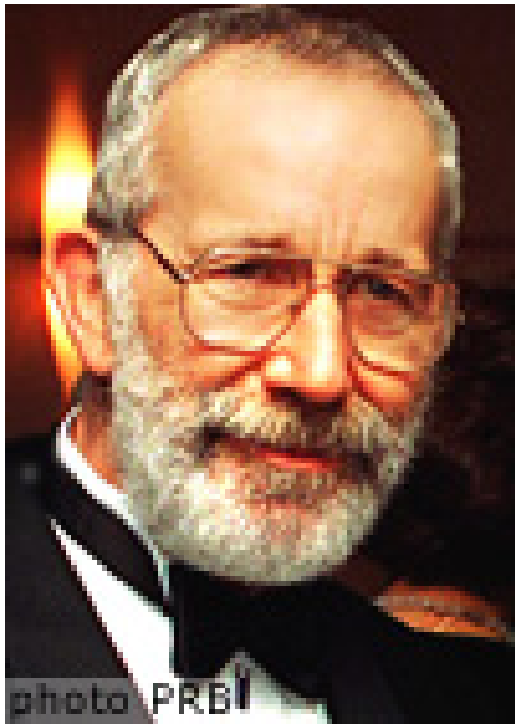
Estimated total species: 1 000 000

The Convention on Biological Diversity
http://www.biodiv.org/convention/default.shtml

The Nobel Prize in Physiology or Medicine 2005

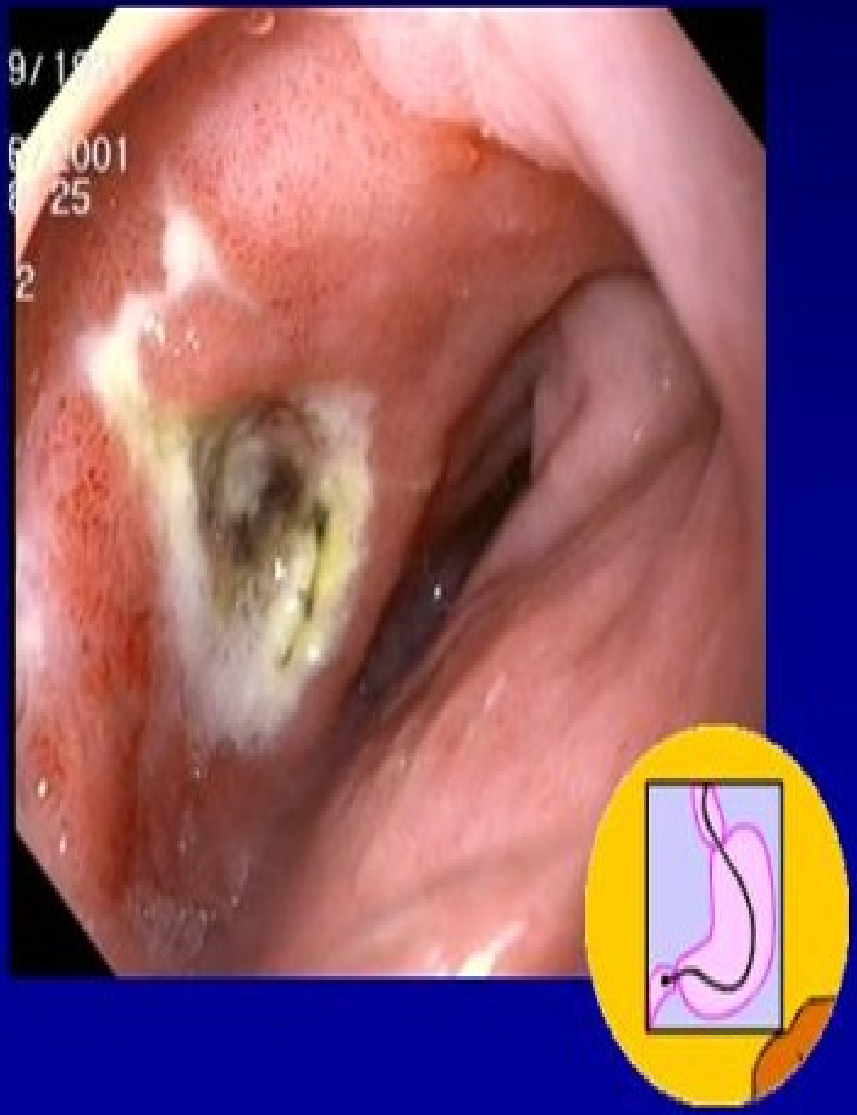
"for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"

