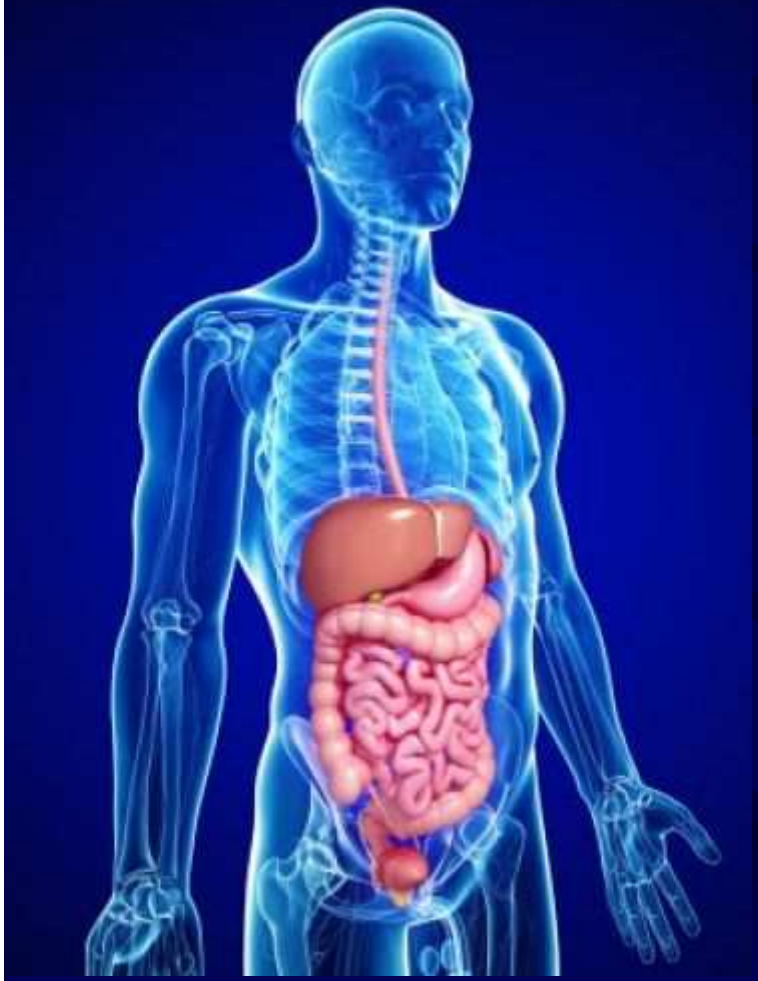
Summer Pathophysiology courses



GASTROINTESTINAL DISORDERS 3

R. BENACKA

Department of Pathophysiology

P.J.Safarik University, KOSICE, SK

PEPTIC ULCER DISEASE (PUD)

Peptic ulcer

- **Definition**
  - **Peptic ulcer -** deep defect in the gastric and duodenal mucosa (∅ 3 mm - several cm) extended even to muscular layer
  - **Peptic erosion** - superfitial mucosal defect (∅ 1-5 mm)
- **Location in GIT**
  - **common:** esophagus, stomach or duodenum,

    Gastric ulcer, Duodenal ulcer, Esophageal ulcer
  - **other:** at the margin of a gastroenterostomy, in the jejunum, Zollinger-Ellison syndrome, Meckel's diverticulum with ectopic gastric mucosa
- **Occurence**
  - 500,000 new cases each year, 5 million people affected in US
  - predominantly older population, peak incidence 55 - 65 years
  - men have 2x higher risk form PUD than women; duodenal PUD more common than gastric ulcers, in women the converse
  - duodenal ulcers occurs 25 - 75 years od age

Symptomatology (common)

Spontaneous

- Dyspepsia persistent, recurrent (not always, e.g. NAIDs ulcers)
- Abdominal discomfort or pain burning or gnawing, epigastric, localised or diffuse, radiate to back or not; hunger pains slowly building up for 1-2 hours; nonspecific, benign ulcers and gastric neoplasm
- Bloating, Fullness, Mild nausea (vomiting relieves a pain)
- Symptoms of Anemia (chronic bleeding, IF- B12 (gastritis))

Meal related

- gastric ulcer pain is aggravated by meals (weight loss)
- duodenal ulcer pain is relieved by meals (do not lose weight)

Emergency

- severe gastric pain well radiating (penetration, perforation)
- bloody vomiting and tarry stool

Characteristics

Gastric ulcer

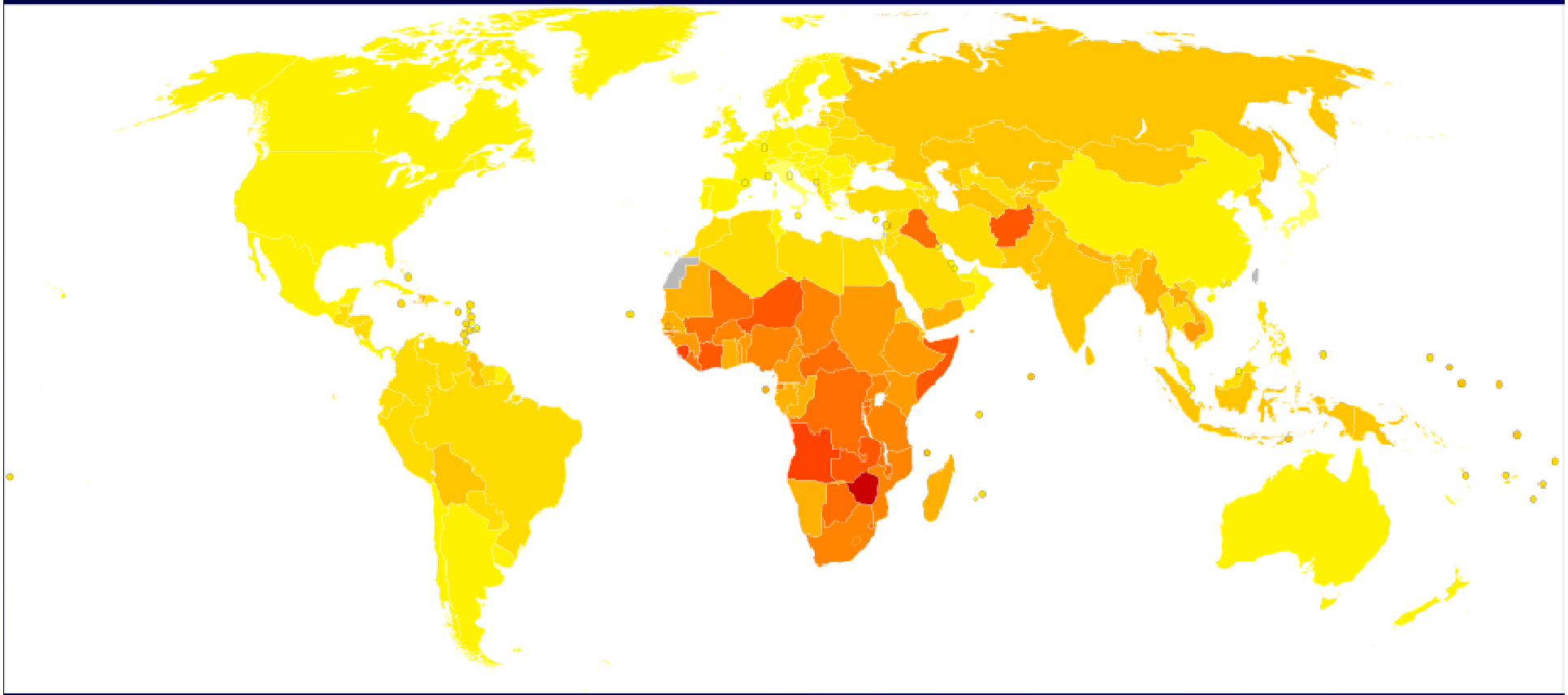
- m: f = 1(2):1 peak 50-60 y.
- pain often diffuse, variable - squizing, heaviness, or sharp puncuating (may absent)
- poorly localized, may radiate to back, 1-3 h after food
- aggravated by meals
- severe gastric pain well radiating indicate penetration or perforation
- seasonal occurence (autumn, spring)

Duodenal ulcer

- m: f = 4:1 peak 30-40 y.
- pain well localized epigastric, chronic, intermittent, relieved by alkalic food
- often late onset 6-8 h after meal or independent (night)
- familiar occurrence
- smokers
- blood O type
- complication - penetration ionto pancreas (pancreatitis)

