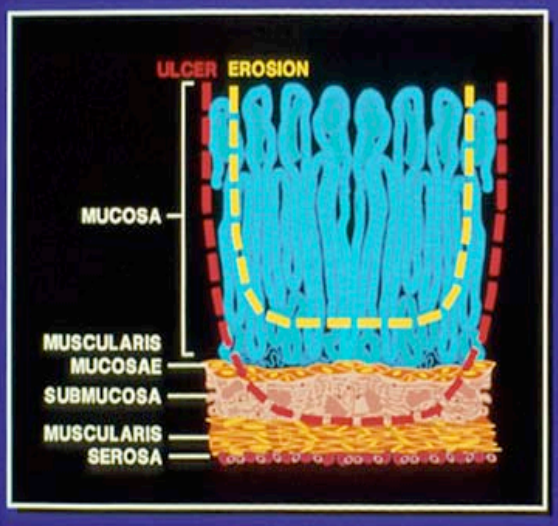
Peptic Ulcer Disease

Timothy C. Wang, M.D.
Chief, Digestive and Liver Diseases
Columbia University Med Center

An Erosion is Superficial to the Muscularis Mucosa While an Ulcer Extends Through the Muscularis Mucosa

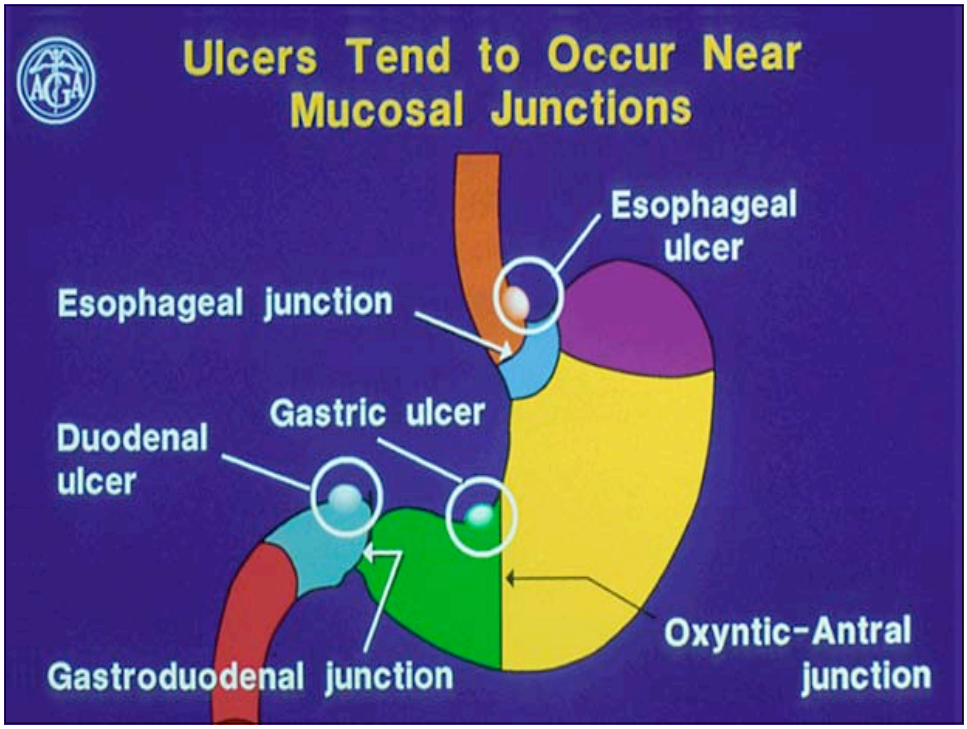


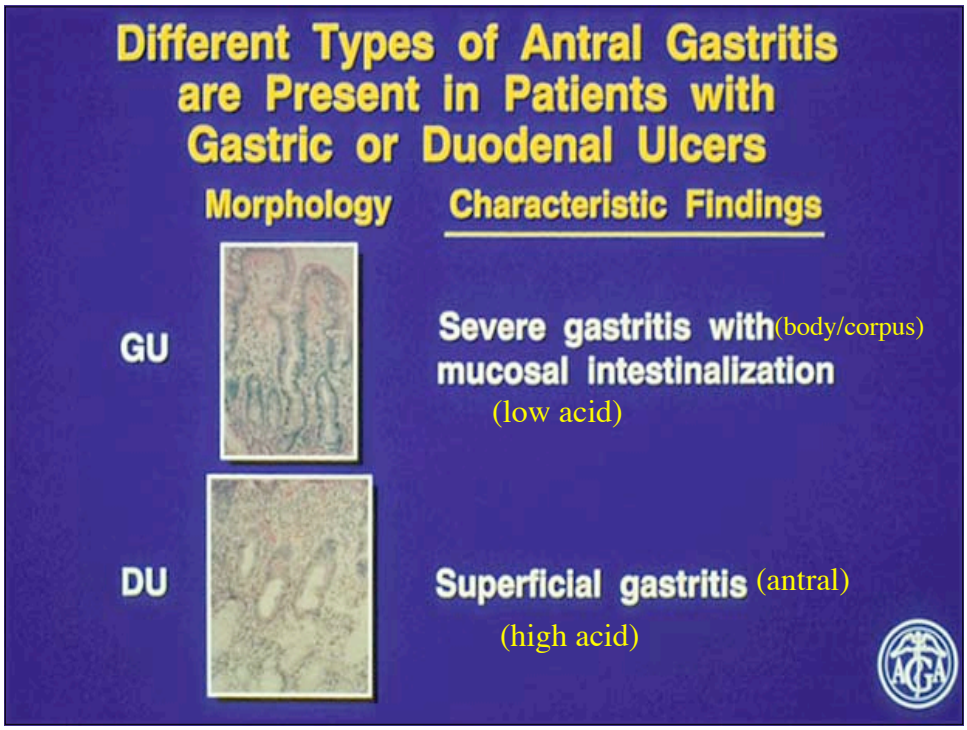


Erosion



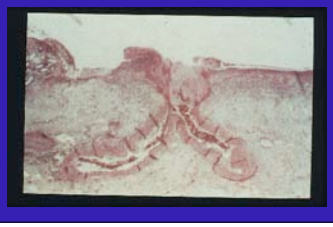
Ulcer


Ulcers Tend to Occur Near Mucosal Junctions
Esophageal ulcer
Esophageal junction
Gastric ulcer
Duodenal ulcer
Oxyntic-Antral junction
Gastroduodenal junction


Different Types of Antral Gastritis are Present in Patients with Gastric or Duodenal Ulcers
Morphology
Characteristic Findings
GU
Severe gastritis with (body/corpus) mucosal intestinalization
(low acid)
DU
Superficial gastritis (antral)
(high acid)

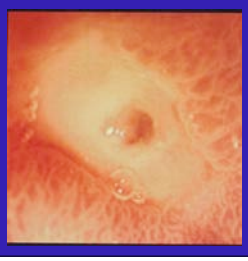
Simple versus Complicated Peptic Ulcer Disease

- Simple ulcers
  - Symptomatic
  - Asymptomatic
- Complicated ulcers
  - Bleeding
  - Perforation
  - Death



- Lifetime PUD prevalence of 10%
- In past, DU 5X as common as GU
- Incidence of GU increases with age
- Overall PUD has been declining

Bleeding ulcer



The Diagnosis of Ulcer Disease by Symptoms Alone is Imprecise

	Prevalence (%)		
	Duodenal Ulcer	Gastric Ulcer	Non-Ulcer Dyspepsia
Epigastric Pain	**~70**	**~70**	**~70**
Nocturnal	50–80	30–45	25–35
Food relief	20–65	5–50	5–30
Episodic	50–60	10–20	30–40
Appetite ↑	10–30	5–10	10–30
Appetite ↓	25–40	40–60	25–40
Belching/bloating	30–65	30–70	40–80

- Ulcers occur without symptoms (10–40%); and ulcer-symptoms occur without ulcer (30–60%)

There is a Low Prevalence of Endoscopically Documented Ulcers in Patients with Dyspepsia