Barry J. Marshall
Australia
b. 1951

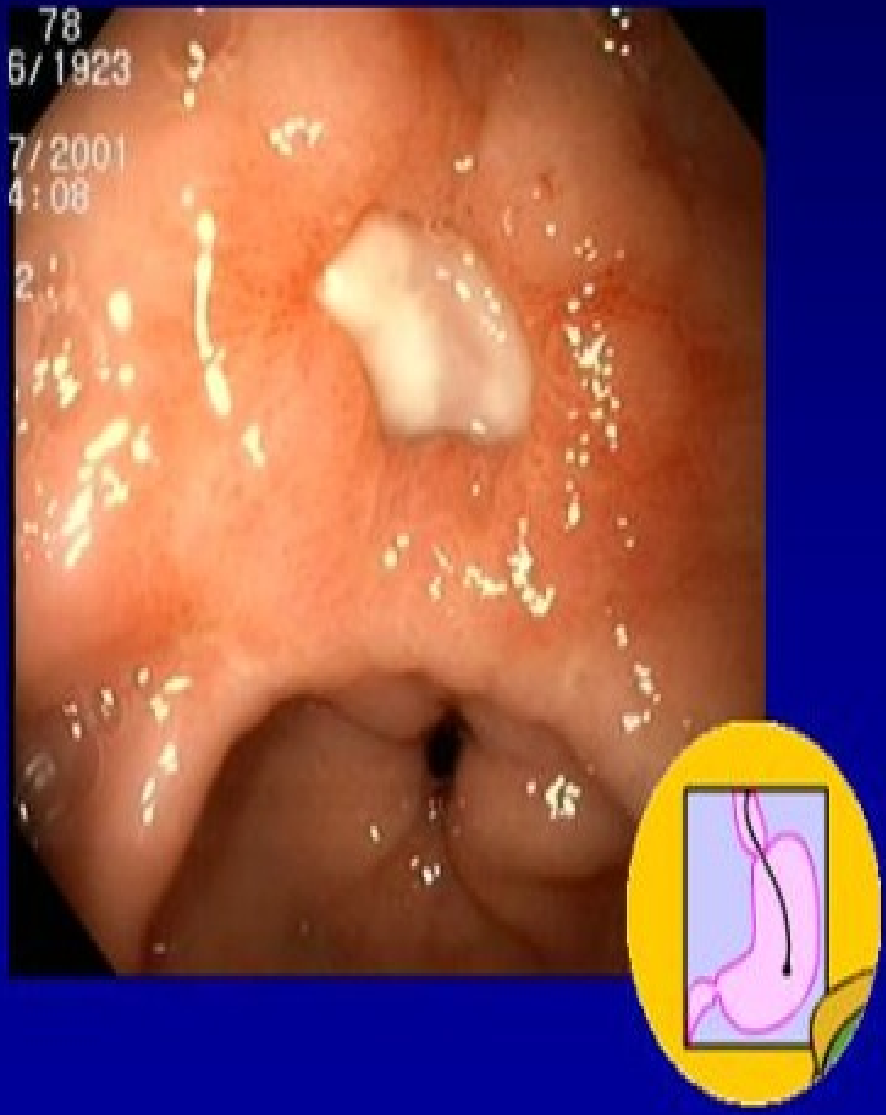


J. Robin Warren
Australia
b. 1937

Duodenal Ulcer (DU)



Gastric Ulcer (GU)



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Prevalence and Incidence of Peptic Ulcer

Prevalance Rate: 1 in 54 or 5 million people in USA

Incidence extrapolations for USA for Peptic Ulcer: 7 per minute

Lifetime risk for Peptic Ulcer: 1 in 10 Americans over lifetime

Probably most common chronic disease of humans. Human populations throughout the world affected. Incidence increases with age and occurs earlier and at increased rates in the developing world and lower socioeconomic groups. Up to 90% of some populations affected.

