# Pathophysiology of GIT I

Oral cavity and salivary glands
Esophagus - GERD
Stomach and duodenum
Peptic ulcer
H. pylori

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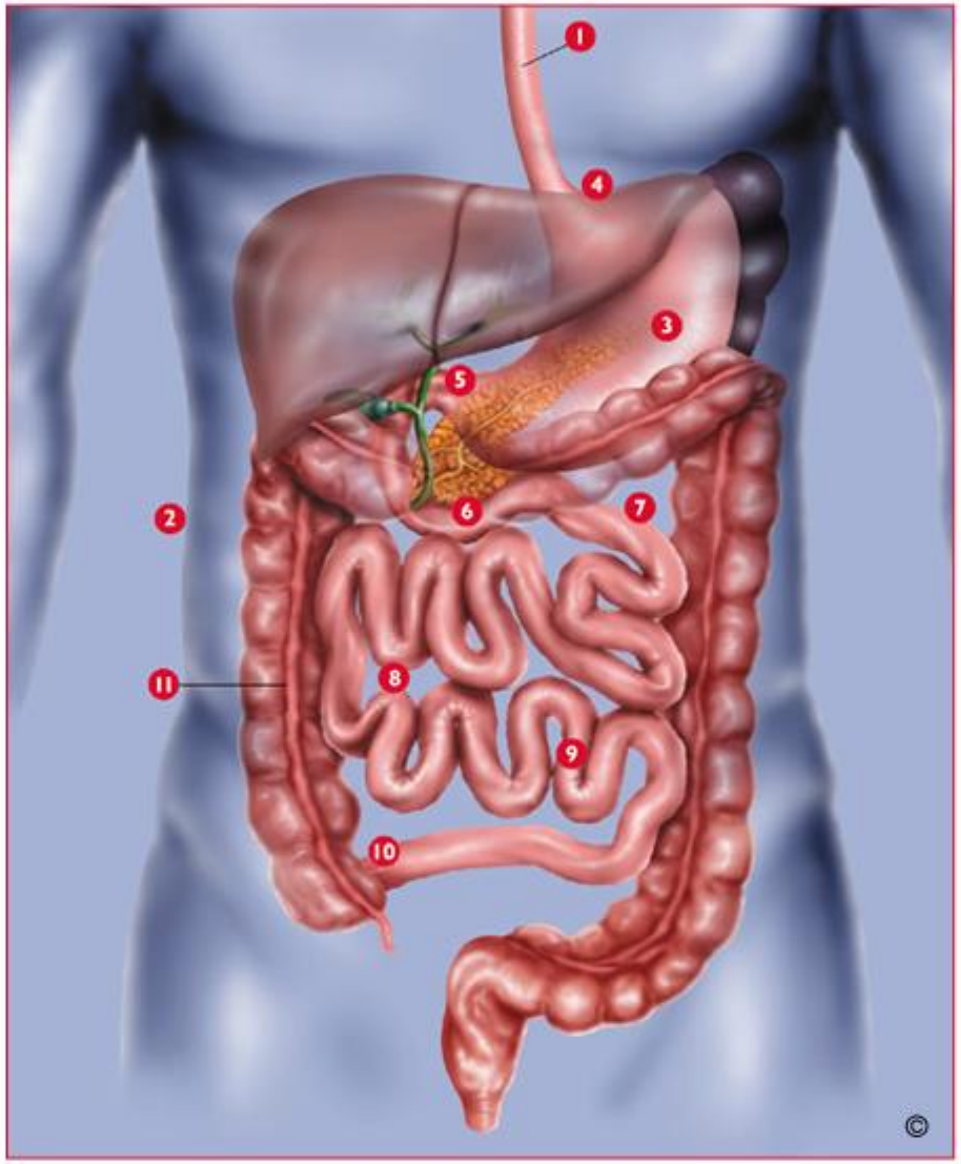
# GIT




- 1- oesophagus
- 2- organs of peritoneal cavity
- 3- stomach (1.5l)
- 4- gastroesophageal junction
- 5- pylorus
- 6- small intestine (4.5 – 6m)
  - 7- duodenum
  - 8- jejunum
  - 9- ileum
- 10- ileocaecal valve
- 11- large intestine
  - ascendant
  - horizontal
  - descendant
  - rectum + anus

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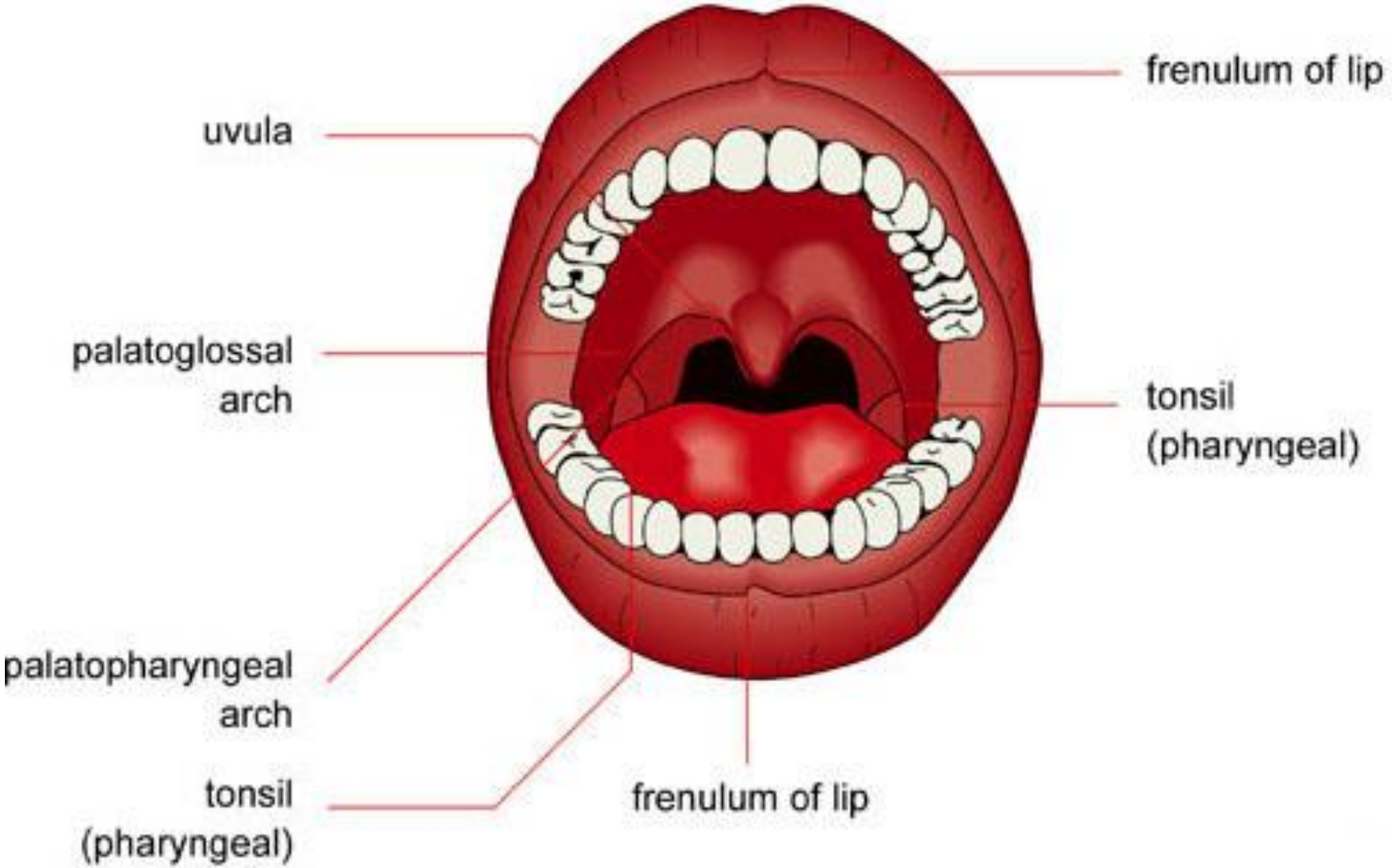
# Pathophysiology of oral cavity

