Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology, Fall 2005
Instructors: Dr. Martin Carey, Dr. Raymond Chung, and Dr. Jonathan Glickman

BRIGHAM AND
WOMEN'S HOSPITAL

Gastrointestinal Pathophysiology Lecture 2005

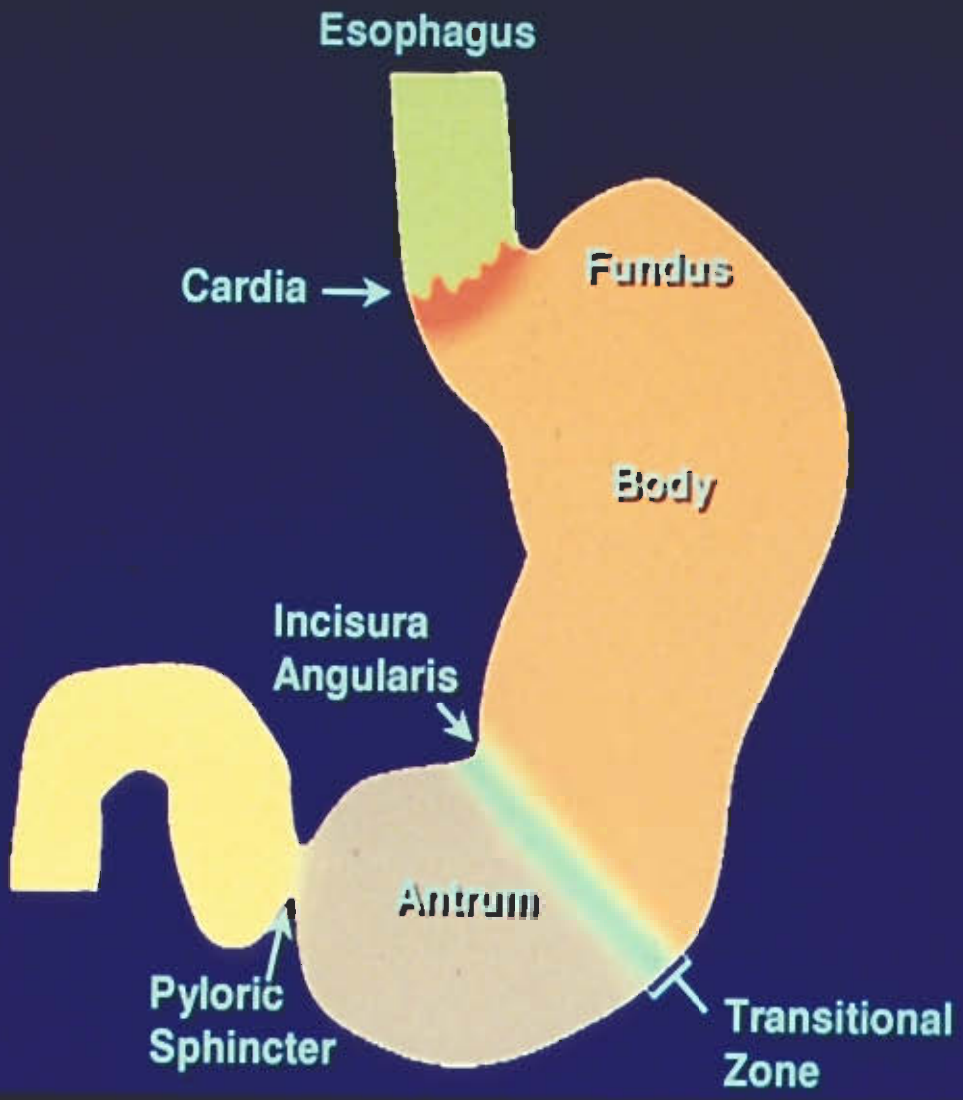
Lisa L. Strate, M.D., M.P.H.
Instructor in Medicine
Department of Gastroenterology

Lecture Overview

- Anatomy / Histology
- Acid secretion
  - Parietal cell
  - Regulation
- Gastric Mucosal Barrier
- Peptic Ulcer Disease (PUD)
  - H. pylori
  - NSAIDs (non steroidal anti-inflammatories)
  - Zollinger Ellison Syndrome
  - Treatment of PUD

Upper GI: Anatomy

Esophagus, Stomach, and Duodenum: Normal Anatomic Outlines and Relationships

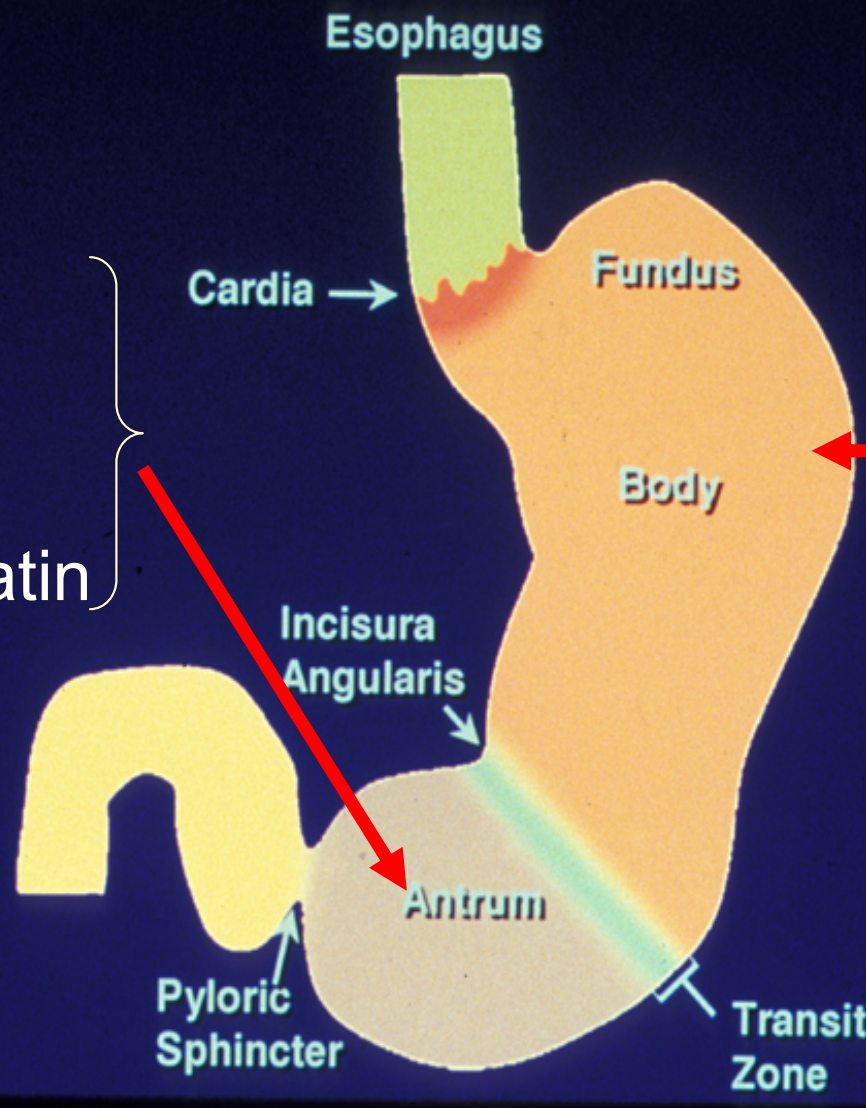


Functions of the stomach

- Bulk storage of undigested food
- Mechanical breakdown of food
- Disruption of chemical bonds
- Preliminary digestion of proteins and carbohydrates
- Production of intrinsic factor
- Protection from pathogens

Upper GI: Anatomy

Esophagus, Stomach, and Duodenum: Normal Anatomic Outlines and Relationships



G cells
- Gastrin

D cells
- Somatostatin

Parietal cells
- HCL, IF

Chief cells
- Pepsinogen

ECL cells
- Histamine

STOMACH AND DUODENUM: NORMAL HISTOLOGY

Mucous cells

G-cell

ANTRAL MUCOSA

CARDIAC MUCOSA

FUNDAL MUCOSA

Mucous cells

Peptic cells

Parietal (oxyntic) cells

DUODENUM with Brunner glands

Parietal Cells

- Oxyntic glands of body and fundus
- Generate large H+ gradient
- Energy-dependent process
- H+-K+ ATPase (Proton Pump)
  - Final step in acid secretion
  - Located on apical membrane along secretory canaliculi

Secretion of Hydrochloric Acid

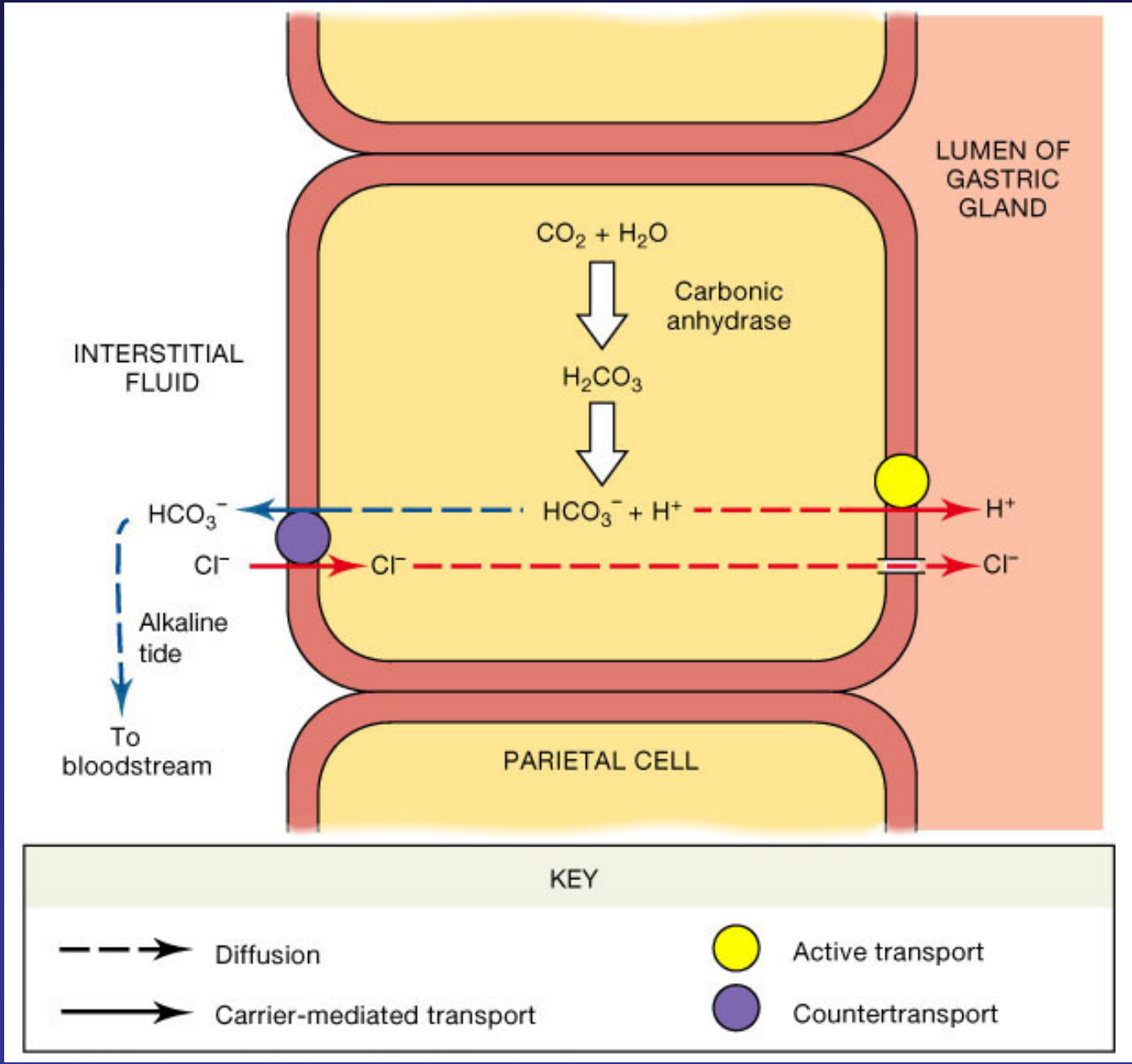
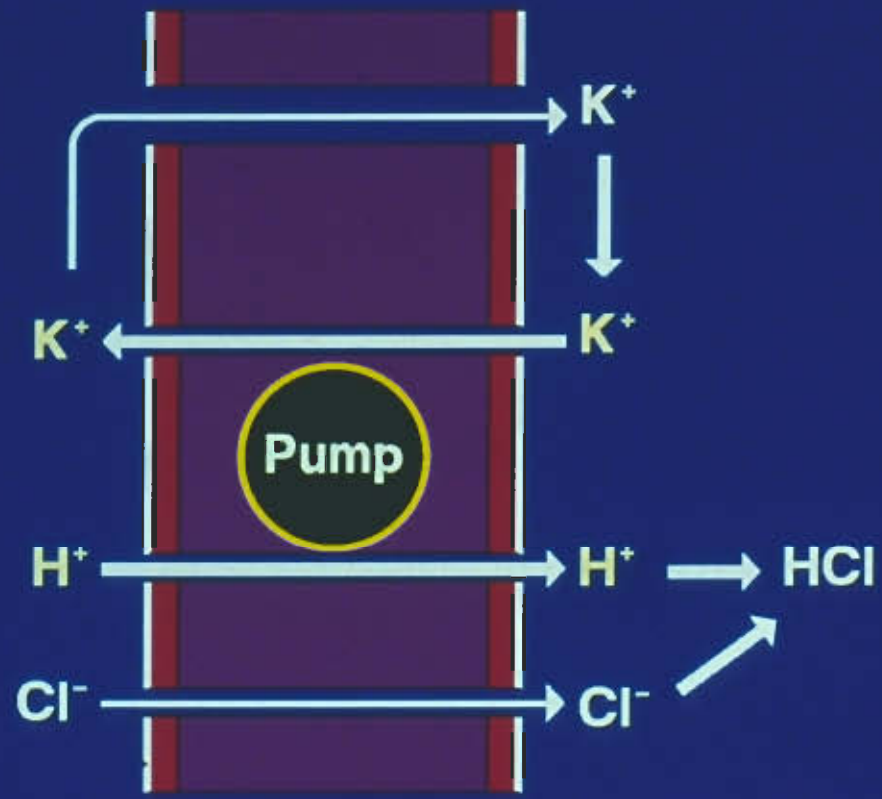
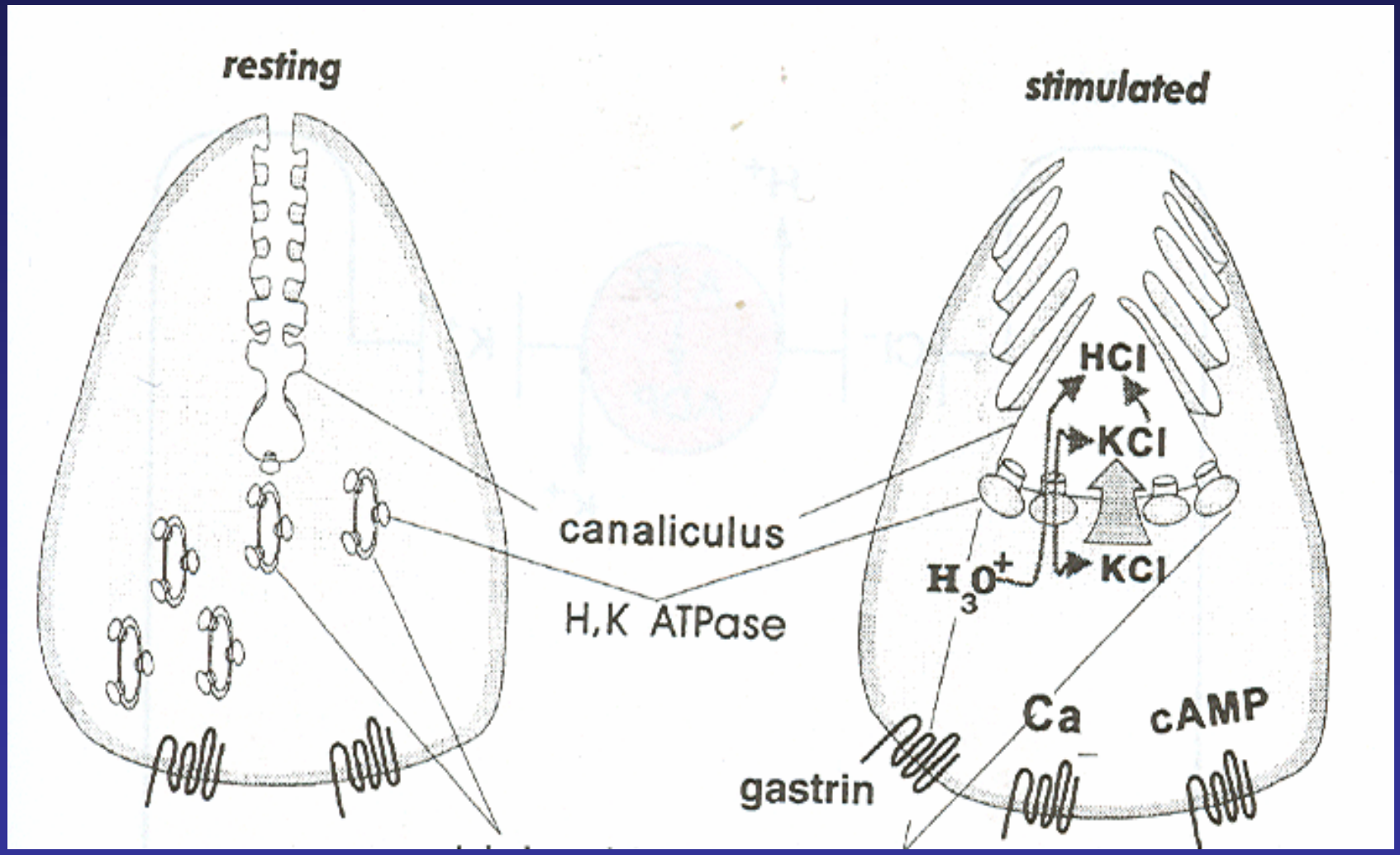


Figure 24.14

The Parietal Cell H^+-K^+ ATPase Secretes H^+ in Exchange for K^+



Transformation of Parietal Cell



M3/ACH Histamine

BASAL ACID OUTPUT (BAO)

- Circadian pattern: lowest in morning (~7am); highest in evening (~11pm)
- Normal < 5 mEq/hour
- Acetylcholine and histamine are the main regulators of basal secretion.
- In most patients with duodenal ulcer disease, the BAO is normal.

