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Definition, Pathogenesis, and Management of That Cursed Dyspepsia

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Dyspepsia

- Umbrella term to refer number of nonspecific symptoms originate from UGI
- Minority: potentially life threatening ↔ Majority: functional
- Difficult to definition and manage functional dyspepsia (FD)

- Crean et al (1994), “Dyspepsia is *episodic recurrent or persist ent* abdominal pain or discomfort, or any other symptoms refe rable to the upper alimentary tract, excluding bleeding or jaun dice, of duration 4 weeks or longer, including abdominal pain/ discomfort, heartburn or other manifestations of gastroesopha geal reflux, anorexia, nausea and vomiting, flatulence or air er uctation (belching, burping or aerophagy), early satiety or und ue repletion after meals, abdominal distension or ‘bloating’

- Overlap? GERD, IBS

Functional dyspepsia (FD)

- Functional = “nonstructural” or “non-organic”
- No gold standard for the definition of FD
- Diagnosis of exclusion after exclusion of all organic causes
- Geographic variation: related in large part to *H.pylori* prevalence
- Problem of misunderstanding on the very symptoms of sufferer
- Physician bias: less commonly used in the US, where FD-type symptoms are designated as GERD.

- Rome I (1989-1994) and II (1999): Any symptoms
  - Reflux type, ulcer type, dysmotility type, unspecified
- Rome III (2006) and IV (2016): More specific
  - Post-prandial distress syndrome (PDS): meal-induced dyspeptic symptoms; bothersome postprandial fullness; early satiety (+epigastric pain or burning that worsens with meals, on Rome IV) for ≥3 d/wk;
  - Epigastric pain syndrome (EPS): occurred in between meals; epigastric pain and/or burning for ≥1 d/wk.

FD: Rome III (2006)

- **Excluded** prominent **heartburn** or satisfied criteria for **IBS**

Table 1. Rome III Functional Gastrointestinal Disorders

A. Functional esophageal disorders
- A1. Functional heartburn
- A2. Functional chest pain of presumed esophageal origin
- A3. Functional dysphagia
- A4. Globus

B. Functional gastroduodenal disorders
- B1. Functional dyspepsia
  - B1a. Postprandial distress syndrome
  - B1b. Epigastric pain syndrome
- B2. Belching disorders
  - B2a. Aerophagia
  - B2b. Unspecified excessive belching
- B3. Nausea and vomiting disorders
  - B3a. Chronic idiopathic nausea
  - B3b. Functional vomiting
  - B3c. Cyclic vomiting syndrome
- B4. Rumination syndrome in adults

C. Functional bowel disorders
- C1. Irritable bowel syndrome
- C2. Functional bloating
- C3. Functional constipation
- C4. Functional diarrhea
- C5. Unspecified functional bowel disorder

D. Functional abdominal pain syndrome

E. Functional gallbladder and Sphincter of Oddi (SO) disorders
- E1. Functional gallbladder disorder
- E2. Functional biliary SO disorder
- E3. Functional pancreatic SO disorder

F. Functional anorectal disorders
- F1. Functional fecal incontinence
- F2. Functional anorectal pain
  - F2a. Chronic proctalgia
    - F2a1. Levator ani syndrome
    - F2a2. Unspecified functional anorectal pain
  - F2b. Proctalgia fugax
- F3. Functional defecation disorders
  - F3a. Dyssynergic defecation
  - F3b. Inadequate defecatory propulsion

G. Functional disorders: neonates and toddlers
- G1. Infant regurgitation
- G2. Infant rumination syndrome
- G3. Cyclic vomiting syndrome
- G4. Infant colic
- G5. Functional diarrhea
- G6. Infant dyschezia
- G7. Functional constipation

H. Functional disorders: children and adolescents
- H1. Vomiting and aerophagia
  - H1a. Adolescent rumination syndrome
  - H1b. Cyclic vomiting syndrome
  - H1c. Aerophagia
- H2. Abdominal pain-related functional gastrointestinal disorders
  - H2a. Functional dyspepsia
  - H2b. Irritable bowel syndrome
  - H2c. Abdominal migraine
  - H2d. Childhood functional abdominal pain
    - H2d1. Childhood functional abdominal pain syndrome
- H3. Constipation and incontinence
  - H3a. Functional constipation
  - H3b. Nonretentive fecal incontinence

- Despite the fundamental change, sensitivity or specificity to identify FD was not different from previous criteria

FD: Rome IV (2016)

- FD should no longer be considered as a single disease entity but rather as a **spectrum** where there is significant **overlap** with **GERD** and **IBS**.