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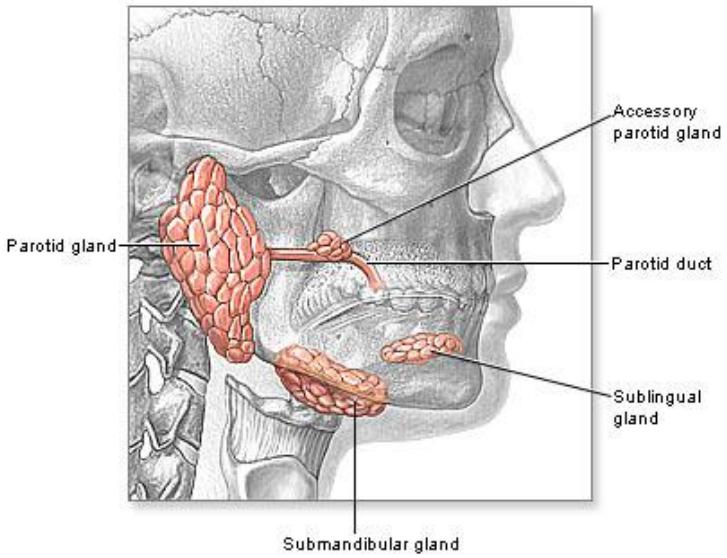
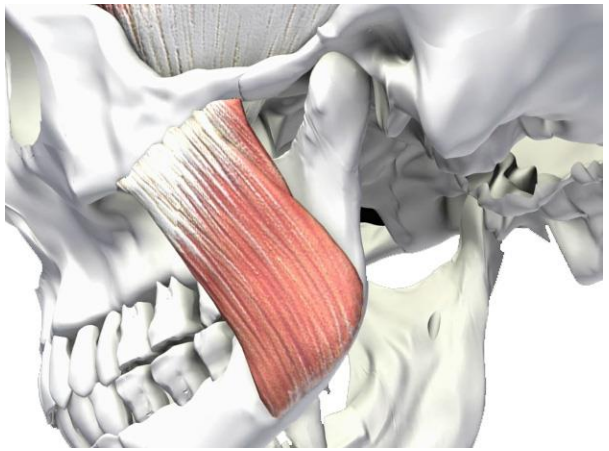
# Pathophysiology of oral cavity



- salivary glands - salivation (1 - 1.5l/day)
  - continual production by small salivary glands
  - large glands secerns only upon stimulus
    - centrum in medulla oblongata → sal. glands (via n. facialis)
    - afferentation from upper centres (cortex, hypothalamus) upon stimuli (taste, smell, chewing, …)
  - enzymes and ions of saliva
    - $\alpha$-amylase (polysaccharides), lipase
    - lysozyme (bactericide)
    - K+, Na+, Cl-, HCO3-
- disease of oral cavity
  - abnormal secretion of saliva
    - ↑ inflammation (e.g. tonsillitis), mechanical irritation
    - ↓ (= xerostomy) - dehydration, Sjögren syndrome, drugs
  - abnormal chewing
    - painful mandibular joint
    - injury of tongue
    - painful teeth
    - mucosal inflammation
  - infections
    - herpetic (HSV-1), bacterial, candidiasis (in immune compromised patients)
  - diseases of temporomandibular joint
    - pain
    - dislocation (habitual)
  - precanceroses and tumors of oral cavity
    - leucoplakia
    - carcinoma – smokers, alcoholics
  - signs of systemic diseases in oral cavity
    - anemia
    - vitamin and iron deficiency
    - malnutrition
    - cyanosis
    - Crohn's disease