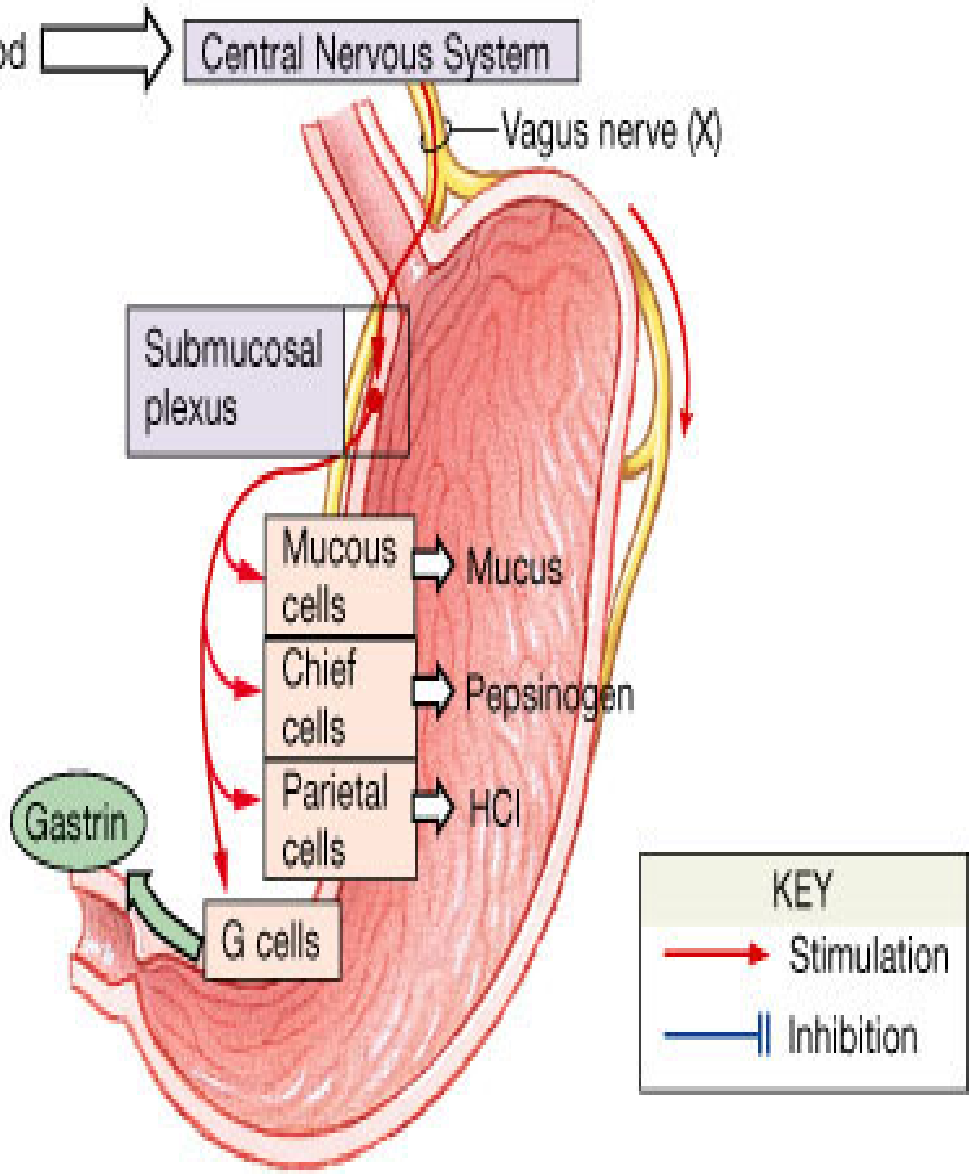
Phases of Acid Secretion

- Cephalic phase
- Gastric phase
- Intestinal phase

Cephalic Phase

(a) The Cephalic Phase Sight, smell, taste, or thoughts of food ⇨ Central Nervous System

Function:
Prepare stomach for arrival of food
Duration:
Short (minutes)
Mechanism:
Neural, via preganglionic fibers in vagus nerve and synapses in submucosal plexus
Actions:
Primary: stimulation of mucus, enzyme, and acid production, leading to increased volume of gastric juice
Secondary: stimulation of gastrin release by G cells



Gastric Phase

(b) The Gastric Phase

Functions:
- Enhance secretion started in cephalic stage; homogenize and acidify chyme; initiate digestion of proteins by pepsin

Duration:
- Long (3–4 hours)

Mechanisms:
- *Neural:* short reflexes triggered by
  - (1) stimulation of stretch receptors as stomach fills
  - (2) stimulation of chemoreceptors as pH increases
- *Hormonal:* stimulation of gastrin release by G cells through parasympathetic activity and presence of peptides and amino acids in chyme
- *Local:* release of histamine by mast cells as stomach fills (not shown)

Actions:
- Increased acid and pepsinogen production; increased motility and initiation of mixing waves

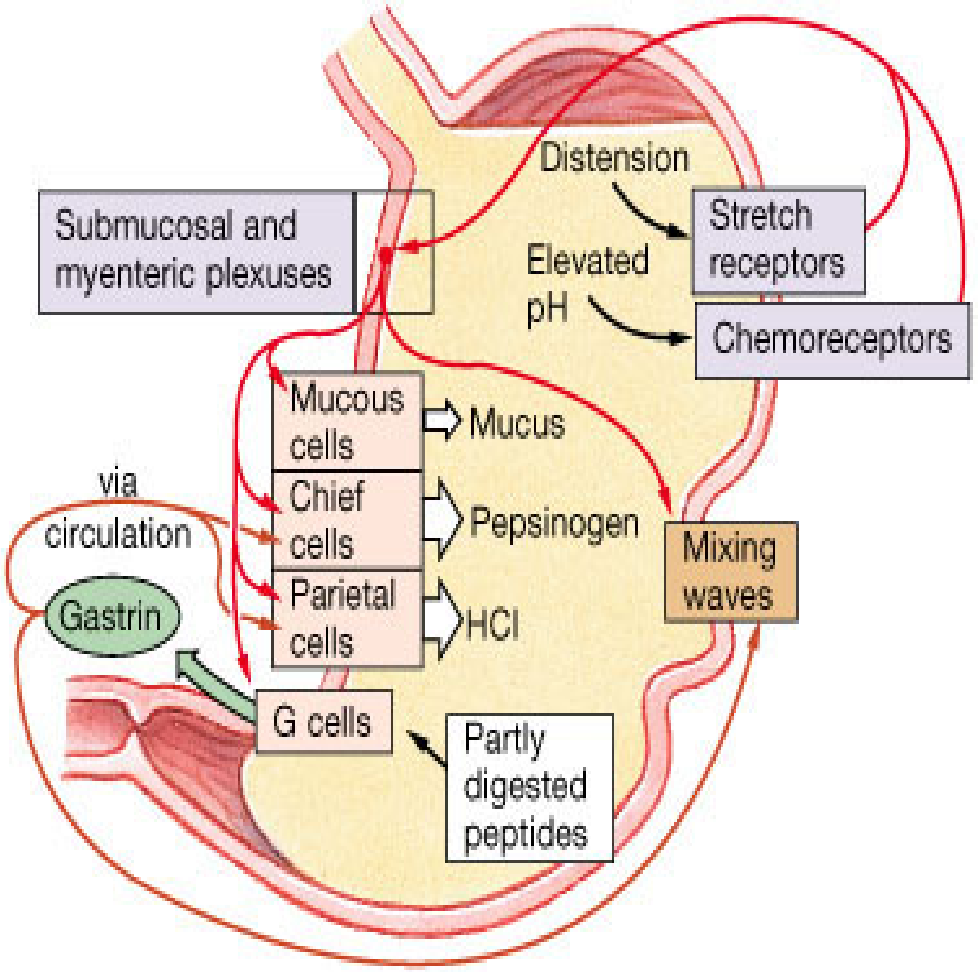


Figure 24.15b

Intestinal Phase

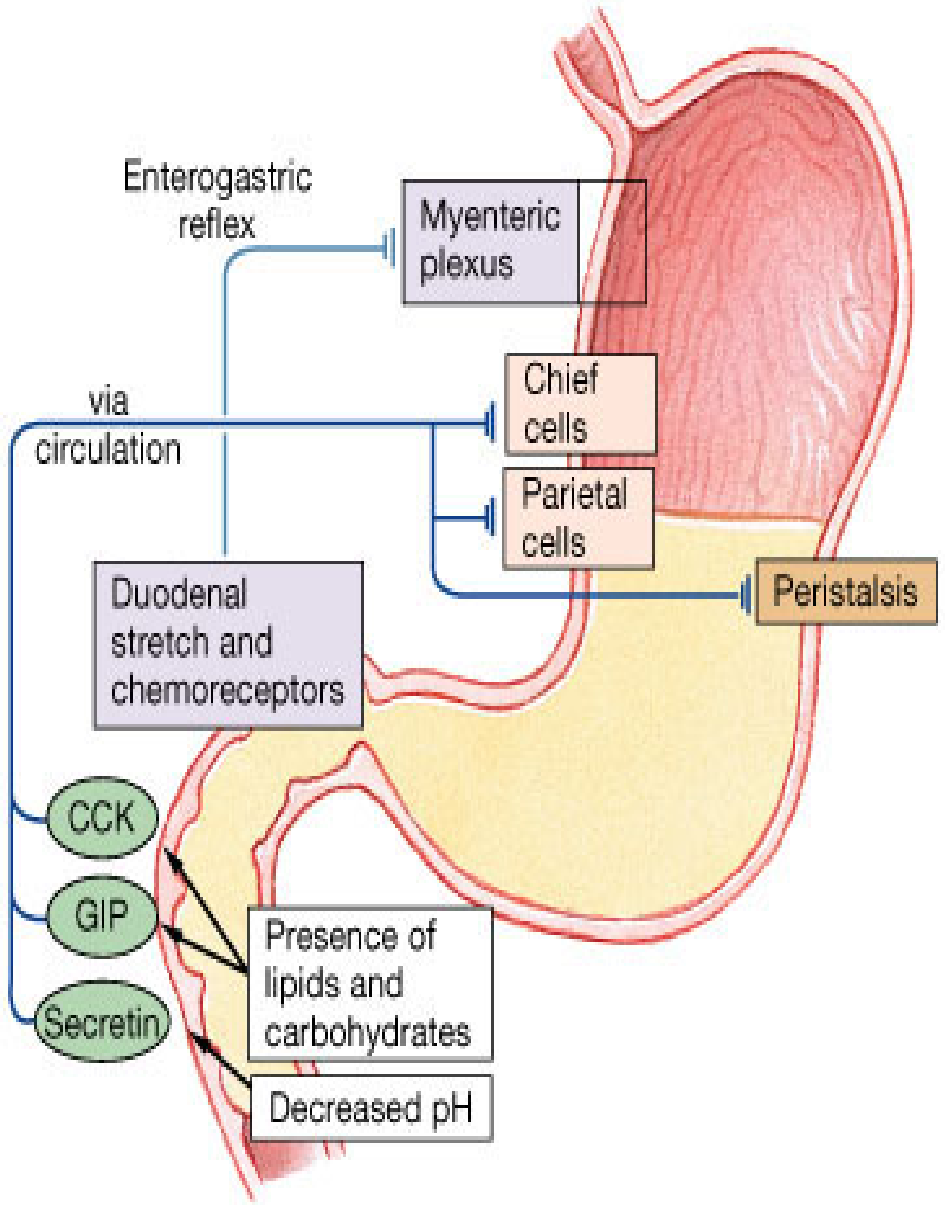
(c) The Intestinal Phase

Function:
Control rate of chyme entry into duodenum

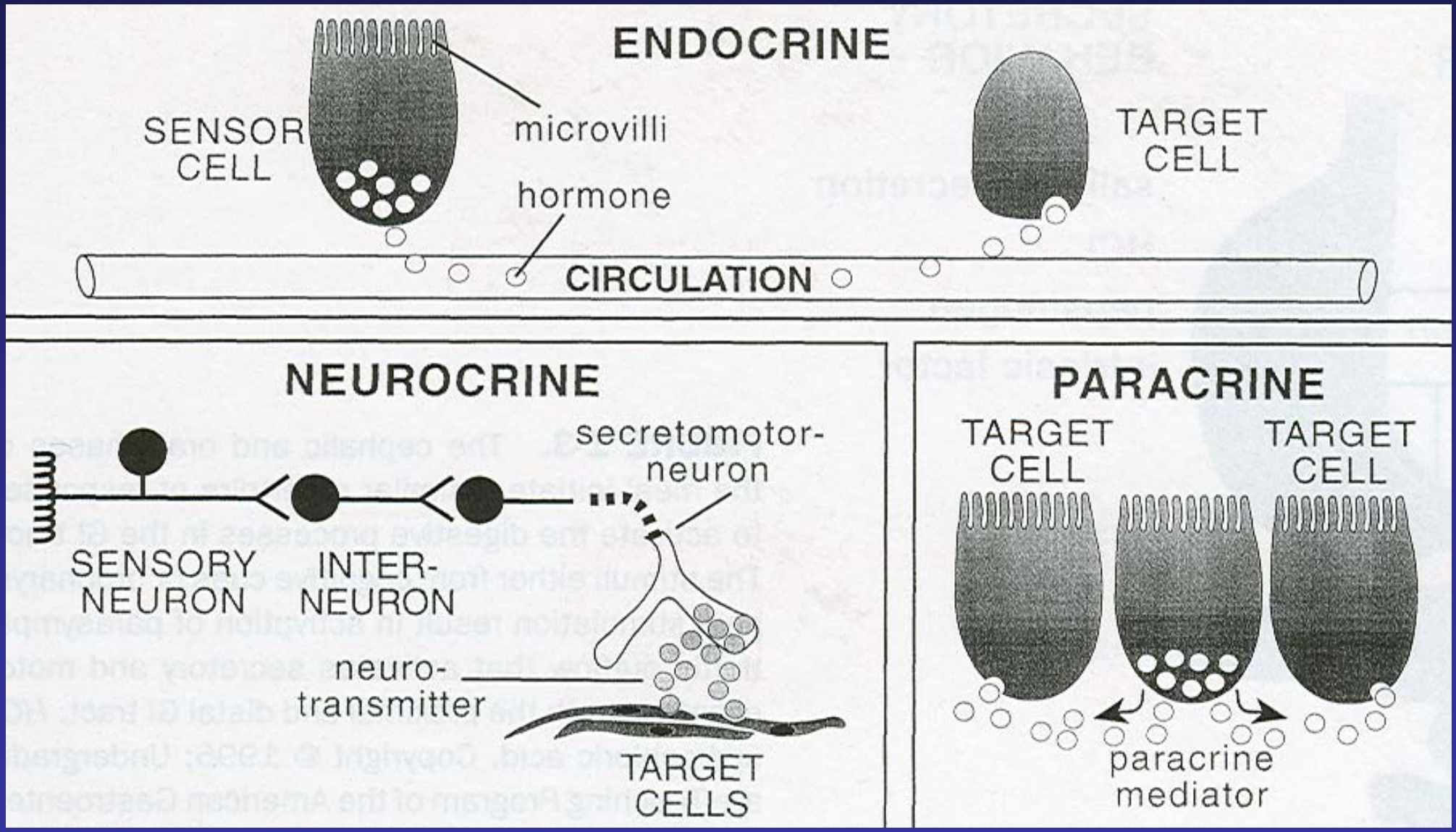
Duration:
Long (hours)

