Peptic Ulcer Disease

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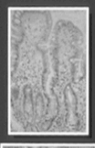
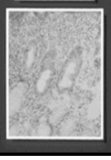
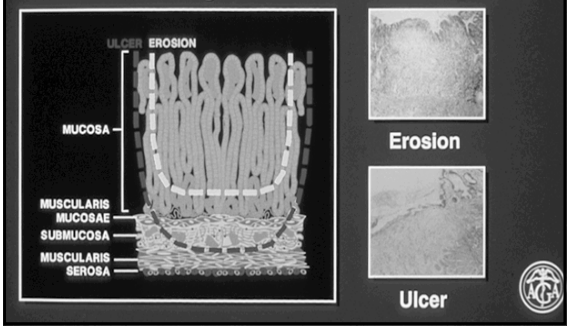
Different Types of Antral Gastritis are Present in Patients with Gastric or Duodenal Ulcers

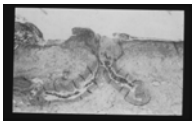
	Morphology	Characteristic Findings
GU		Severe gastritis with mucosal intestinalization (body/corpus) (low acid)
DU		Superficial gastritis (antral) (high acid)

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

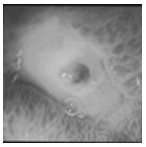


Simple versus Complicated Peptic Ulcer Disease

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

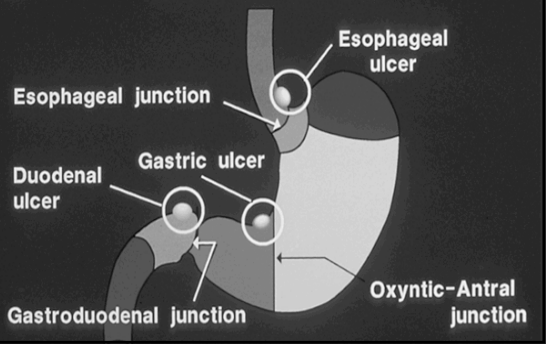


- Lifetime PUD prevalence of 10%
- In past, DU 5X as common as GU
- Incidence of GU increases with age
- Overall PUD has been declining



Bleeding ulcer

Ulcers Tend to Occur Near Mucosal Junctions



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

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

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

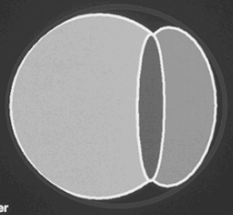
Cigarette Smoking is Strongly Associated with Ulcer Disease

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 3 Major Causes of Ulcer Disease



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

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 secretio 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

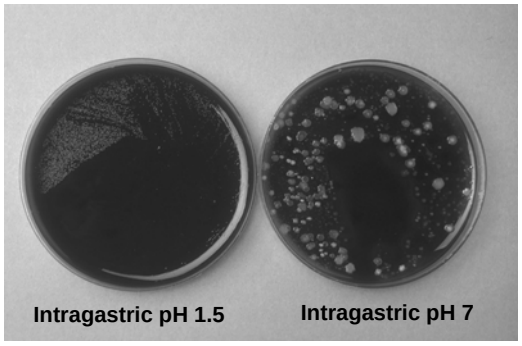
Role of acid (HCl) in the stomach

- 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

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

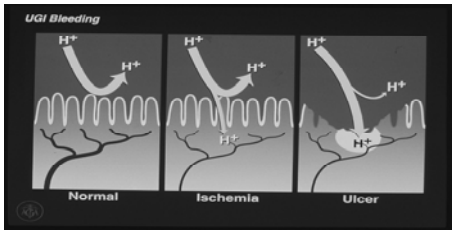
DATE	PERSON	EVENT
• 1910	Schwarz	"No acid, no ulcer"
• 1915	Sippy	Proposed bedrest, hourly feedings of milk and antacids
• 1920	Popielsky	Described stimulation of gastric acid secretion by histamine
• 1950's	Code MacIntosh	Proposed other secretogogues stimulated acid secretion by releasing histamine
• 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