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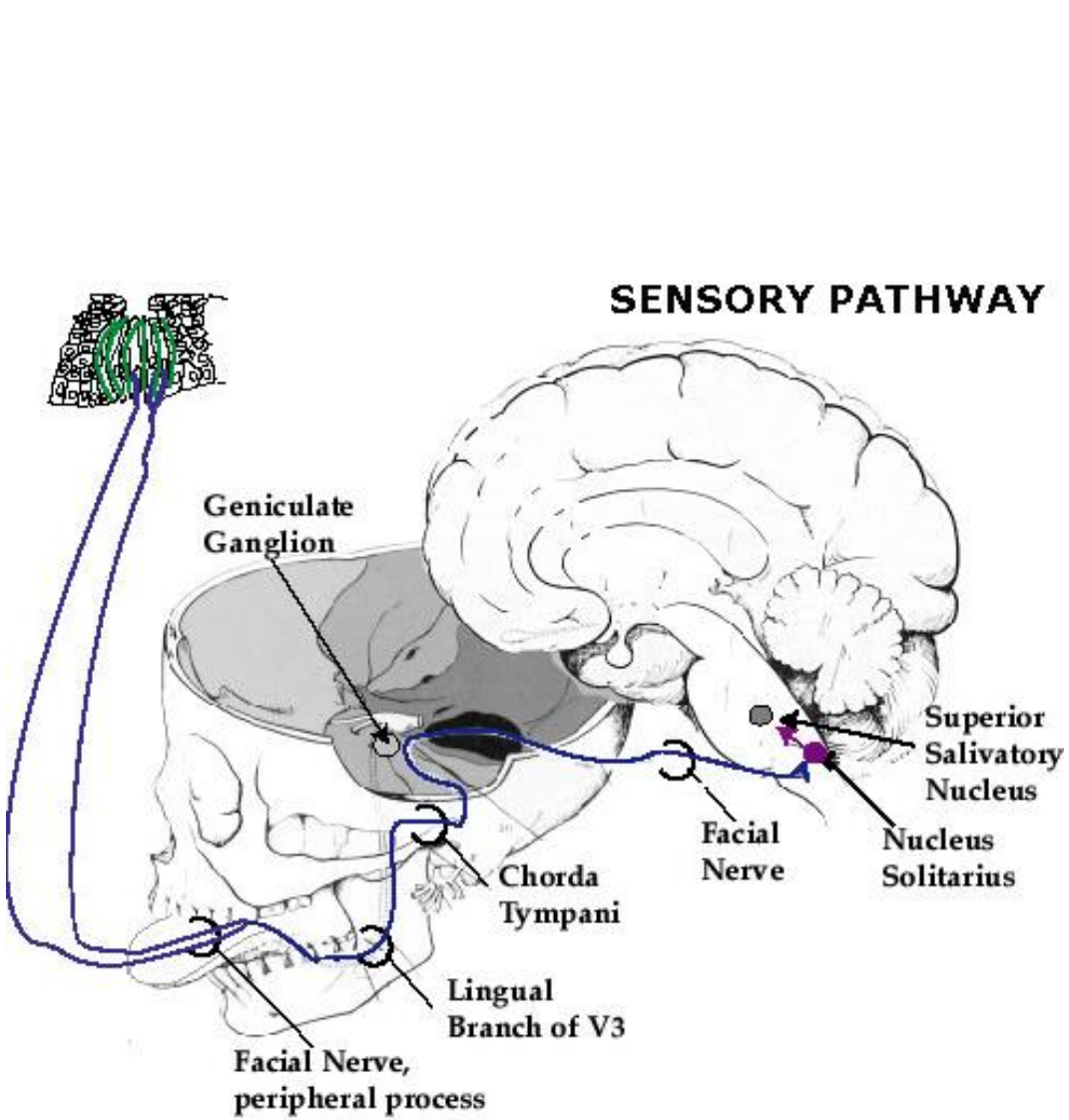
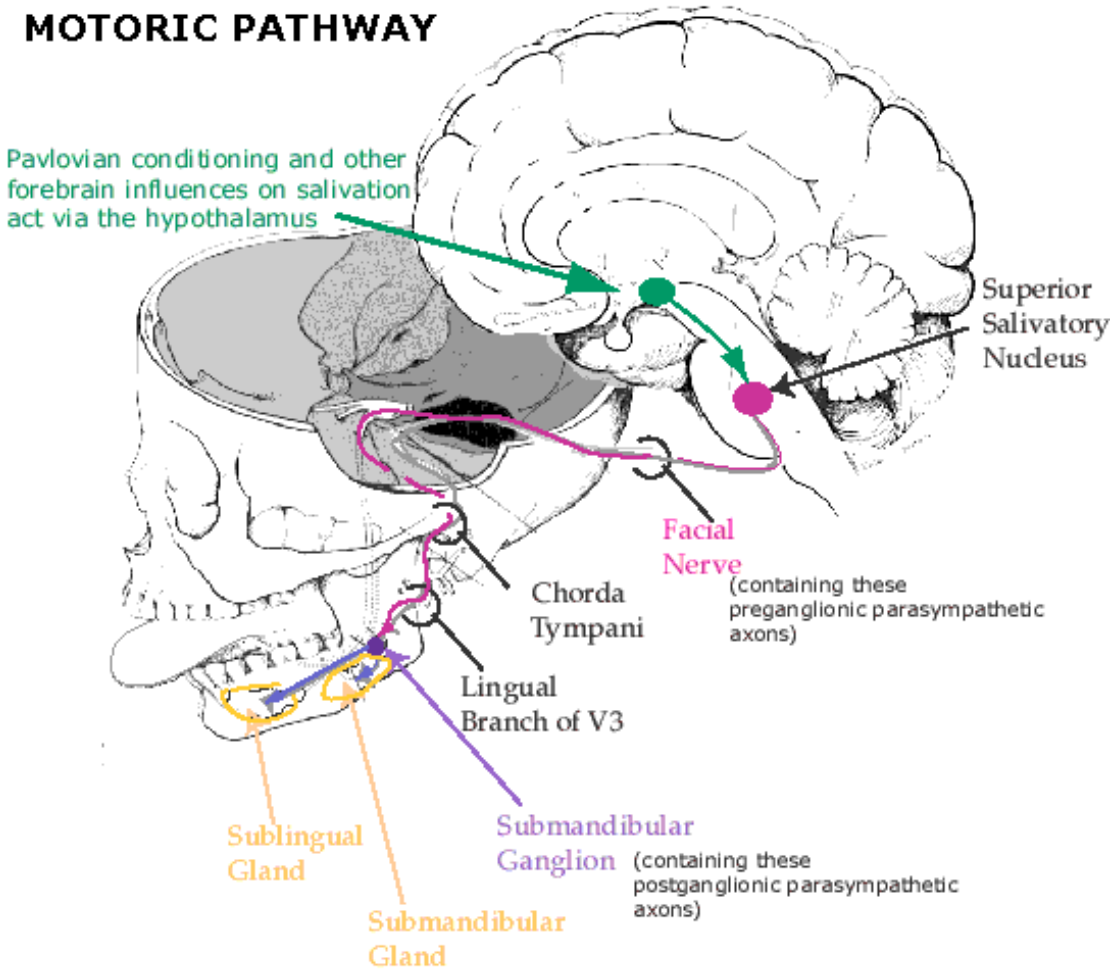
# Reflexive salivation

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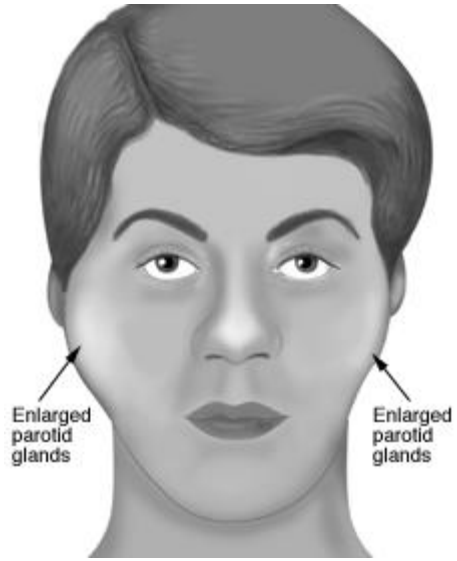
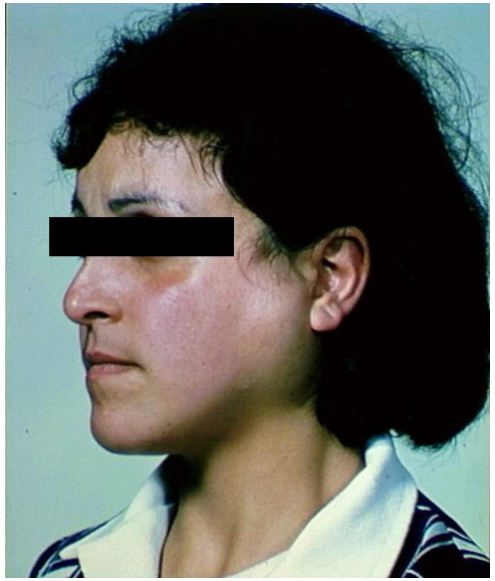
# Sjögren syndrome

- syn. keratoconjunctivitis sicca
- autoimmune reaction against salivary (xerostomy) and tear glands (xerophtalmy)
  - initiated by viral infection?
- symptoms
  - difficulties of chewing and swallowing
  - difficult talking
  - dry cough
  - irritation, eye burning, foreign body feeling and reddening of eye
  - sometimes accompanied by joint and muscle pain
- SS can coexist with other autoimmune diseases
  - rheumatoid arthritis
  - systemic lupus erythematodes
  - thyreopathy