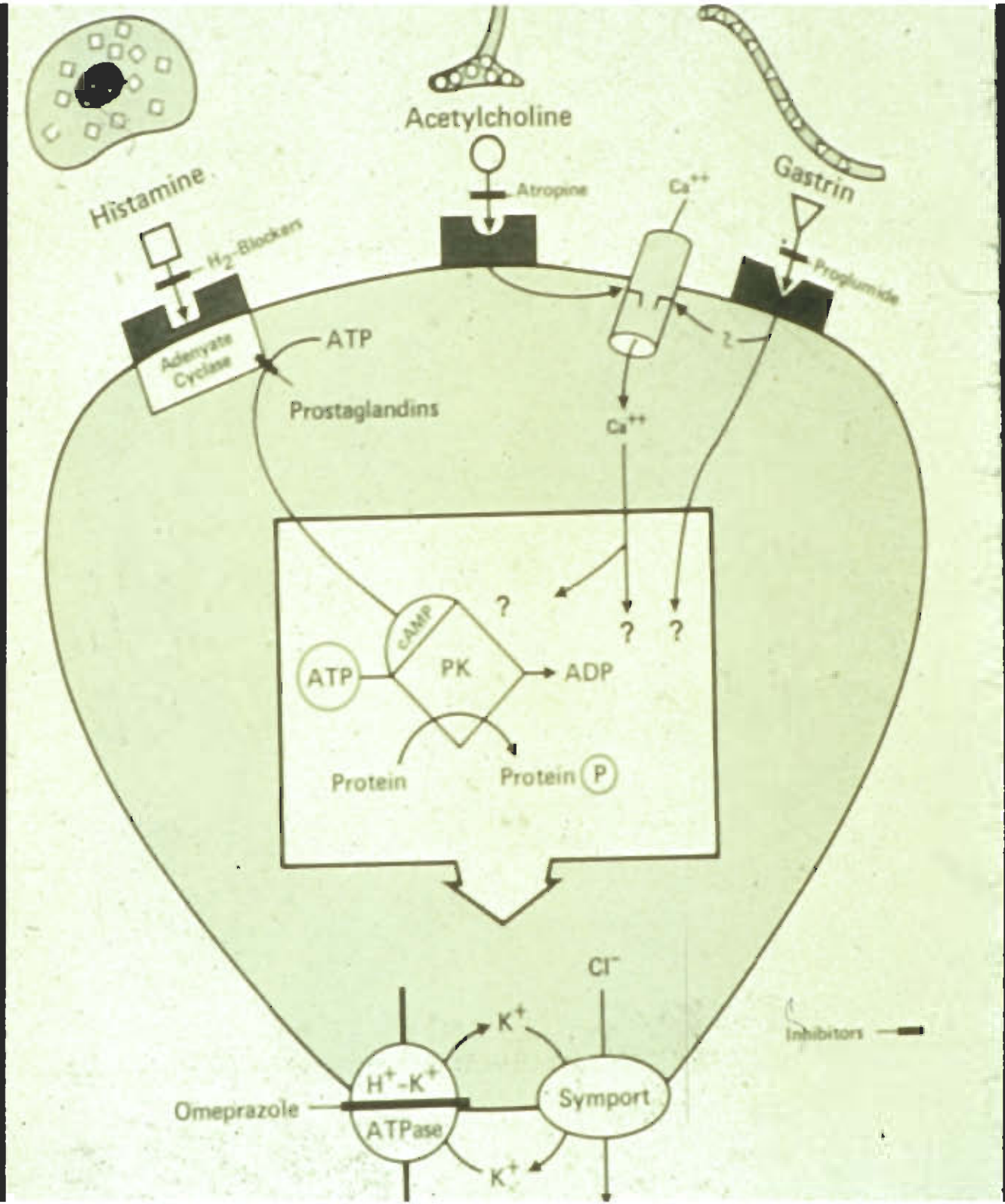
Mechanisms:
Neural: short reflexes (enterogastric reflex) triggered by distension of duodenum
Hormonal:
Primary: stimulation of cholecystokinin (CCK), gastric inhibitory peptide (GIP), and secretin release by presence of acid, carbohydrates, and lipids
Secondary: release of gastrin stimulated by presence of undigested proteins and peptides (not shown)

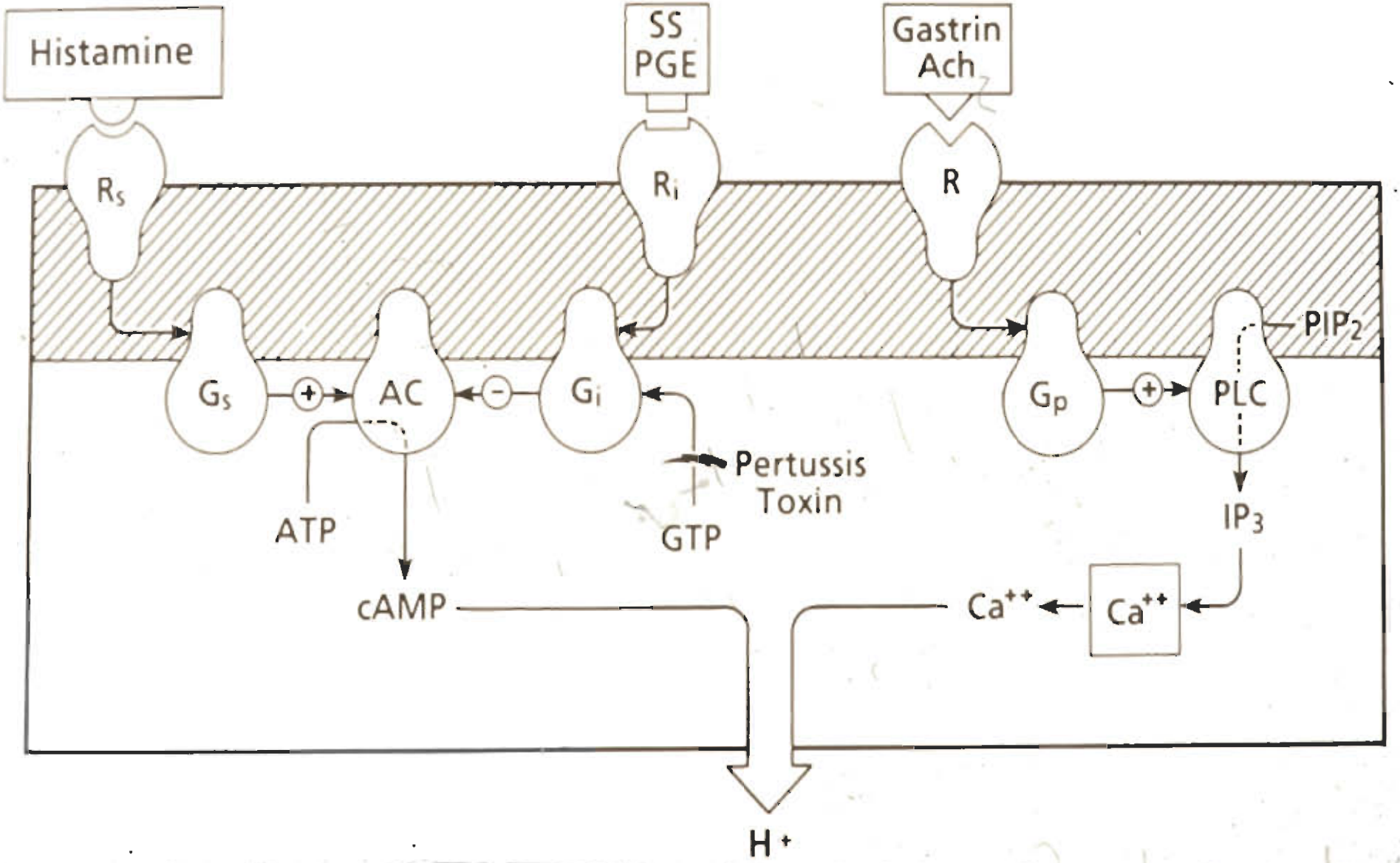
Actions:
Feedback inhibition of gastric acid and pepsinogen production; reduction in gastric motility



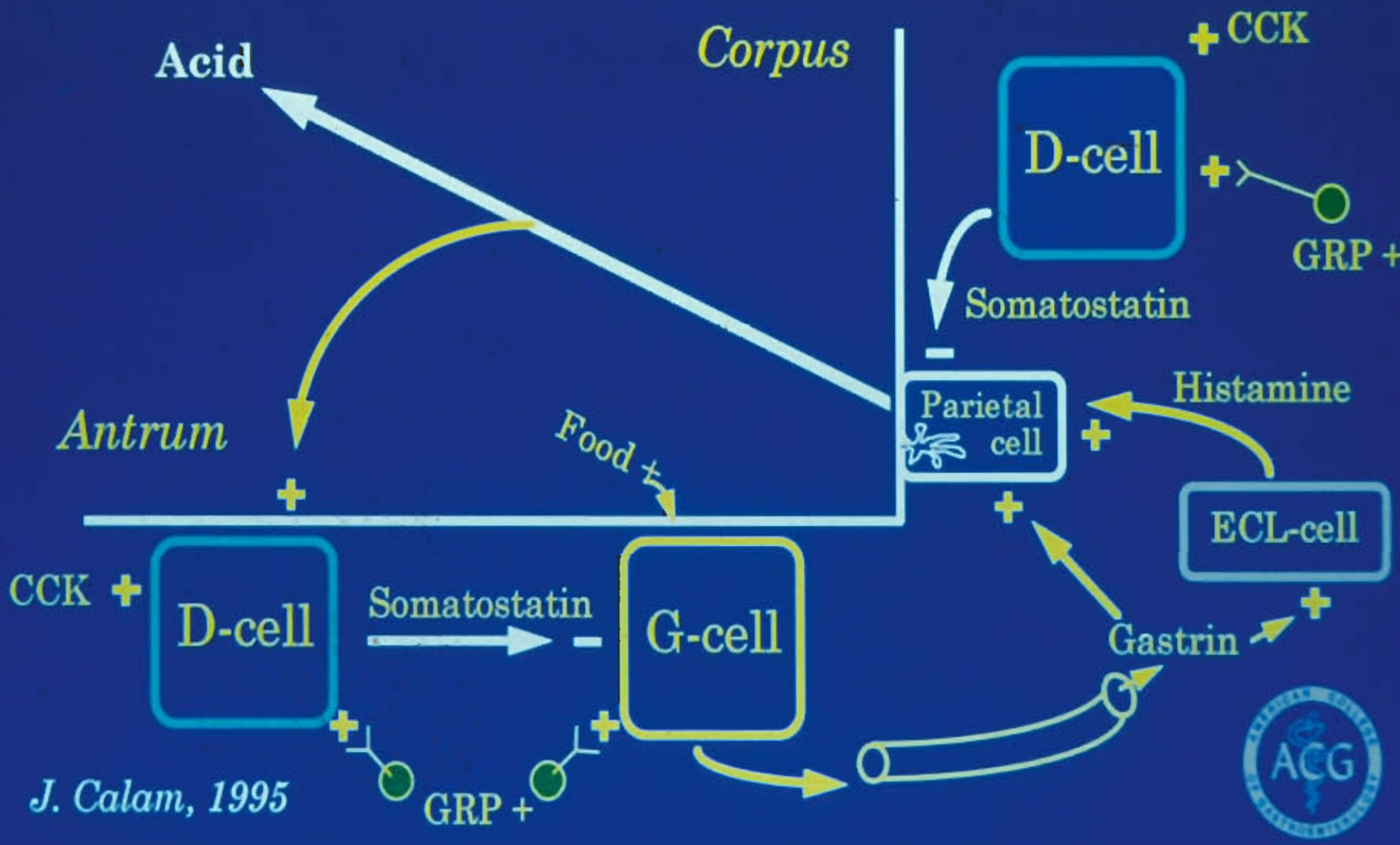
Control Mechanisms of the GI tract




Acetylcholine
Histamine
Gastrin
Atropine
H_2-Blocker
Proglumide
Ca^{++}
Adenylate Cyclase
ATP
Prostaglandins
Ca^{++}
?
?
?
cAMP
ATP
PK
ADP
Protein
Protein (P)
Cl^-
K^+
H^+-K^+ ATPase
Omeprazole
Symport
K^+
Inhibitors


Histamine
SS
PGE
Gastrin
Ach
R_s
R_i
R
G_s
AC
G_i
G_p
PLC
PIP_2
ATP
cAMP
GTP
Pertussis
Toxin
IP_3
Ca^{++}
Ca^{++}
H^+

ACID SECRETION - PATHOPHYSIOLOGY



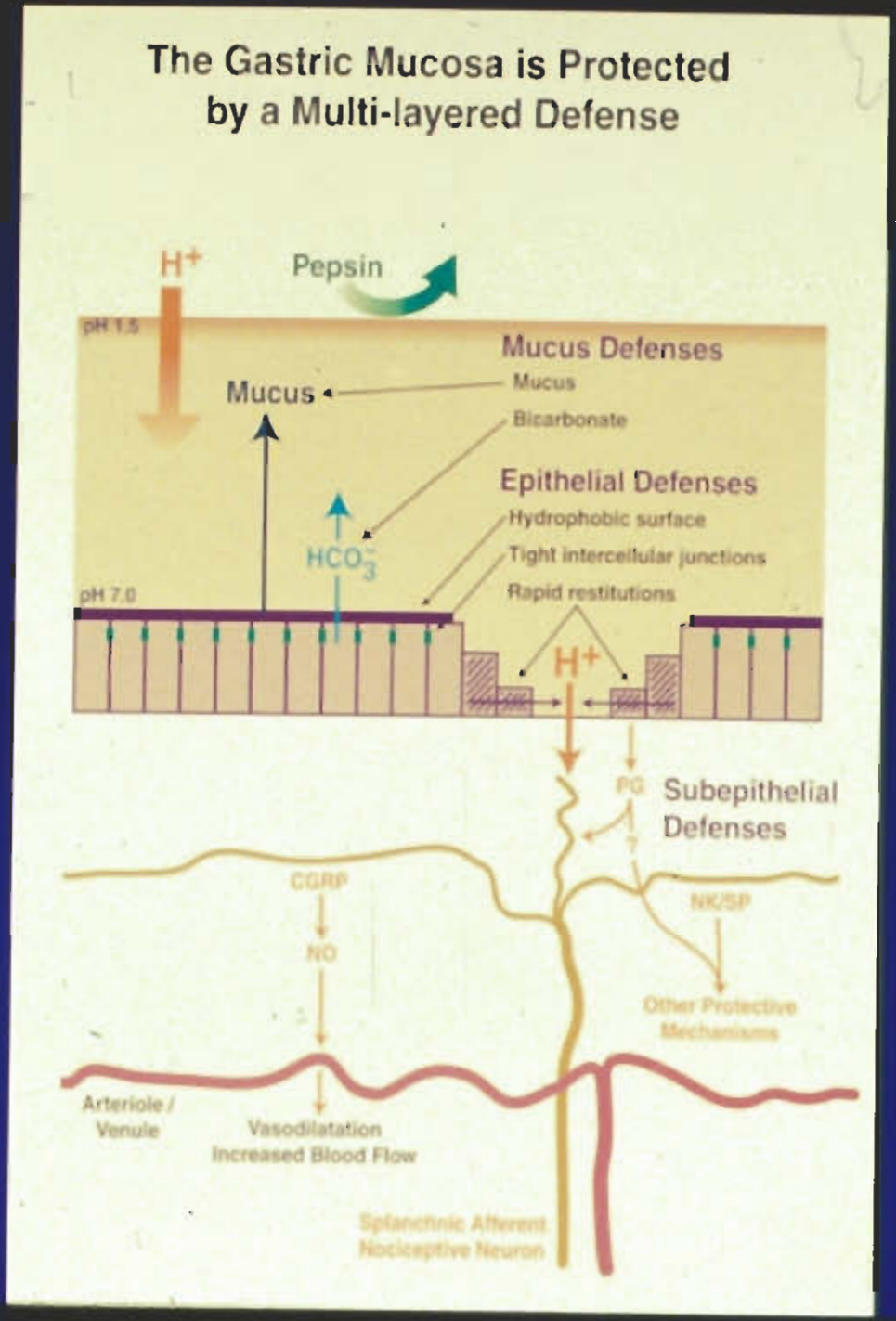
Chief Cells

- Located in the body and fundus
- Secrete pepsinogens (pepsinogen I & II)
  - Inactive precursors of pepsins
- Gastric acid converts pepsinogen to pepsin
  - Unfolding reveals catalytic site
- Inactivated at pH > 6
- Digests ~ 15% of dietary protein

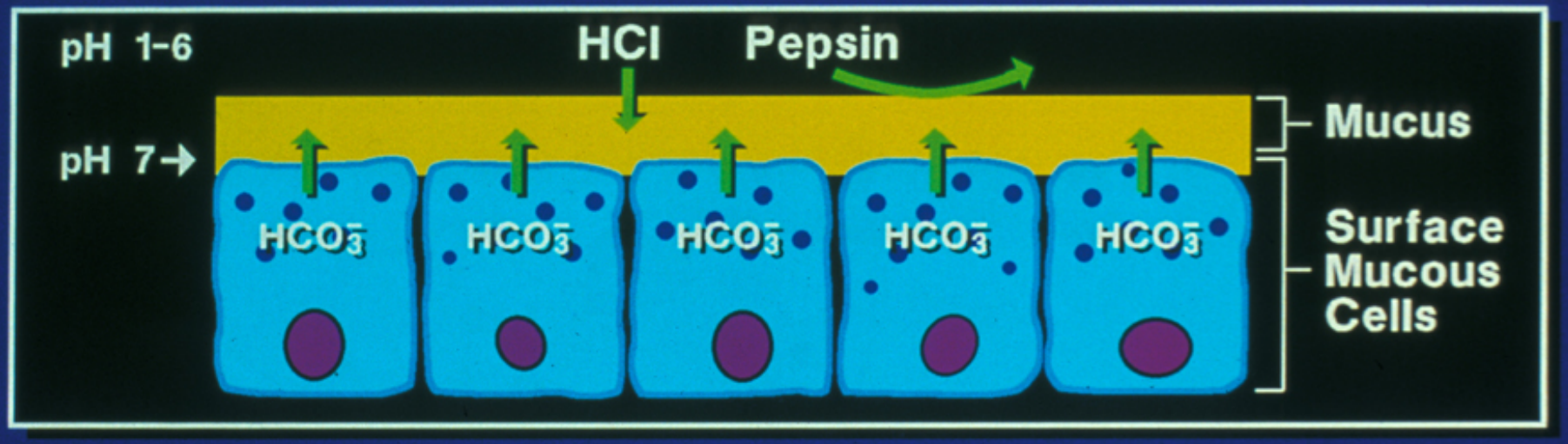
Gastric Mucosal Barrier

- Bicarbonate
- Mucus
- Phospholipids in cell membrane
- Tight junctions
- Rapid cell renewal/restitution
- Mucosal blood flow
- Growth factors, prostaglandins, nitric oxide