Effect of pH on intragastric bacteria



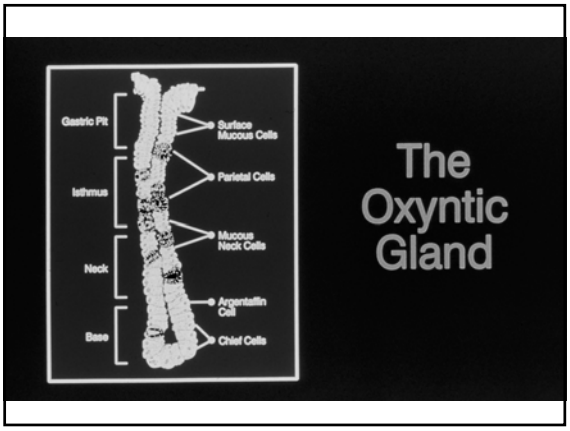
No Acid, No Ulcer

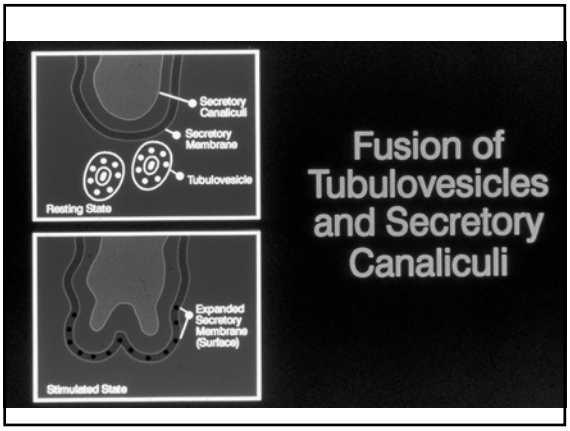
- Schwarz (1910): "Ohne saueren Magensaft, kein pepticsches Geschwur"
- Hyperacidity only in some patients (e.g.DU, ZE) but acid is a factor in most patients with PUD



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





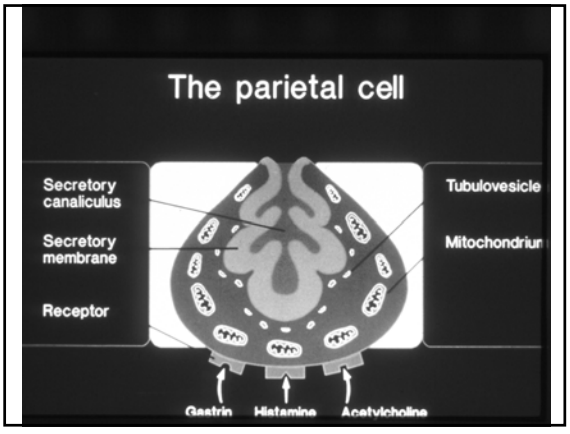
Parietal cells

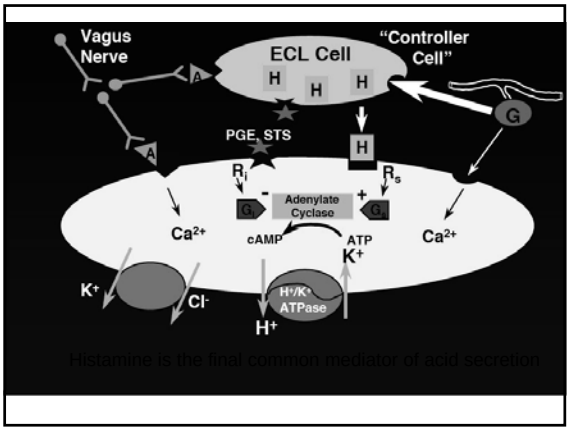
- Human stomach contains ~ 1 billion parietal cells
- Large (25 μm in diameter) oval shaped cells located in mid region of oxyntic glands
- Major function is the secretion of acid
- Three main ultrastructural features:
  - numerous mitochondria
  - tubulovesicles
  - secretory canaliculi

Integrated control of acid secretion

Three levels of regulation of acid secretion:

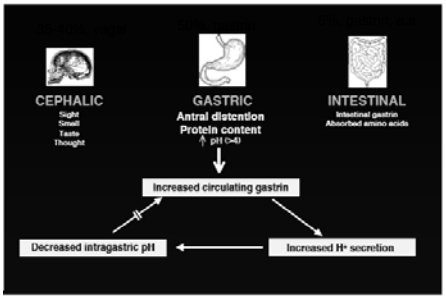
- Neural control - acetylcholine
  - cephalovagal and local intragastric reflex arcs
- Hormonal control
  - endocrine (gastrin) or paracrine (somatostain, histamine)
- Local direct factors
  - positive (+) factors - amines/amino acids, gastric distention
  - negative (-) factors - increased acid or low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