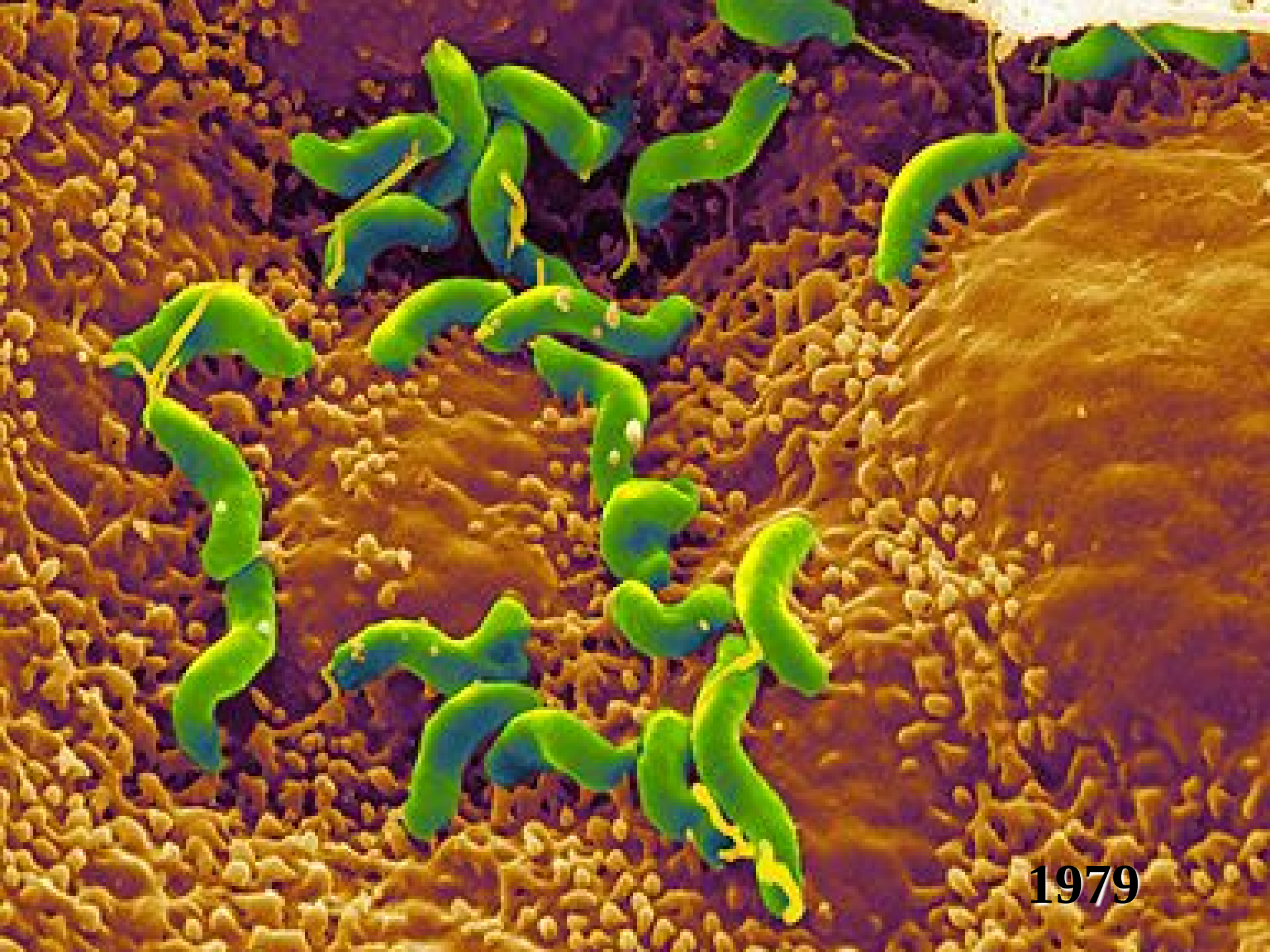
.... en 1987!