The Gastric Mucosa is Protected by a Multi-layered Defense

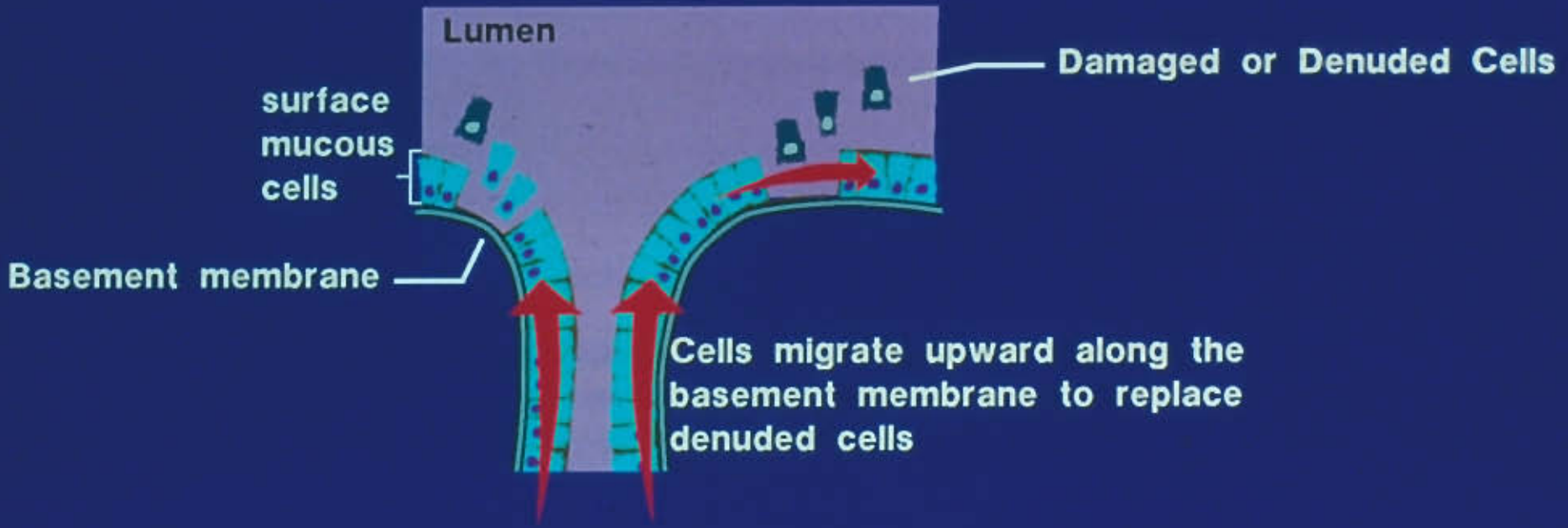


The Upper Gastrointestinal Mucosa is Covered by a Layer of Mucus



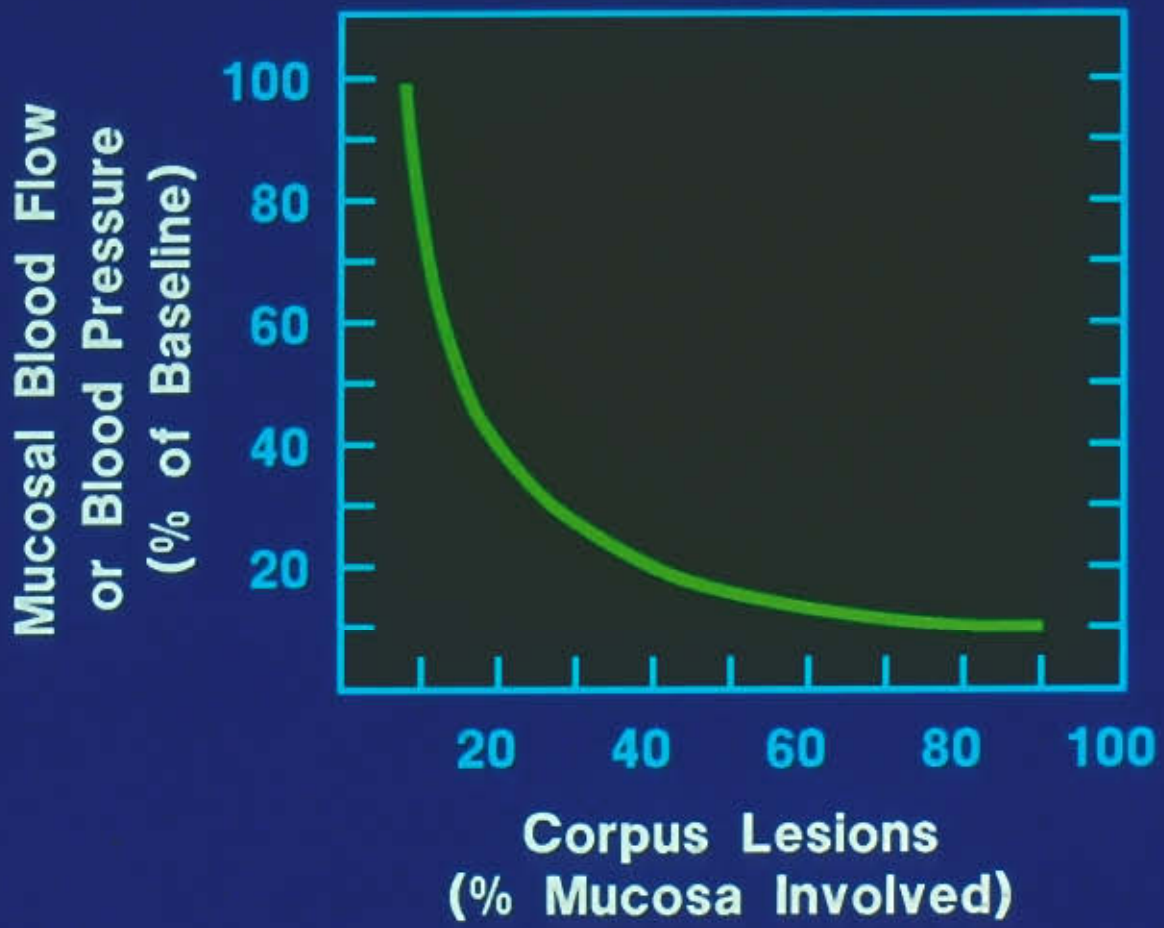
- Unstirred, thin layer of mucus (glycoproteins and water), bicarbonate and surface phospholipids
  - Chemical and physical barrier
- Mucus and bicarbonate secreted by mucus cells
  - Stimulants similar to those for gastric acid

Damaged Gastric Mucosal Cells are Replaced Rapidly by Migration of Surface Mucous Cells Along the Basement Membrane



- This process is referred to as restitution or reconstitution
- It occurs within minutes both *in vivo* and *in vitro*

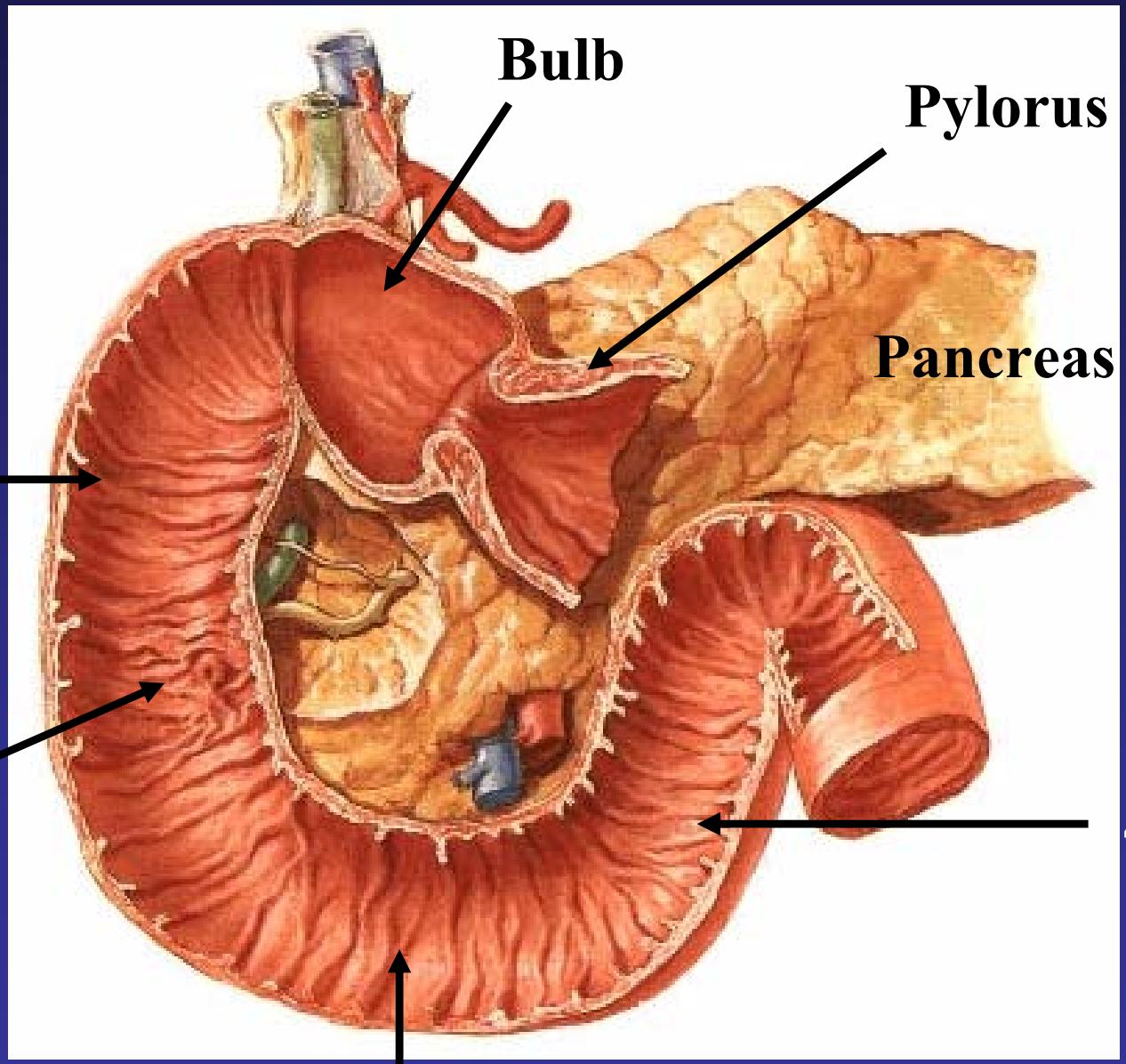
Decreased Mucosal Blood Flow Accentuates Gastric Mucosal Injury



Prostaglandins

- Arachidonic acid $\xrightarrow[\text{(COX)}]{\text{cyclooxygenase}}$ Prostaglandins (PE_2)
- Mediators of inflammation
- Normal functioning in a variety of tissues
- In the stomach:
  - Mucus and bicarbonate secretion
  - Blood flow
  - Cellular repair / restitution
  - Surface phospholipid layer
  - Inhibit parietal cells at high concentrations

Anatomy: Duodenum



Duodenum

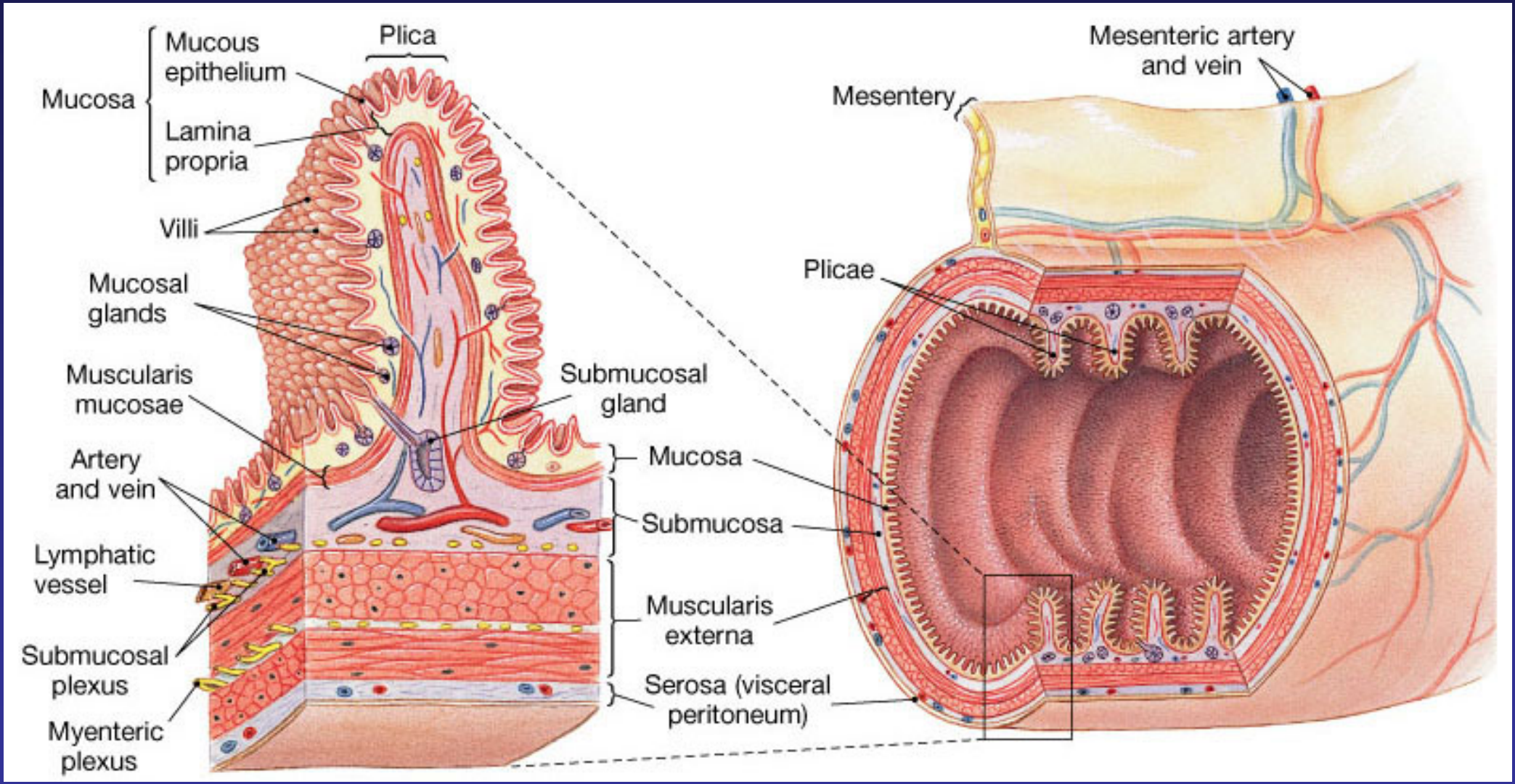
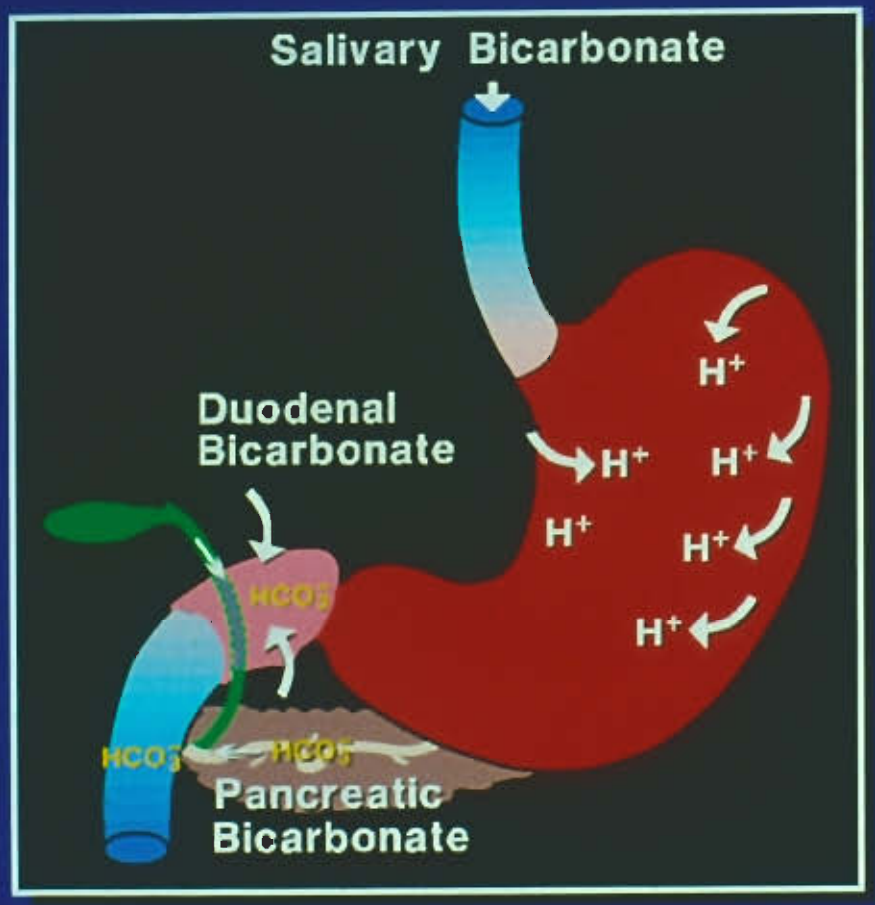
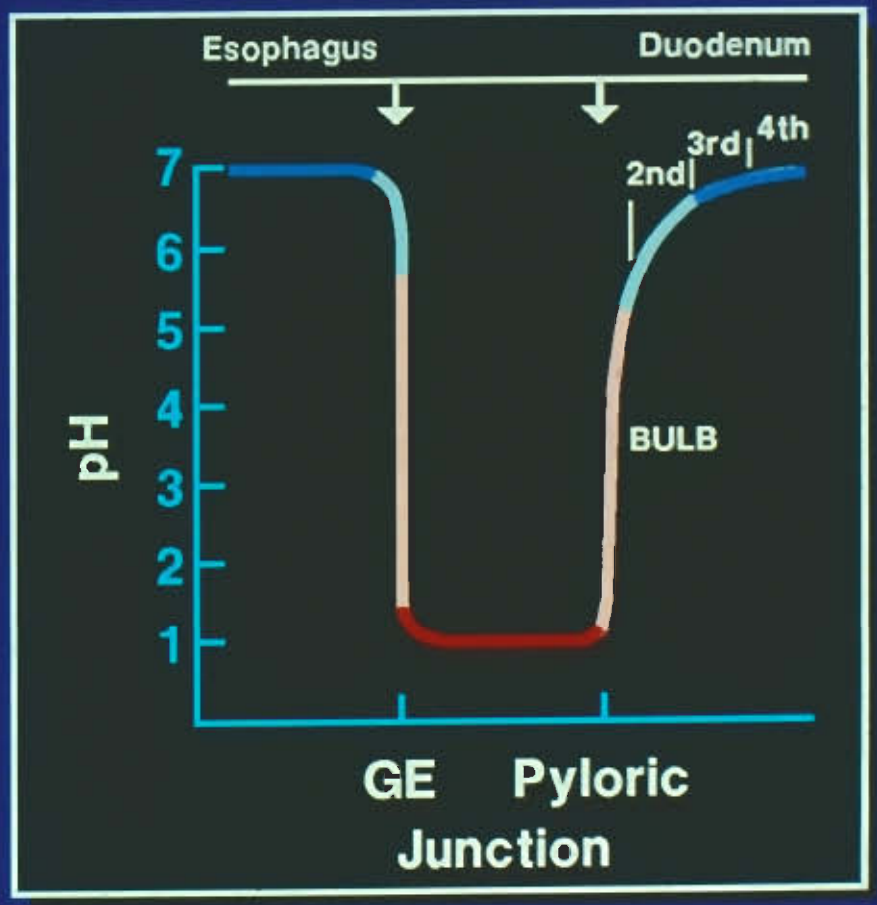