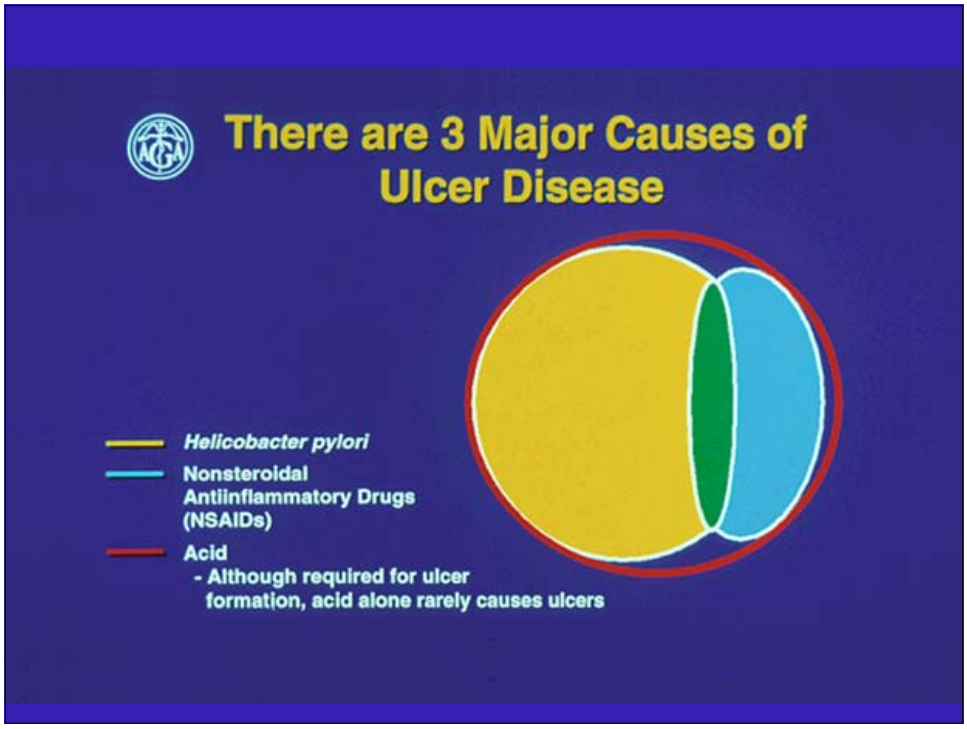
- About 3% of family physician visits are for dyspepsia
- Endoscopic findings in patients with dyspepsia:

Duodenal Ulcer	15–30%
Gastric Ulcer	5–10%
Gastroduodenitis	25–50%
Normal	15–50%

- Dyspepsia is an imprecise symptom complex that includes: epigastric pain/discomfort, nausea, belching, and bloating

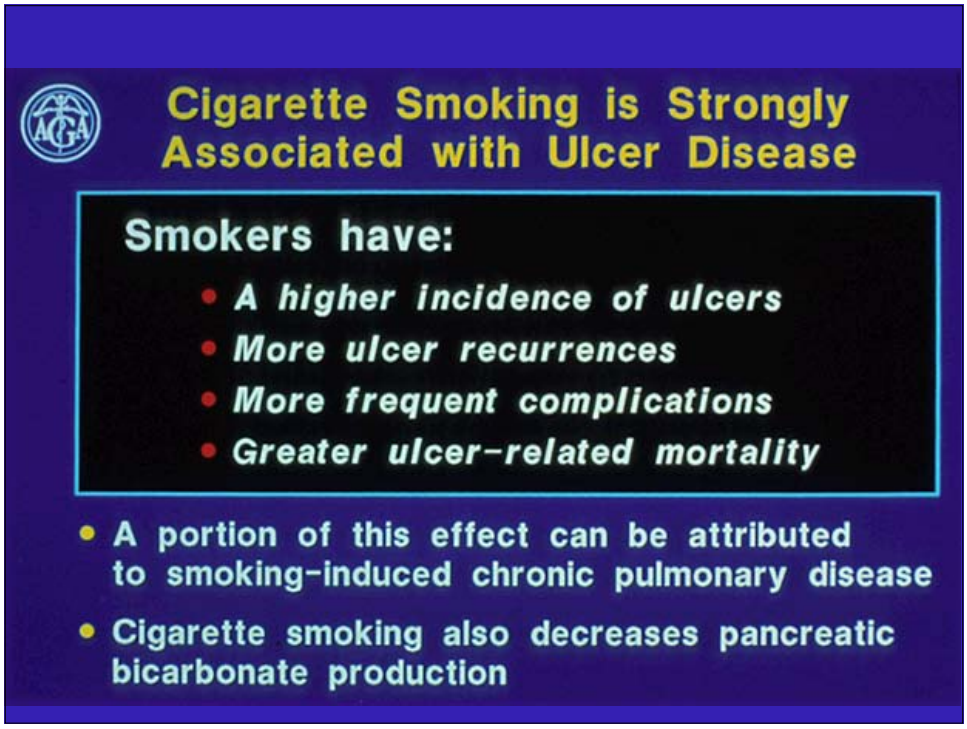
There are Many Non-Ulcer Causes of Dyspepsia

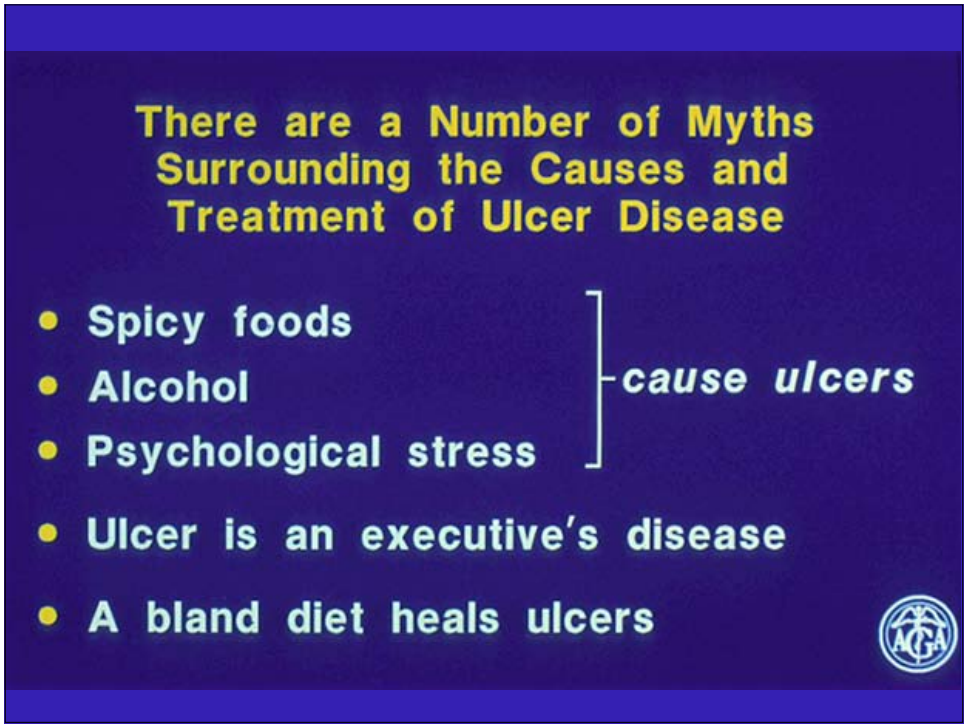
- Idiopathic dyspepsia ("Non-ulcer dyspepsia")
- Gastroesophageal reflux
- Drugs
- Pregnancy
- Delayed gastric emptying
- Biliary and/or pancreatic diseases
- Mesenteric ischemia



Causes of Peptic Ulcer Disease

- H. pylori infection *
- NSAIDs *
- Stress ulcers (Cushing's, Curling's, ischemia)
- Increased gastrin: (Zollinger-Ellison, retained gastric antrum, antral G-cell hyperplasia)
- Increased histamine: Systemic mastocytosis, foregut carinoid tumors, leukemia
- Massive small bowel resection, renal failure, cirrhosis, COPD


Cigarette Smoking is Strongly Associated with Ulcer Disease
Smokers have:
A higher incidence of ulcers
More ulcer recurrences
More frequent complications
Greater ulcer-related mortality
A portion of this effect can be attributed to smoking-induced chronic pulmonary disease
Cigarette smoking also decreases pancreatic bicarbonate production


There are a Number of Myths Surrounding the Causes and Treatment of Ulcer Disease
Spicy foods
Alcohol
Psychological stress
cause ulcers
Ulcer is an executive's disease
A bland diet heals ulcers