Epidemiology of PUD

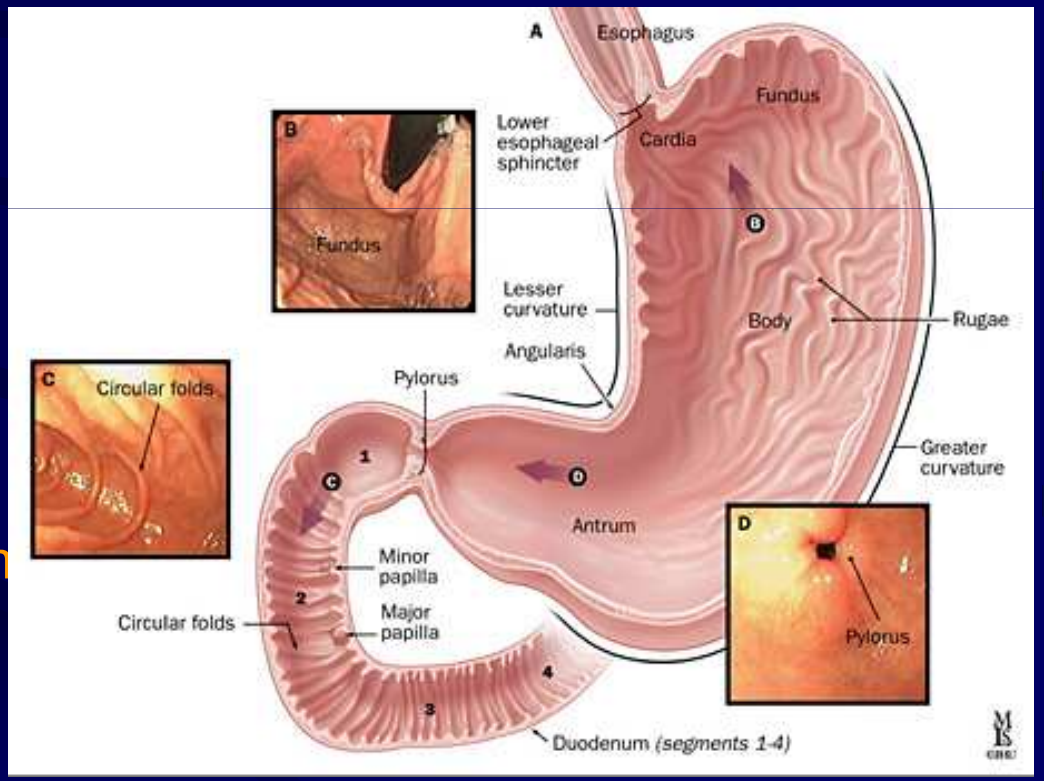
Characteristics



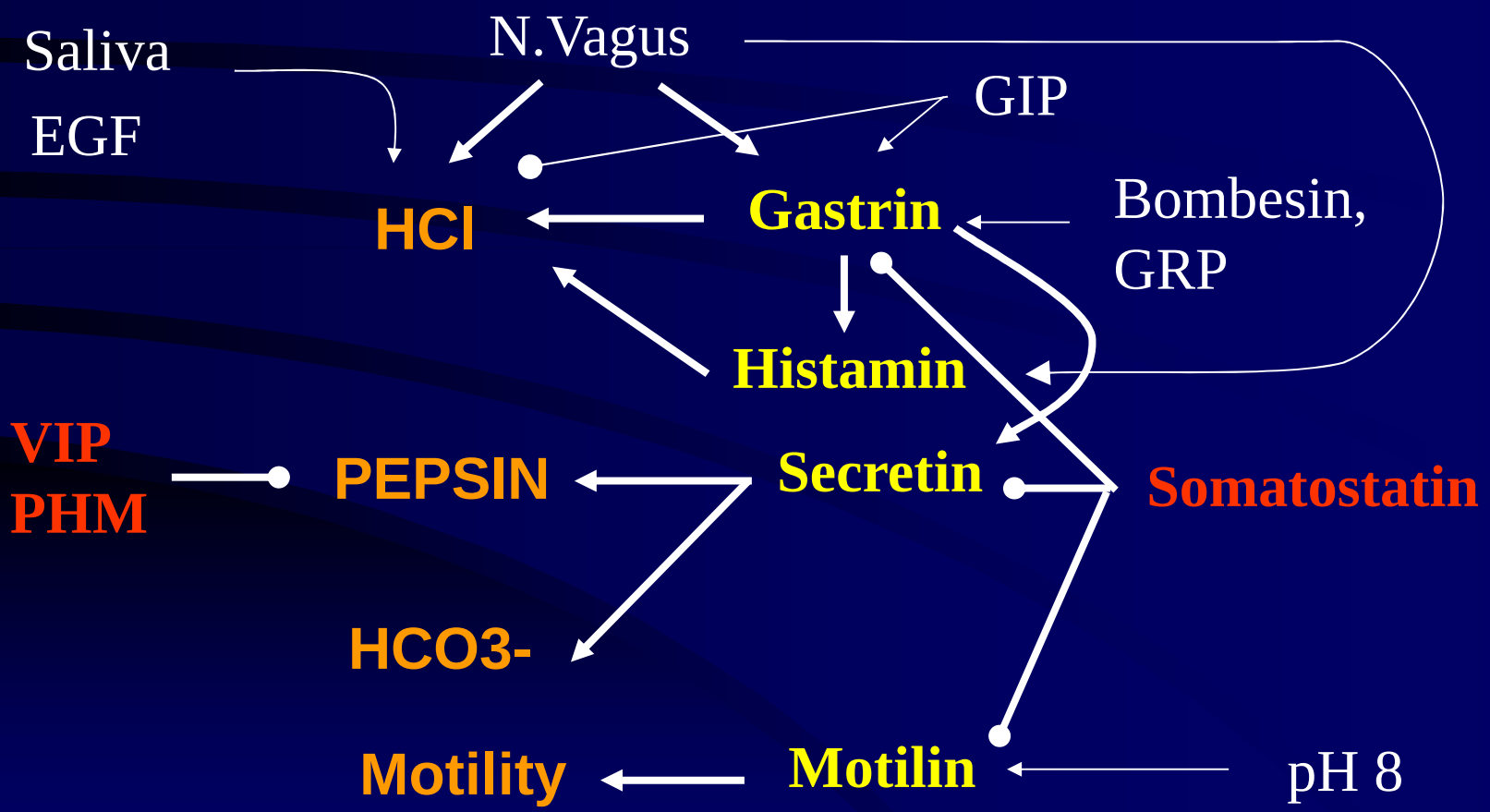
Etiopathogenetical considerations

Gastro-duodenal physiology

- **Anatomy (stomach - antrum, body , fundus)**
- **Components of gastric juice**
  - Salts, Water
  - Hydrochloric acid
  - Pepsins
  - Intrinsic factor
  - Mucus
- **Components of duodenal juice**
  - Enzymes (trypsin, chymotrypsin
  - Water
  - HCO_3^-
  - Bile acids, bilines



Regulation of digestive activity



Hydrochlorid acid production

- Secreted by parietal cells
- Stimulated by endogenous substances

  Gastrin I, II (G) -gastrin cells

  Acetylcholin (M1) - vagi

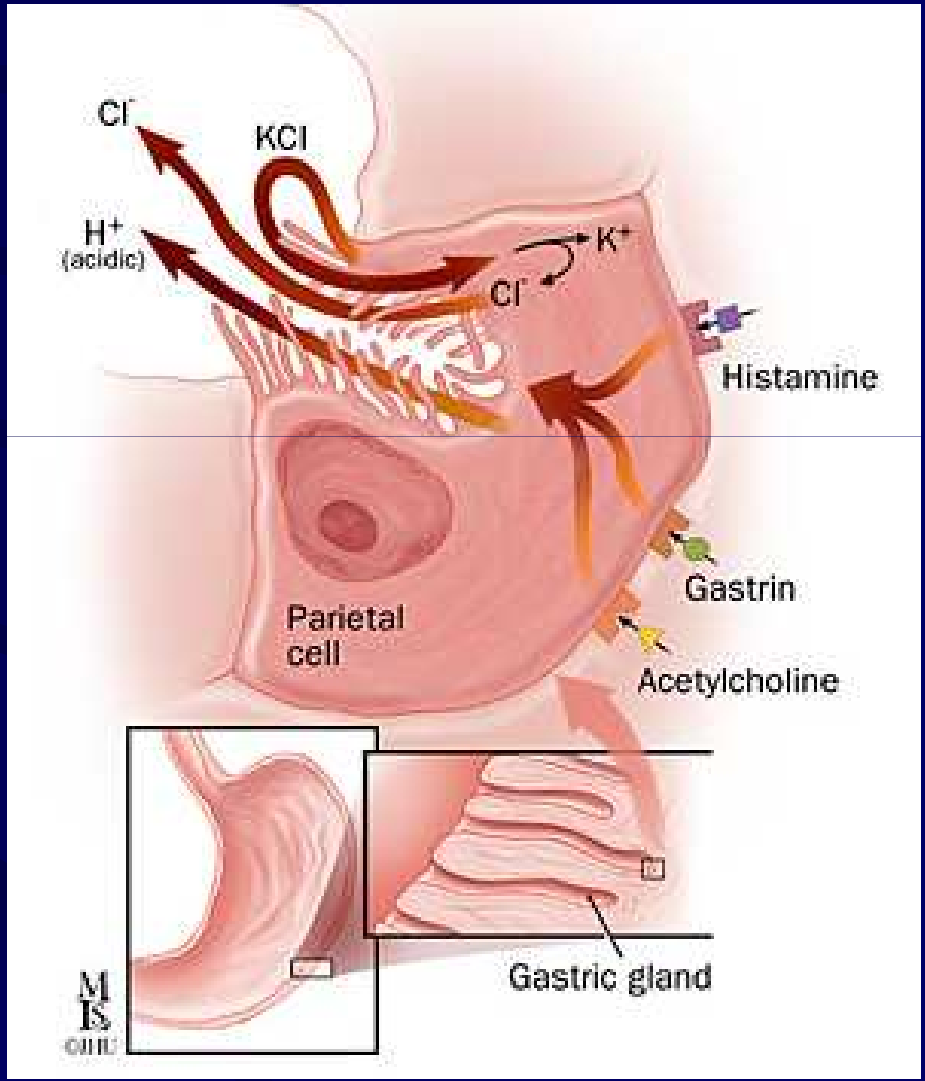
  Histamine (H2)

  Prostaglandins (E2, I2),

  Norepinephrin

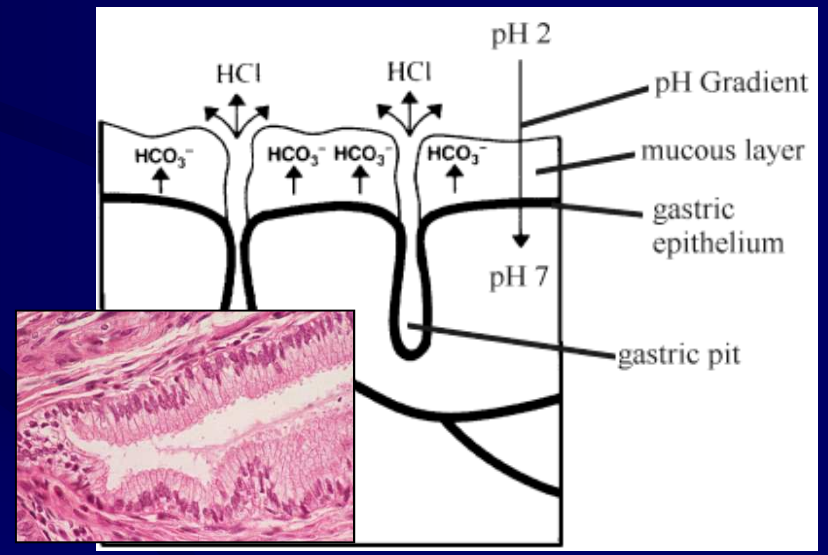
- Functions

- converts pepsinogen into active pepsins
- provide low pH important for protein breakdown
- keeps stomach relatively free of microbes



(2) Mucosal protection

- Gastric mucus - 0,1-0,5 mm soluble vs. gel phase
  - mucin (MUC1, MUC2, MUC5AC, and MUC6 produced by collumnar epithelium
  - gel thickness prostaglandins (PG E2) ⬆ COX I inhibitors ⬇
- Bicarbonate (HCO_3^-) secretion
  - collumnar epithelium in stomach, pancreatic juice to duodenum
  - enters the soluble and gel mucus, buffers H^+ ions
- Mucosal (epithelial) barrier
  - mechanical support aginst H+
- Blood supply into mucose
  - removal of H^+ ions
  - supply wioth HCO_3^-



Break through mucosal defence

- First line defense (mucus/bicarbonate barrier)
- Second line defense (epithelial cell mechanisms barrier function of apical plasma membrane)
- Third line defense (blod flow mediated removal of back diffused H+ and supply of energy)