Figure 24.3

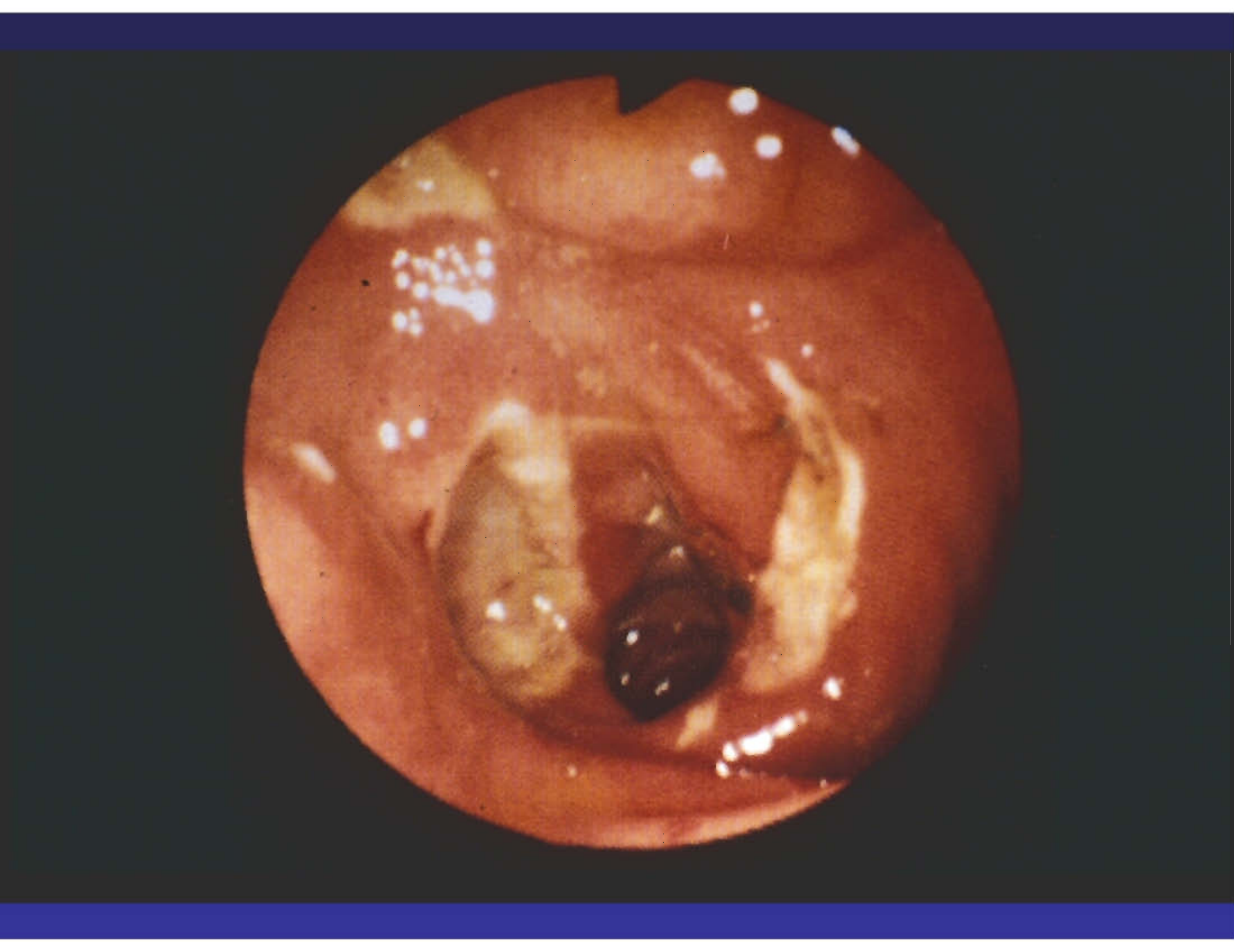
High [H^+] is Confined to the Stomach and Duodenal Bulb





Peptic Ulcer Disease Epidemiology

- 5-10% lifetime risk in U.S.
- 500,000 hospital stays/ year
- 2.5 million physician visits/ year
- 3-5,000 deaths/ year
- 3.3 billion dollars/ year



Clinical Presentation: PUD

Symptoms

- Pain
- Dyspepsia
- Nausea
- Vomiting

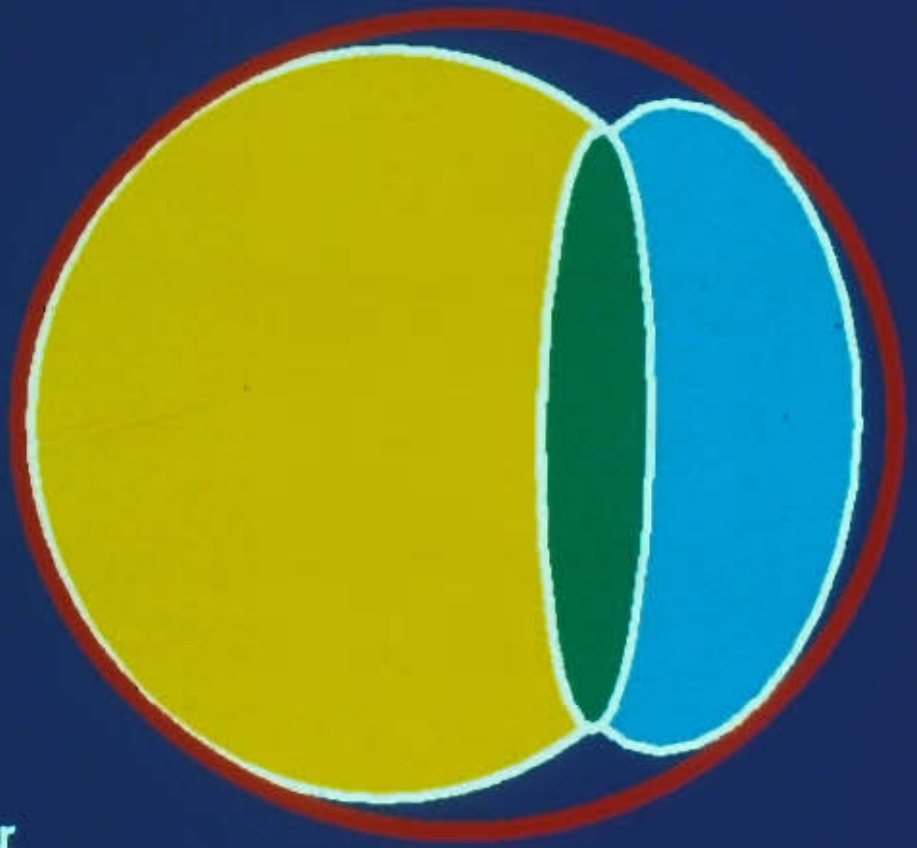
Complications

- Bleeding
- Perforation
- Obstruction

Factors Influencing Mucosal Integrity

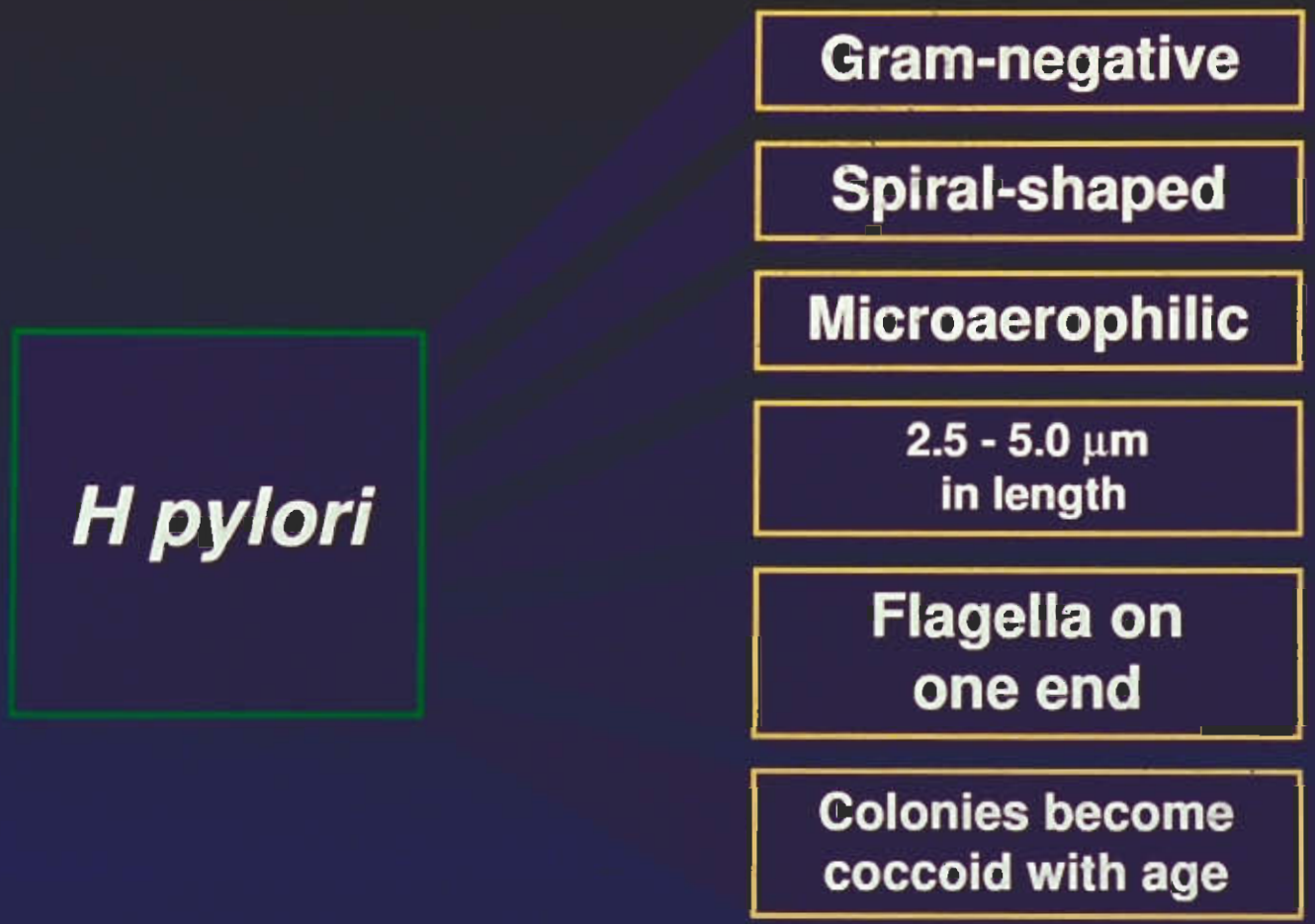
Protective (Defensive)	Deleterious (Aggressive)
Bicarbonate secretion	Acid secretion
Mucus production	H. pylori infection
Prostaglandin synthesis	NSAIDs
Mucosal blood flow	Smoking
Cell turnover & repair	Tissue ischemia/hypoxia
Growth Factors	Genetic factors
Intercellular tight junctions	Bile salts

There are 3 Major Causes of Ulcer Disease

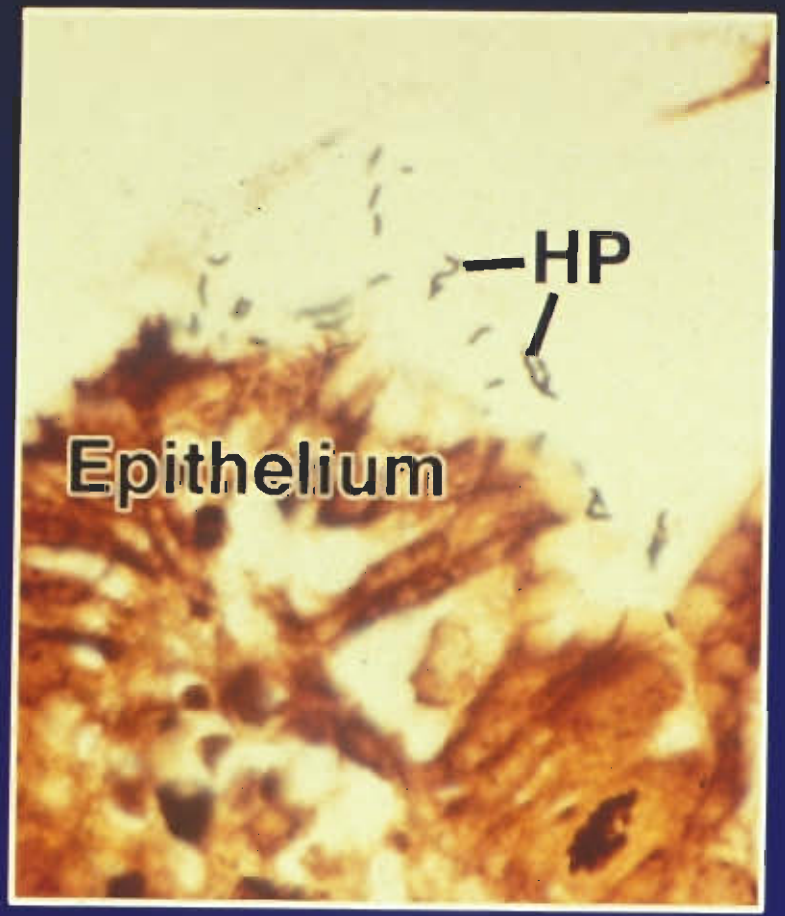


- *Helicobacter pylori*
- Nonsteroidal Antiinflammatory Drugs (NSAIDs)
- Acid
  - Although required for ulcer formation, acid alone rarely causes ulcers

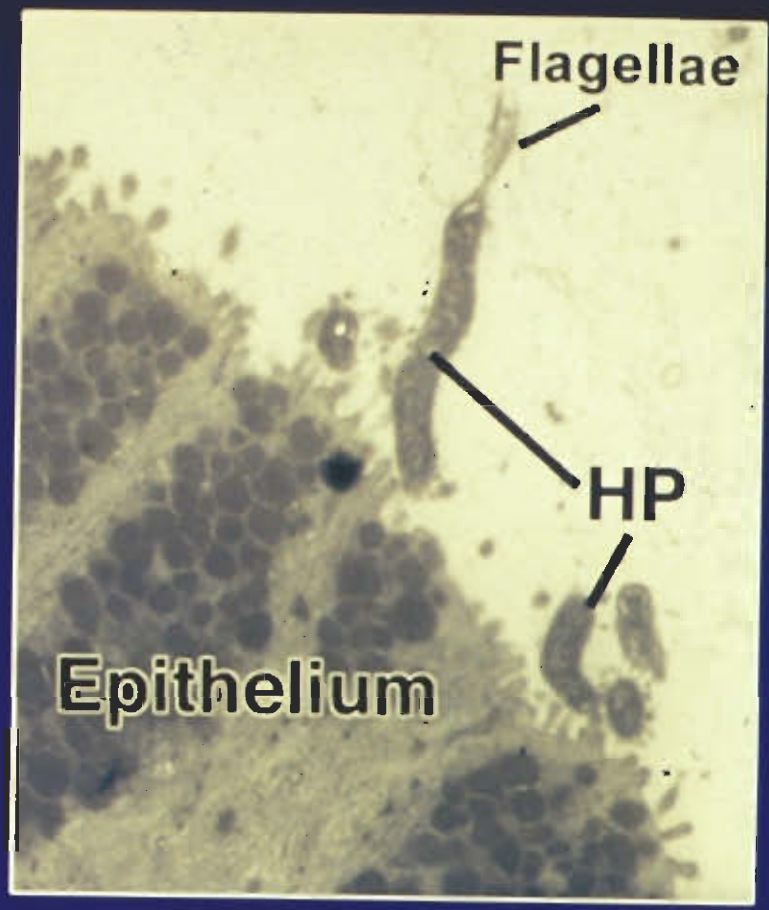
H pylori – the Organism



Helicobacter pylori: Curved Organisms (HP) with Flagellae Over Gastric Epithelium



Light Microscopy



Electron Microscopy

Discovery of *H pylori*

Research interest comes and goes...