HISTORY OF THE STUDY OF ACID SECRETION AND PEPTIC ULCER DISEASE

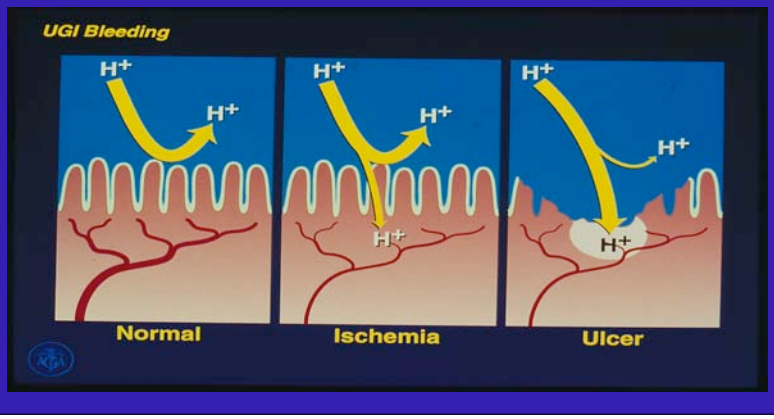
DATE	PERSON	EVENT
• 1st cent	Plinius	Used coral powder for dyspepsia
• 17th cent	Von Helmont	Recognized acid in gastric juice
• 1822-33	Beaumont	1. Confirmed gastric juice had HCL 2. Proposed mental effects on gastric secretion 3. Proposed chemical digestion of food
• 1824	Prout	Identified HCL in gastric juice
• 1882	Quincke	Introduced "peptic ulcer disease"
• 1893	Golgi	Recognized the parietal cell as the source of acid secretion
• 1890's	Pavlov	Demonstrated cephalic and gastric phases of acid secretion
• 1905	Edkins	Discovered "gastrin" - antral mucosal extract that stimulated acid secretion

HISTORY OF THE STUDY OF ACID SECRETION AND PEPTIC ULCER DISEASE (con't)

DATE	PERSON	EVENT
• 1910	Schwarz	"No acid, no ulcer"
• 1915	Sippy	Proposed bedrest, hourly feedings of milk and antacids
• 1920	Popielsky	Described stimulation of gastric acid secretion by histamine
• 1950's	Code MacIntosh	Proposed other secretogogues stimulated acid secretion by releasing histamine
• 1960's	Kahlson	Gastrin and food stimulated HDC activity and by releasing histamine
• 1964	Gregory	Determined chemical structure of gastrin
• 1970's	Grossman	Proposed the interaction hypothesis-synergy between secretogogues
• 1974	Black	Introduced the first effective H2 receptor antagonist

No Acid, No Ulcer

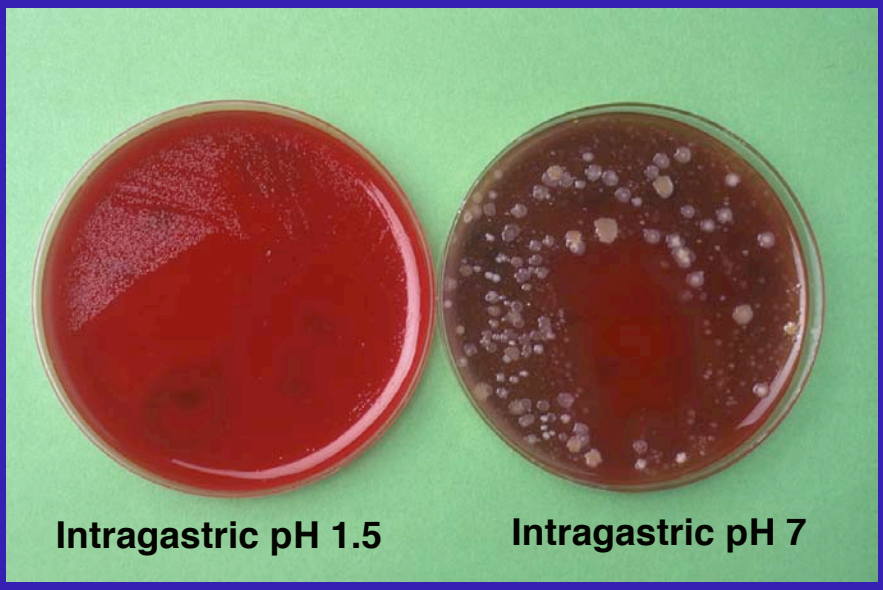
- Schwarz (1910): “Ohne saueren Magensaft, kein pepticsches Geschwur”
- Hyperacidity only in some patients (e.g.DU, ZE) but acid is a factor in most patients with PUD



Role of acid (HCl) in the stomach

- Helps to kill prey that is ingested live
- Small role in protein digestion through activation of pepsin
- Some bacteriostatic action - helps to sterilize the gastric contents
- Gastric juice also contains bicarbonate, pepsinogen, intrinsic factor, prostaglandins, K+, Na+, mucins, and trefoil proteins

Effect of pH on intragastric bacteria



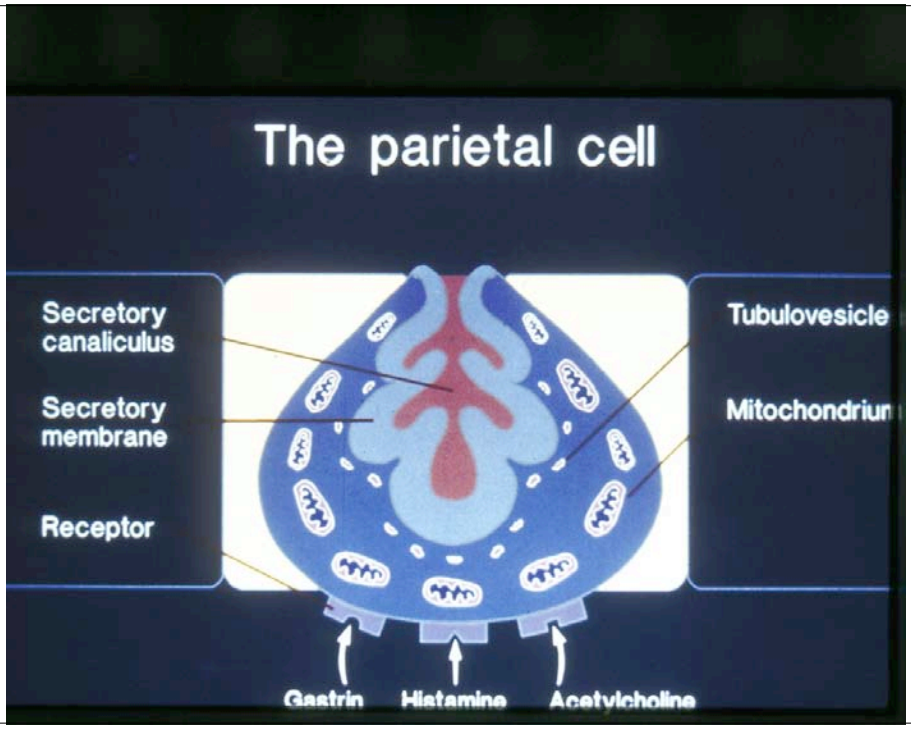
Fundamentals of acid secretion

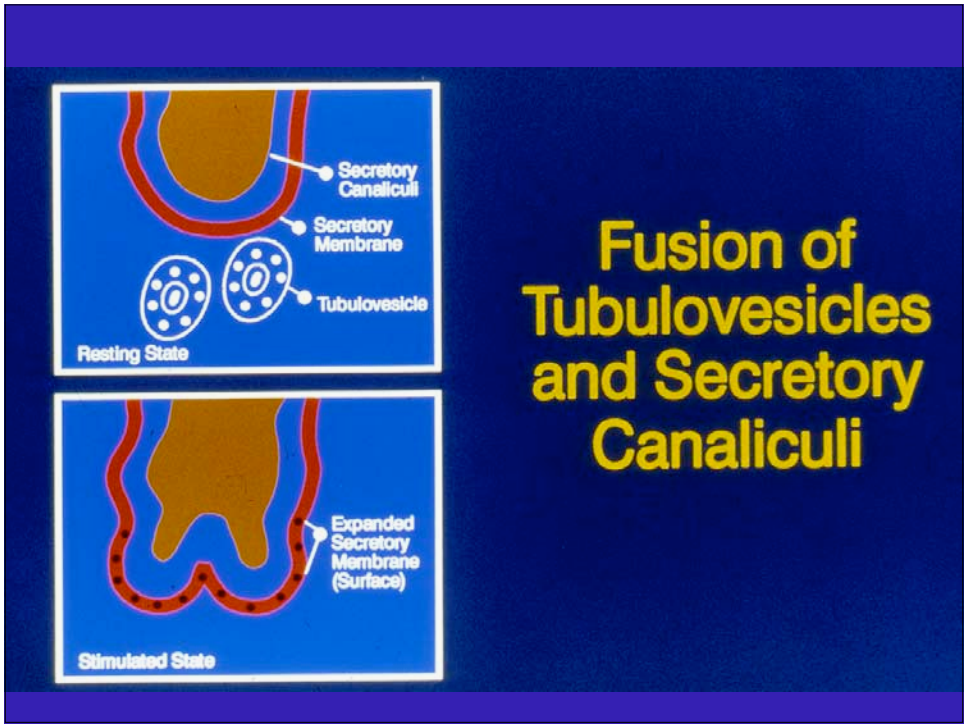
- The human stomach produces 1-1.5 liters of gastric juice per day
- Highly acidic with pH of ~0.8 (160 mM H+)
- Acid secreted across a concentration gradient of 2.5 million fold
- Active transport process requiring tremendous energy
- Transport achieved by H+K+ATPase pump