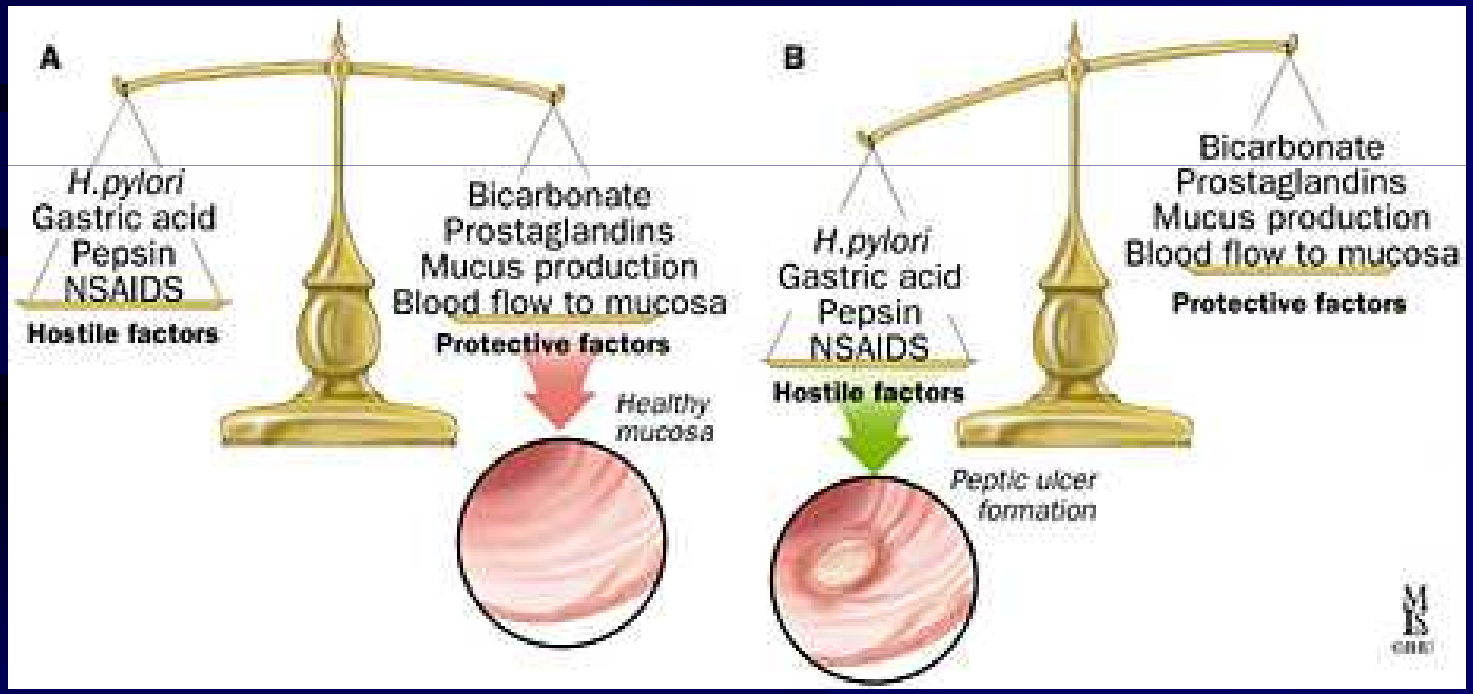
  if not working → Epitelial cell injury
- First line repair - restitution
- Second line repair - cell replication

  if not working → Acute wound formation
- Third line repair - wound healing

  if not working → Ulcer formation

Etiopathogenesis

- Ballance between hostile and protective factors
- ”No gastric acid, no peptic ulcer”- misconception



Etiopathogenesis

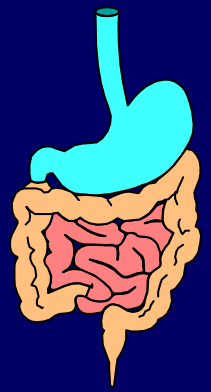
⬆ Agressive factors

- Helicobacter pylori
- Nonsteroidal Anti Inflammatory Drugs (NSAIDs)
- Cushing ulcer (adrenocorticosteroids)
- Hyperacidity (abnormalities in acid secretion)

⬇ Protective factors

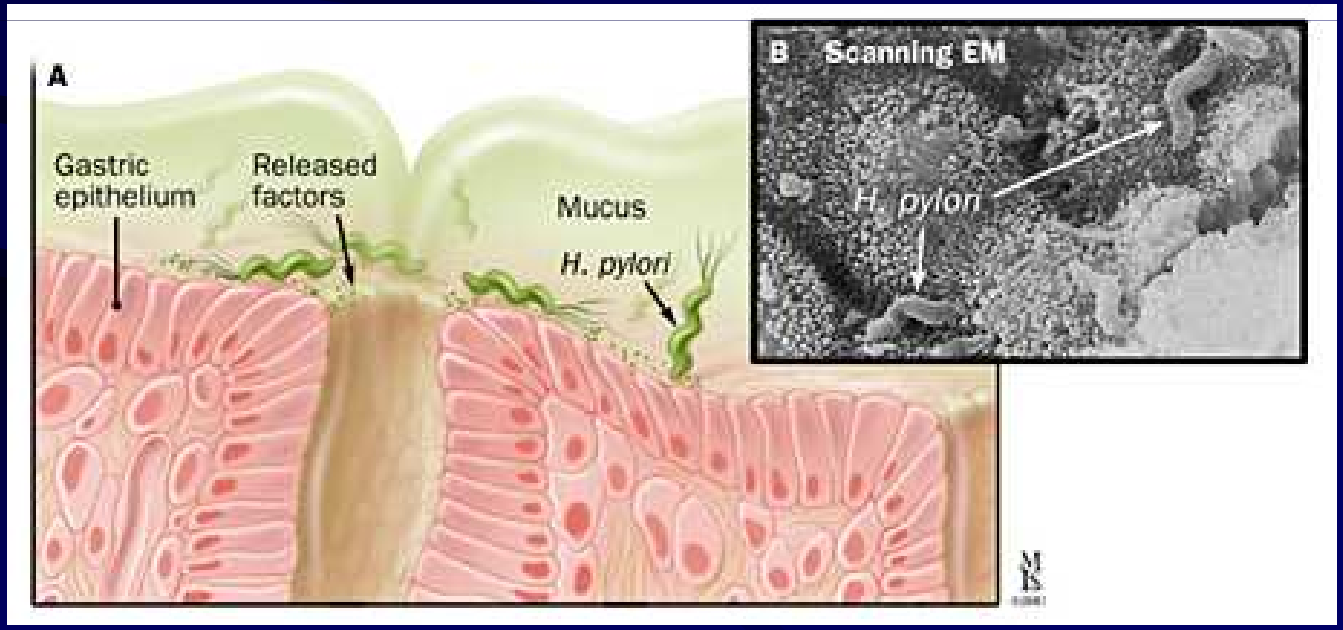
- Curling ulcer (stress, gastric ischemia)
- Abnormalities in gastric motility, duodenal-pyloric reflux, GERD
- NSAIDs (abnormality in mucus production)

Etiopathogenesis



CAUSES

(1) Helicobacter pylori

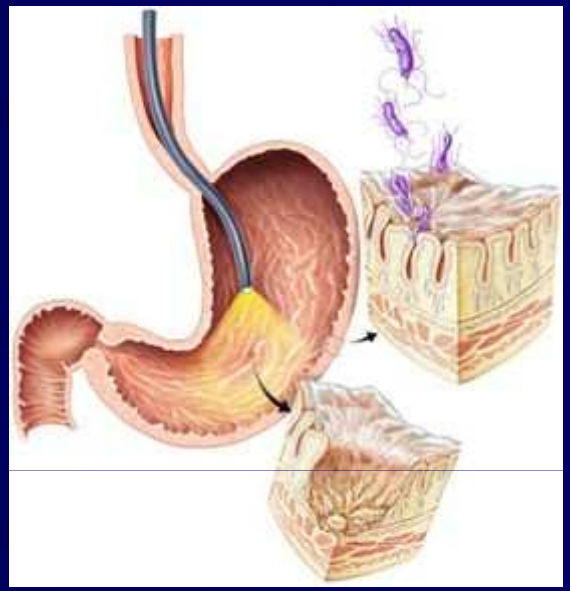


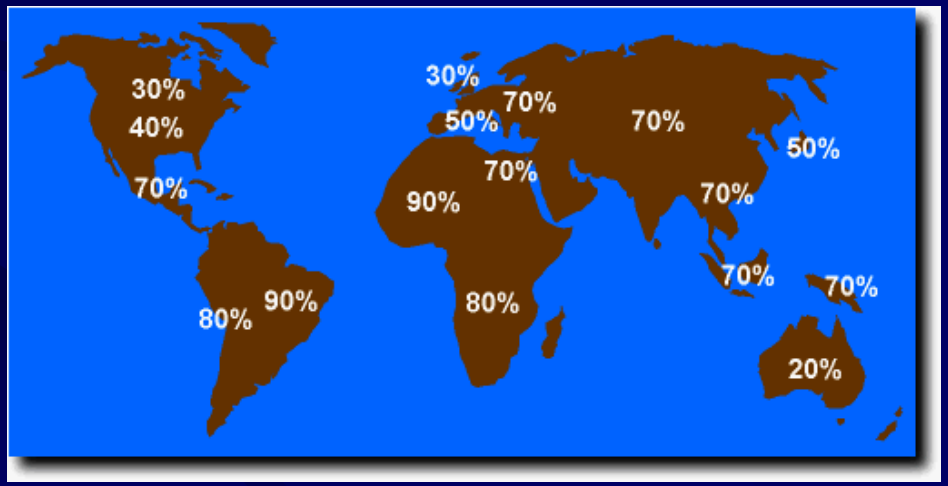
(1) Helicobacter pylori

- Barry Marshall & Robin (1982)
- Gram - curved rod, weakly virulent, likes acid enviroment, produces urease
- acquired in children (10% - 80%), highest in developing countries (contaminated water ?)
- Positive in > 90% of duodenal ulcer and >80% of gastric ulcer (maily diabetics)
- Large percentage of people infected, but not all develop peptic ulcer

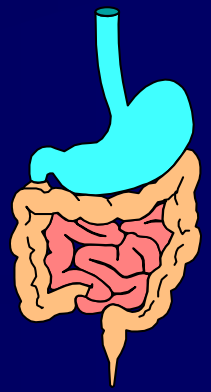
Mechanisms:

- Role in ulcer (or cancer) controversial - gastritis
  - leaking proof hypothesis
  - gastrin link hypothesis
  - ammonia production





Etiopathogenesis



CAUSES

(1) Helicobacter pylori

(2) Nonsteroidal Anti Inflammatory Drugs

(2) NSAIDs

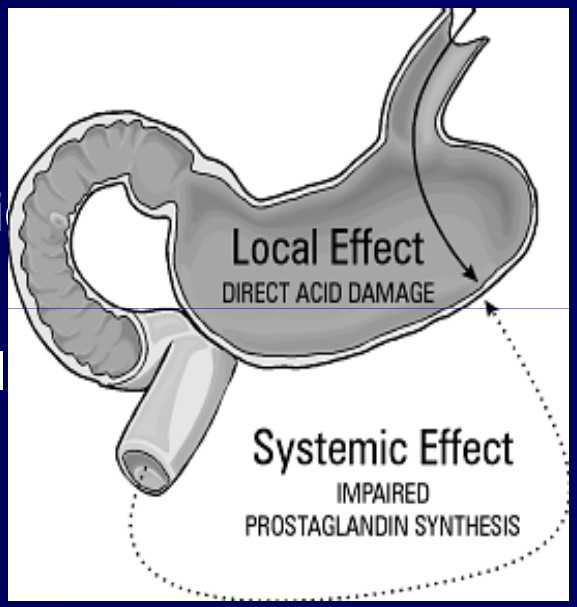
- Associated with < 5% of duodenal ulcer, ~ 25% of gastric ulcer
- inhibition of **cyclooxygenase-1 (COX-1)**

  cyclo-oxygenase-1 - permanently expressed in cells

  cyclo-oxygenase-2 - inducible inflammatory enzyme

Prostaglandins

- increase mucous and bicarbonate producti
- inhibit stomach acid secretion,
- increase blood flow within the stomach wal
- **Mechanisms:**