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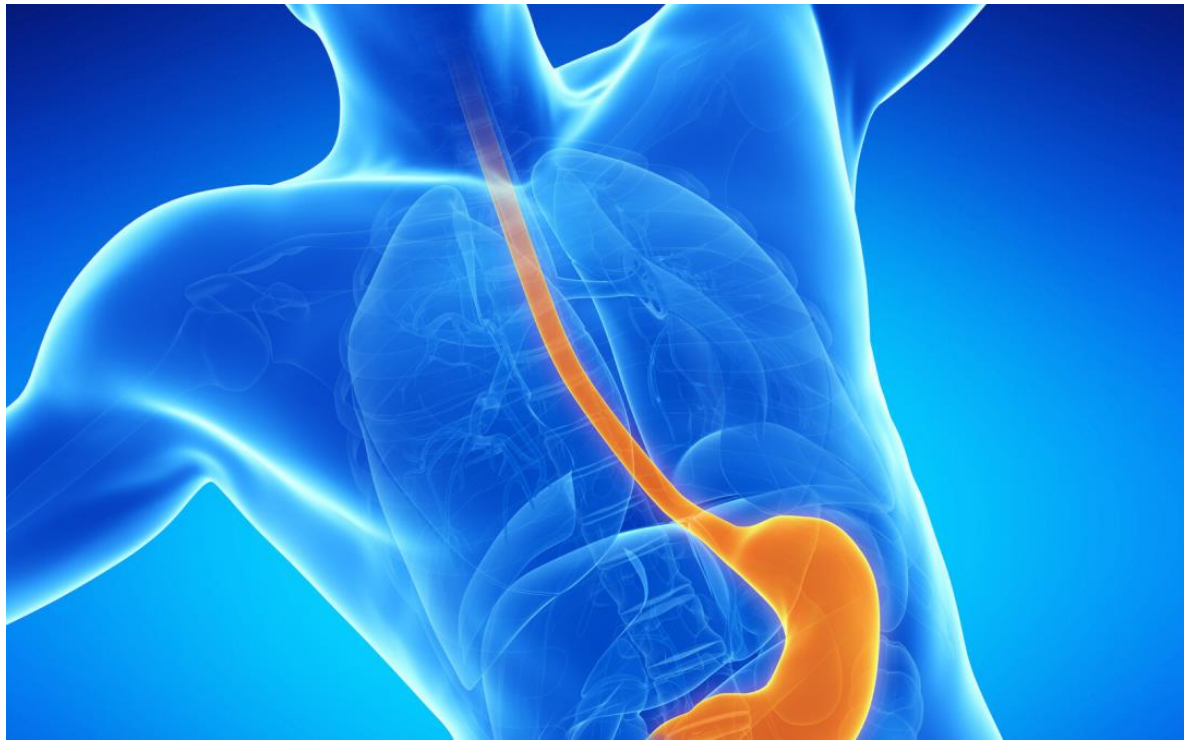

# OESOPHAGUS

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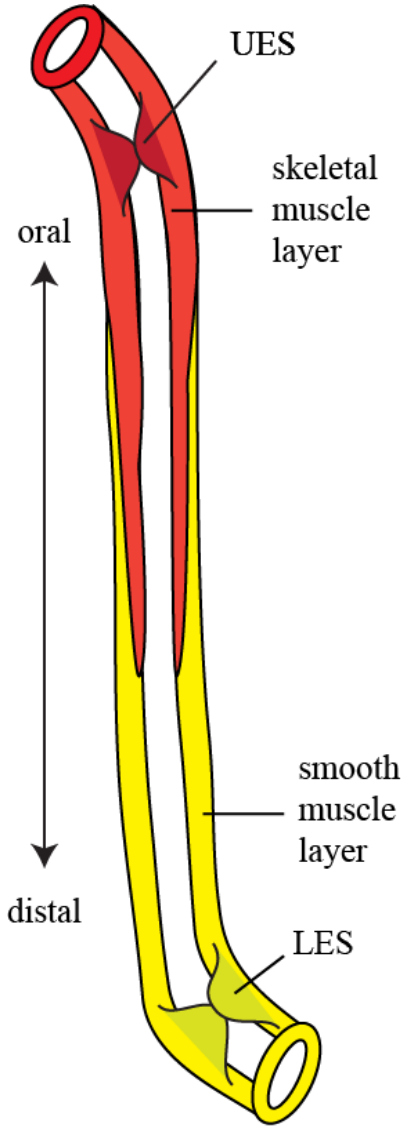
# Anatomy and histology of oesophagus

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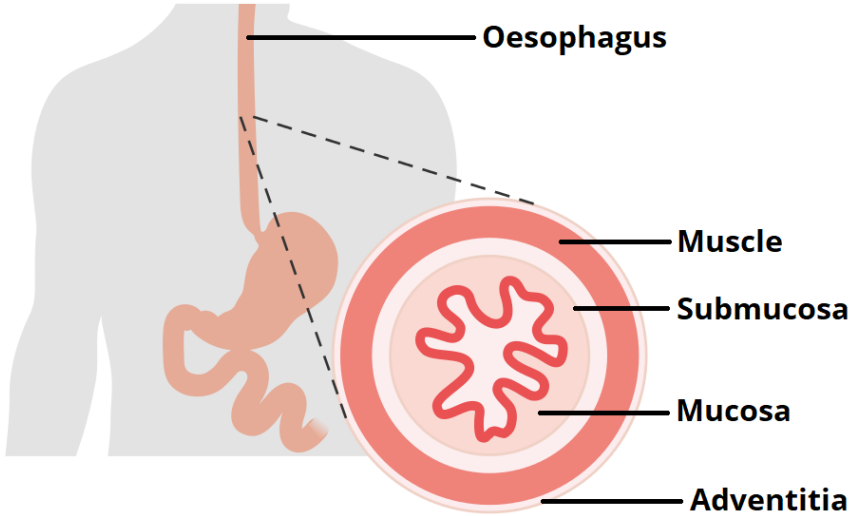


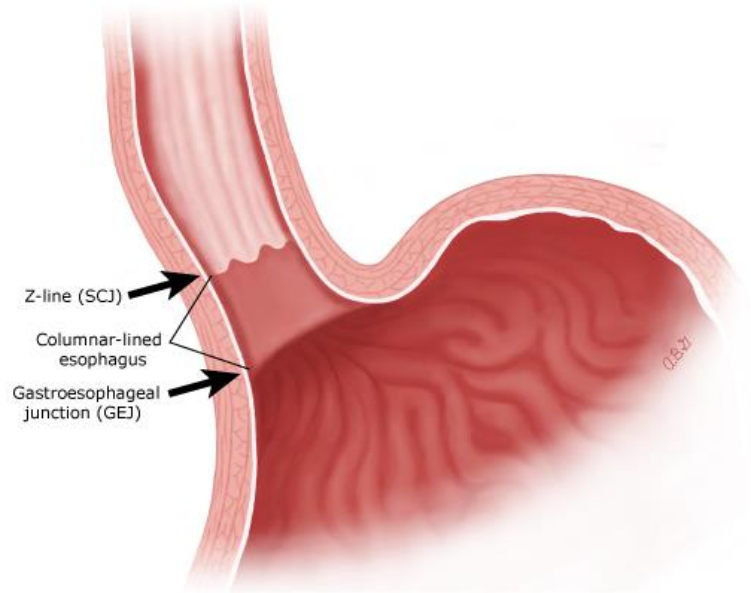


- anatomy and histology
  - upper 1/3 striated muscle
    - upper sphincter (m. cricopharyngeus)
  - bottom 2/3 smooth muscle
    - lower sphincter (smooth muscle)
  - epithelial lining
    - upper 2/3 non-keratinised squamous epithelium
      - squamous carcinoma
    - in a very terminal part cylindrical epithelium
      - adenocarcinoma
    - the squamocolumnar junction (SCJ or Z-line) is the visible line formed by the juxtaposition of squamous and columnar epithelia
    - the gastroesophageal junction (GEJ) is the imaginary line at which the oesophagus ends and the stomach begins