Parietal cells

- Human stomach contains ~ 1 billion parietal cells
- Large (25 mm in diameter) oval shaped cells located in mid region of oxyntic glands
- Major function is the secretion of acid
- Three main ultrastructural features:
  - numerous mitochondria
  - tubulovesicles
  - secretory canaliculi

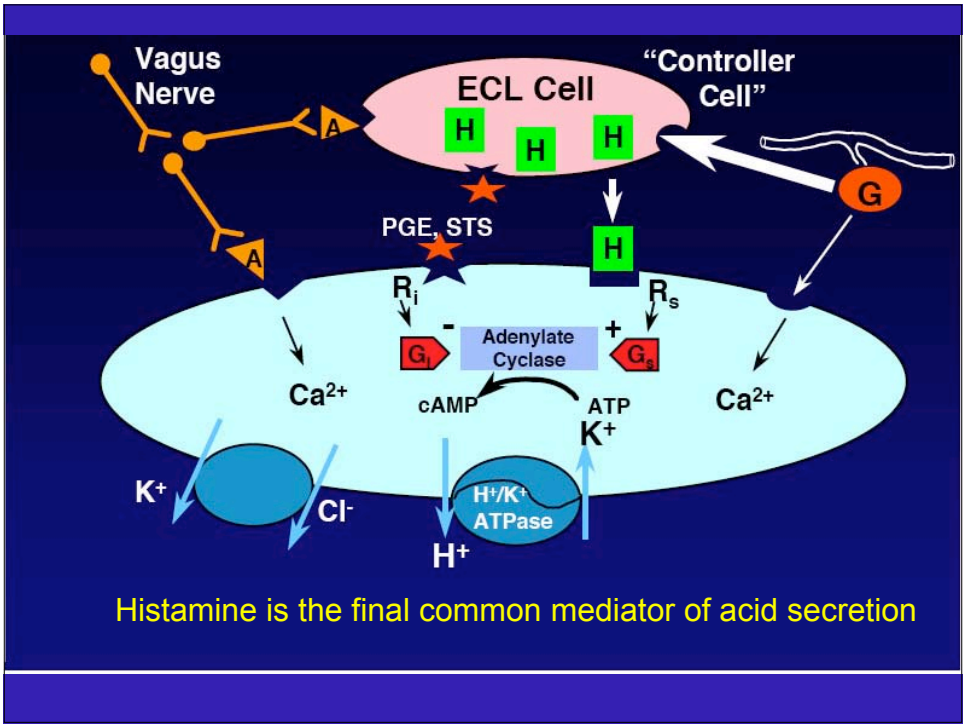

The parietal cell
Secretory canaliculus
Secretory membrane
Receptor
Tubulovesicle
Mitochondrium
Gastrin
Histamine
Acetylcholine


Secretory Canaliculi
Secretory Membrane
Tubulovesicle
Resting State
Expanded Secretory Membrane (Surface)
Stimulated State
Fusion of Tubulovesicles and Secretory Canaliculi

Integrated control of acid secretion

Three levels of regulation of acid secretion:

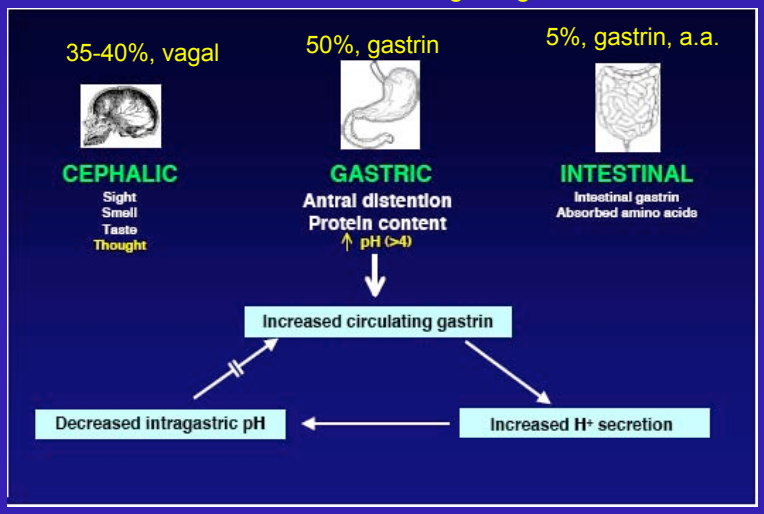
- Neural control - acetylcholine
  - cephalovagal and local intragastric reflex arcs
- Hormonal control
  - endocrine (gastrin) or paracrine (somatostain, histamine)
- Local direct factors
  - positive (+) factors - amines/amino acids, gastric distention
  - negative (-) factors - increased acid or low pH

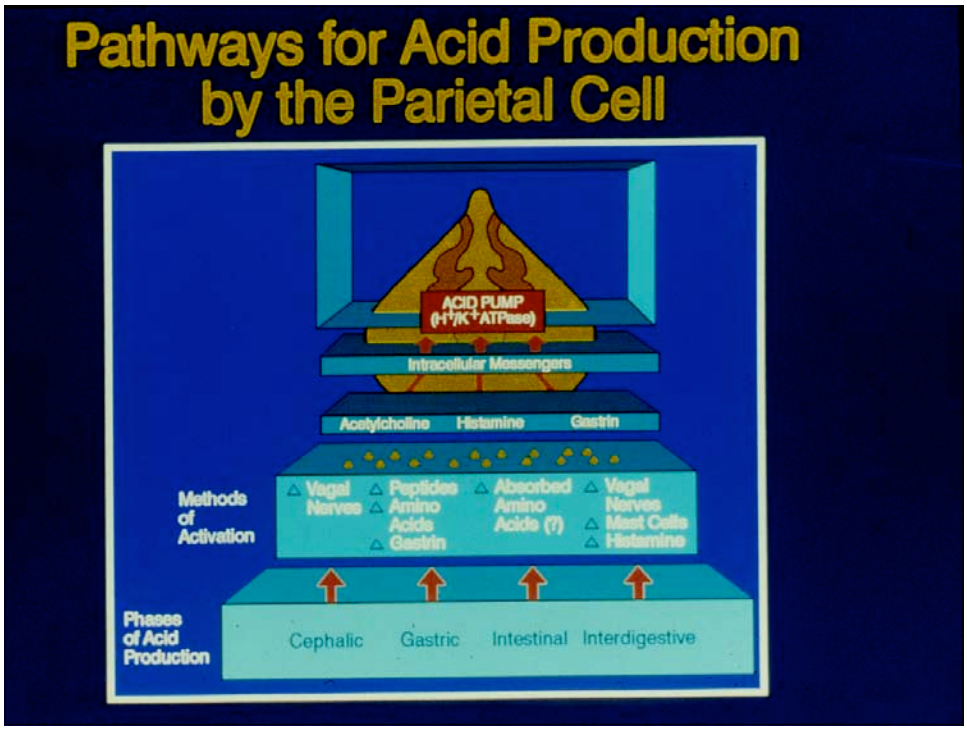


Histamine is the final common mediator of acid secretion

Phases of gastric acid secretion

- Interdigestive phase
  - –basal acid secretion -vagal regulation



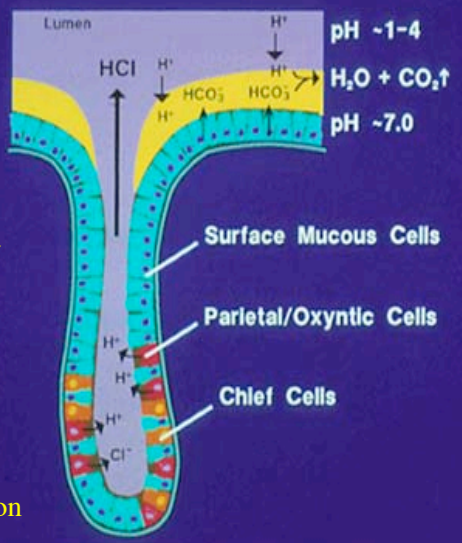


Why the stomach does not digest itself

- Acid is through a mucus gel layer through narrow “viscous fingers” which prevent back diffusion of acid due to a change in viscosity at the lower lumenal pH.