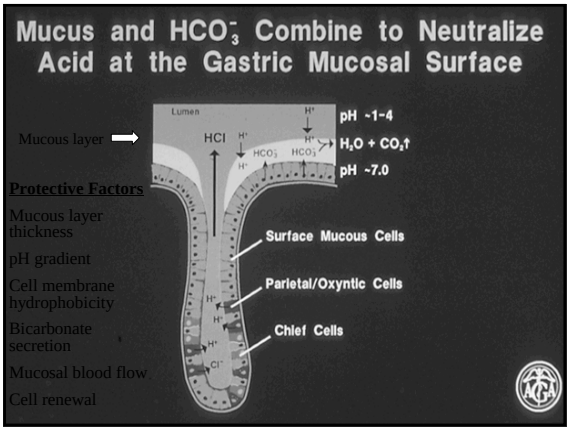


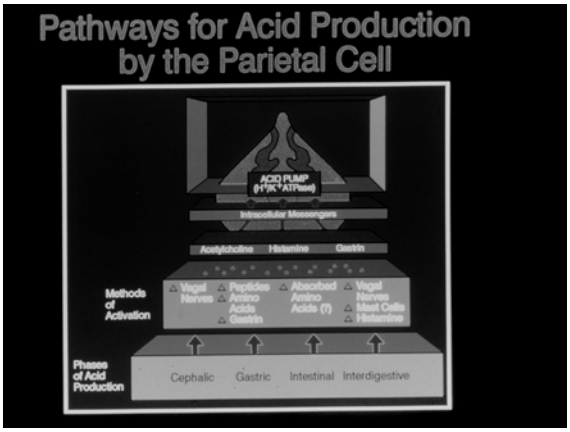


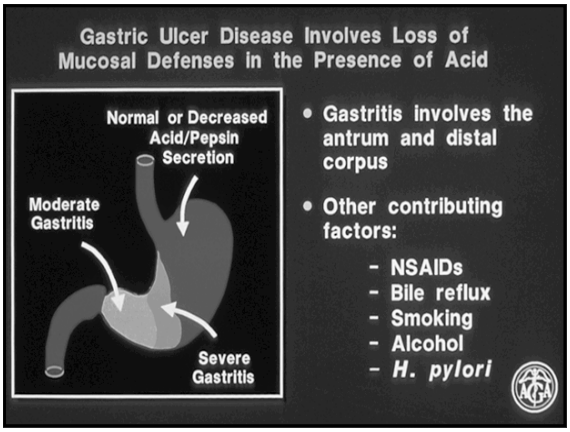
Phases of gastric acid secretion

- Interdigestive phase
  - –basal acid secretion -vagal regulation





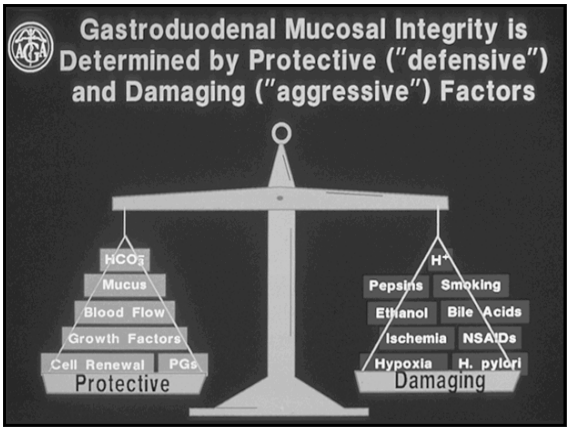


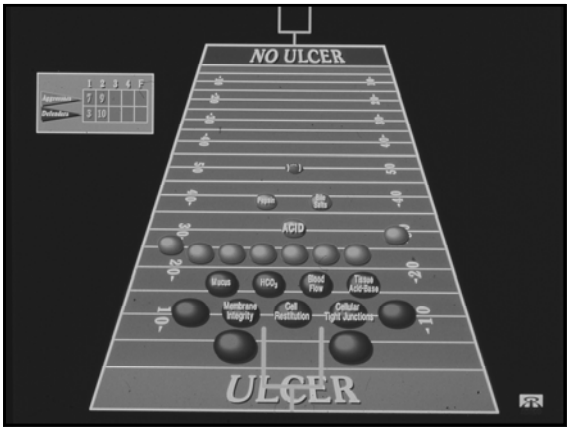


Why the stomach does not digest itself

- 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.