Local injury

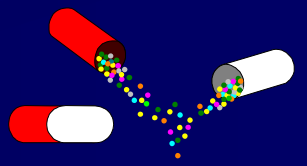
- direct (weak acids, back diffusion of H^+)
- inderect (reflux of bile containing metabolites)

Systemic injury (predominant)

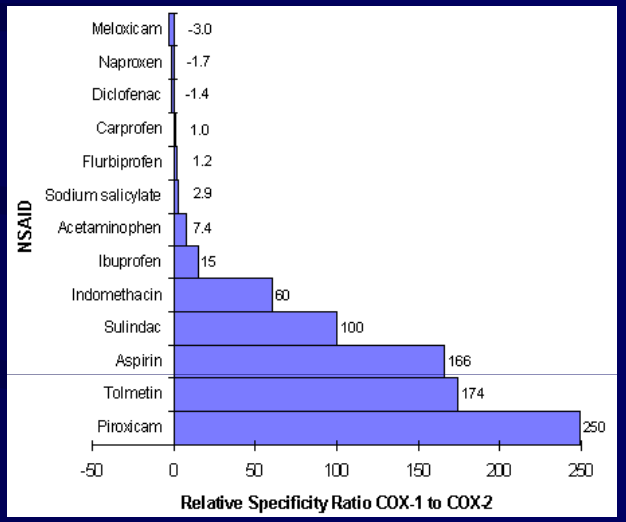
- decreased synthesis of mucosal prostaglandins PGE2, PGI2

NSAID users: incidence of H. pylori in patients with gastric ulcers < duodenal ulcers

NSAIDs - COX I inhibitors

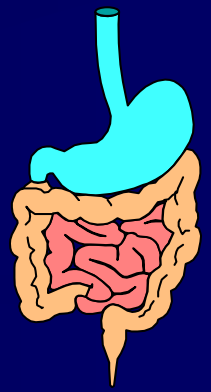


Class	Examples
acetylsalicylic acid	aspirin
acetic acids	diclofenac indomethacin ketorolac nabumetone sulindac tolmetin
fenamates	meclofenamate mefenamic acid
oxicams	piroxicam
propionic acids	ibuprofen ketoprofen naproxen oxaprozin



Ulcer Risk by Specific NSAIDs		
Lowest Risk	**Medium Risk (see note)**	**Highest Risk**
Nabumetone (Relafen) Etodolac (Lodine) Salsalate Sulindac (Clinoril)	Aspirin Ibuprofen (Motrin, Advil, Nuprin, Rufen) Naproxen (Aleve, Naprosyn, Naprelan, Anaprox) Diclofenac (Voltaren) Tolmetin (Tolectin)	Flurbiprofen (Ansaid) Piroxicam (Feldene) Fenoprofen Indomethacin (Indocin) Meclofenamate (Meclomen) Oxaprozin Ketoprofen (Actron, Orudis KT

Etiopathogenesis



CAUSES

(1) Helicobacter pylori

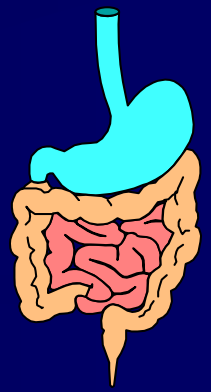
(2) Nonsteroidal Anti Inflammatory Drugs

(3) Hyperacidity - Zollinger Ellison sy.

(3) Hyperacidity

- Gastrinoma (Zollinger-Ellison sy.) **peptic ulcers (0.1% o fall cases) mainly in unusual locations (e.g. jejunum)**
  - **gastrin-producing islet cell tumor of the pancreas (gastrinoma) (50%), duodenum (20%), stomach, peripancreatic lymph nodes, liver, ovary, or small-bowel mesentery (30%).**
  - **in 1/4 patients part of the multiple neoplasia syndrome type I (MEN I)**
  - **hypertrophy of the gastric mucosa, massive gastric acid hypersecretion**
  - **diarrhea** (steatorrhea from acid inactivation of lipase)
  - **gastroesophageal reflux** (episodic in 75% of patients)
- Hypercalcaemia (?)
  - **i.v. calcium infusion in normal volunteers induces gastric acid hypersecretion. Calcium stimulates gastrin release from gastrinomas.**
  - **benefitial effect of parathyreoidectomy**

Etiopathogenesis



CAUSES

(1) Helicobacter pylori

(2) Nonsteroidal Anti Inflammatory Drugs

(3) Hyperacidity - Zollinger Ellison sy.

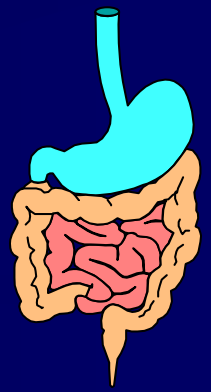
(4) Other factors

(4) Other

Rarely, certain conditions may cause ulceration in the stomach or intestine, including:

- radiation treatments,
- bacterial or viral infections,
- physical injury
- burns (Curling ulcer)

Etiopathogenesis



SUSCEPTIBILITY FACTORS

(1) Genetic factors

Genetic Factors

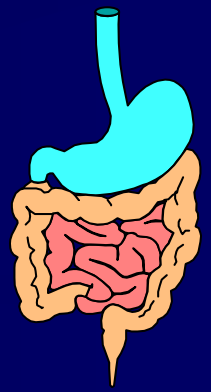
Genetic predisposition for ulcer itself

- **Familiar agreggation of ulcer disease is modest**
  in first-degree relatives 3x greater incidency
  39% pure genetic factors; 61% individual factors (stress, smoking)
  Finnish twin cohort (13888 pairs)
  (Räihä et al.,Arch Intern Med., 158(7), 1998)
- 20–50% of duodenal ulcer patients report a positive family history; gastric ulcer patients also report clusters of family members who are likewise affected

Genetic predisposition for H. pylori

- Genetic influences for peptic ulcer are independent of genetic influences important for acquiring *H pylori* infection
  (Malaty et al., Arch Intern Med. 160, 2000)
- increased incidence of H. Pylori caused ulcers in people with type O blood

Etiopathogenesis

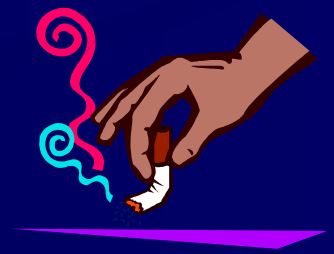


SUSCEPTIBILITY FACTORS

(1) Genetic factors

(2) Smoking

Smoking

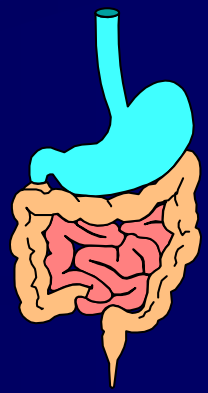


- correlation between cigarette smoking and complications, recurrences and difficulty to heal gastric and duodenal PUD
- smokers are in about 2x risk to develop serious ulcer disease (complications) than nonsmokers
- invovement of smoking itself in ulcer etiology „*de novo*“ controversial (?) (? Stress associated with smoking)

Mechanisms

- smoking increases acid secretion, reduces prostaglandin and bicarbonate production and decreases mucosal blood flow
- cigarette smoking promotes action of H. pylori (co-factors) in PUD

Etiopathogenesis

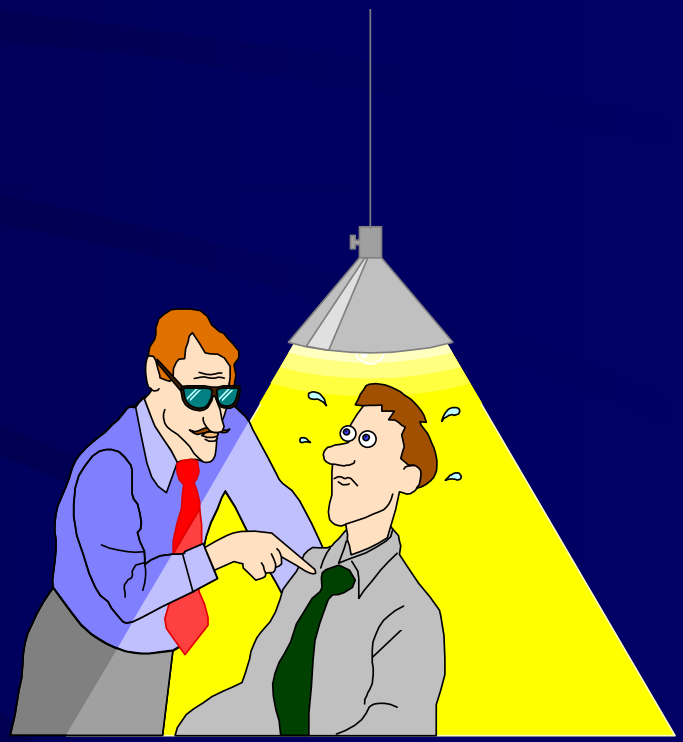


SUSCEPTIBILITY FACTORS

(1) Genetic factors

(2) Smoking

(3) Stress



Stress

Animal studies

- inescapable stress - related ulcer (H. Selye)

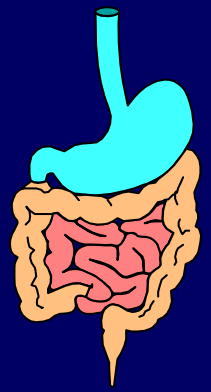
Human studies

- social and psychologic factors play a contributory role in 30% to 60% of peptic ulcer cases
- conflicting conclusions ? (”ulcer-type” personality, A-type persons, cholerics, occupational factors - duodenal ulcer)
- long-term adrenocorticoid treatment

Background

- stress-related acute sympathetic, catechlaminergic and adrenocortical response (GIT ischemia)
- increases in basal acid secretion (duodenal ulcers)

Etiopathogenesis



SUSCEPTIBILITY FACTORS

(1) Genetic factors
(2) Smoking
(3) Stress
(4) Coffee and acidic beverages
(5) Chronic alcoholism

Other factors

- **COFFEE AND ACID BEVERAGES**
  - Coffee (both caffeinated and decaffeinated), soft drinks, and fruit juices with citric acid induce increased stomach acid production
  - no studies have proven contribution to ulcers, however consuming more than three cups of coffee per day may increase susceptibility to H. Pylori infection

- **ALCOHOL**
  - mixed reports (some data have shown that alcohol may actually protect against H. Pylori)
  - intensifies the risk of bleeding in those who also take NSAIDs

Causes - conclusions

Gastric ulcer

- ↑ mucous permeability to H+
- not necessary hyperacidity, even anacidity
- ↑ gastrin (in hypoacidity)
- delayed gastric emptying
- duodeno-antral regurgitation
- (bile acids)