Bhaskar KR et al, Nature 1992;360:458

Mucus and HCO_3^- Combine to Neutralize Acid at the Gastric Mucosal Surface

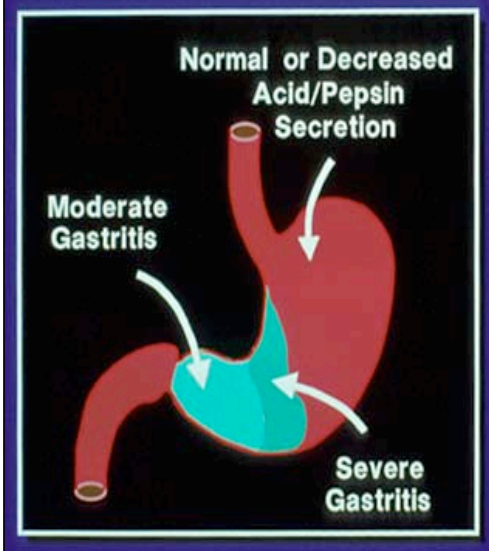


Mucous layer

Protective Factors

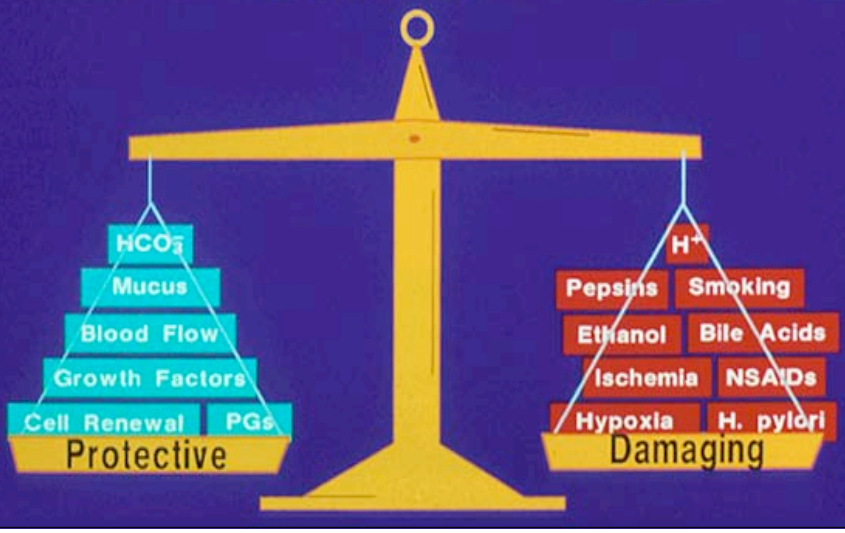
- Cell membrane hydrophobicity
- Mucosal blood flow
- Cell proliferation
- Mucous layer thickness
- pH gradient
- Glutathione
- Bicarbonate secretion

Gastric Ulcer Disease Involves Loss of Mucosal Defenses in the Presence of Acid

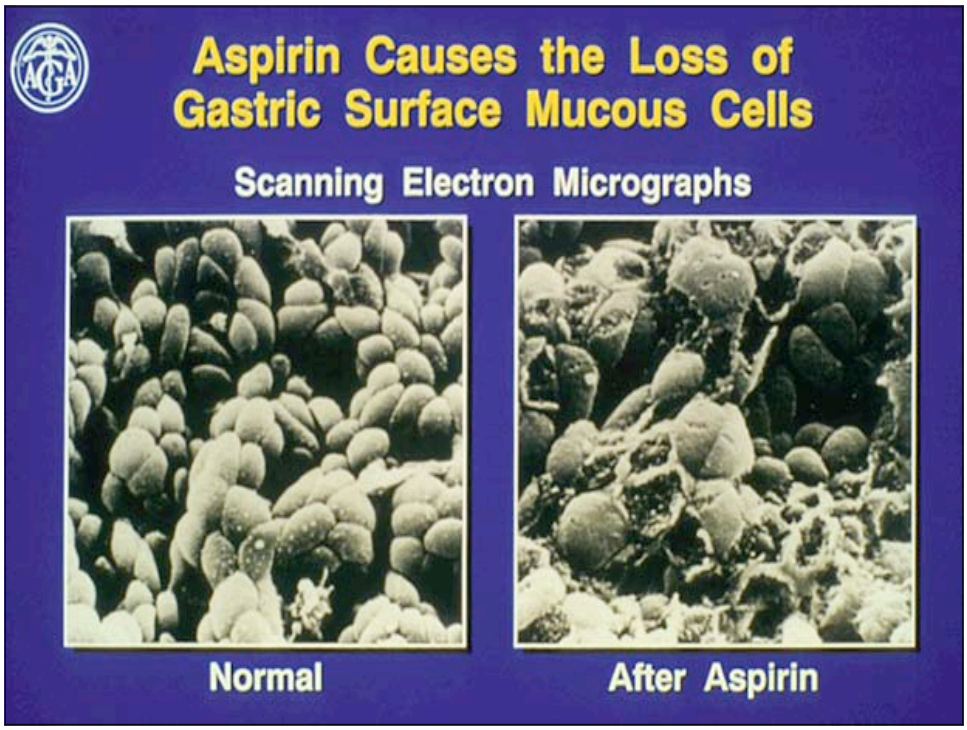


- Gastritis involves the antrum and distal corpus
- Other contributing factors:
  - NSAIDs
  - Bile reflux
  - Smoking
  - Alcohol
  - *H. pylori*

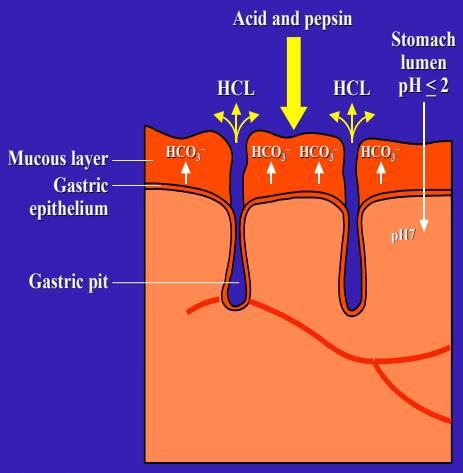
Gastroduodenal Mucosal Integrity is Determined by Protective ("defensive") and Damaging ("aggressive") Factors




NO ULCER
1 2 3 4 F
Aggressors
Defenders
7 9
3 10
Pepsin
Bile Salts
ACID
Mucus
HCO_3
Blood Flow
Tissue Acid-Base
Membrane Integrity
Cell Restitution
Cellular Tight Junctions
ULCER


Aspirin Causes the Loss of Gastric Surface Mucous Cells
Scanning Electron Micrographs
Normal
After Aspirin

Normal Gastric Protective Mechanisms



Collins, 1990.

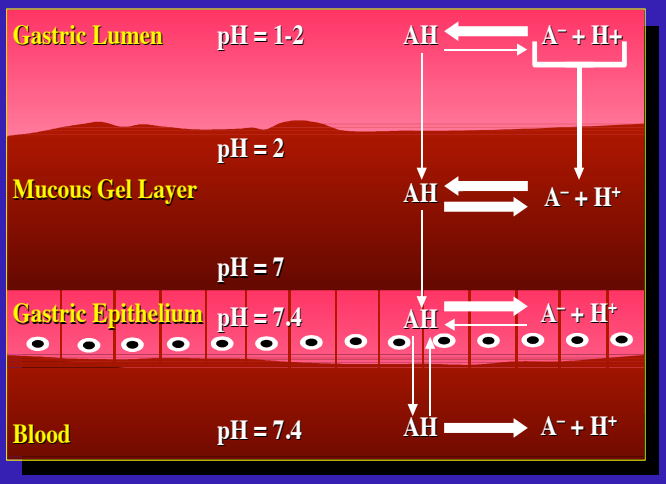
Protective factors: all are PG dependent

- Mucous layer thickness
- pH gradient
- Cell membrane hydrophobicity
- Bicarbonate secretion
- Mucosal blood flow

Mechanisms of NSAID Injury

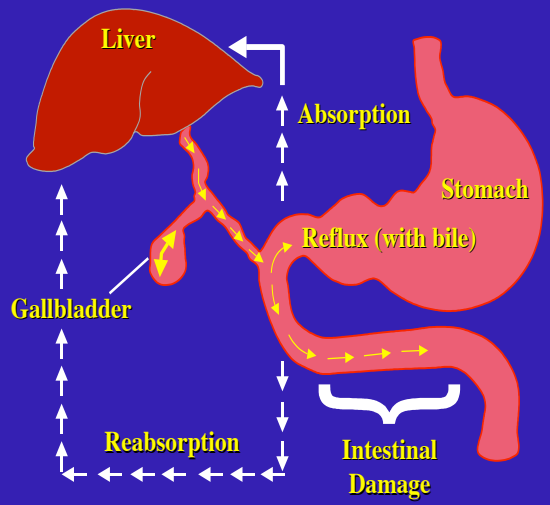
- Topical injury
  - Ion trapping: rapid, compound specific
  - Enterohepatic recirculation
- Prostaglandin depletion
  - Systemic effect
- Neutrophil Activation
  - Increased neutrophil vascular adherence mediated by increased TNFα and ICAM
- Combination renders mucosa vulnerable to acid

Ion Trapping of Acidic NSAIDs



Schoen. *Am J Med*. 1989;86:449.