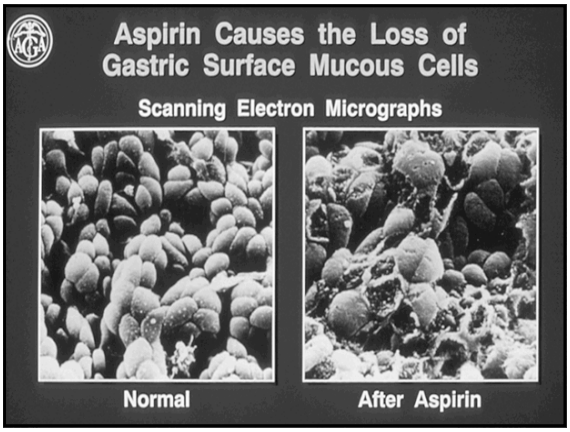
Bhaskar KR et al, Nature 1992;360:458



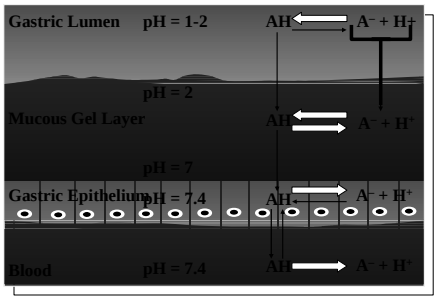


Mechanisms of NSAID Injury

- 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

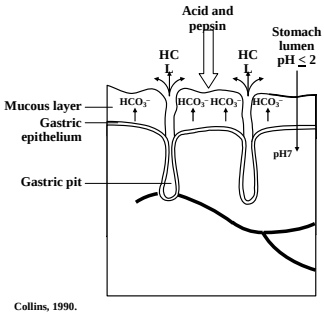


Ion Trapping of Acidic NSAIDs



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

Normal Gastric Protective Mechanisms

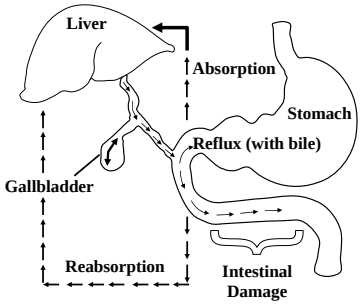


Collins, 1990.

Protective factors: all are PG dependent

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

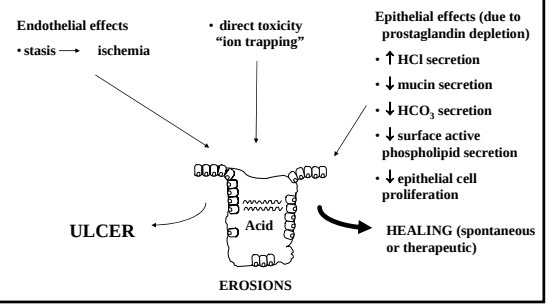
Indirect Topical Exposure Via Enterohepatic Circulation



NSAIDs Excreted in Bile

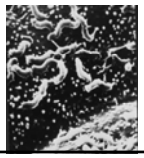
- Indomethacin
- Diclofenac
- Naproxen
- Piroxicam
- Sulindac
- Oxaprozin
- Ketorolac

Pathogenesis of NSAID-Induced Ulcer



H. pylori Timeline

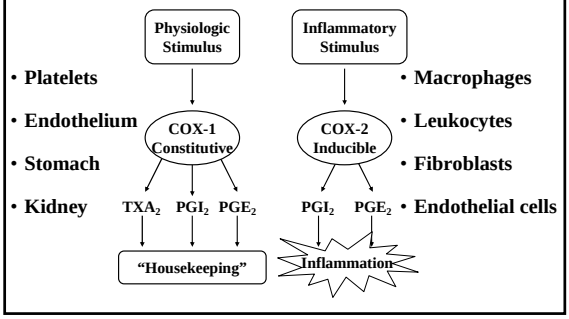
- Early 1900's — Discovery of human gastric bacteria
- 1920-1980 — Rediscovery of gastric bacteria
- 1982 — Isolation and culture of *C. pyloridis* by Marshall and Warren
- 1987 — Eradication reduces DU recurrence
- 1989 — Bacteria are renamed *H. pylori*
- 1990's — Association of *H. pylori* with gastric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



Helicobacter pylori

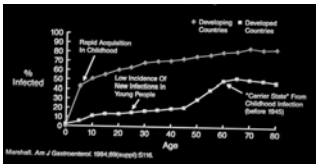
Marshall & Warren

Cyclooxygenase Isoenzymes



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

Risk factors for serious NSAID-related Peptic Ulcer Disease

- Age > 60 years
- History of previous ulcer or GI bleeding
- Concomitant 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 belongs to a larger family of *Helicobacter sp.*