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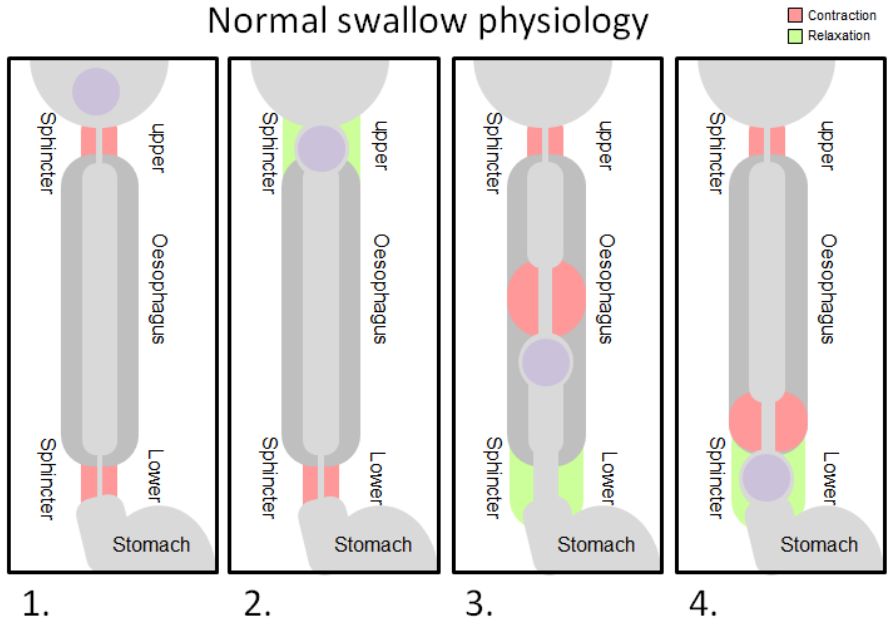
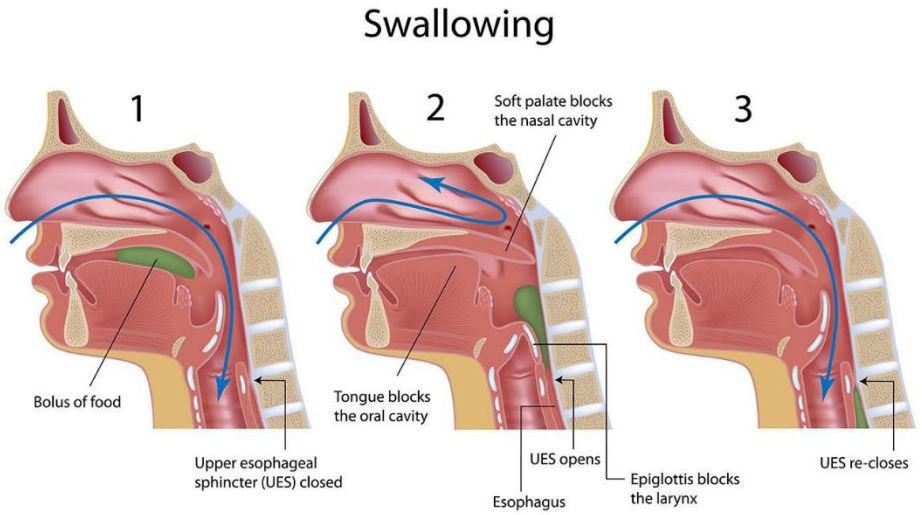
# Motility of oesophagus




- normal motility = contractions occurring in the oesophagus, which propel the food bolus forward toward the stomach
  - swallowing reflex
    - oral, pharyngeal and oesophageal phase
  - voluntary peristaltics
- high-resolution oesophageal manometry is an examination of the oesophageal motility
  - measuring pressures generated by the oesophageal muscles and the sphincters
- disorders of motility and swallowing
  - **dysphagia** (oropharyngeal or oesophageal)
    - 1) functional – often to liquid or both liquid and solids
      - e.g. scleroderma, amyotrophic lateral sclerosis or vegetative neuropathy in diabetes mellitus, Parkinson's disease, stroke, multiple sclerosis, myasthenia gravis
    - 2) mechanical obstruction – very often to solids
      - achalasia, strictures (reflux. esophagitis or irradiation), scleroderma, peptic ulcer, tumours
  - **odynophagia**
    - painful swallowing
  - **globus pharyngeus**
    - persistent or intermittent non-painful sensation of having a lump or foreign material in the throat }e.g. pill, food bolus,

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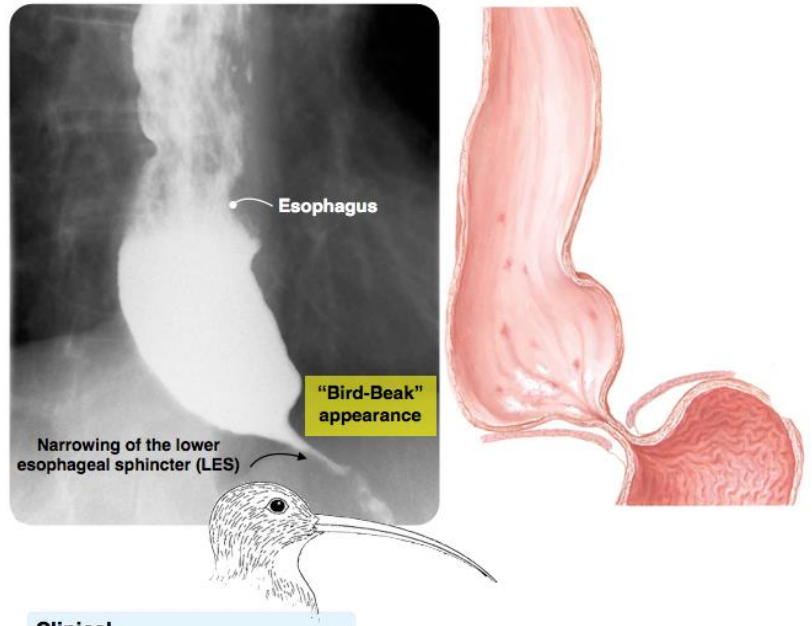
# Disorders of oesoph. motility

- achalasia
  - inability to relax lower oesoph. sphincter + lack of peristaltics
    - due to inborn or acquired impairment of inhibitory neurons of myenteric nerve plexus (Meissneri) and production of nitric oxide (NO) by NO synthase
  - causes – idiopathic, neurodegenerative, autoimmune, infection (viral, parasitic)
    - example - Chagas disease
      - common in Middle and Latin America
        - affect approx. 15 mil. people
        - 25% of Latin-American population endangered
      - infection by parasite Trypanosoma cruzi
        - incest born
      - acute phase – only swelling in the site of bite
        - e.g. periorbitaly
      - chron. stage
        - GIT (megacolon and megaoesophagus)
        - heart (dilated cardiomyopathy)
      - later stages malnutrition and heart failure
      - dementia