Indirect Topical Exposure Via Enterohepatic Circulation



NSAIDs Excreted in Bile

Indomethacin
Diclofenac
Naproxen
Piroxicam
Sulindac
Oxaprozin
Ketorolac

Pathogenesis of NSAID-Induced Ulcer

Endothelial effects
- stasis ischemia

- direct toxicity "ion trapping"

Epithelial effects (due to prostaglandin depletion)
- ↓ HCl secretion
- ↓ mucin secretion
- ↓ HCO_3 secretion
- ↓ surface active phospholipid secretion
- ↓ epithelial cell proliferation

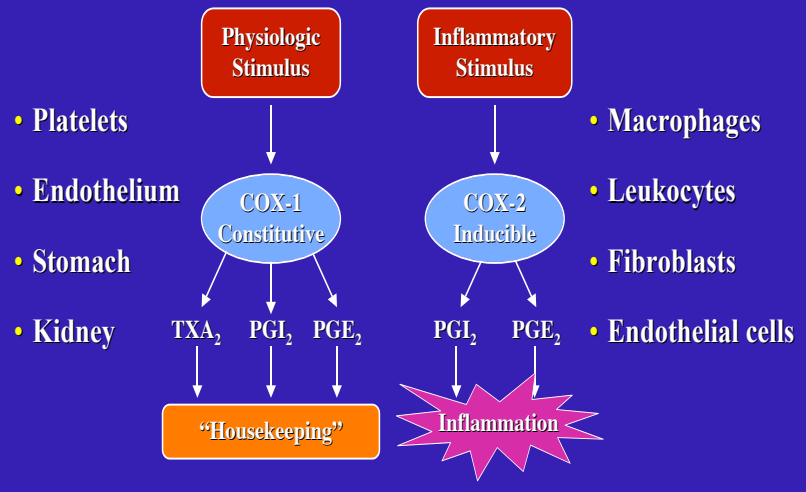


ULCER

EROSIONS

HEALING (spontaneous or therapeutic)

Cyclooxygenase Isoenzymes



Risk factors for serious NSAID-related Peptic Ulcer Disease

- Age > 60 years
- History of previous ulcer or GI bleeding
- Concomittant use of anticoagulants or glucocorticoids
- High dose NSAID therapy
- Use of multiple NSAIDs
- Severity of underlying disease

- High (9%) risk of major complications if 4 or more risk factors
- PPI prophylaxis for patients at high risk for NSAID ulcers

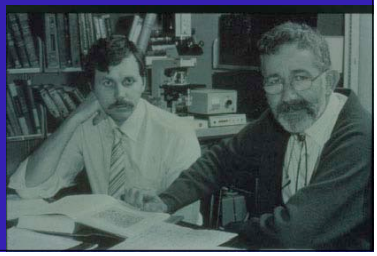
H. pylori Timeline

- Early 1900's — Discovery of human gastric bacteria
- 1920-1980 — Rediscovery of gastric bacteria
- 1982 — Isolation and culture of *C. pyloridis* by Marshall and Warren
- 1987 — Eradication reduces DU recurrence
- 1989 — Bacteria are renamed *H. pylori*
- 1990's — Association of *H. pylori* with gastric cancer and MALT lymphoma
- 1997 — Complete genome sequence of *H. pylori*



Helicobacter pylori

Marshall & Warren



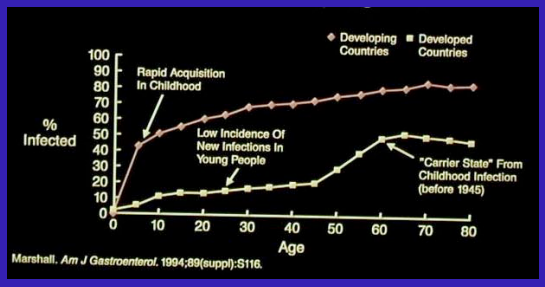
BJM demonstrates that H. pylori causes gastritis



Figure 6. Ulcer Tales. A Comic describing the Self Ingestion of Helicobacter.
Notes: This page shows Neil Noakes saying "Dr Marshall you're crazy" and I am saying "There is no other way."

Epidemiology of *H. pylori*

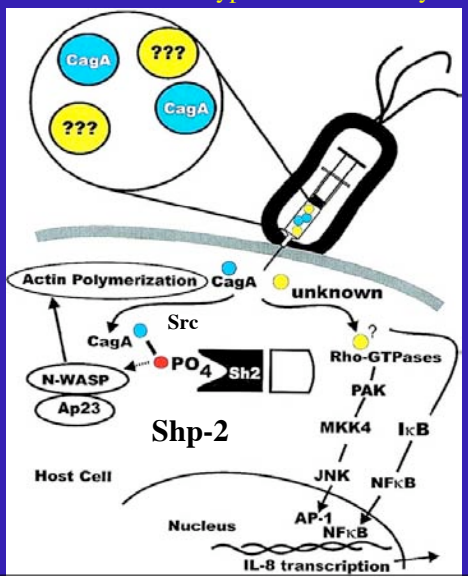
- Universal in developing countries but declining in incidence in industrialized nations



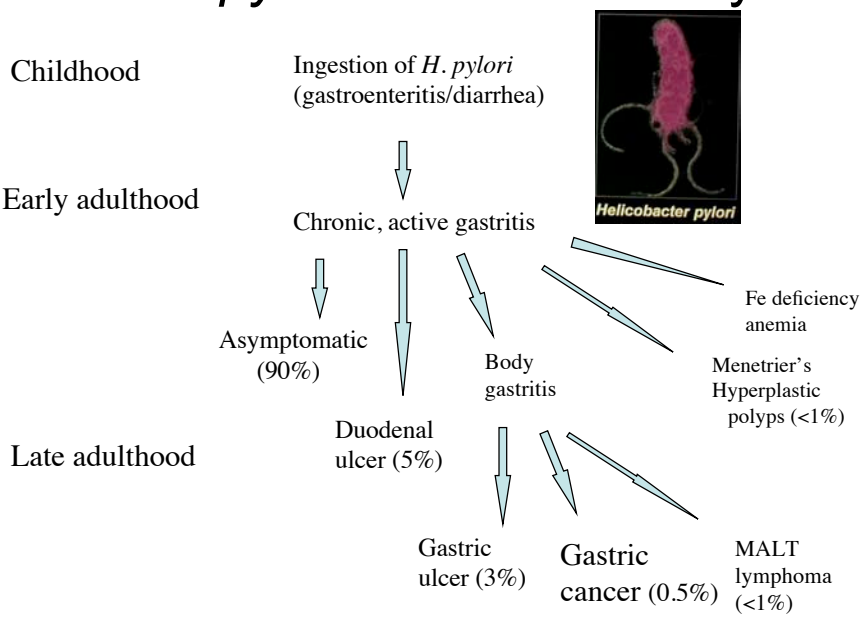
- Cohort effect explains higher rates in older adults in the U.S.
- Early childhood the major window for acquisition; low rates in older children & adults
- Transmission is person-to-person
  - Familial clustering (passed among siblings older-younger)
  - High rates in institutions with crowding & poor sanitation
- Fecal-oral versus oral-oral transmission

CagA Protein from *Helicobacter pylori* Is a Trojan Horse to Epithelial Cells

- Keys for survival
  - Acid tolerant (urease, UreI)
  - Motile (multiple flagella)
- Important attributes
  - Attachment (32 Hop adhesins, including BabA)
  - Other virulence factors: VacA, picB/cagE
  - Genes regulated by slipped-strand mispairing
  - Uses molecular hydrogen for energy



H. pylori: Natural History



H. pylori and gastritis

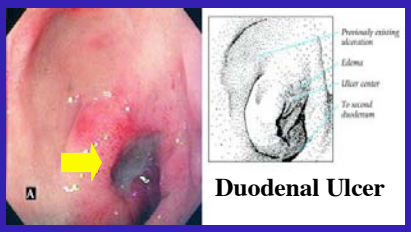
- **Acute infection may result in hypochlorhydria**
- **Active, chronic (type B) gastritis invariably present with *H. pylori***
- **Causal relationship established (Koch's postulates):**
  - **Eradication of *H. pylori* eliminates gastritis**
  - **Ingestion of *H. pylori* by 2 volunteers**
- **Mild superficial gastritis usually asymptomatic**

ALL HP INFECTIONS ARE NOT ALIKE: HISTOLOGY IS KEY

- **Superficial pangastritis (mixed gastritis) without disease**
  - **Normal acid**
- **Antral predominant gastritis**
  - **Increased acid (DU)**
- **Body gastritis (± atrophy) - Decreased acid (GU, gastric cancer)**
- **Multifocal atrophy with intestinal metaplasia**
  - **Decreased acid (gastric cancer)**

H. pylori and Peptic Ulcer Disease

- PUD develops in only 5-10% of HP -infected patients.
- In the past, HP found in 95% (DU) & 80% (GU) patients.
- Recent U.S. studies, declining prevalence of HP in PUD.
- More NSAID (+) and HP(-) / NSAID (-) ulcers.
- Recurrence of PUD decreased markedly by HP eradication.
- U.S. studies suggest that 20% recur after HP eradication.