Table 2. Functional Gastrointestinal Disorders: Disorders of Gut–Brain Interaction

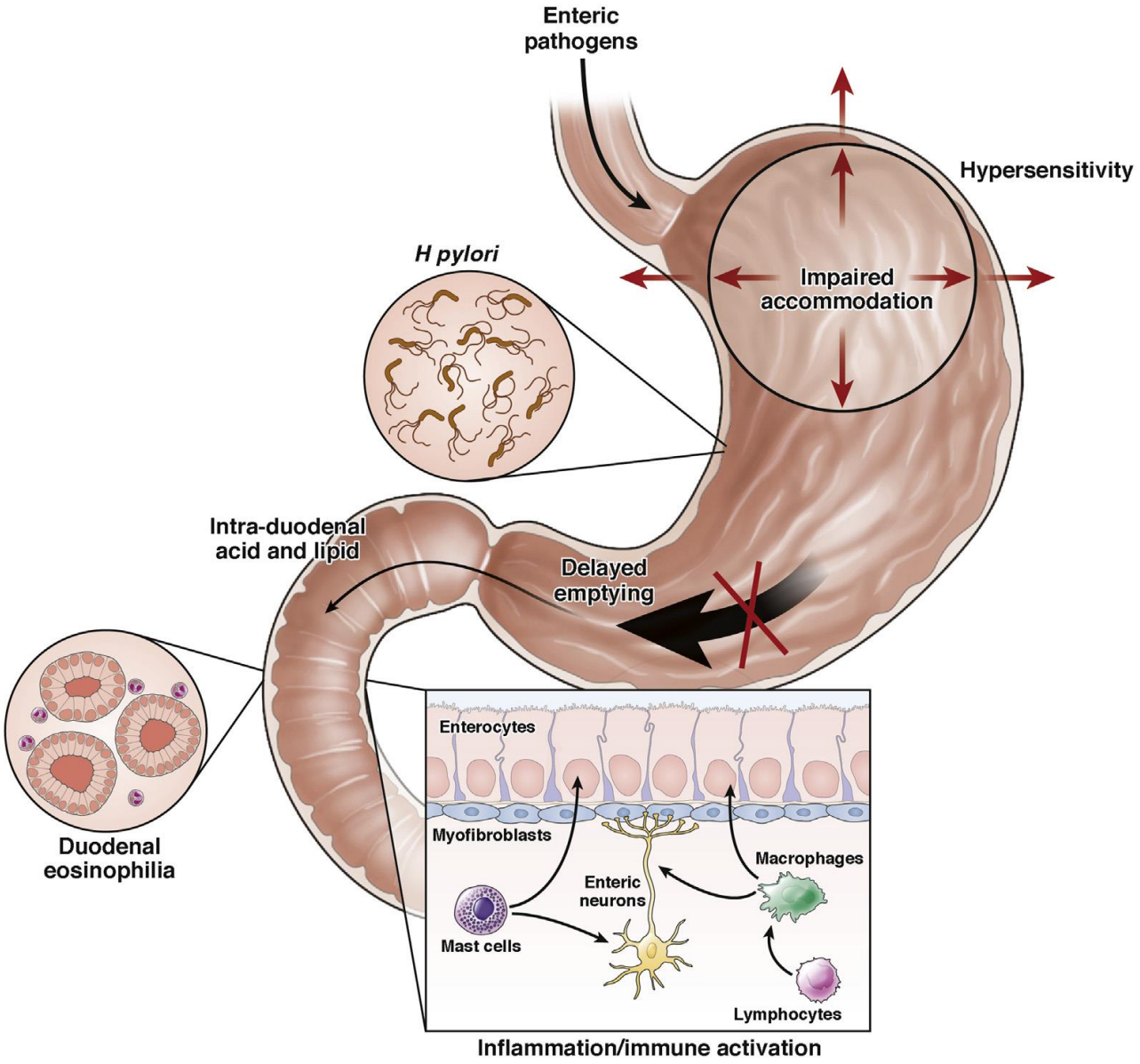
A. Esophageal Disorders	
A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	
B. Gastroduodenal Disorders	
B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome (PDS)	B3a. Chronic nausea vomiting syndrome (CNVS)
B1b. Epigastric pain syndrome (EPS)	B3b. Cyclic vomiting syndrome (CVS)
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome (CHS)
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	
C. Bowel Disorders	
C1. Irritable bowel syndrome (IBS)	C2. Functional constipation
IBS with predominant constipation (IBS-C)	C3. Functional diarrhea
IBS with predominant diarrhea (IBS-D)	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits (IBS-M)	C5. Unspecified functional bowel disorder
IBS unclassified (IBS-U)	C6. Opioid-induced constipation
D. Centrally Mediated Disorders of Gastrointestinal Pain	
D1. Centrally mediated abdominal pain syndrome (CAPS)	
D2. Narcotic bowel syndrome (NBS)/ Opioid-induced GI hyperalgesia	

- Bothersome; occur more frequently than normal population

Epidemiology of FD

- Prevalence: 10~30% (problem of definition)
- Global pooled prevalence: 21%
- Higher in: women, smokers, NSAID users, *H. pylori*-positive pts.
- Western (ulcer-like, reflux-like) > Eastern (dysmotility like)
- SES tends to low in western, while high in Eastern.
- H. pylori eradication is more effective for Sx in Eastern.
- Higher economic impact in Western.