**Clinical**
- Dysphagia (solids, liquids)
- Difficulty belching
- Chest pain
- Regurgitation of undigested food
- Dyspepsia
- Aspiration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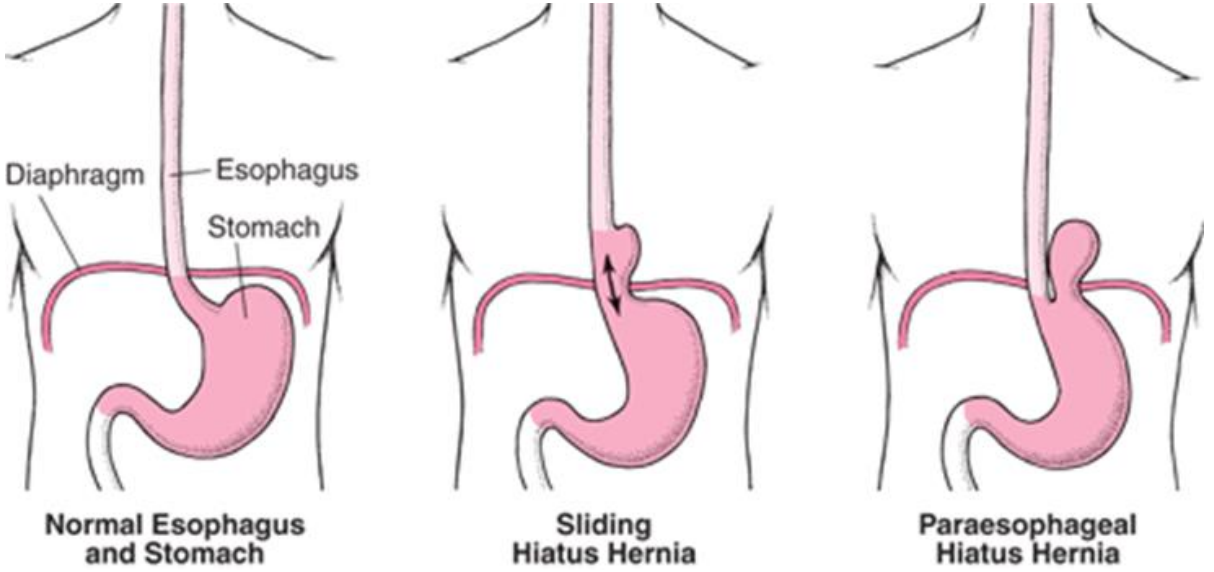
# Hiatal hernias

- protrusion (herniation) of the part of the stomach through the opening in the diaphragm into chest cavity (posterior mediastinum)
  - 1) sliding
  - 2) rolling (paraoesophageal)
- risk factors
  - inborn larger diaphragm hiatus
  - obesity
  - increased intraabdominal pressure (e.g. chron. obstipation)
  - gravidity
- complications
  - acute complete herniation
  - gastroesophageal reflux and Barrett's oesophagus

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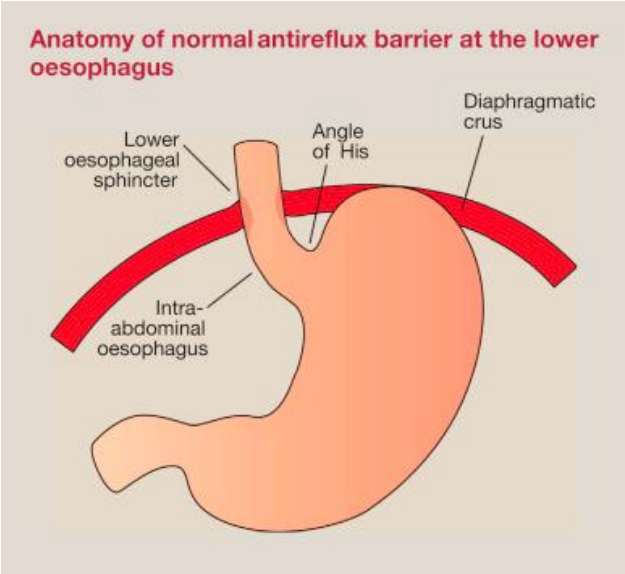
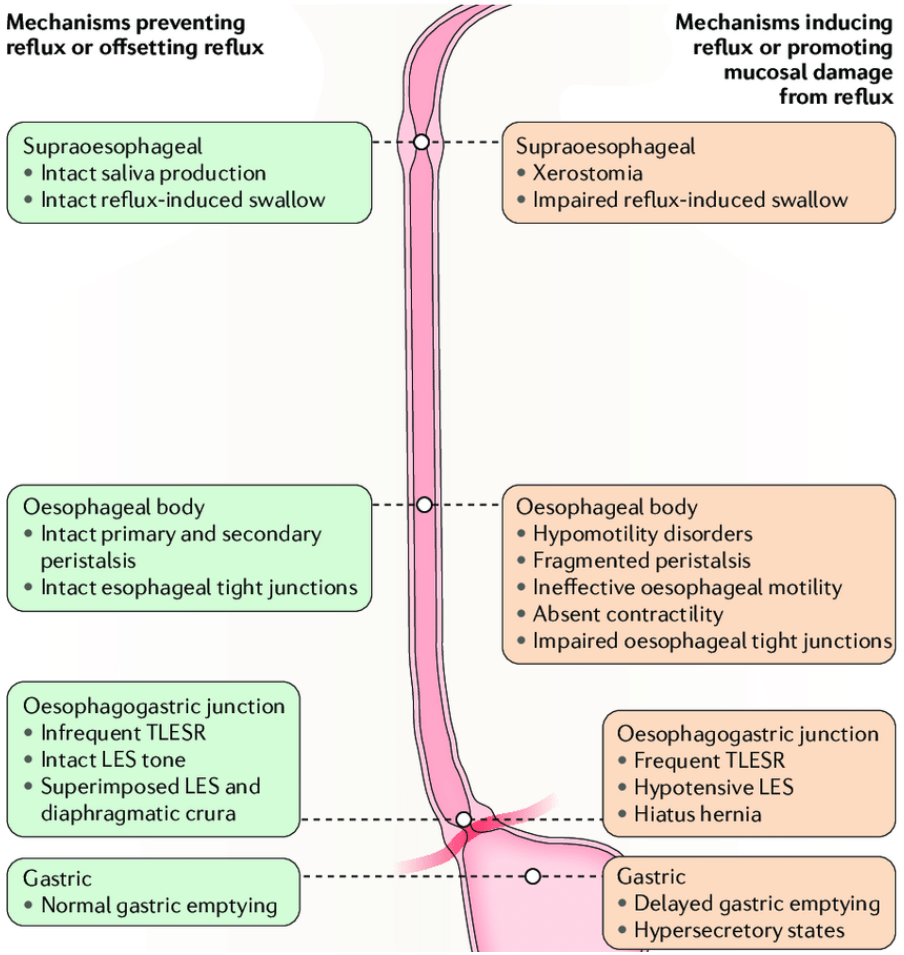
# Gastroesophageal reflux disease(GERD)