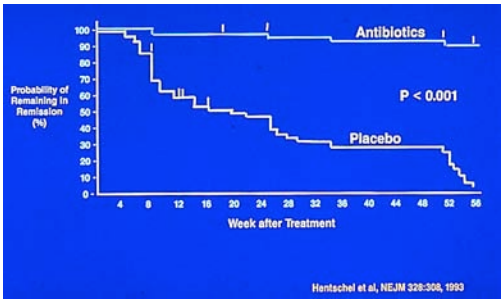
Duodenal Ulcer

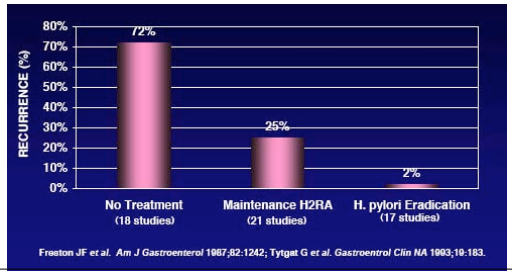
Gastric Ulcer



Eradication of *H. pylori* in Recurrent Duodenal Ulcer

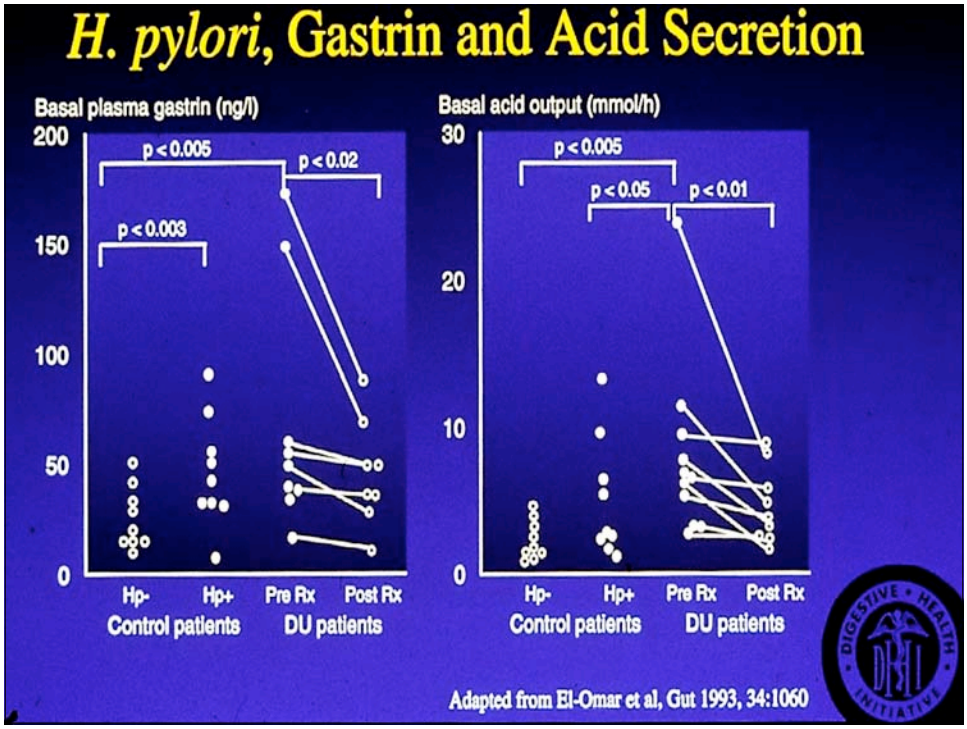
- Use of triple antibiotics to eradicate *H. pylori* is superior to acid suppression in the prevention of recurrent D.U.

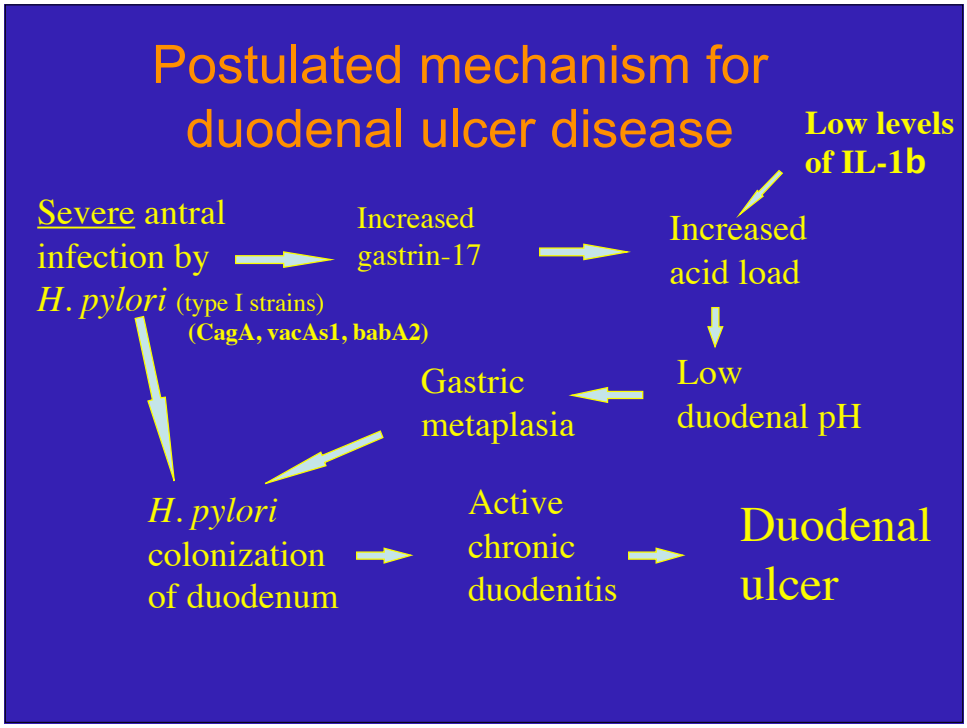




Pathogenesis of *H. pylori*-dependent duodenal ulcer disease

- Need for severe, antral-restricted gastritis
- Increases in gastrin/ gastric acid
  - Role for incompletely processed gastrins
- Host genetics: noninflammatory IL-1b genotypes
- Role of Type I strains (cagA, vacAs1, babA2), type IV secretion and dupA
- Duodenal colonization by *H. pylori* (in areas of gastric metaplasia)


H. pylori, Gastrin and Acid Secretion
Basal plasma gastrin (ng/l)
200
150
100
50
0
p < 0.005
p < 0.02
p < 0.003
Hp-
Hp+
Pre Rx
Post Rx
Control patients
DU patients
Basal acid output (mmol/h)
30
20
10
0
p < 0.005
p < 0.05
p < 0.01
Hp-
Hp+
Pre Rx
Post Rx
Control patients
DU patients
Adapted from El-Omar et al, Gut 1993, 34:1060


Postulated mechanism for duodenal ulcer disease
Low levels of IL-1b
Severe antral infection by H. pylori (type I strains)
(CagA, vacAs1, babA2)
Increased gastrin-17
Increased acid load
Low duodenal pH
Gastric metaplasia
H. pylori colonization of duodenum
Active chronic duodenitis
Duodenal ulcer

H. pylori and gastric cancer

- Declining in the U.S.,
- 2nd leading cause of cancer-related mortality worldwide.
- *H. pylori*: odds ratio of 3- to 20-fold.
- Animal models (ferrets, Mongolian gerbils, and mice) confirm the carcinogenicity of *Helicobacter.*
- HP classified by the IARC as a class I carcinogen
- Eradication may potentially reduce gastric cancer risk.