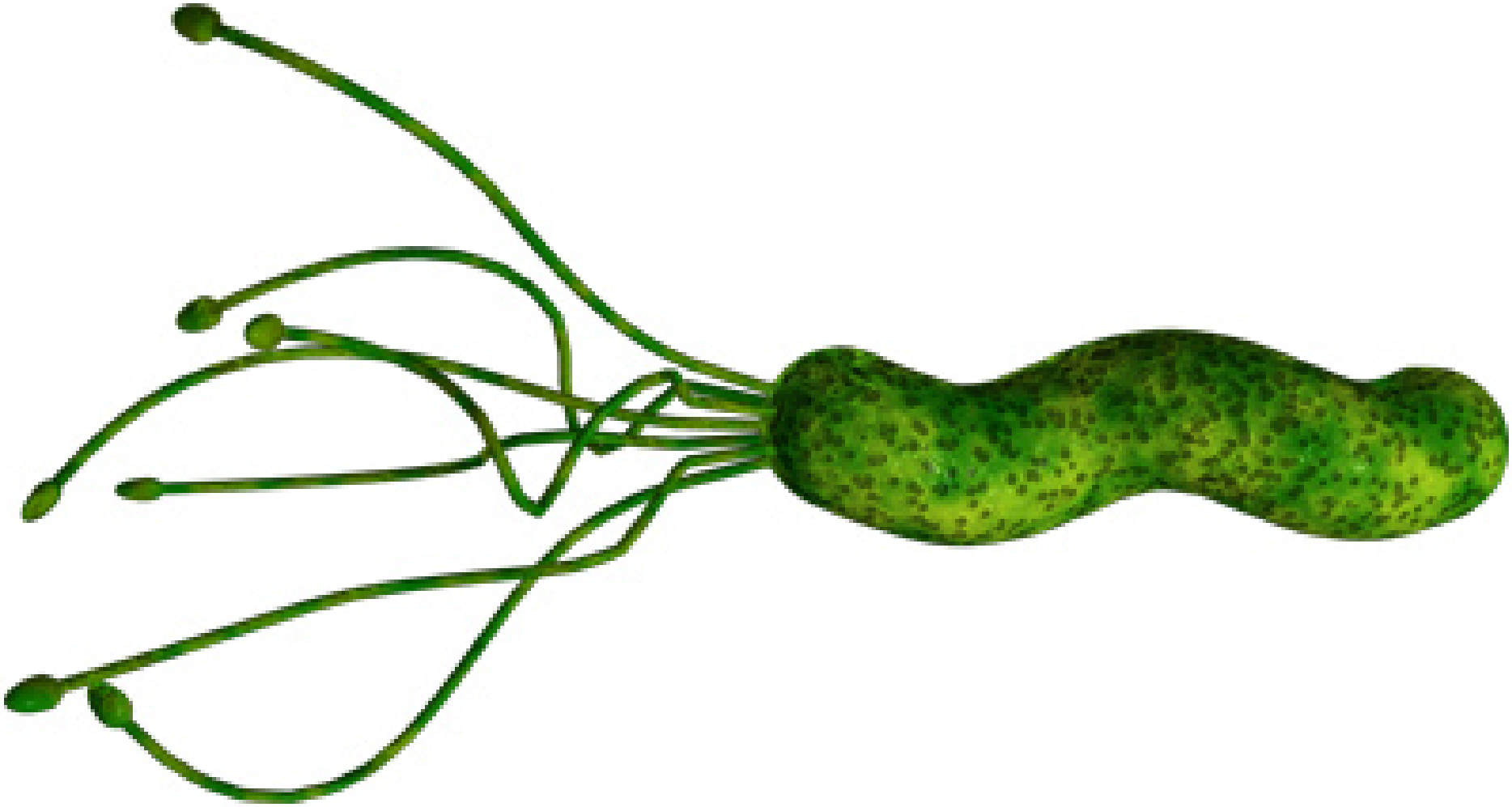
Excerpts from Causes of Peptic Ulcer: a Selective Epidemiological Review by M. Susser, published in the Journal of Chronic Diseases, *Vol. 20 pp. 435-456, 1967*

"...certain patterns of relationships were more common in 'ulcer' families. **Thus the mothers of ulcer patients tended to have psychogenic symptoms, and to be striving, obsessional, and dominant in the home; fathers tended to be steady, unassertive, and passive."**

"The description of these families...emphasizes the conflict in duodenal ulcer patients between **dependence engendered by a powerful mother and demands of adult roles."**