- 1984 Marshall & Warren - prove
- 1975 Steer - in ulcer patients
- 1954 Palmer - disputes finding
- 1938 Doenges - in humans
- 1896 Salomon - in cats/dogs
- 1893 Bizzozero - in dogs

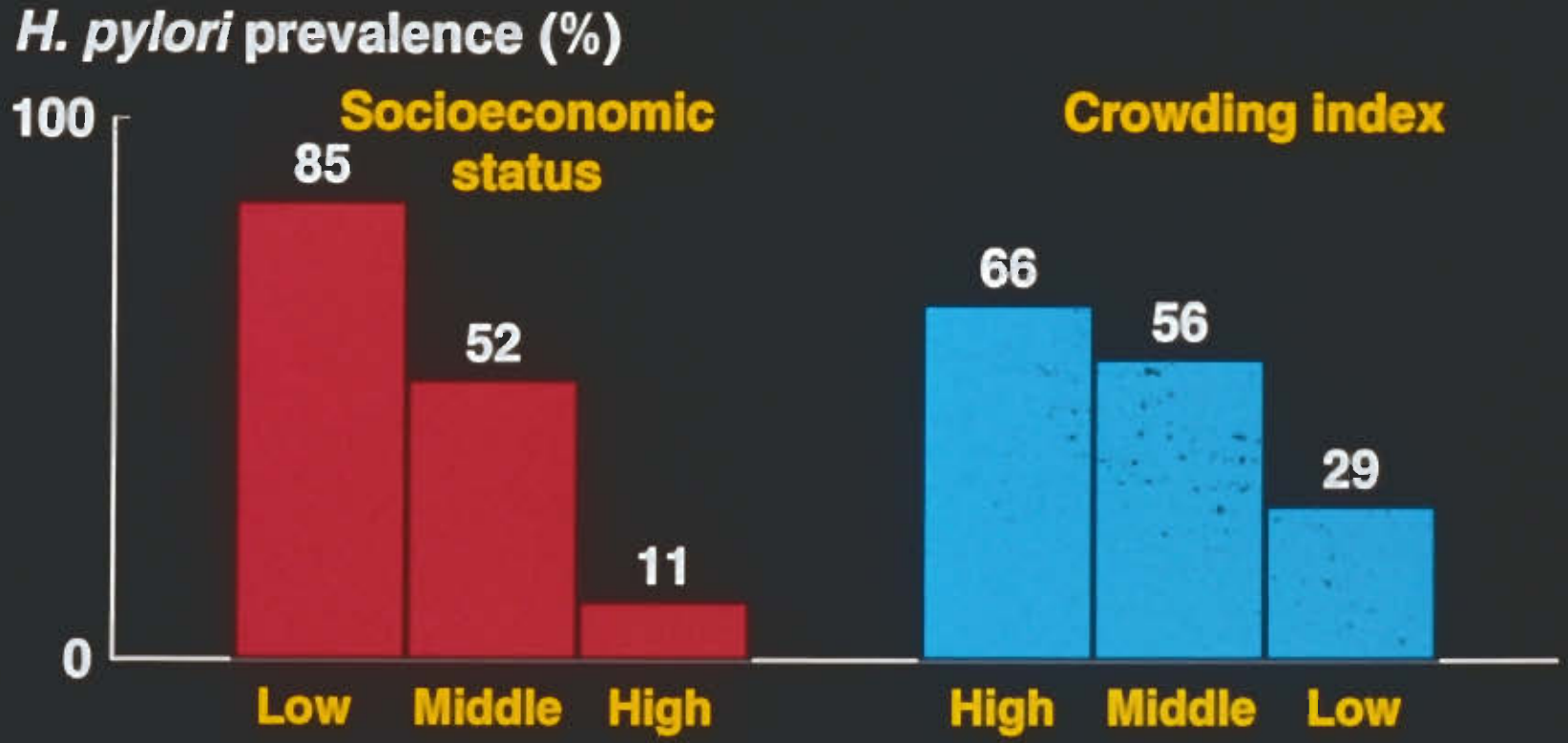
Koch's Postulates – Proof

Requirement	Marshall's Fulfillment
1. Observe microorganism in every case of disease	• Observes spiral bacilli in gastric biopsy specimens from patients with GU, DU, and gastritis
2. Isolate and grow in culture	• Grown over Easter weekend in 1984 after 34 failures
3. Culture reproduces disease when animal inoculated	• Marshall ingests culture; endoscopically-confirmed gastritis 10 days later
4. Observe in and recover from the experimentally diseased animal	• *H pylori* taken from Marshall biopsy grown in culture

Epidemiology and Transmission

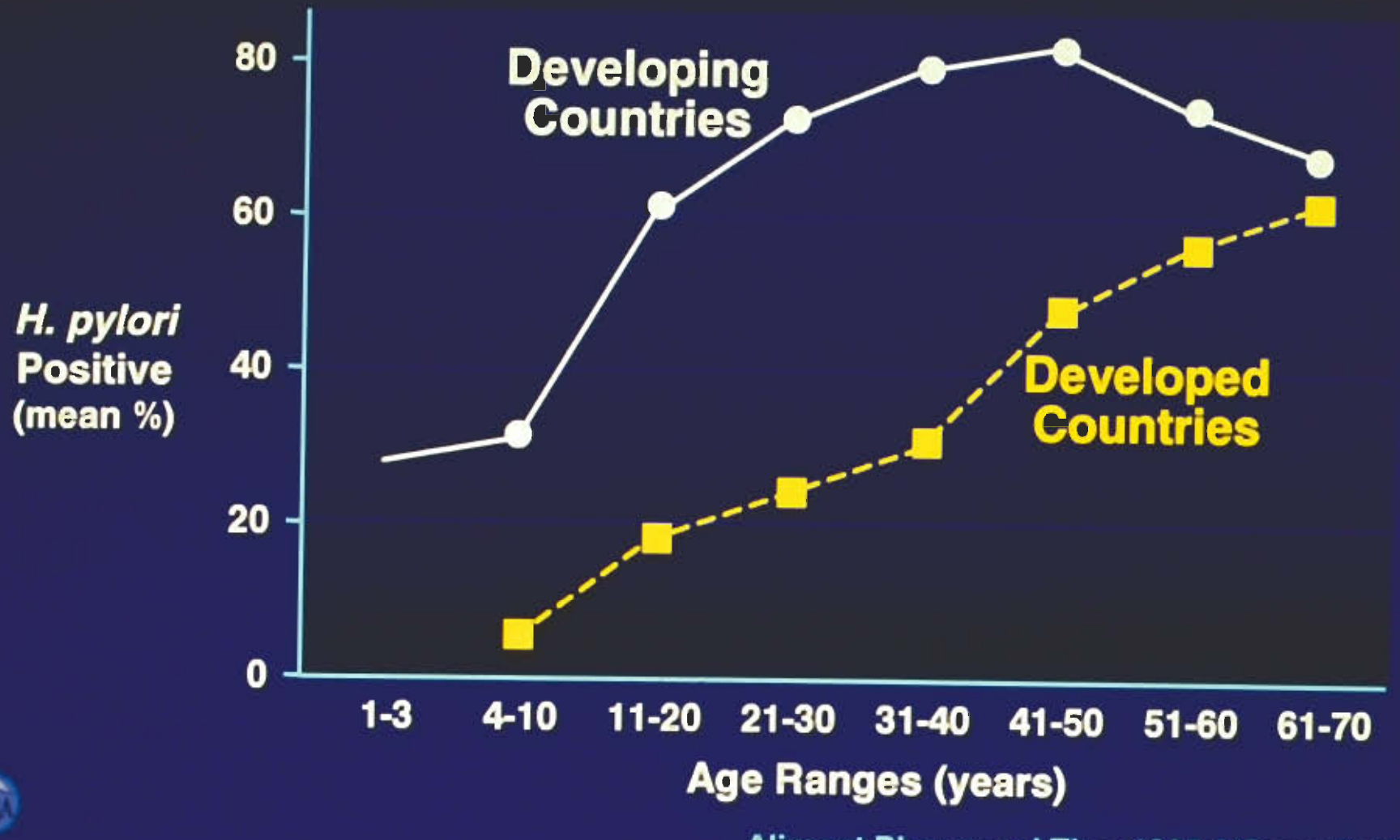
- Overall prevalence closely correlated with socioeconomic conditions
- Prevalence is >80% many developing countries as compared to 20-50% industrialized countries – decreasing substantially over recent decades
- Infection acquired by oral ingestion of the bacteria
- Direct transmission from person to person occurs from vomitus, saliva, feces, and water supply

H. pylori prevalence related to childhood, socioeconomic status and crowding



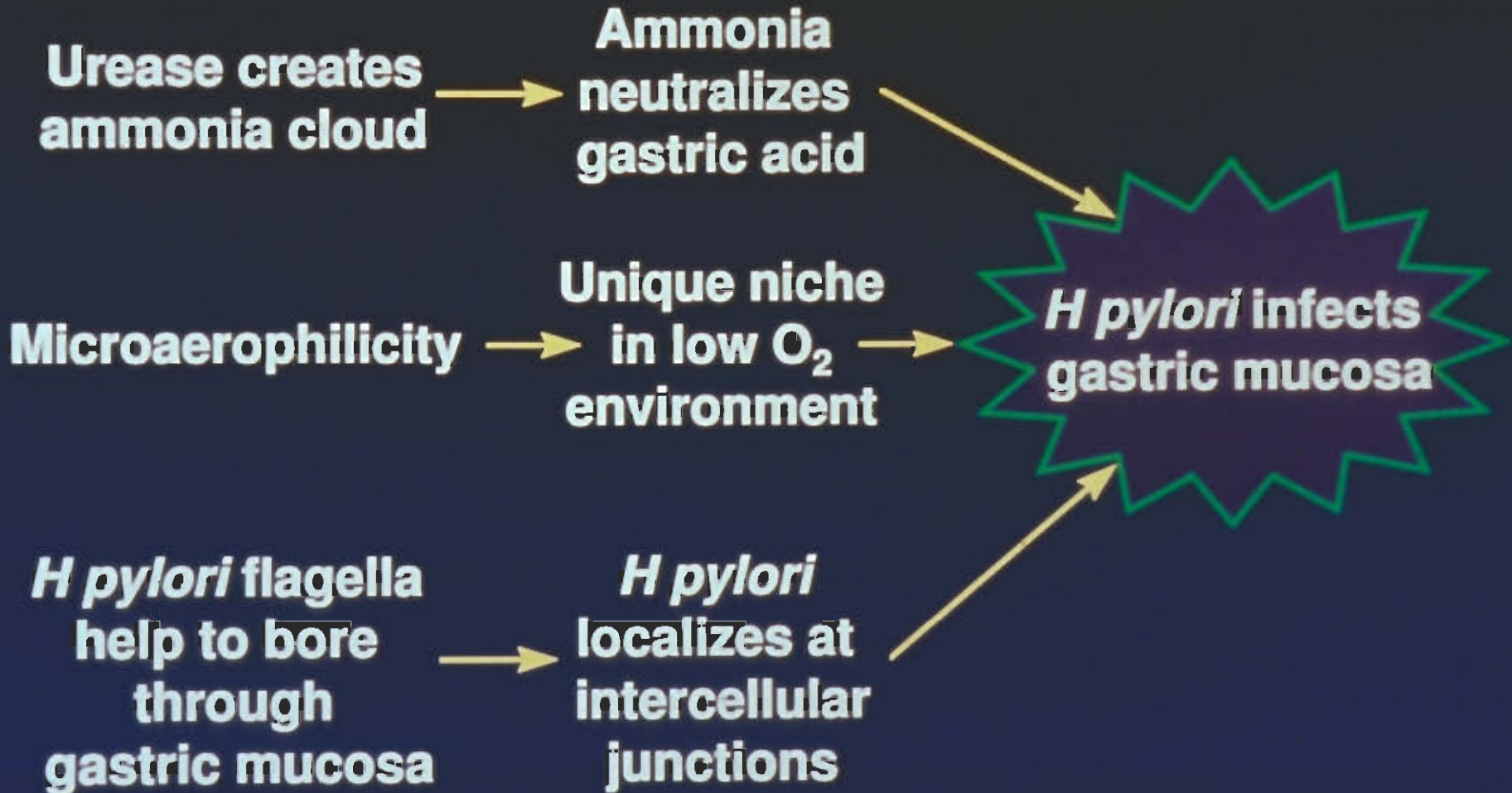
Malaty and Graham, 1994

Prevalence of *Helicobacter pylori* Infection In Developing vs Developed Countries

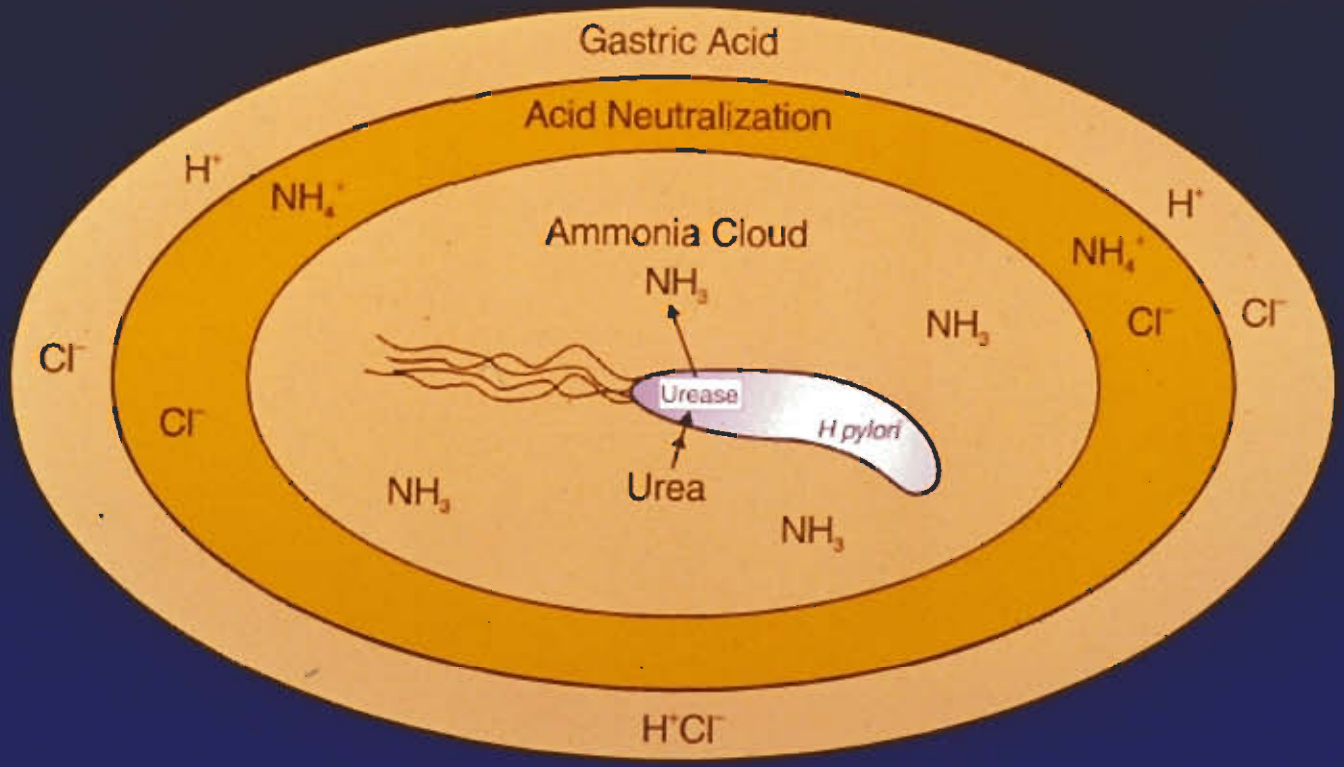


Aliment Pharmacol Ther 1995;9(Supp 2):33

How Does *H pylori* Survive?



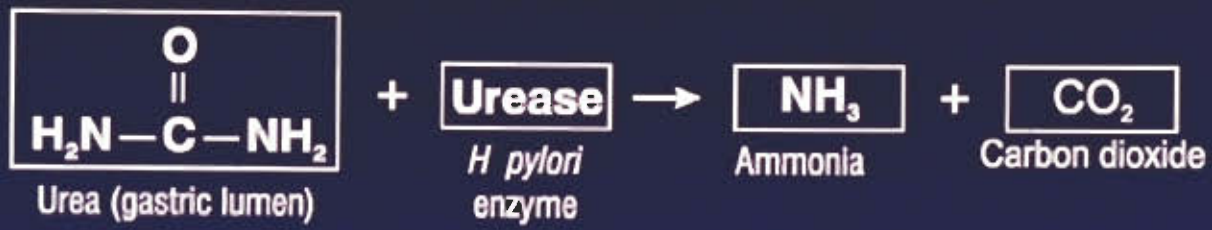
Protected by an Ammonia Cloud



[Adapted from Lee, 1994]

From Urea to Ammonia... to Neutralization

Ammonia Production



Gastric Acid Neutralization

acidic pH **neutral pH**

[Adapted from Mobley et al, 1991]