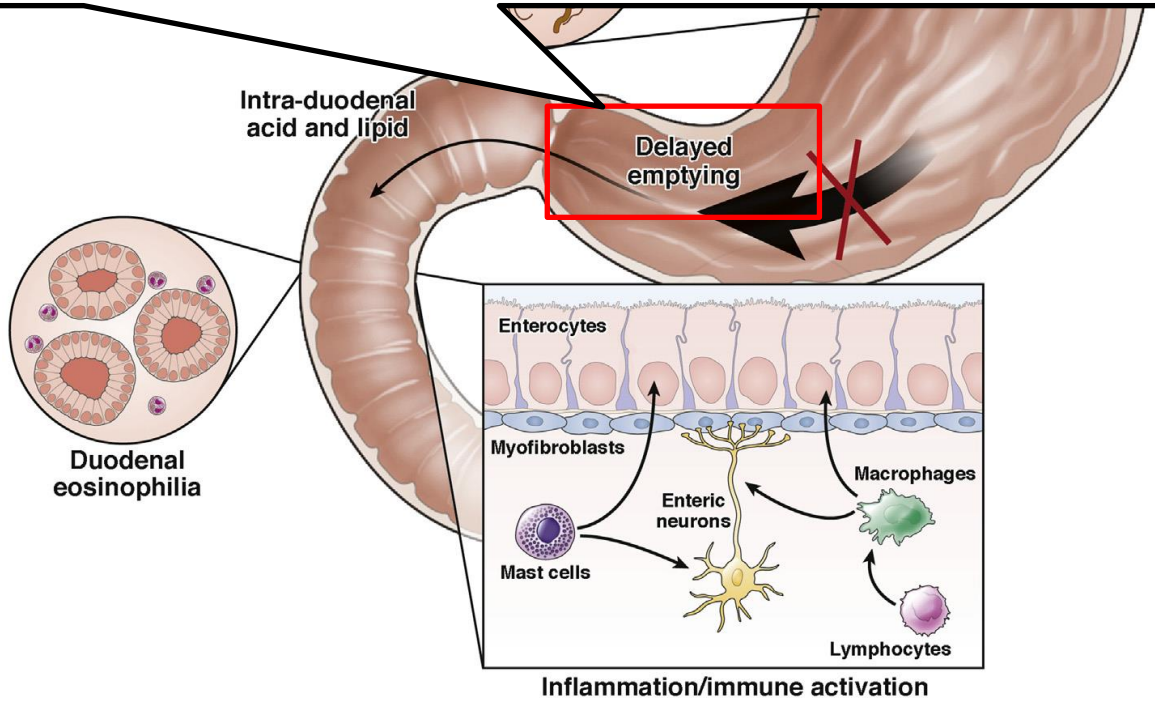
Pathophysiology of FD



Pathophysiology of FD

Delayed gastric emptying

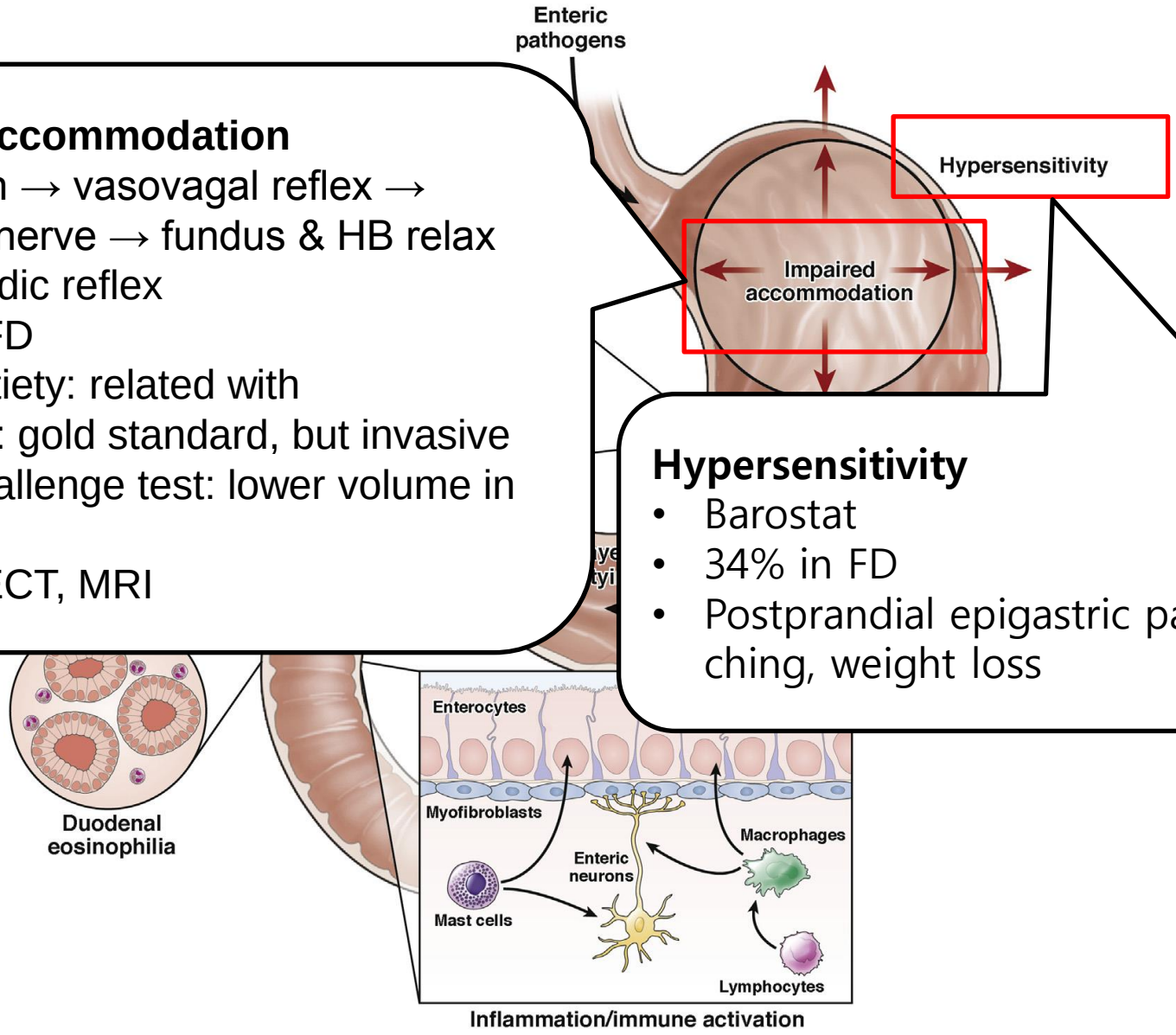
- Traditionally, thought to be one of the main players.
- 20~50% among dyspepsia sufferers
- 1.5 times slower on gastric emptying of solid than control subjects
- Symptom overlap between PDS and idiopathic gastroparesis
- Post-prandial fullness: related with delayed gastric emptying vs. other symptoms: not related with delayed gastric emptying
- Paradoxically rapid gastric emptying in small population