Duodenal ulcer

- ↑ number of parietal cells
- ↑ gastrin only after meat
- ↓ HCO_3^- production
- hyperacidity
- rapid gastric emptying
- ↓ neutralisation of acid →
- 80-90% H. pylori

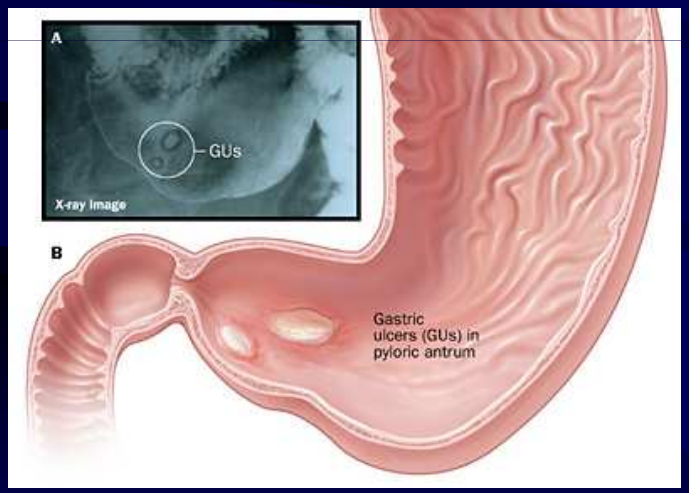
Lack of protective factors predominate

Predominance of agressive factors

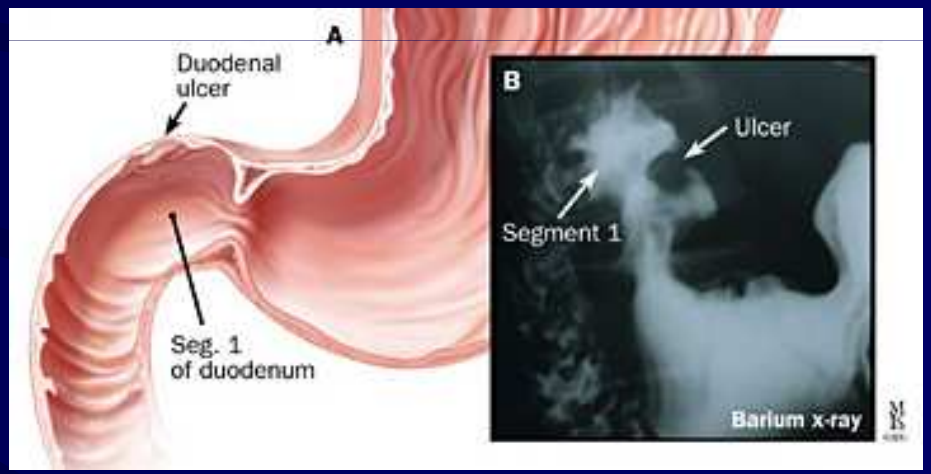
Peptic Ulcer Disease - Diagnosis

(1) Radiological Diagnosis

- In use until 70's: barium x-ray or upper GI series
- 30% false results



Prepyloric peptic ulcer



Duodenal peptic ulcer

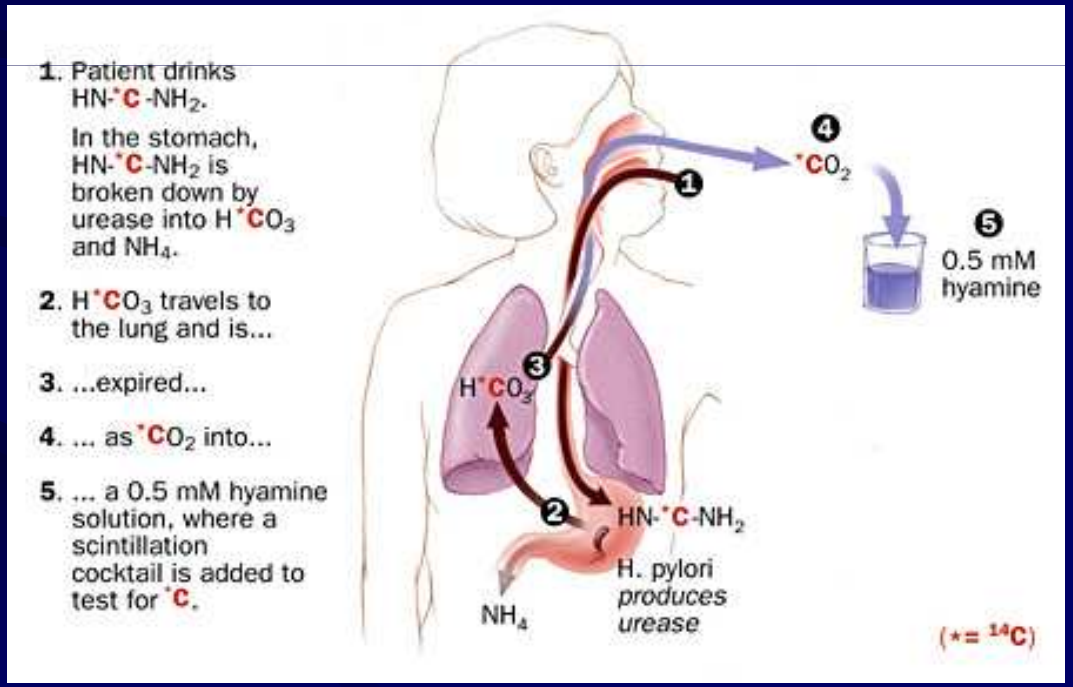
Peptic Ulcer Disease - Diagnosis

(2) Laboratory Diagnosis

refractory (to 8 weeks of therapy) or recurrent disease

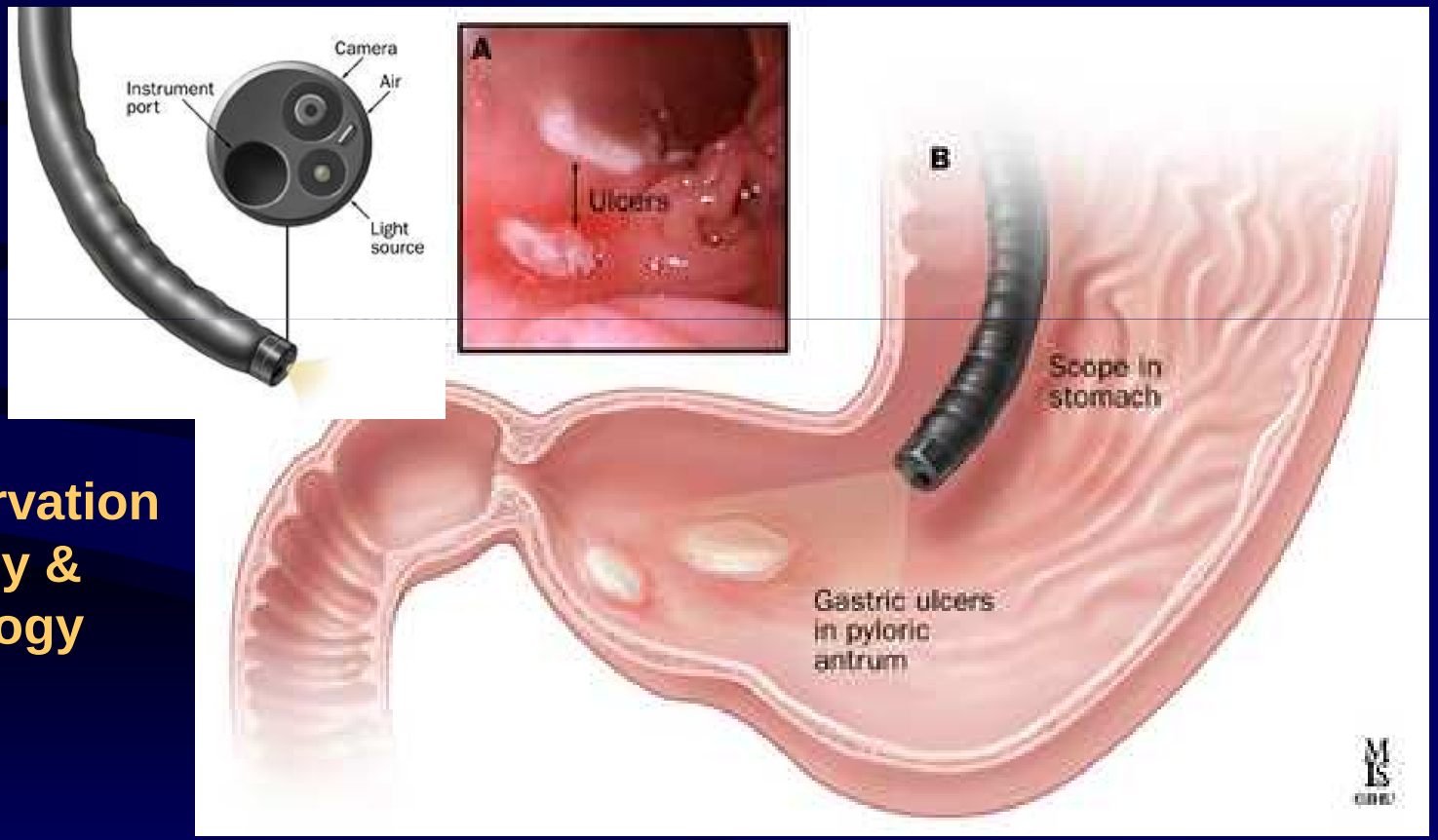
- basal gastric acid output (?hypersecretion)
- gastrin calcium (gastrinoma, MEN)
- biopsies of gastric antrum (H. pylori)
- serologic tests (H.pylori) IgG, IgA
- urea breath tests (H.pylori)