"The variations in peptic ulcer in different geographical, historical, and social contexts are unequivocal evidence of the influence of ways of life in this disease. The specific elements that contribute to the variations probably include diet, alcohol, cigarette smoking, emotional strain, personality, and genotype... . **This does not exclude the possibility that a major single causal effect awaits discovery."**


1979



Warren J. R. (1983)
Unidentified curved bacilli on gastric epithelium in active chronic gastritis
Lancet (i): 1273

Marshall B. J. & Warren J. R. (1984)
Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration
Lancet (i): 1311-1314

« I preferred to believe my eyes, not the medical textbooks of the medical fraternity »

R. Warren (2002)

Koch's Postulates

I. The organism, a germ, should always be **found microscopically** in the bodies of animals having the disease and in that disease only; it should occur in such numbers and be distributed in such a manner as to explain the lesions of the disease.

II. The germ should be obtained from the diseased animal and **grown outside the body.**

III. **The inoculation of these germs**, grown in pure cultures, freed by successive transplantations from the smallest particle of matter taken from the original animal, **should produce the same disease in a susceptible animal.**

IV. The germs should be found in the diseased areas so produced in the animal.

Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ (1985)

Attempt to fulfil Koch's postulates for pyloric Campylobacter.

A volunteer with histologically normal gastric mucosa received pyloric campylobacter by mouth. A mild illness developed, which lasted 14 days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day. The syndrome of acute pyloric campylobacter gastritis is described. It is proposed that this disorder may progress to a chronic infection which predisposes to peptic ulceration.

Med J Aust. 1985 Apr 15;142(8):436-9.

PATHOGENIC PROPERTIES OF *HELICOBACTER PYLORI*

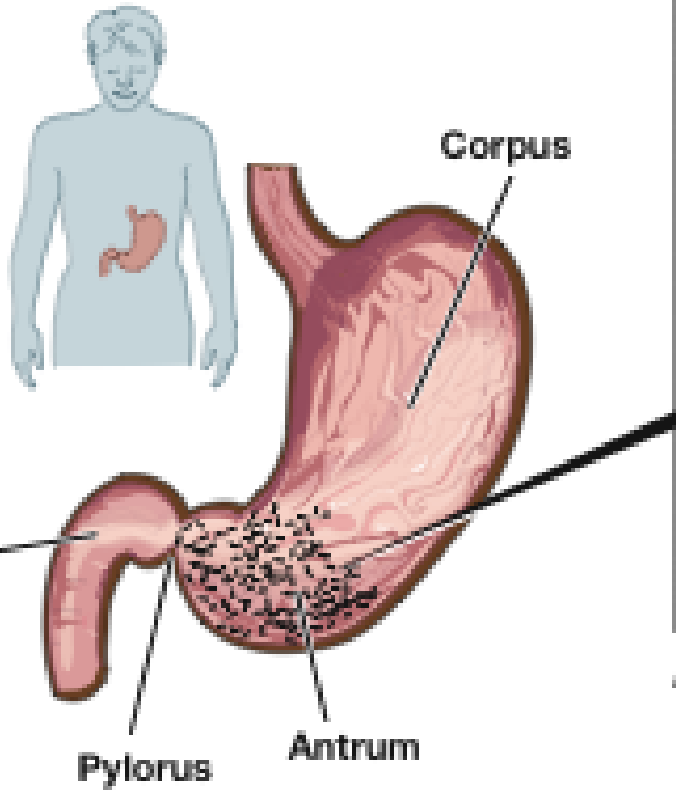
- ➢- Adheres to gastric epithelium
- ➢- Lives within mucous gel layer overlying gastric epithelium
- ➢- Penetrates intercellular junctions
- ➢- Invades gastric glands and canaliculi of parietal cells
- ➢- Produces cytotoxins that may play role in pathogenicity
- ➢- Induces epithelial cytolysis and disrupts intercellular junctions
- ➢- Increases permeability of mucous layer to hydrogen ions and pepsin
- ➢- Enables gastric acid and pepsin to create ulcer craters
- ➢- Evades host immune defenses
- ➢- Damages tissue
- ➢- Secretes urease to produce ammonia, which protects it from gastric acid