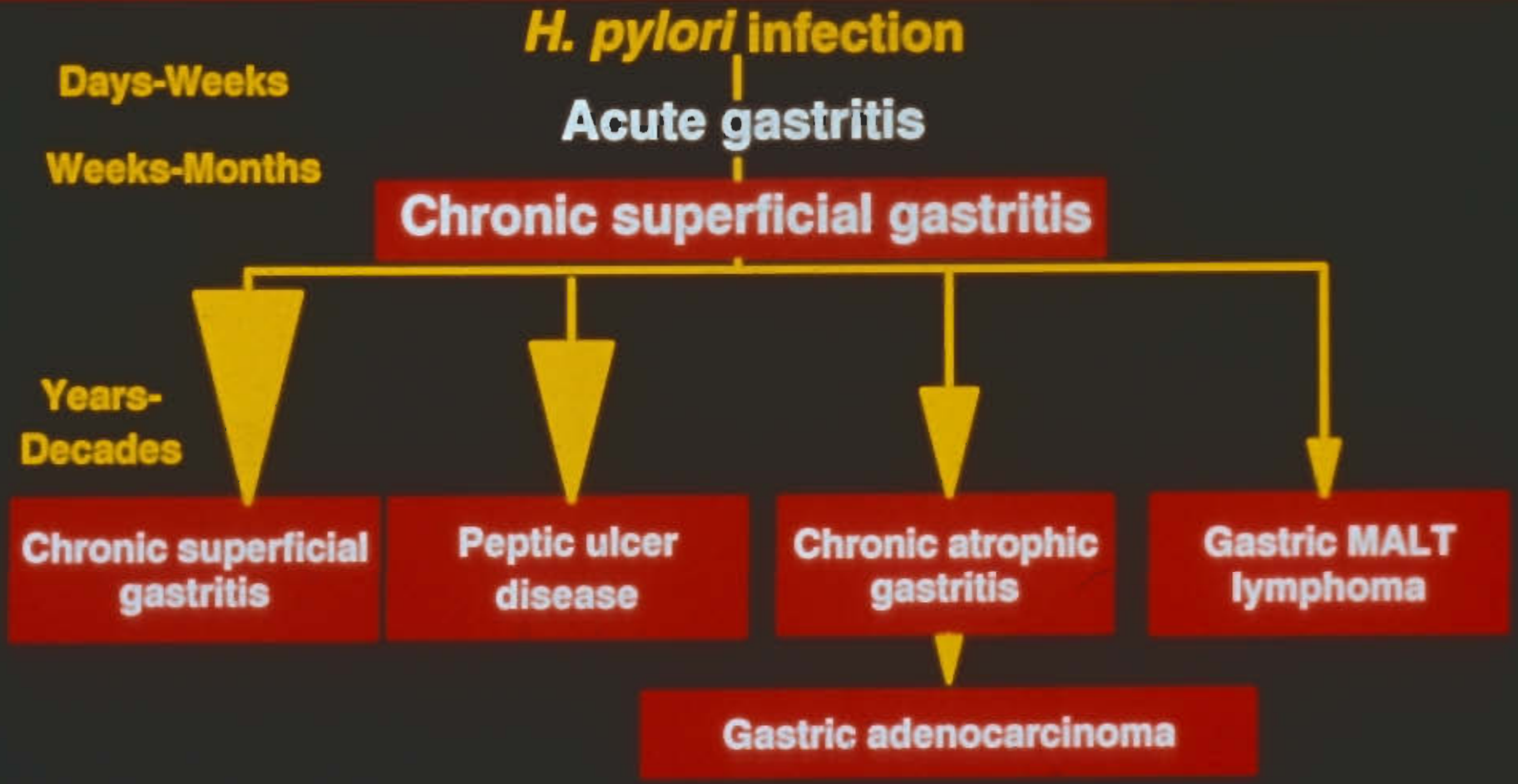
Pathogenic Mechanisms of H. Pylori

Feature	Mechanism
Flagella	Penetration of mucus layer
Adhesins	Attachment to mucosa
Urease enzyme	Neutralization of acid
Cytotoxins (cag A, vacA)	Inducement of tissue injury
Lipopolysaccharide	Inhibition of mucin synthesis
Interleukins (IL-1, IL-8)	Recruitment of neutrophils
Tumor necrosis factor	Alteration in microvascular permeability

H. Pylori Infection Natural History

- Asymptomatic in most individuals
- Most infections occur in childhood
- Spontaneous clearance is rare
- Re-infection after cure is rare
- Chronic gastritis is seen in nearly all

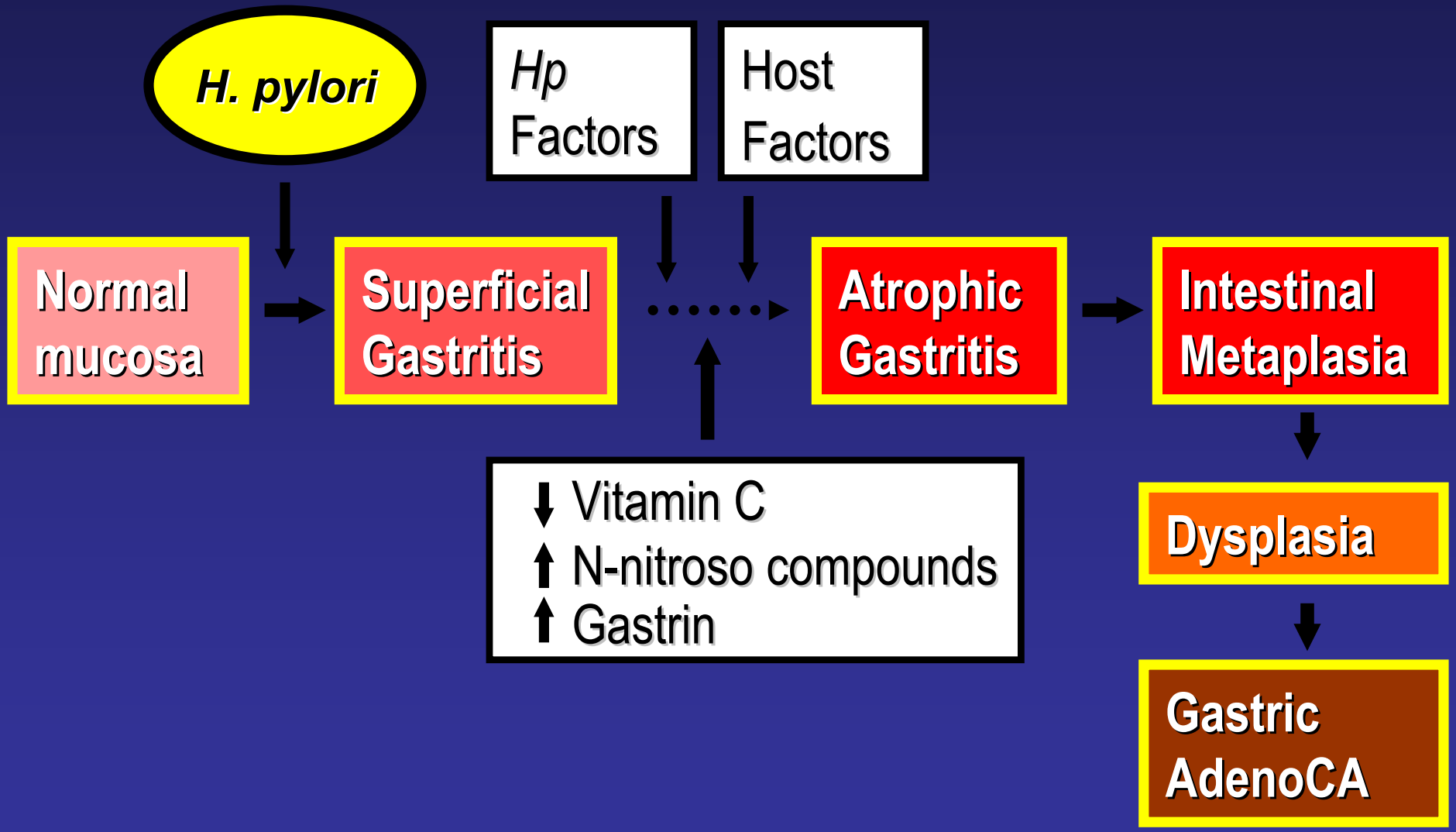
H. pylori: Association with gastroduodenal disease



H. Pylori and PUD

- Most common cause of PUD
- Lifetime risk 3% in U.S. 25% in Japan
- 70% recurrence without treatment
- 2-4% after successful treatment
- Antral gastritis $\rightarrow$ Duodenal ulcer
- Body gastritis $\rightarrow$ Gastric ulcer $\rightarrow$ Atrophy $\rightarrow$ Metaplasia

Proposed Model of Gastric Carcinogenesis



Indications for H. Pylori Eradication

Definite	Probable	Not Recommended
Active duodenal ulcer	Atrophic gastritis	Asymptomatic
Active gastric ulcer	Dyspepsia	Extraintestinal disease
Personal hx gastric CA	FmHx gastric CA	Prevention of gastric CA
Prior GU/DU	Patient Request	Longterm PPI
Intestinal metaplasia		
MALT Lymphoma		
NSAID therapy & Hx of PUD		

Diagnostic Tests for Helicobacter pylori

	Sensitivity (%)	Specificity (%)	Cost ($)
Noninvasive			
ELISA, serum	90	85	40-100
Urea breath test	95	90	250-350
Stool antigen assay	90	90	60
Invasive			
Biopsy urease test	90	98	6-20
Histology	95	98	60-250
Culture	90	100	150

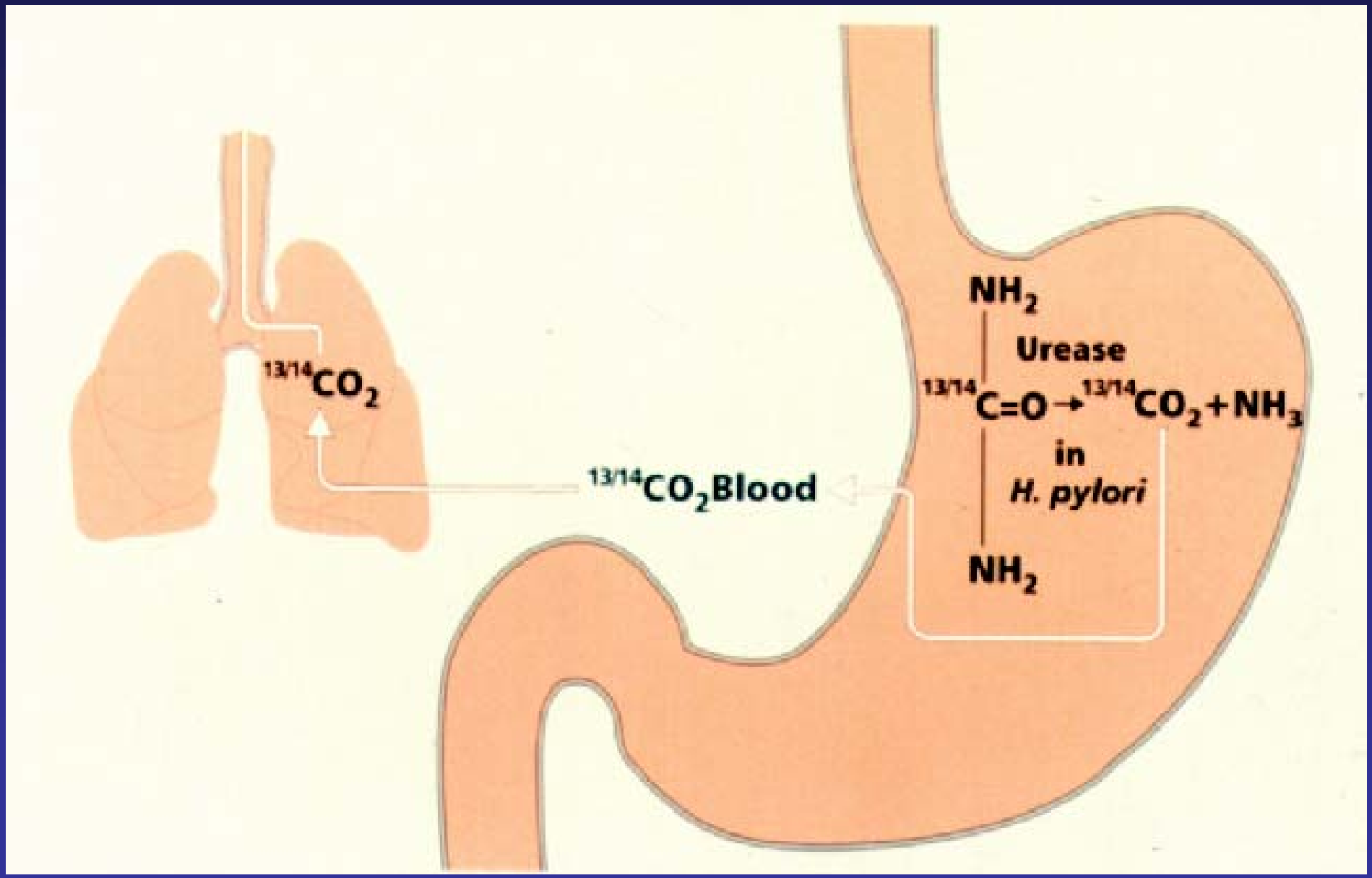
Serology

- Test of choice when endoscopy is not indicated
  - Noninvasive
  - Inexpensive
  - Good sensitivity/specificity
- IgG antibodies
  - ELISA (laboratory)
  - Immunoassay (office)
- Limited usefulness in follow-up testing for eradication

Urea Breath Tests (^{13}C and ^{14}C)

- Test of choice to confirm *H. pylori* eradication
  - Noninvasive
  - Less expensive than endoscopy
  - Samples entire stomach
- False-negative results may occur shortly after treatment

Principle of the ^{13}C- or ^{14}C-urea breath test



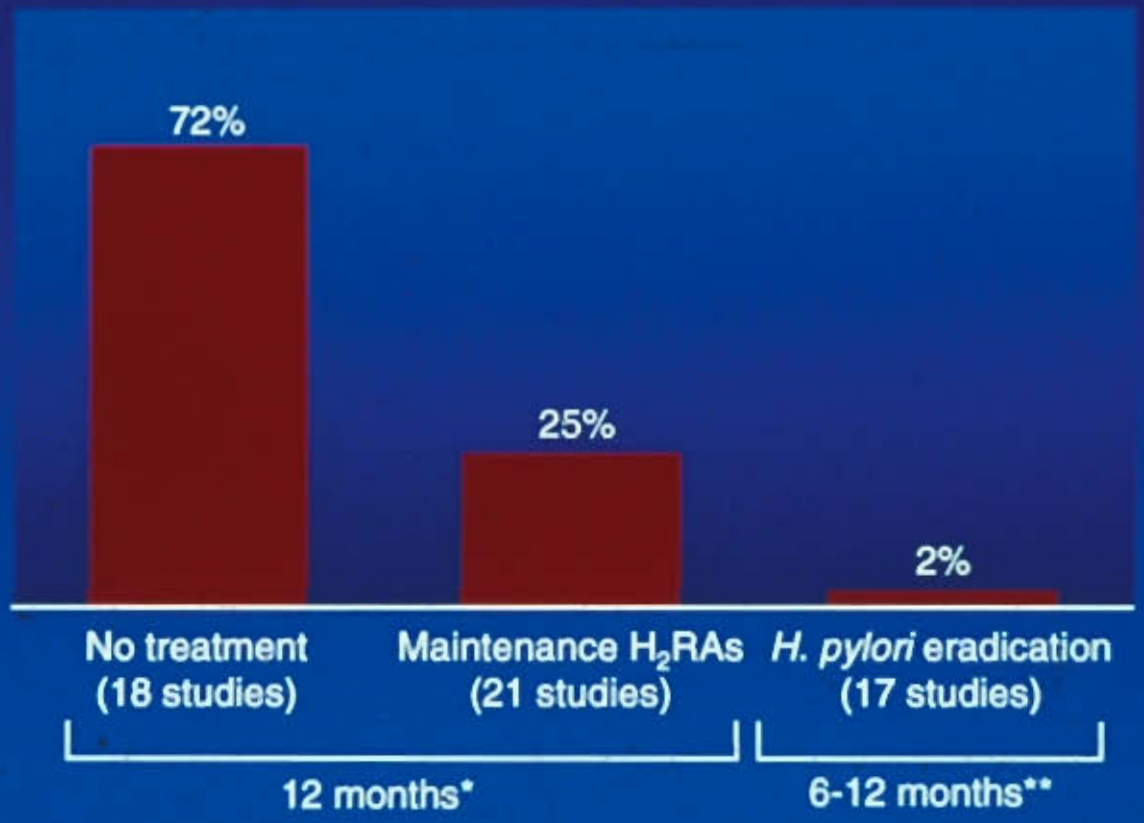
Culture

- Culture gastric tissue
- Can perform antibiotic sensitivity testing on isolates
- Limitations
  - Not widely available
  - Requires laboratory expertise
  - Relatively expensive
  - Delayed diagnosis

H. Pylori Treatments

	Eradication (%)
Monotherapy	
Amoxicillin or Clarithro or Metronidazole	15-20
Dual therapy	
PPI + Clarithromycin	50-80
PPI + Amoxicillin	50-90
Triple therapy	
Bismuth + Metronidazole +Tetracycline	82-96
Bismuth + Metronidazole +Amoxicillin	75-90
Bismuth + Clarithromycin +Tetracycline	95
PPI + Metronidazole + Clarithromycin	80-90
PPI + Clarithromycin + Amoxicillin	80-90
PPI + Metronidazole + Amoxicillin	80-90
H2RA + Metronidazole + Amoxicillin	90
Quadruple therapy	
Bismuth + Metronidazole + Tetracycline + PPI	94-98
Bismuth + Metronidazole + Tetracycline + H2RA	85-95

Duodenal Ulcer Recurrence: Results of Three Strategies



*Freston, Am J Gastroenterol 1987:82(12):1242

**Data from Tytgat and Rauws, Gastroenterol Clin NA 1993;19:183

How much NSAID use is there in the US?

- 21 million US adults have symptomatic OA[1]
  - leading cause of work-related disability, and disability in patients aged >65 years
- 70% of people aged >65 years take NSAIDs at least weekly. 34% take at least 1 tablet per day[3]
- 111,400,000 prescriptions annually for NSAIDs[4]
- $4.8 billion in annual drug costs[3]

[1] Lawrence et al, Arthritis Rheum 1998; 41: 778
[2] Gucione, Am J Pub Health 1994; 84: 351
[3] Talley et al, Dig Dis Sci 1995; 40: 1345
[4] Laine, Gastroenterology 2001; 120: 594

How do NSAIDs cause gastric injury?