Lasts 20 minutes, highly sensitive



Peptic Ulcer Disease - Diagnosis

(3) Endoscopic Diagnosis - stomach

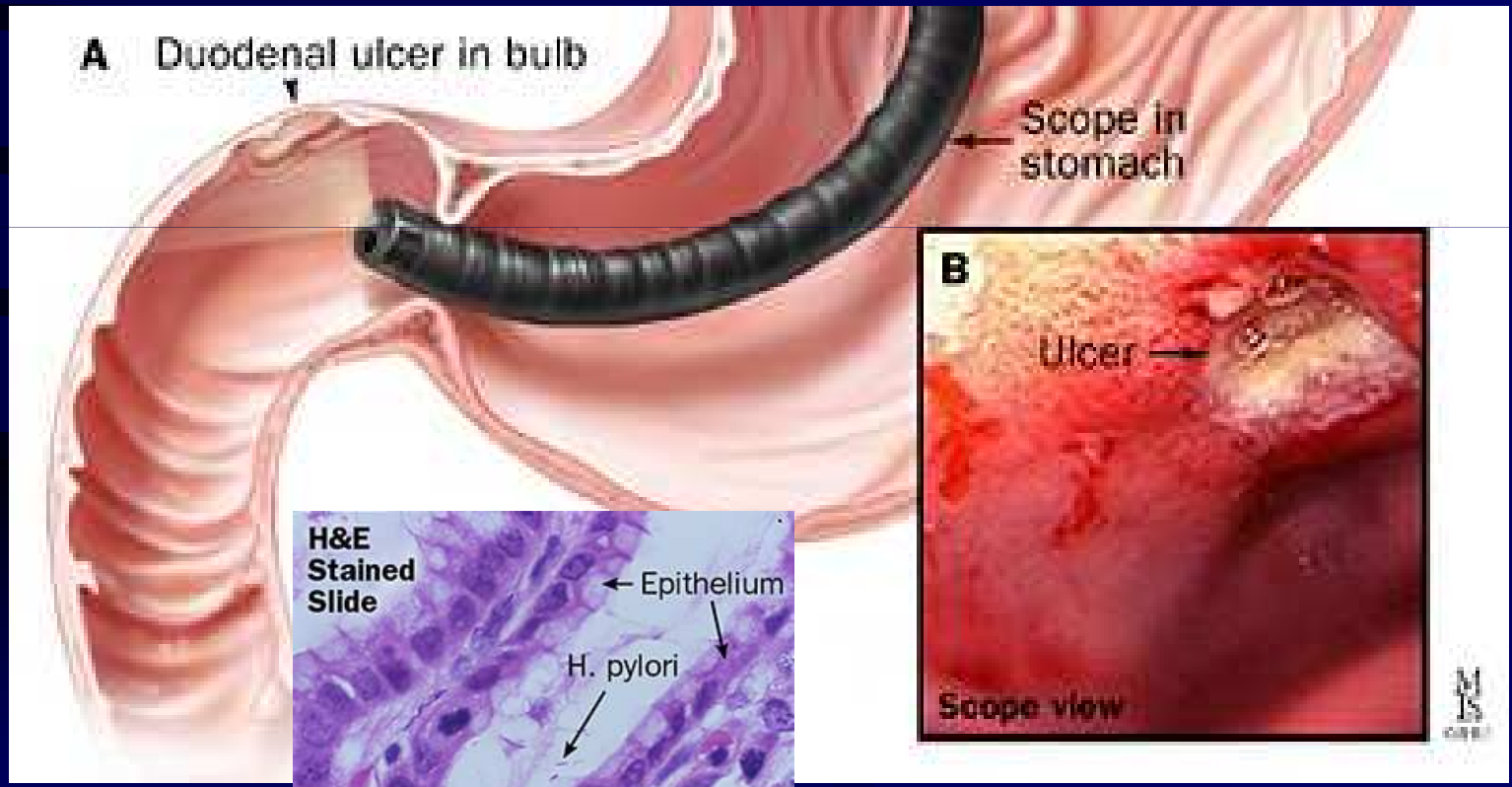


- Observation
- Biopsy & histology

Today's principal diagnostic method

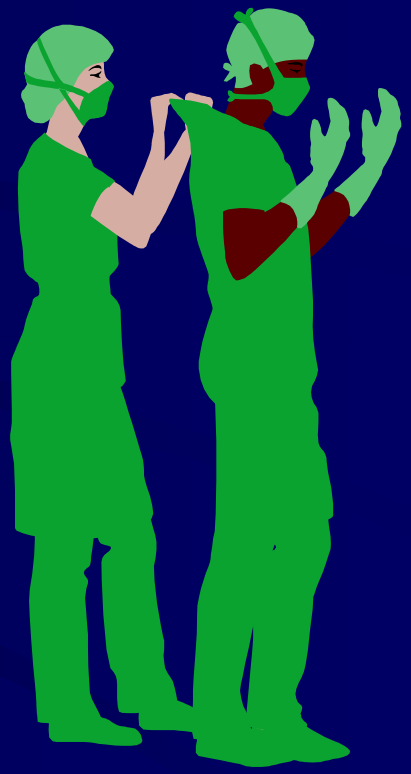
Peptic Ulcer Disease - Diagnosis

(3) Endoscopic Diagnosis - duodenum



Peptic Ulcer Disease -Therapy

- Medical therapy
- Surgery
- Endoscopic Therapy



Peptic Ulcer Disease -Therapy

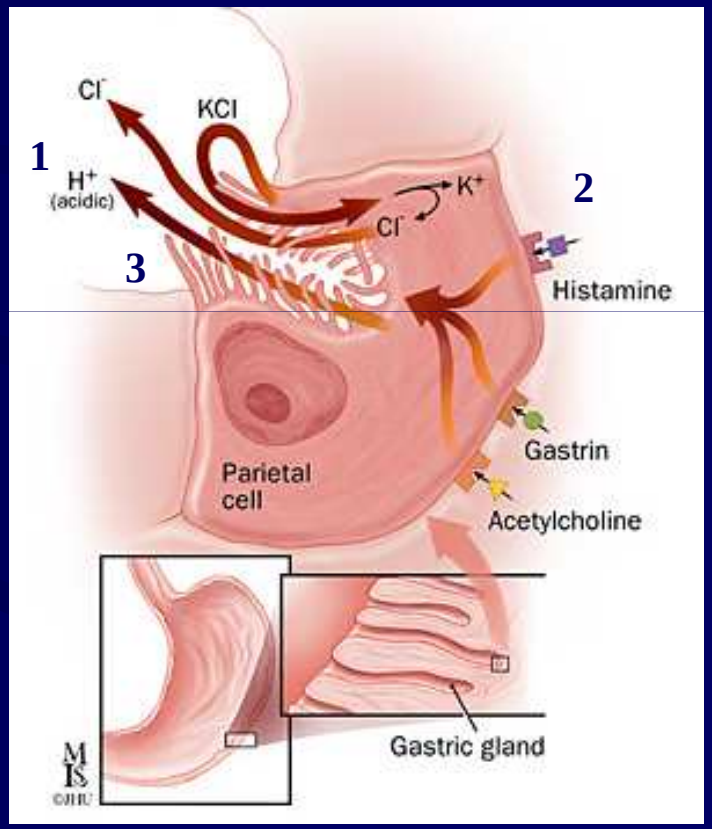
(1) Medical therapy - principles

1) reduce gastric acidity by mechanisms that inhibit or neutralize acid secretion,
2) coat ulcer craters to prevent acid and pepsin from penetrating to the ulcer base,
3) provide a prostaglandin analogs to maintain mucus
4) remove environmental factors such as NSAIDs and smoking,
5) reduce emotional stress (if possible)

Peptic Ulcer Disease -Therapy

Medical therapy -

1) Antacids - large doses required 1 and 3 hours after meals, magnesium hydroxide -diarrhoea
2) Histamine H2-receptor antagonists - cimetidine, ranitidine, famotidine and nizatidine
3) Proton pump inhibitors - resistant to other therapies,prevent NSAID-gastroduodenal ulcers, omeprazole lansoprazole
4) Prostaglabdin stimulators - Sucralfate, Misoprostol