- anti-reflux barrier
  - lower oesoph. sphincter
  - mucosal rugae
  - angel between stomach and oesophagus
  - oesoph. peristaltics
- GERD = retrograde passage of gastric content up to oesophagus (or further up to mouth and respiratory tract) where it acts aggressively
  - due to HCl, enzymes – proteases (pepsin) and event. bile (when dudodeno-gastric reflux also present)
- occasional reflux appears in healthy subjects
- risk is substantially higher in the presence of hiatal hernia
- symptoms (oesoph. reflux disease)
  - subjective
    - dysphagia
    - heart burn (pyrosis)
    - abdominal discomfort or pain
    - throat pain
  - objective
    - burping
    - regurgitation
      - risk of aspiration, respiratory infection
    - cough
    - vomiting
- complications of GER
  - reflux esophagitis
    - ulcers, strictures, bleeding
  - Barrett's oesophagus
    - approx. 10% patients with GER
  - adenocarcinoma

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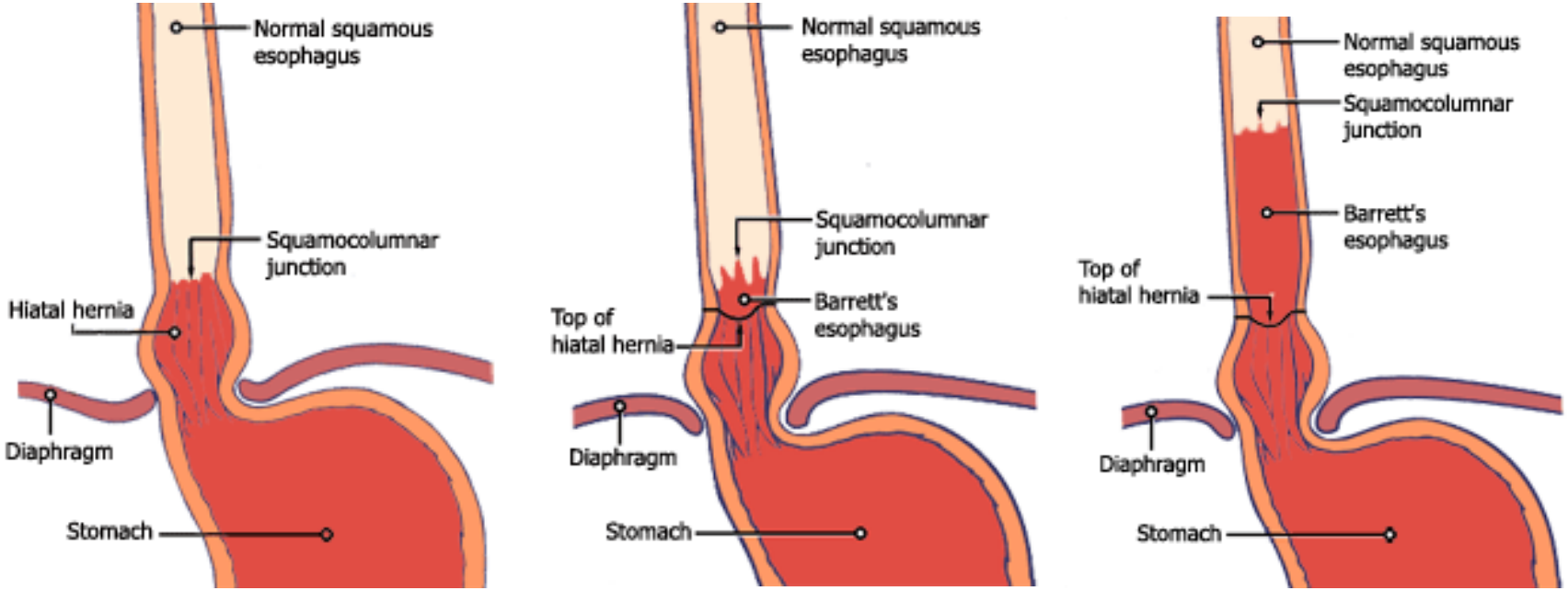
# Barrett's oesophagus

- metaplasia of mucosa in long term GER
  - squamous epithelium changes to cylindrical
- ↑ risk of adenocarcinoma
  - up to 40x higher than in healthy subjects
- pathogenesis not clear
  - suspected error of differentiation of pluripotent stem cells

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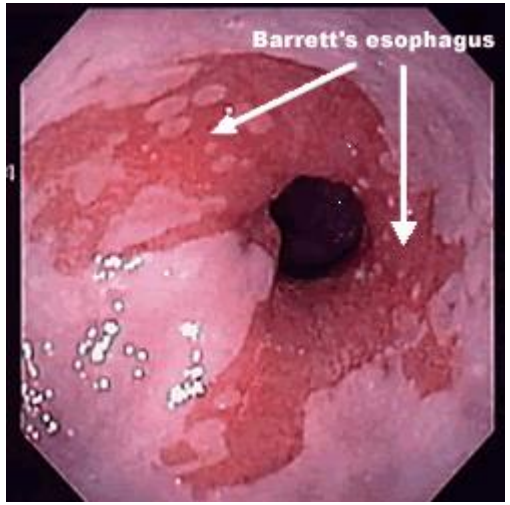
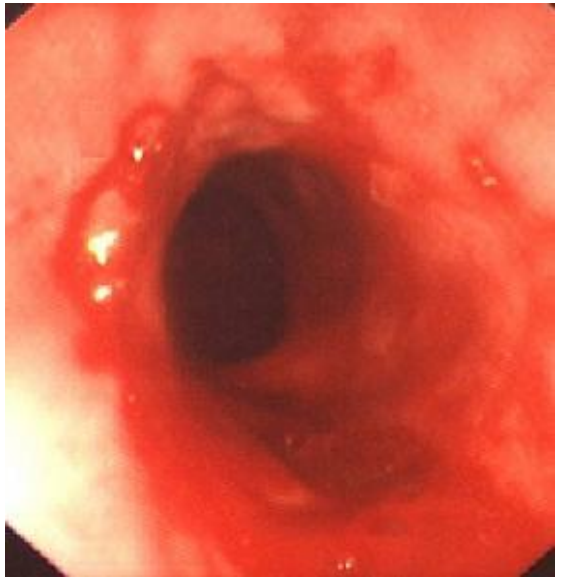
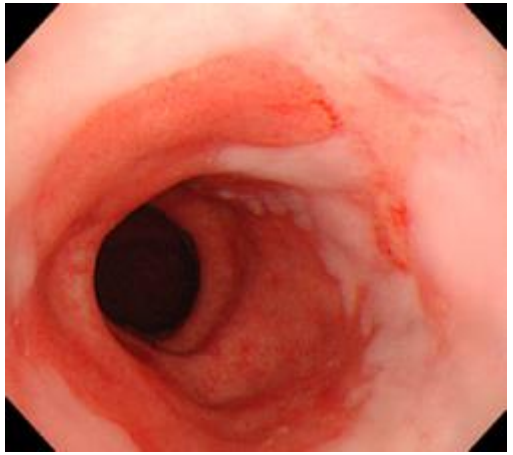
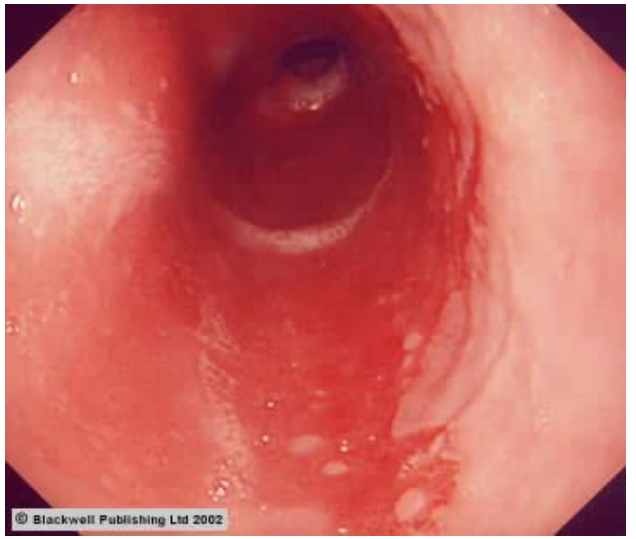
# Barrett´s oesophagus