Topical

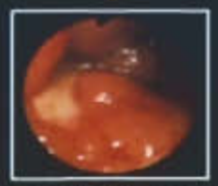
- Intragastric pH <2.5
  - ionization of NSAID
  - inhibition cell metabolism
- ↑ cell permability

Inhibition of protective PGs

- Reduction in:
  - mucosal blood flow
  - mucin
  - phospholipid
  - HCO_3^-
- ↓ cell restitution

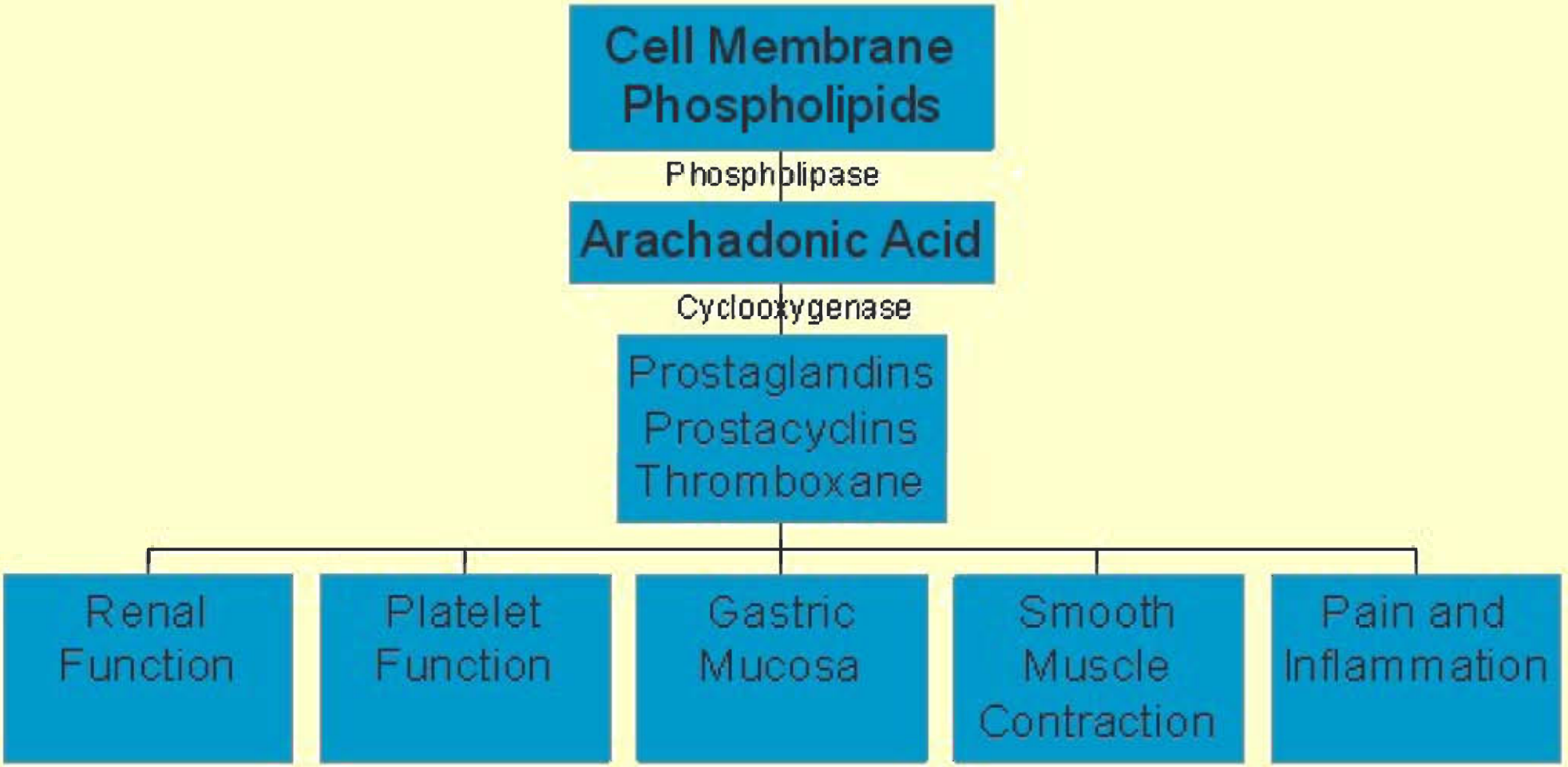
Microvascular injury

- Inhibits NO
- Ischemia
- Free radicals

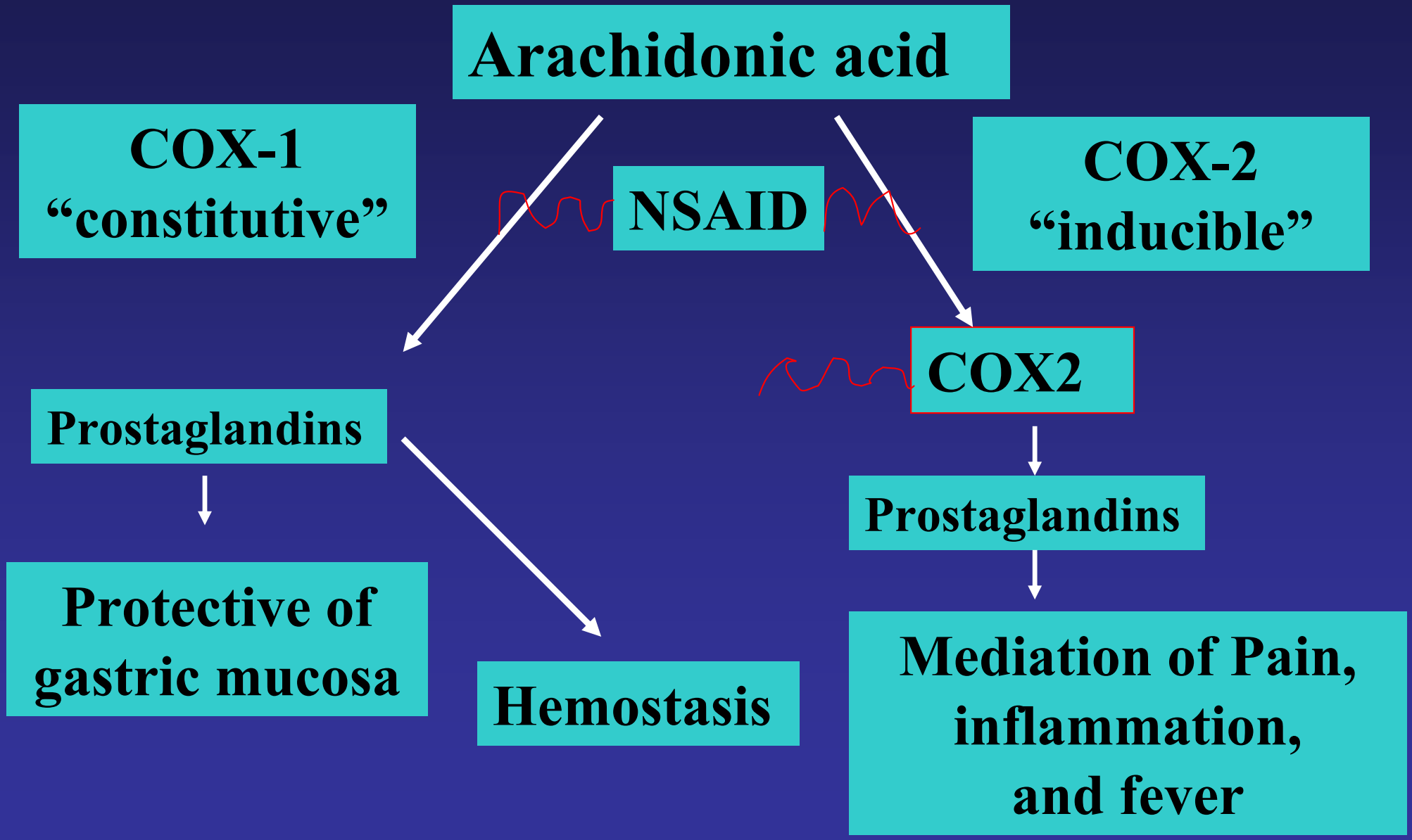


Mucosal damage and ulceration

Prostaglandin production



Mechanisms of NSAIDS vs COX2 Inhibitors



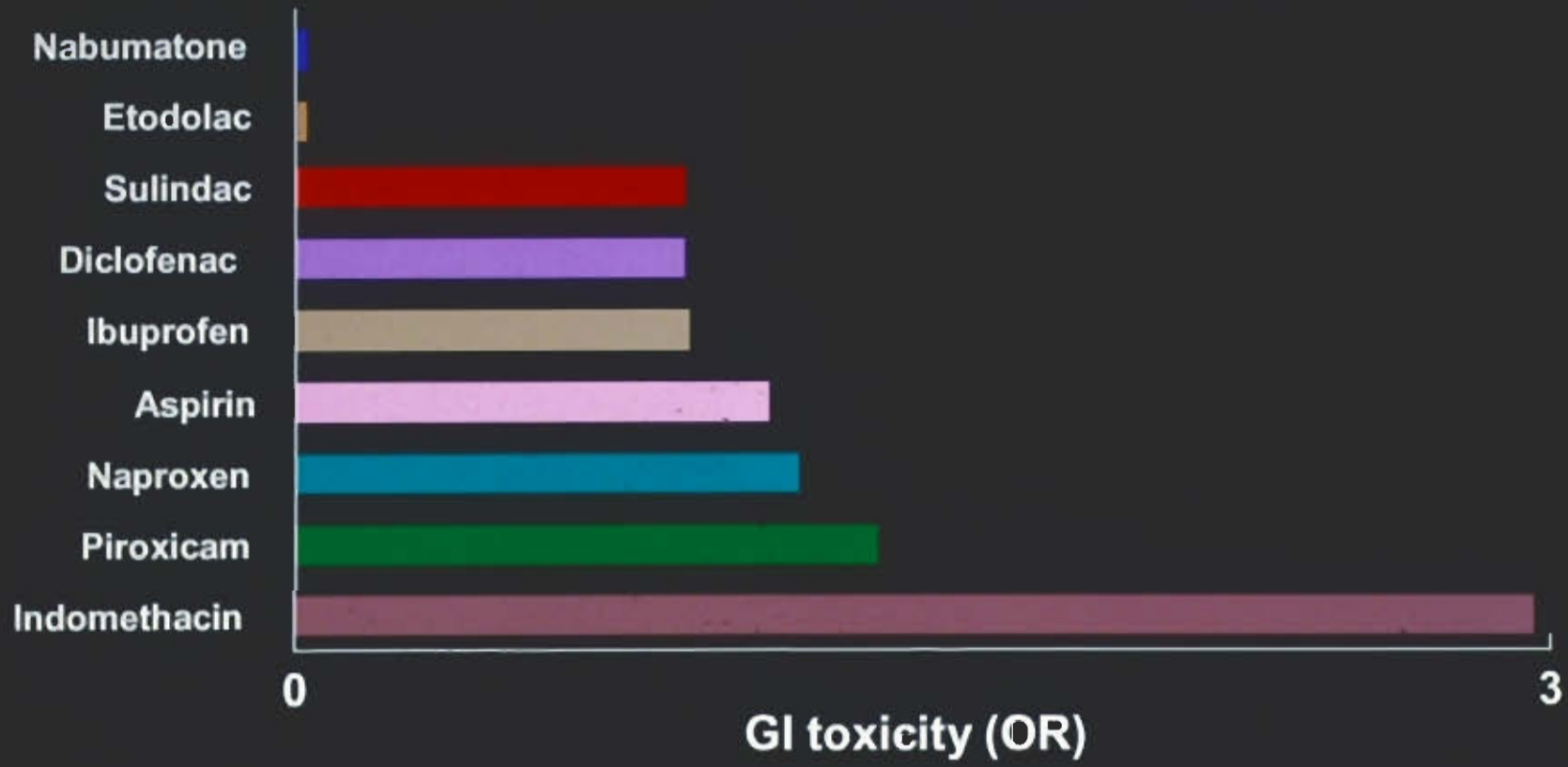
Cox-2 Selective Inhibitors

- ↓ gastrointestinal toxicity
  - Fewer symptomatic and endoscopic ulcers
  - Safety lost with high doses and low-dose aspirin use
- ↑ risk of major cardiovascular events
  - Inhibit prostacyclin
    - ↑ platelet aggregation & ↓ vasodilation
  - No inhibition of thromboxane A2
    - ↑ platelet aggregation & ↓ vasodilation

Ulcer complications with celecoxib and NSAIDs in aspirin users

Silverstein et al, JAMA 2000; 284: 1247

Are some NSAIDs safer than others?



Singh et al, Arthritis Rheum 1997; 40: 5115

Risk Factors for NSAID Ulcers

- NSAID
  - Type
  - Dose
  - Duration
- Age > 70
- Corticosteroid use
- Anticoagulant use
- History of PUD
- H. pylori infection

Zollinger Ellison Syndrome

- Accounts for < 0.1% of all duodenal ulcers
- Classic triad
  - Ulcers in unusual locations or multiple ulcers
  - Hypersecretion of acid
  - Non-beta islet cell tumor of pancreas (gastrinoma)
- 20-25% ZES pts have MEN type I syndrome
  - Parathyroid, pituitary, pancreatic islet cell tumors

Diagnosis of ZES

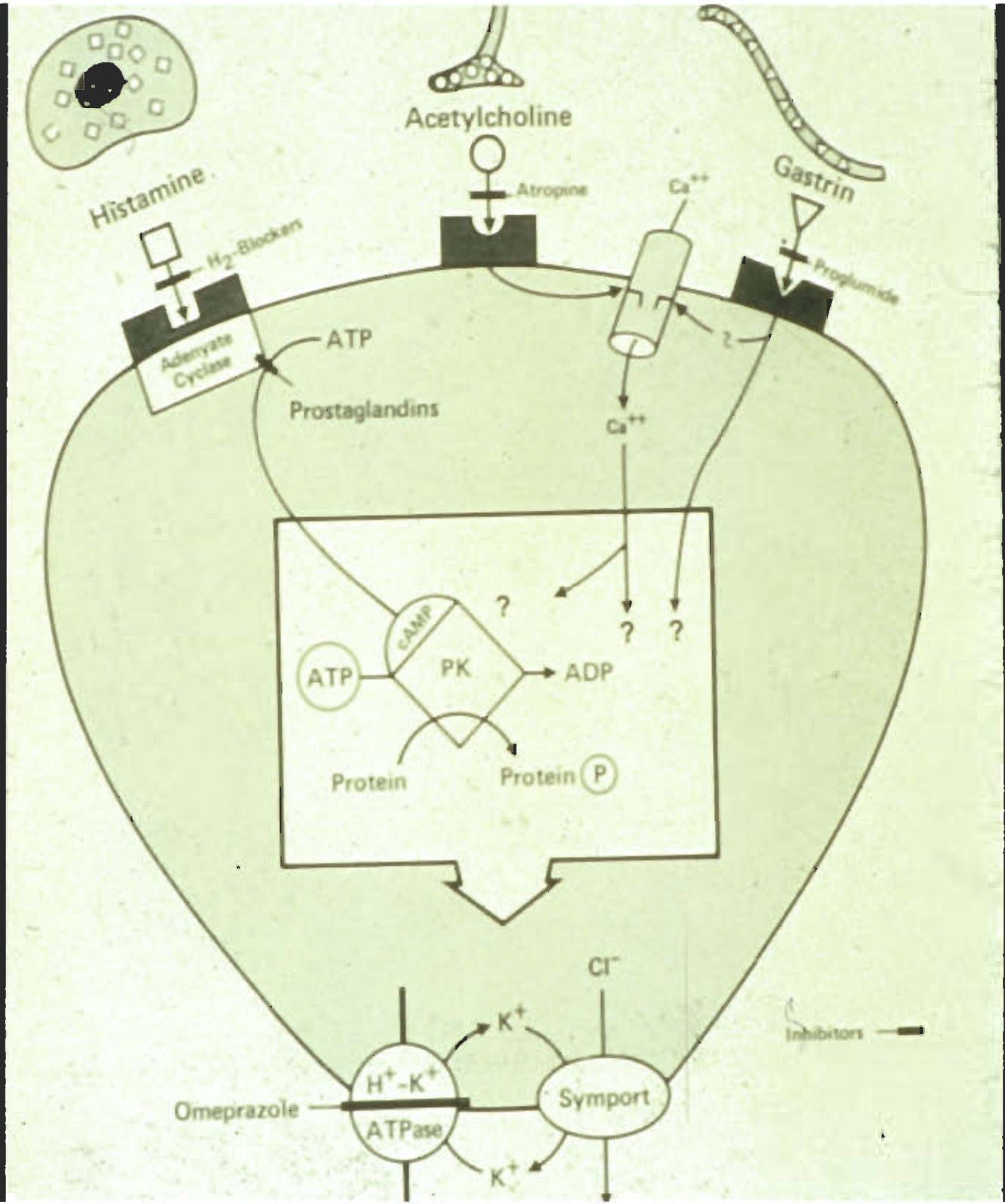
- Evaluation:
  - Fasting serum gastrin (off all acid suppressive meds)

    Gastrin level > 1000 pg/ml
  - Secretin Stimulation Testing

    Gastrin rise >200 pg/ml
- Tumor localization: CT scan, Octreotide scan, EUS, angiography, arterial stimulation venous sampling, intraoperative palpation and transillumination

Treatment of PUD

- Eradicate H. pylori
- Stop NSAID or switch to less toxic drug and/or use prophylactic therapy
- Acid suppression (PPI) 4-6 wks
  - Continue in patients on NSAID/aspirin or with complicated ulcer disease
- Stop smoking


Acetylcholine
Histamine
Gastrin
Atropine
H_2-Blocker
Proglumide
Ca^{++}
Adenylate Cyclase
ATP
Prostaglandins
Ca^{++}
?
?
?
cAMP
ATP
PK
ADP
Protein
Protein (P)
Cl^-
K^+
H^+-K^+ ATPase
Omeprazole
Symport
K^+
Inhibitors

Medications for PUD: Proton Pump Inhibitors (PPIs)

- Most potent acid inhibitors
- Time release absorption from sm. intestine
- Concentrated in canaliculus of parietal cell
- Activated when pH < 1.5
- Covalently & irreversibly bind H+-K+ ATPase
- Pump inhibited until new pump synthesized
- Regardless of degree of pump stimulation

H_2 Antagonists

- Less effective than PPIs
- Bind histamine receptor on parietal cell
- Bind to cytochrome P450

Misoprostol

- Prostaglandin E_1 analog
- ↑ mucosal protection & ↓ acid secretion
- Very effective in preventing NSAID PUD
- Limited by side effects & frequent dosing

Sucralfate

- Basic salt compound
- Polymerizes into paste and adheres to damaged mucosa
- No effect on acid secretion

Antacids

- First medical therapy used for PUD
- Neutralize luminal acid
- Brief duration of action