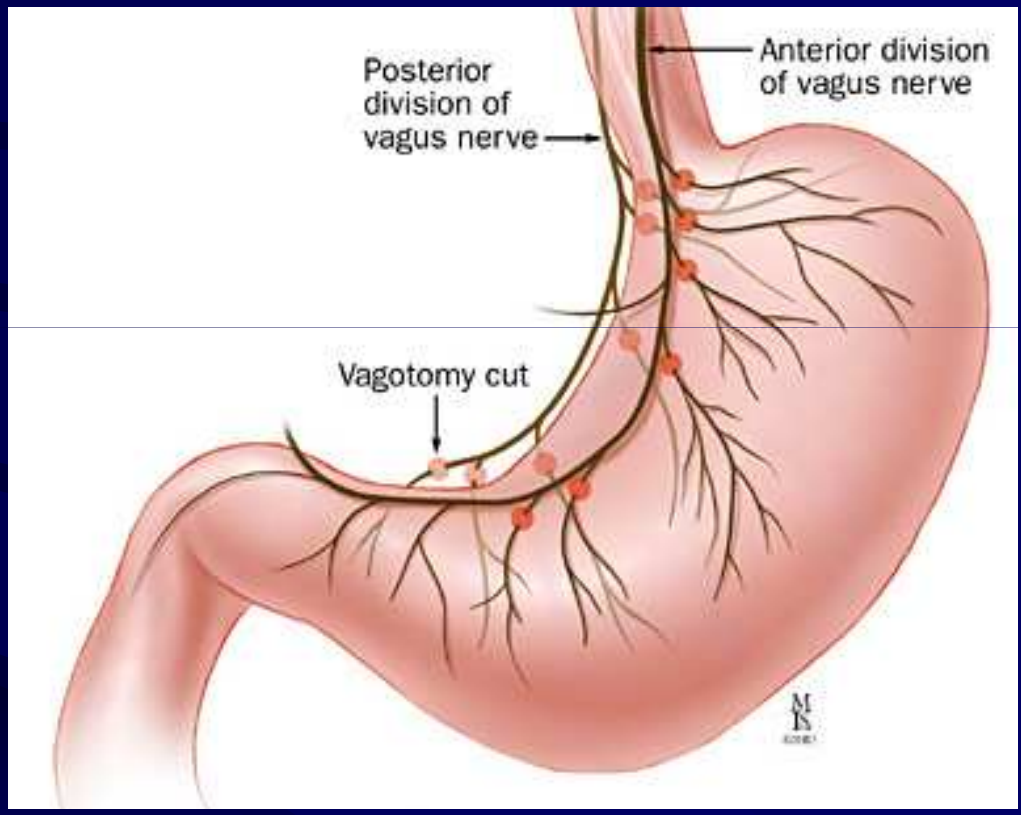


Peptic Ulcer Disease - Therapy

Surgery

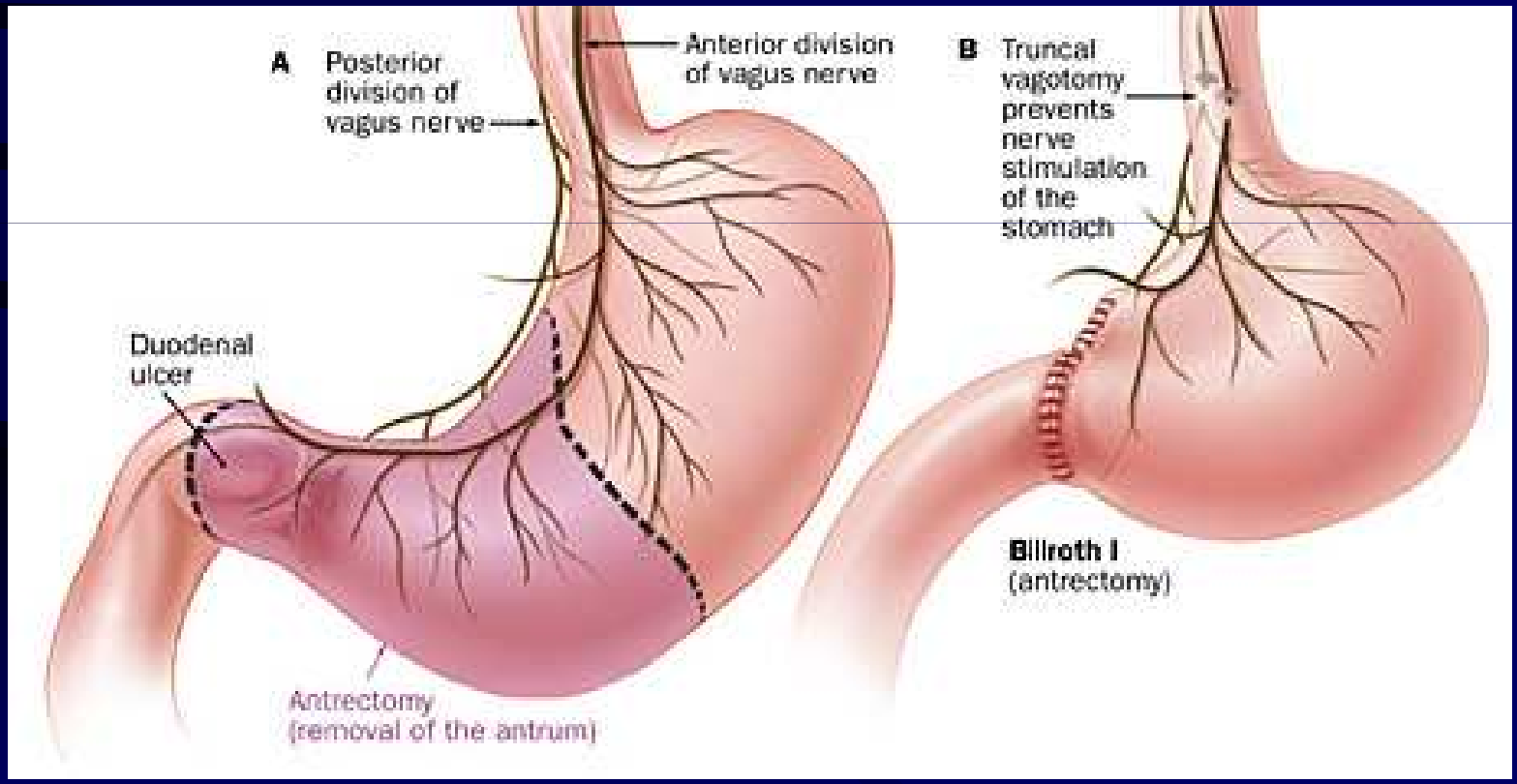
- Vagotomy

total
selective
super-selective



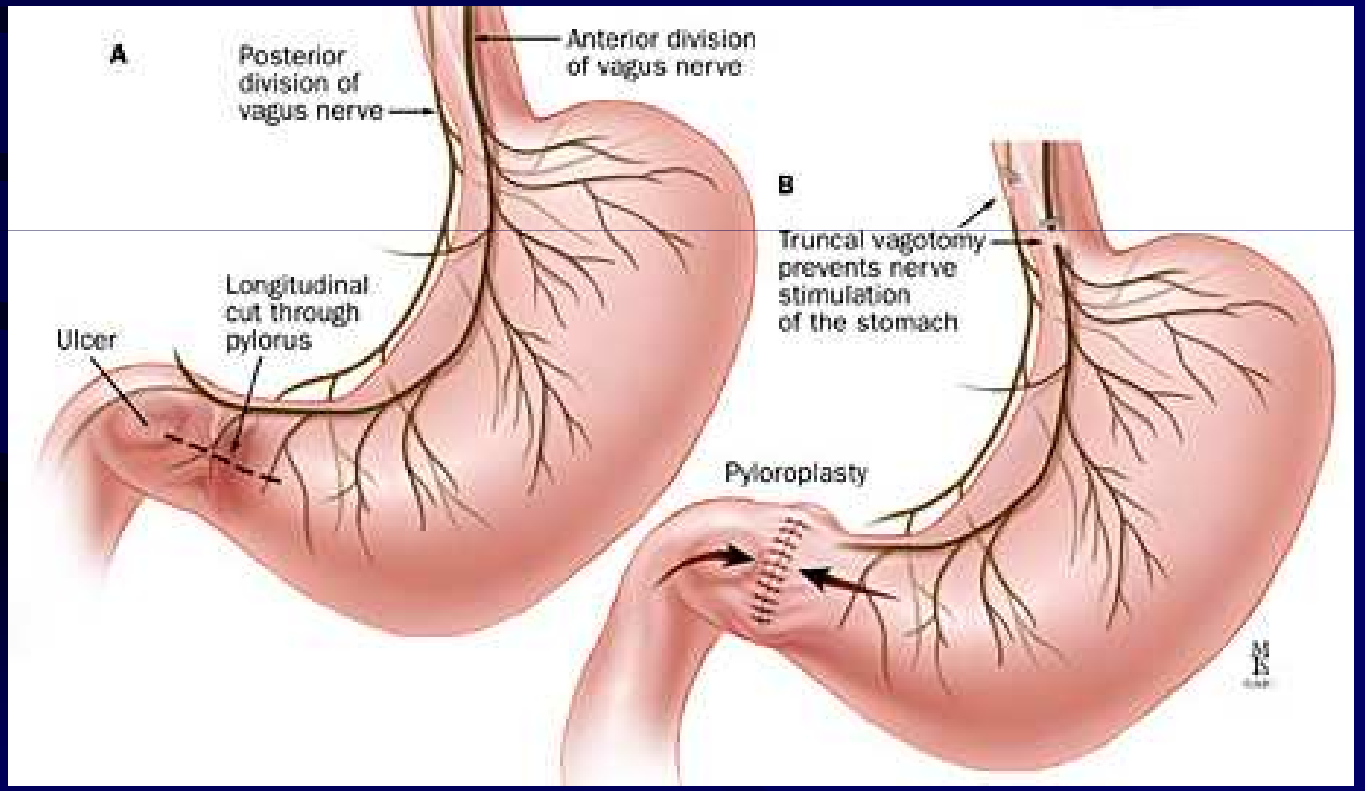
Peptic Ulcer Disease - Therapy

Surgery Bilroth I (antrectomy) + vagotomy



Peptic Ulcer Disease - Therapy

Surgery Pyloroplasty + truncal vagotomy

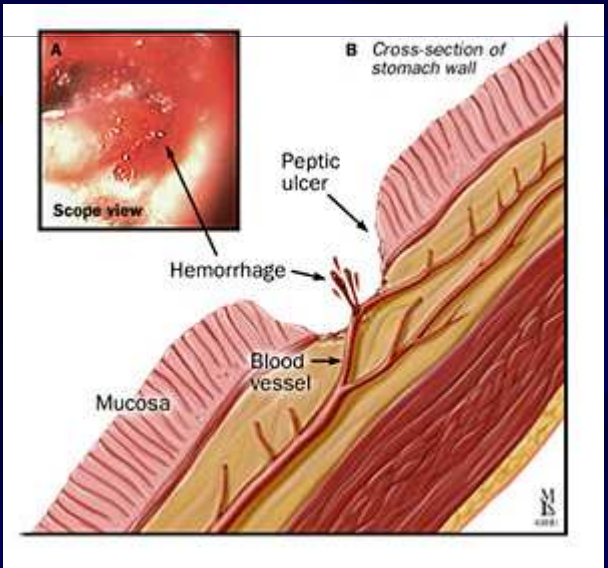


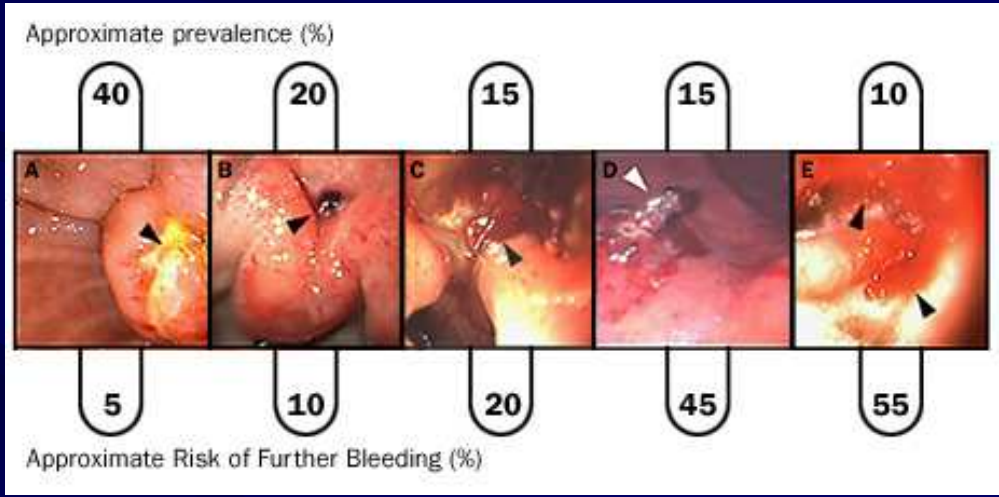
Complications

- Hemorrhage
- Perforation
- Penetration
- Gastric outlet obstruction

Haemorrhage

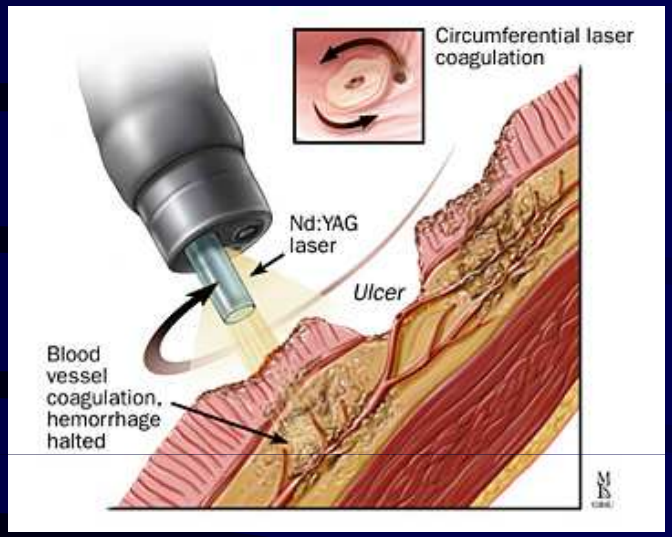
- **Most common,** 5–20% of patients, duodenal> gastric ulcers, men > women, **75**% stops spontaneously, 25% need surgery
- **Vomiting of blood**
- **Melena**