Pathophysiology of FD

Impaired accommodation

- Ingestion → vasovagal reflex → nitrergic nerve → fundus & HB relax
- Antrofundic reflex
- 40% in FD
- Early satiety: related with
- Barostat: gold standard, but invasive
- Drink challenge test: lower volume in FD
- US, SPECT, MRI



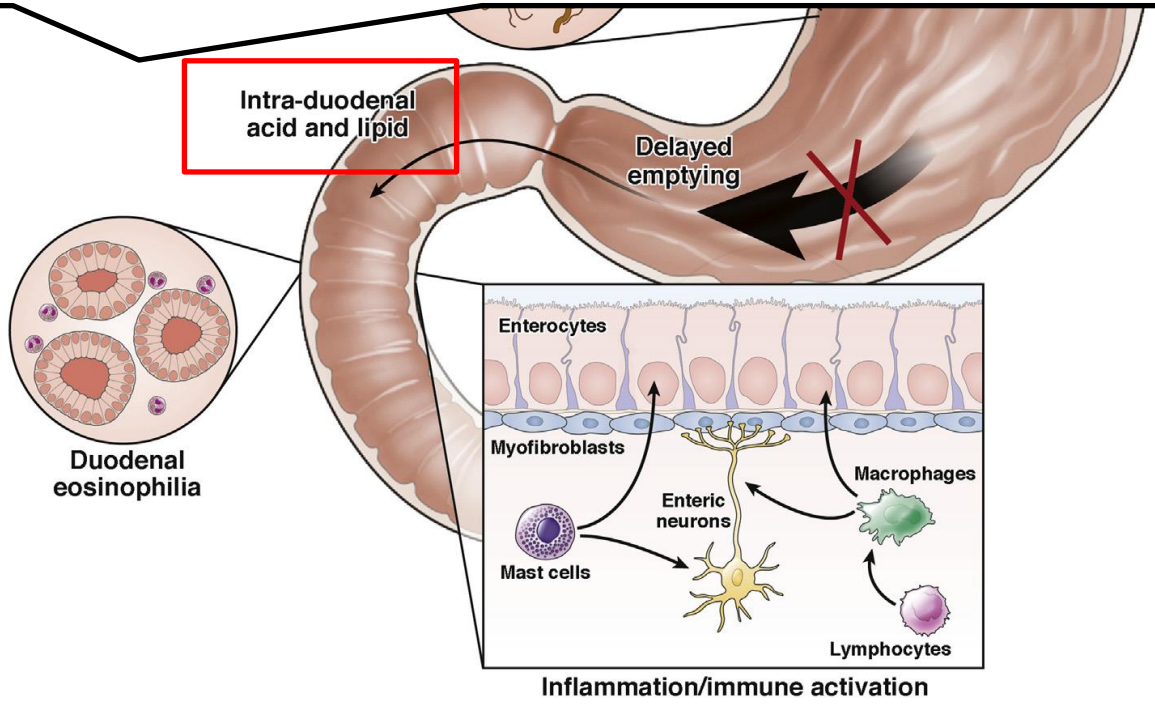
Hypersensitivity

- Barostat
- 34% in FD
- Postprandial epigastric pain, bel ching, weight loss

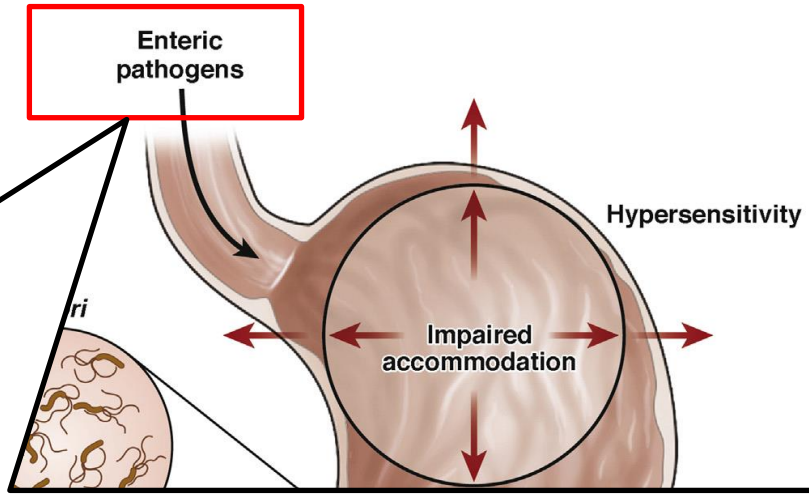
Pathophysiology of FD

Duodenal hypersensitivity to acid and lipid

- 59% of FD developed nausea during a brief period of duodenal acid perfusion
- reduced clearance of exogenously administered acid from the duodenal bulb