Humans
- *H. pylori*
- ***H. heilmanni***

Mouse
- ***H. hepaticus***
- ***H. bilis***
- ***H. rodentium***
- *H. typhlonius*
- *H. ganmani*
- ***H. rappini***

Ferret
- *H. mustaelae*

Rat
- *H. trogontum*
- *H. bilis*

Chicken
- ***H. pullorum***

Hamster
- *H. cinaedi*
- *H. cholecystus*
- *H. aurati*
- *H. mesocricetorum*

Cat
- *H. felis*

Woodchuck
- *H. marmotae*

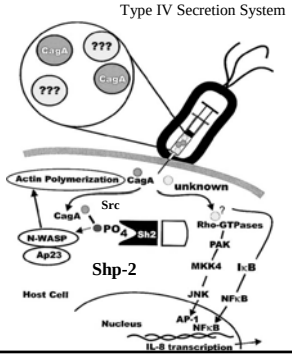
Gerbil
- *H. bilis*
- *H. hepaticus*

Dog
- *H. fennelliae*
- *H. canis*

Other
- *H. canadensis*
- *H. winghamensis*

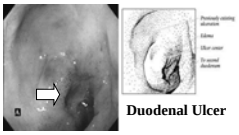
CagA Protein from *Helicobacter pylori* Is a Trojan Horse to Epithelial Cells

- 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



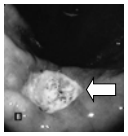
H. pylori and Peptic Ulcer Disease

- 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.

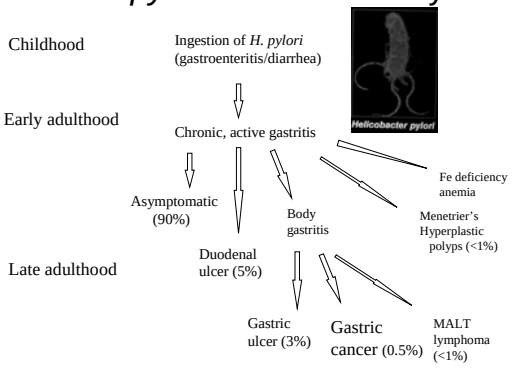


Duodenal Ulcer

Gastric Ulcer

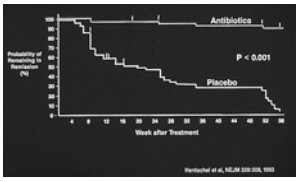


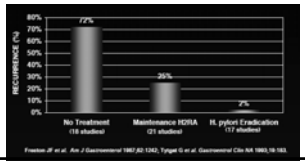
H. pylori: Natural History



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.





H. pylori and gastritis

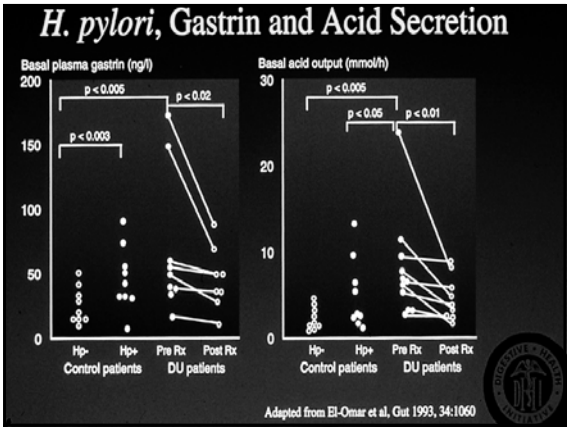
- **Acute infection may result in hypochlorhydria**
- **Active, chronic (type B) gastritis invariably present with *H. pylori***
- **Causal relationship established (Koch's postulates):**
  - **Eradication of *H. pylori* eliminates gastritis**
  - **Ingestion of *H. pylori* by 2 volunteers**
- **Mild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

ALL HP INFECTIONS ARE NOT ALIKE: HISTOLOGY IS KEY

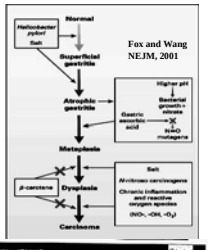
- **Superficial pangastritis (mixed gastritis) without disease**
  - **Normal acid**
- **Antral predominant gastritis**
  - **Increased acid (DU)**
- **Body gastritis (± atrophy) - Decreased acid (GU, gastric cancer)**
- **Multifocal atrophy with intestinal metaplasia**
  - **Decreased acid (gastric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