Helicobacter pylori

— the bacterium causing peptic ulcer disease

Infection

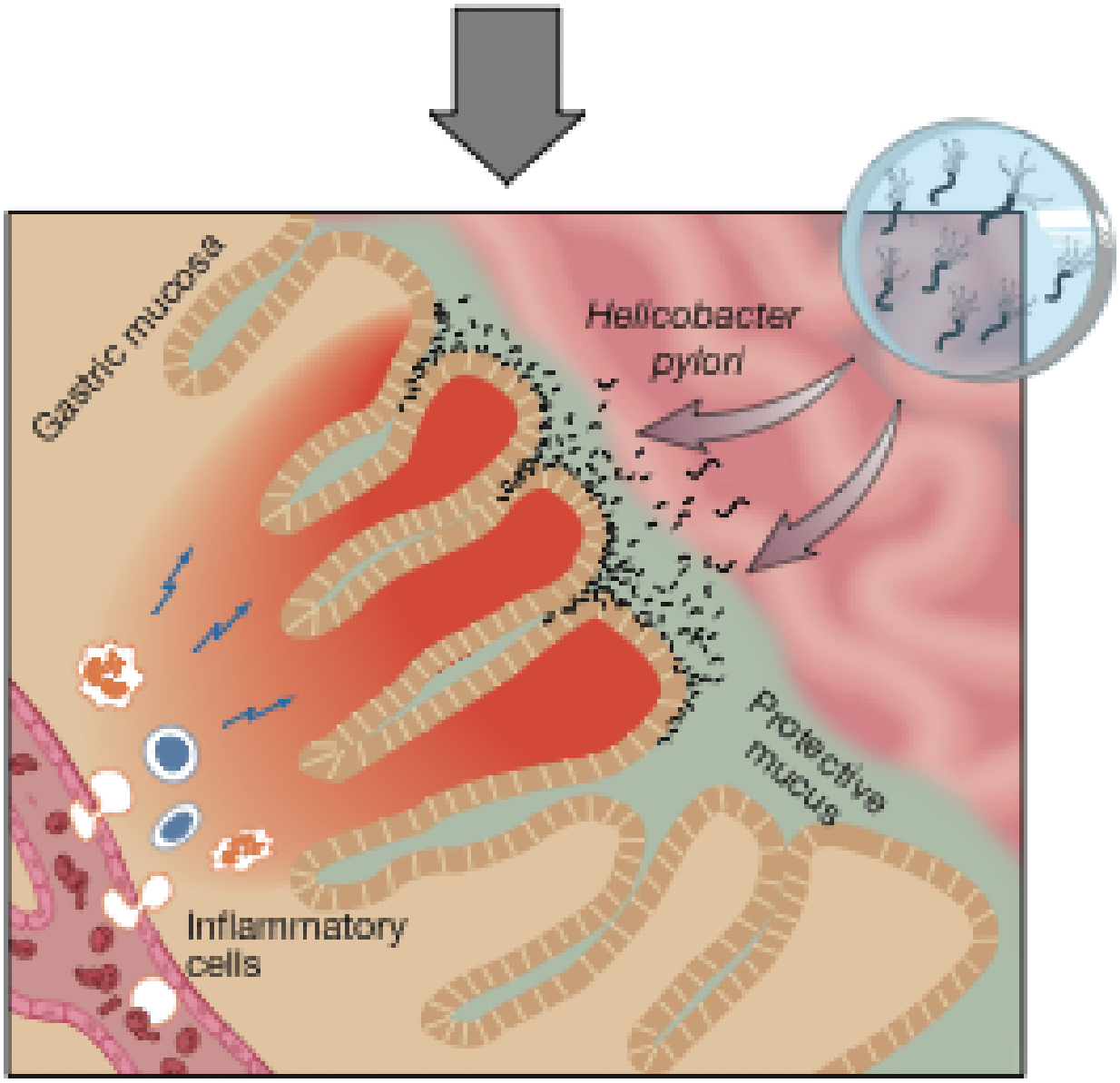
Helicobacter pylori infects the lower part of the stomach, antrum.



Helicobacter pylori

Inflammation

Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.



Ulcer

Gastric inflammation may lead to duodenal or gastric ulcer. Severe complications include bleeding ulcer and perforated ulcer.