- Directly via duodenal receptors and sensory nerves or indirectly through feed back changes in proximal gastric function
- intraduodenal infusion of lipids sensitized the stomach to distention and prov oked symptoms of fullness, discomfort, and nausea

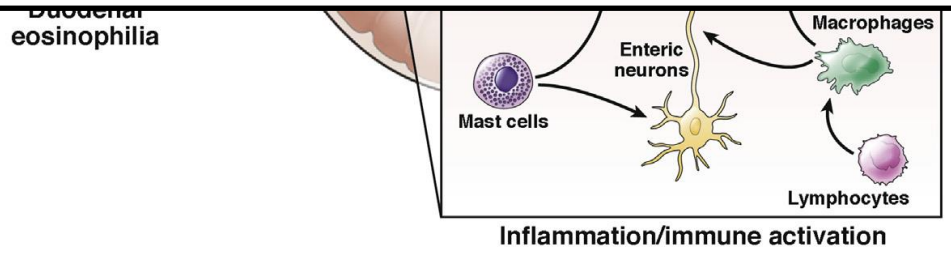


Pathophysiology of FD



Postinfectious

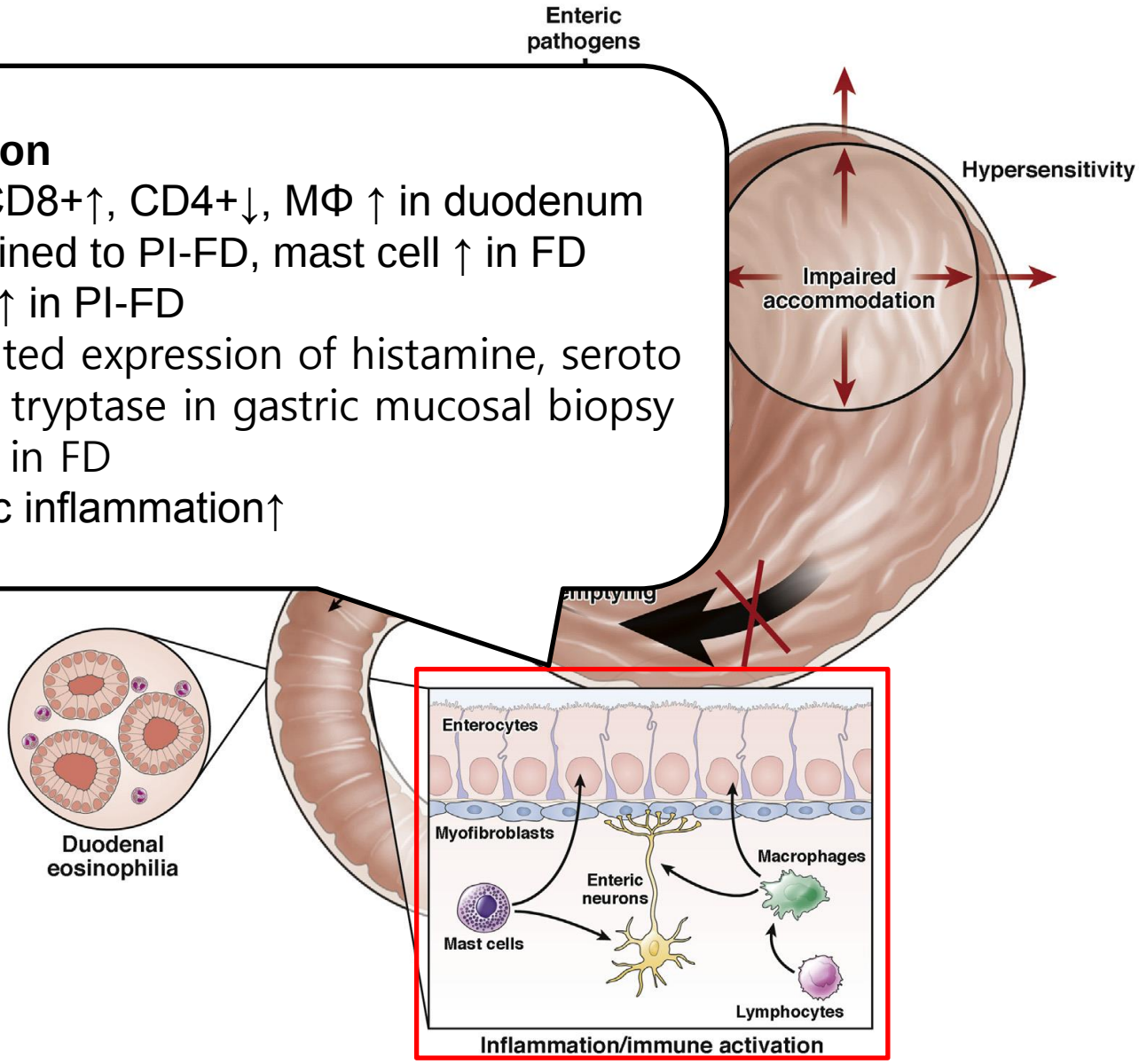
- *De novo* development of FD following an enteric infection
- Early satiety, nausea, weight loss; symptoms were attributed to impaired acco mmodation resulting from dysfunction of gastric nitrergic neurons.
- *Salmonella enteritis:* the relative risk for the development of FD was 5.2
- *Giardia lamblia* infection has been shown to provoke visceral hypersensitivity and delay gastric emptying