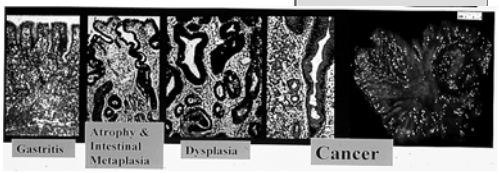
Pathogenesis of *H. pylori*-dependent duodenal ulcer disease

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



Helicobacter pylori is a Class I Carcinogen





Postulated mechanism for duodenal ulcer disease

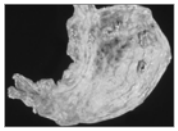
Low levels of IL-1β

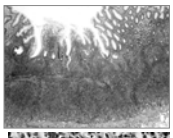
Severe antral infection by *H. pylori* (type I strains) **(CagA, vacAs1, babA2)** → Increased gastrin-17 → Increased acid load → Low duodenal pH → Gastric metaplasia

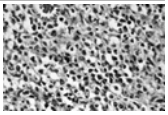
H. pylori colonization of duodenum → Active chronic duodenitis → Duodenal ulcer

H. pylori and Gastric 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

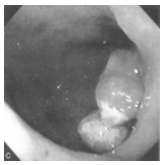




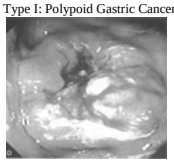


H. pylori and gastric cancer

- 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.



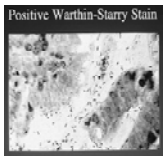
Type I: Polypoid Gastric Cancer

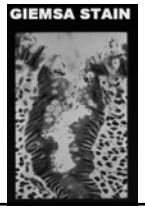


Type II:Exophytic Gastric Cancer

Diagnostic tests for *H. pylori*

- Noninvasive
  - Serology (ELISA, immunoblot)
  - UBT (C13 or C14)
- Invasive (require endoscopy)
  - Rapid urease assay
  - Histology (Warthin-Starry, Giemsa, Immunohistochemistry
  - Culture, PCR analysis
- Newer noninvasive
  - e.g. H. pylori stool antigen (HpSA)





H. pylori treatment regimens

PPI Triple Regimens (7-14 days)

- OAC (omeprazole/amoxicillin/clarithromycin) 89-95%
- LAC (lansprazole/amoxicillin/clarithromycin) 90-95%
- MOC (metronidazole/omeprazole/clarithromycin) 87-91%

Quadruple Regimens (7-14 days)

- PPI/BMT (omeprazole plus bismuth/metronidazole/ tetracyline) 98%
- RBC-AC (ranitidine/bismuth citrate/amoxicillin/ clarithromycin) 90-95%

There are Clinical Features that Can Distinguish ZE Syndrome from DU

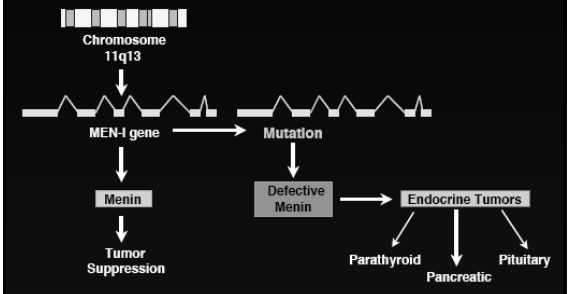
FEATURE	MECHANISM(s)
• Diarrhea • Weight loss/steatorrhea	↑ gastric acid secretion ↓ duodenal/jejunal pH Inactivation of lipase Mucosal inflammation
• Large gastric folds	Trophic effect of gastrin
• Large amounts of gastric secretions	Secretory effect of gastrin
• Family history of endocrine tumor, ↑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

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

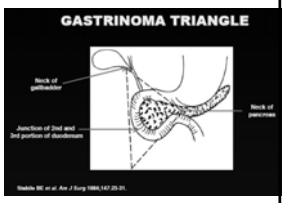
- The tumors produce gastrin (G17 & G34); referred to as "gastrinomas"
- Tumors localized usually to head of pancreas, duodenal wall or regional lymph nodes
- About one-half of gastrinomas are multiple and two-thirds malignant
- About one-fourth have multiple endocrine neoplasia syndrome (MEN I) – tumors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

MEN-I SYNDROME



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%



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