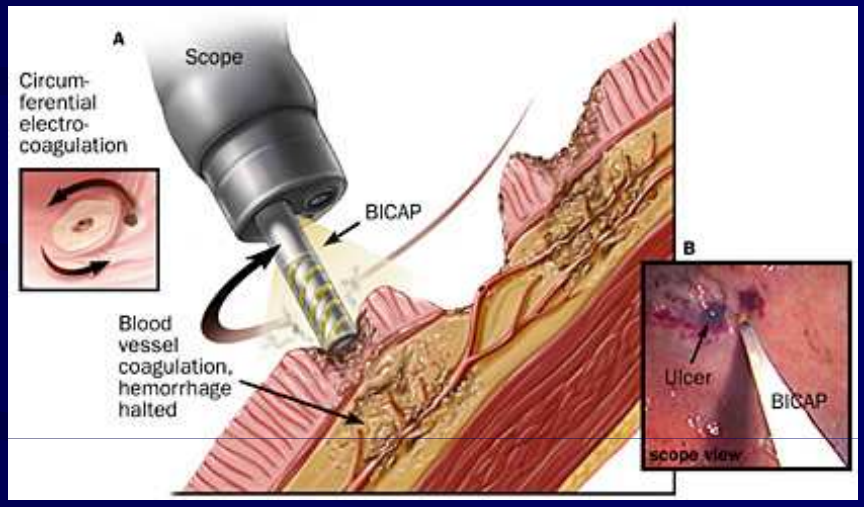


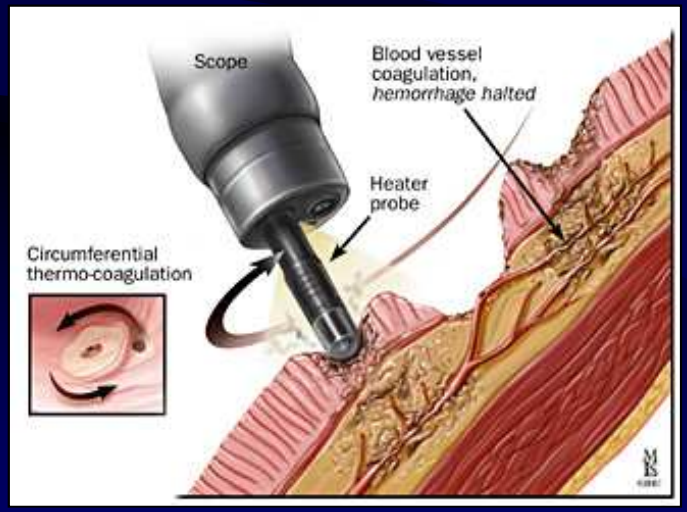
Haemorrhage (treatment)

Laser coagulation

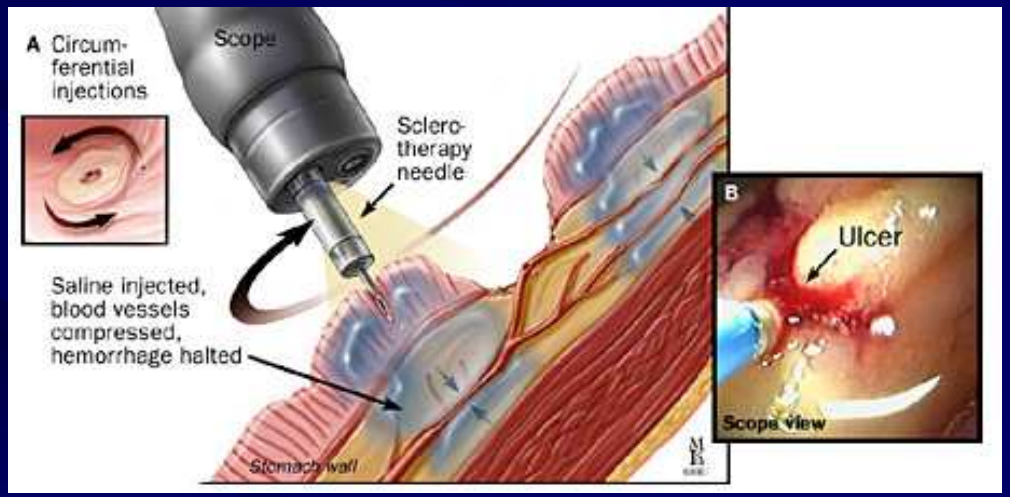


Electro- coagulation





Thermo- coagulation



Sclerotherapy

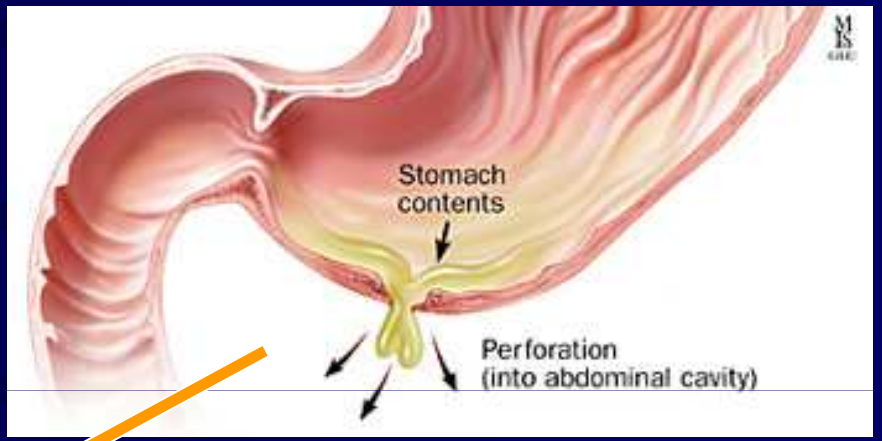
Perforation and penetration

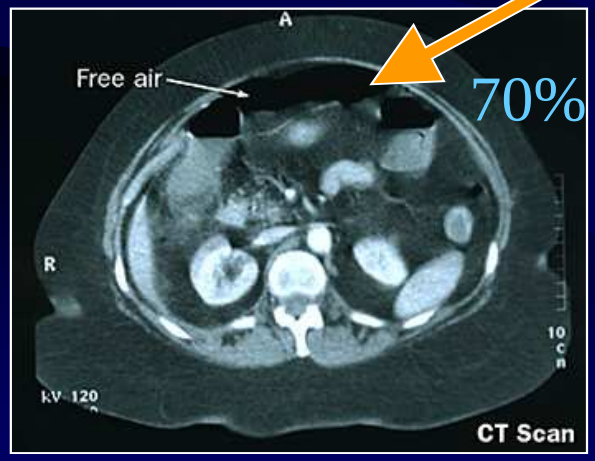
Perforation

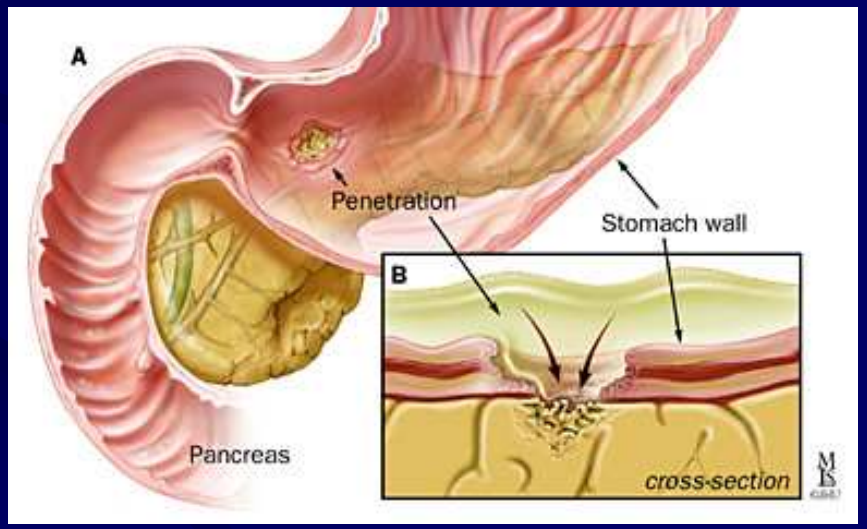
- 5–10% ulcers, in 15% die
- peritonitis
- gastric > duodenal ulcers

Penetration

- 5-10% of perforating ulcers
- pancreas, bile ducts, liver, small or large intestine

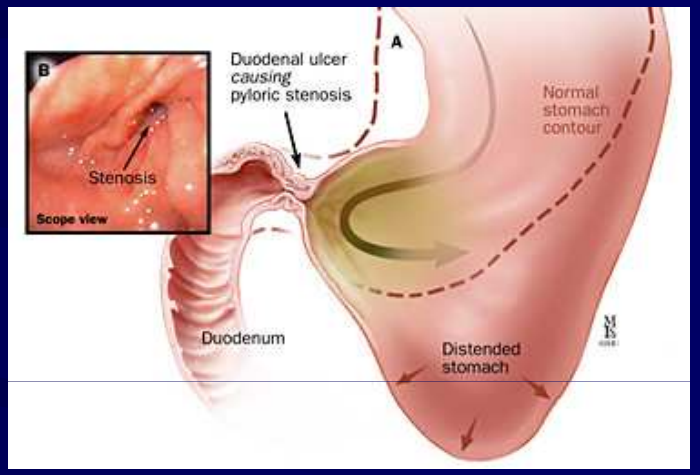


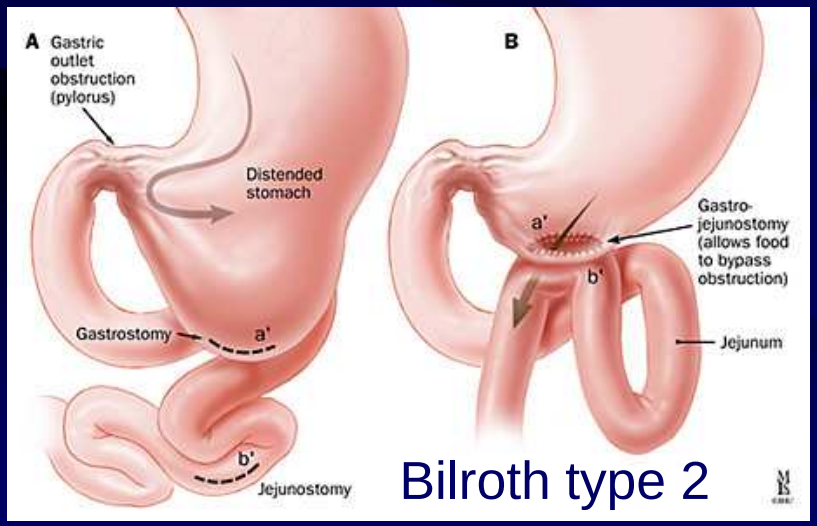




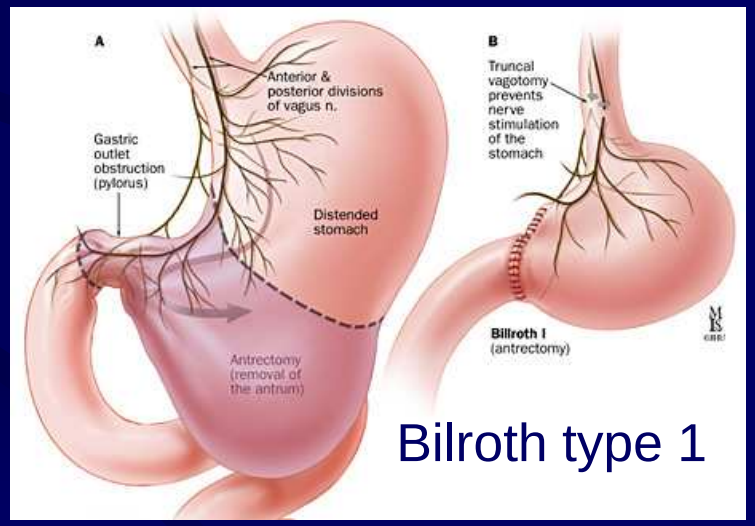
Gastric outlet obstruction

- 5% ulcers, pyloric stenosis
- inflammation, scarring
- duodenal > gastric ulcer
- endoscopic ditation
- surgery





Bilroth type 2



Bilroth type 1