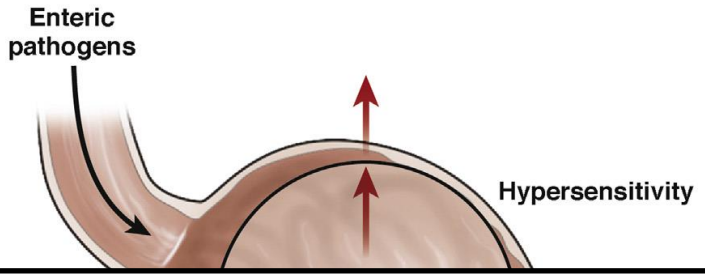
Pathophysiology of FD

Inflammation

- PI-FD: CD8+↑, CD4+↓, MΦ ↑ in duodenum
- Not confined to PI-FD, mast cell ↑ in FD
- EC cells↑ in PI-FD
- Augmented expression of histamine, seroto nin, and tryptase in gastric mucosal biopsy samples in FD
- Systemic inflammation↑

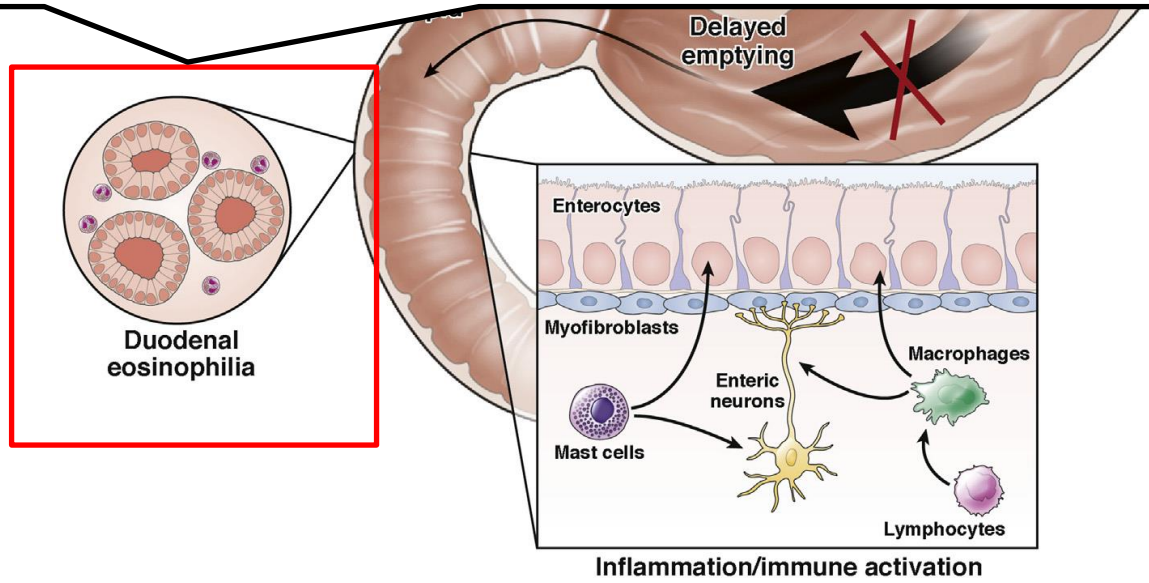


Pathophysiology of FD

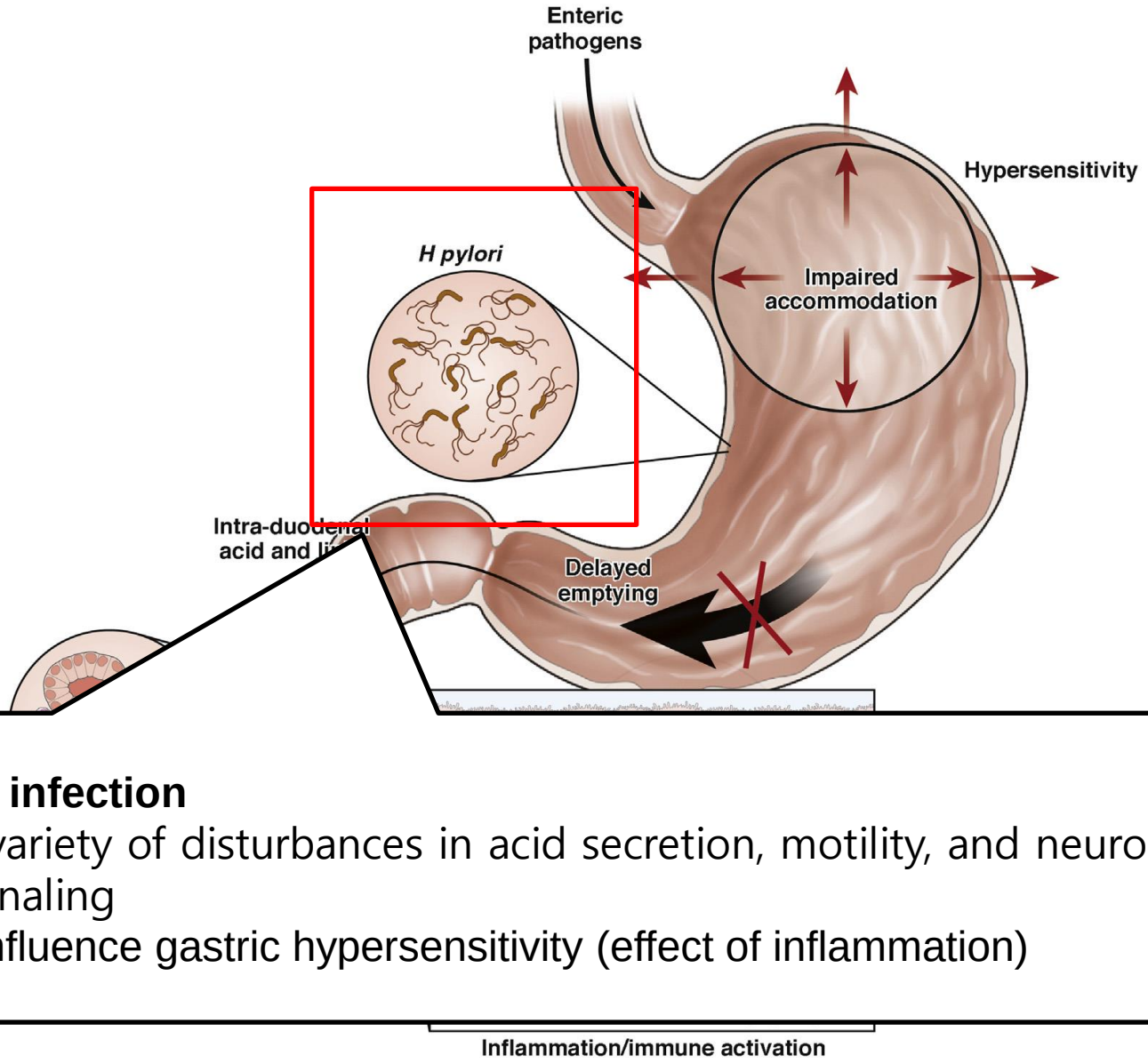


Duodenal eosinophilia (not gastric)

- OR for the FD in subjects with high duodenal bulb Eo counts was 11.7
- Early satiety, postprandial fullness: 2nd portion
- Abdominal pain: bulb & 2nd portion
- Related with PDS and allergy



Pathophysiology of FD



***H. pylori* infection**

- via a variety of disturbances in acid secretion, motility, and neuroendocrine signaling
- may influence gastric hypersensitivity (effect of inflammation)