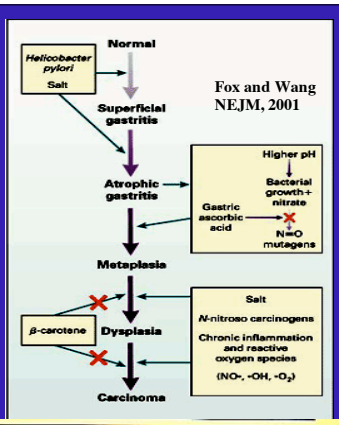


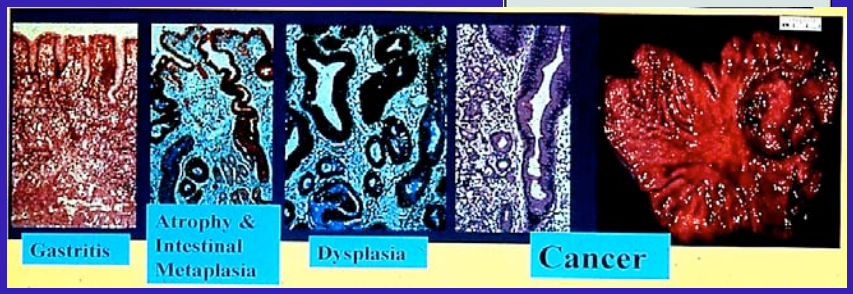
Type I: Polypoid Gastric Cancer



Type II:Exophytic Gastric Cancer

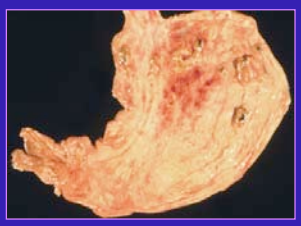
Helicobacter pylori is a Class I Carcinogen

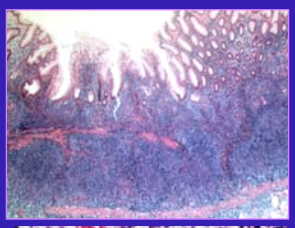


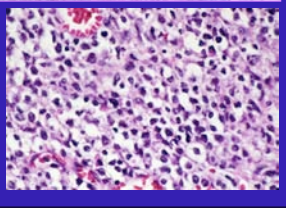


H. pylori and Gastric MALT Lymphoma

- MALT = Mucosa-associated lymphoid tissue
- (MALT) lymphoma of the stomach: a rare tumor strongly associated with *H. pylori* infection
- *H. pylori* gastritis harbors the clonal B cell that eventually gives rise to MALT lymphoma (NEJM 1998)
- Eradication of *H. pylori* leads to regression of early MALT lymphomas in 60-92% of cases
- Tumors in the distal stomach and that are superficial (stage 1 T1) are most likely to respond to antibiotics

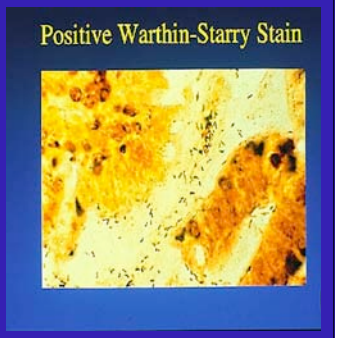


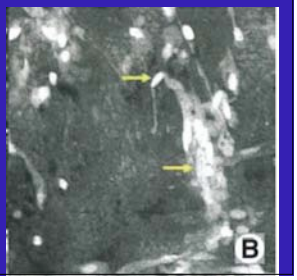




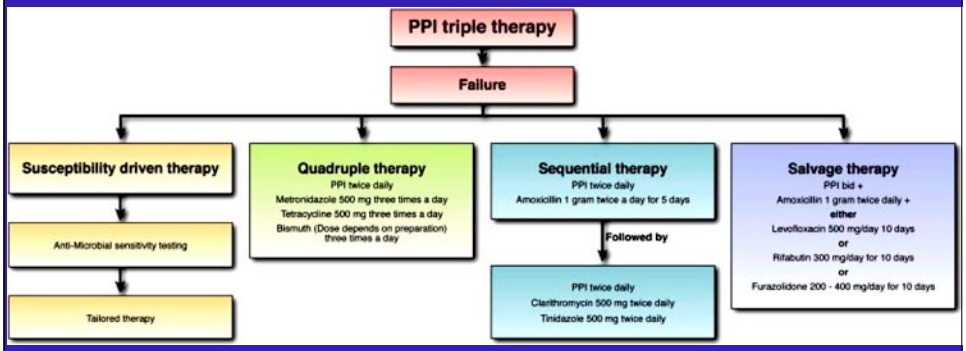
Diagnostic tests for *H. pylori*

- Noninvasive
  - Serology (ELISA, immunoblot)
  - UBT (C13 or C14)
  - H. pylori stool antigen (HpSA)
- Invasive (require endoscopy, minimum 3 biopsies)
  - Rapid urease assay
  - Histology (Warthin-Starry, Giemsa, immunostaining
  - Culture, PCR analysis
  - endomicrosopy





Treatment strategies for HP



PPI Triple Regimens - PPI plus two antibiotics (clarithromycin plus amoxicillin or metronidazole)

LAC (lansprazole/amoxicillin/clarithromycin) dose packet most commonly used in U.S.

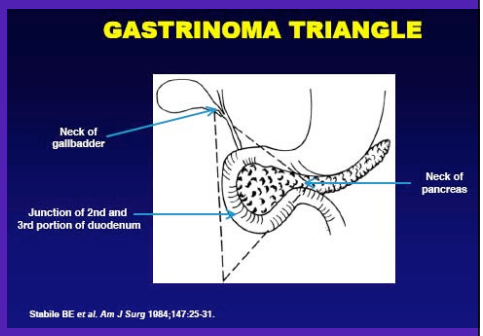
Zollinger-Ellison Syndrome is a Clinical Triad Consisting of:

- Gastric acid hypersecretion
- Severe peptic ulcer disease (in >90%)
- Non-beta islet cell tumors of the pancreas

- The tumors produce gastrin (G17 & G34); referred to as "gastrinomas"
- Tumors localized usually to head of pancreas, duodenal wall or regional lymph nodes
- About one-half of gastrinomas are multiple and two-thirds malignant
- About one-fourth have multiple endocrine neoplasia syndrome (MEN I) - tumors of parathyroid, pituitary, and pancreatic islets

Gastrinoma

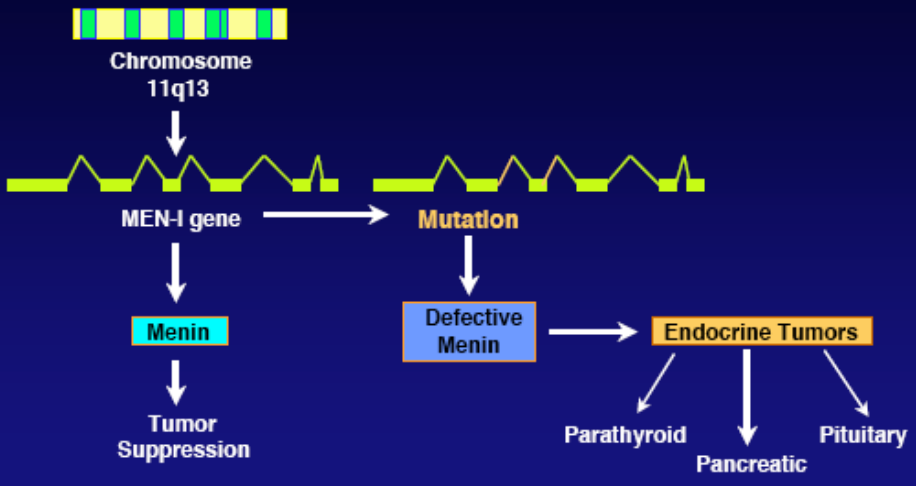
- Described by Zollinger and Ellison in 1955
- 80-90% of tumors in "gastrinoma triangle"
  - Duodenal wall - 40-50%
  - Pancreas - 20-25%
  - Stomach and jejunum - rare
  - Extrapancreatic, extraintestinal - 10-20%
- Range from microscopic (44%) to 20 cm
- Ulcers often distal to duodenal bulb
- Diarrhea in 30-50%
- GERD in 50-70%



There are Clinical Features that Can Distinguish ZE Syndrome from DU

FEATURE	MECHANISM(s)
• Diarrhea • Weight loss/steatorrhea	↑ gastric acid secretion ↓ duodenal/jejunal pH Inactivation of lipase Mucosal inflammation
• Large gastric folds	Trophic effect of gastrin
• Large amounts of gastric secretions	Secretory effect of gastrin
• Family history of endocrine tumor, ↑ Ca^{++}	MEN I - parathyroid tumor/hyperplasia
• Intractable or post-surgical recurrences of ulcer disease	Acid hypersecretion due to gastrin-secreting tumor

MEN-I SYNDROME



ZOLLINGER-ELLISON SYNDROME
Diagnosis

Diagnosis of ZES established by:

Compatible clinical presentation *must* be present (PUD, diarrhea, severe GERD)

Hyperchlorhydria: > 15 mEq H^+/h in unoperated patient; BAO:MAO > 0.6

Hypergastrinemia: fasting > 1000 pg/ml