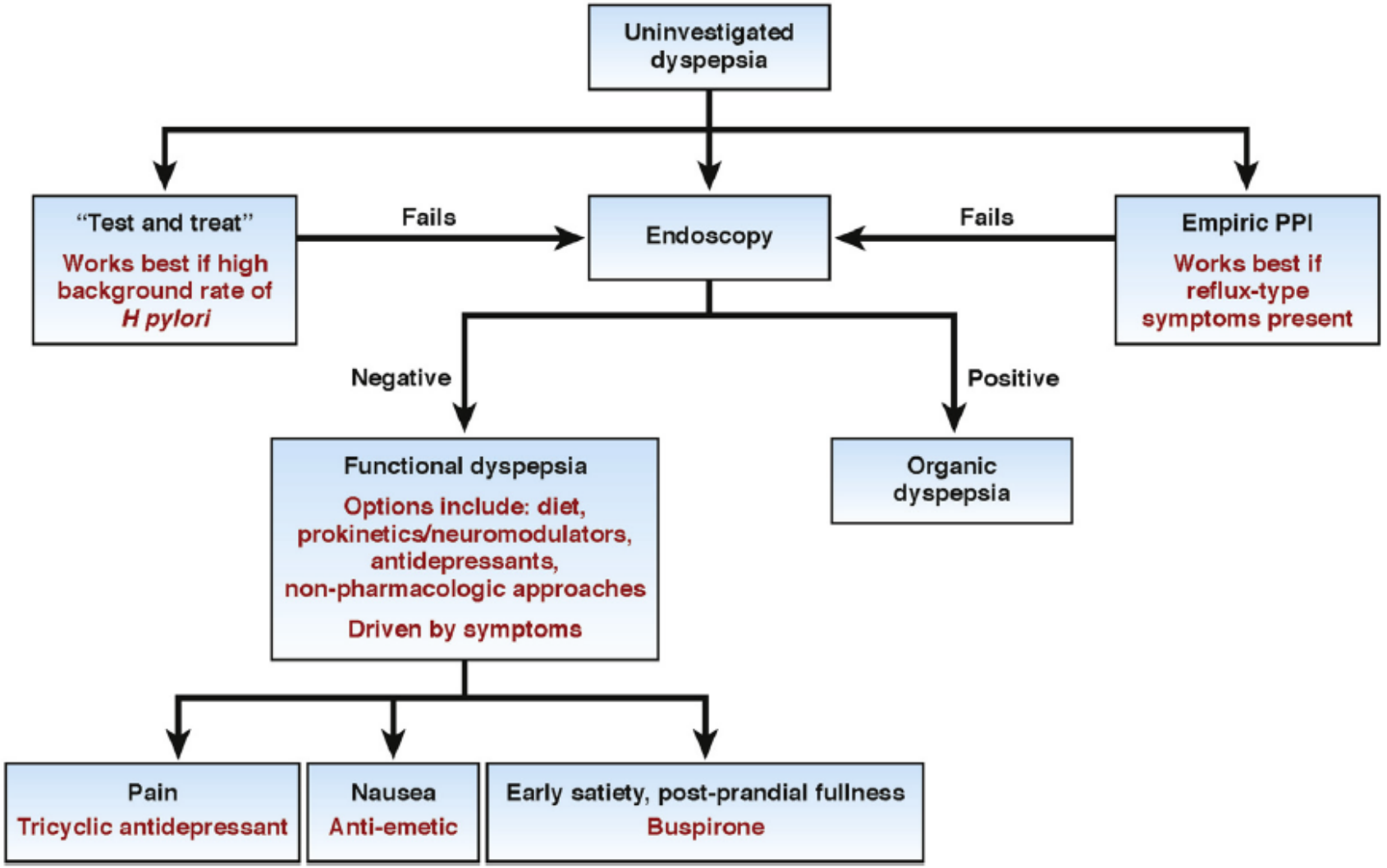
Pathophysiology of FD

- Psychosocial: stress, anxiety, depression
- Diet: salty, hot
- Lifestyle: tobacco, alcohol, NSAID
- Ehlers-Danlos type III

Management of FD

- **Reassure** (must not belittle)
- **Diet**: Visceral adiposity, canned food, alcohol weekly, high fat, salt, fermentable oli gosaccharides, disaccharides, monosaccharides, and polyols, carbonated drinks, h ot spices
- **Antidepressants**: TCA (not SSRI); amitriptyline 50 mg qd > escitalopram 10mg
  (ulcer-like epigastric pain & normal gastric emptying)
- **Eradication of *Helicobacter pylori***: small population (10%) but significant
- **Prokinetic agents**: ~~metoclopramide, domperidone, mosapride,~~
  cinitapride > domperidone in post-prandial fullness, early satiation, bloating
  itopride: meta-analysis, phase II, (not in phase III)
  acotiamide: phase II, large multicenter phase III in Japan (post-prandial distress, early satiation, bloating)
- **Enhancing gastric accommodation**: buspirone (post-prandial fullness, early satiation, bloating)
- **Nonpharmacologic therapies**: psychotherapy, acupuncture (high risk of bias)
- **Herbal medicine**: Iberogast (Germany), Rikkunshito (Japan), Menthacarin
- **Novel approaches**: cannabinoid-1 receptor, a novel target

Dyspepsia: a Clinical Guide



Conclusion

- Dyspepsia is difficult to define and manage