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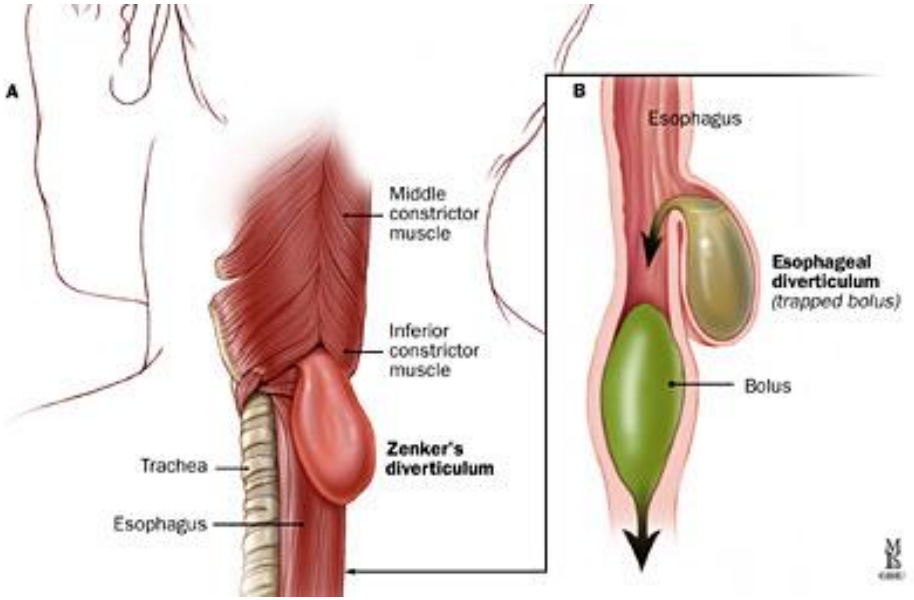
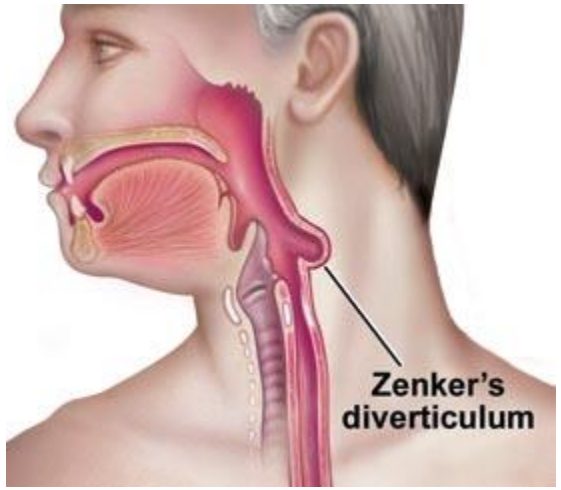
# Oesophageal diverticuli

- according to the mechanism of development
  - traction
  - passion
  - combined
- according to localization
  - hypopharyngeal
    - Zenker's (pulsion)
      - false (only mucosa)
      - regurgitation without dysphagia
      - risk of aspiration
  - epibronchial
    - often due to traction by mediastinal lymph node in TBC
  - epiphrenic
    - due to increased intraluminal pressure
    - regurgitation of fluid at night

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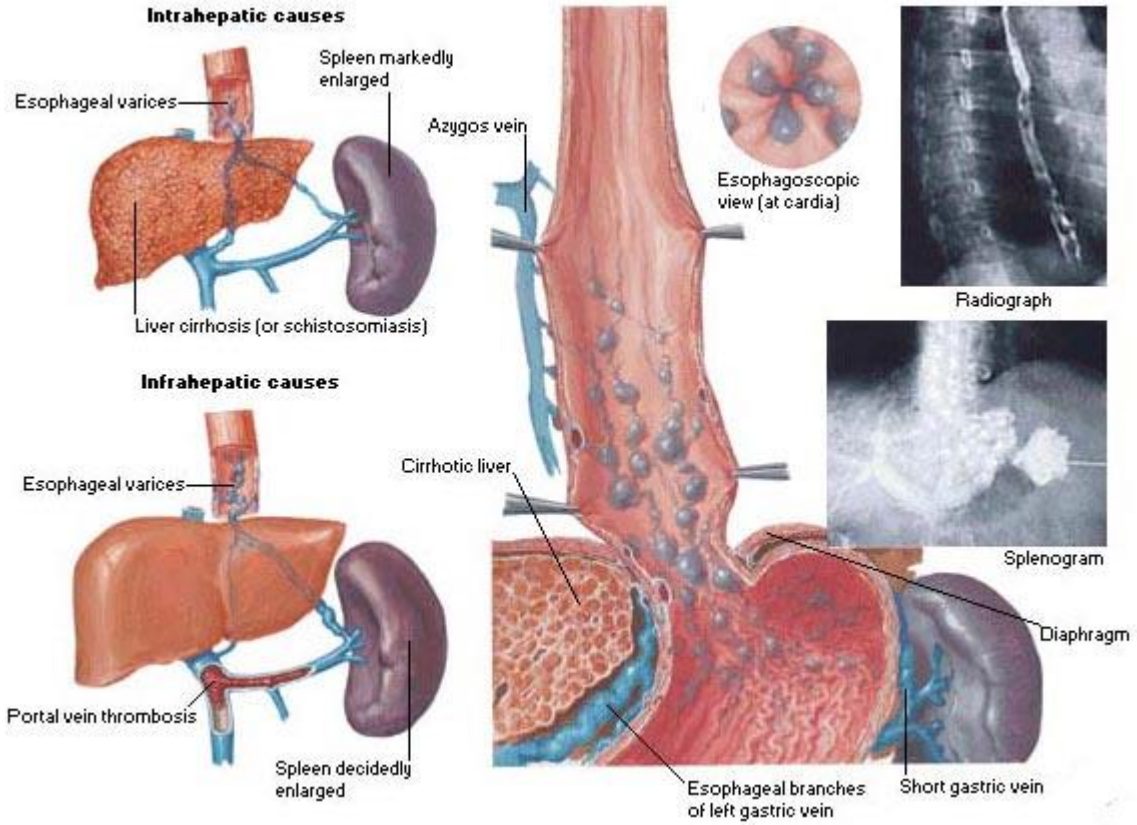
# Oesophageal varices

- due to portal hypertension (increased pressure in v. portae)
  - pre-hepatic (congestive heart failure)
  - hepatic (liver cirrhosis)
  - post-hepatic (thrombosis of v. portae)
- blood circumvents liver and enters the syst. circulation (lower v. cava) via
- portocaval anastomoses
- risk of bleeding from superficially located veins

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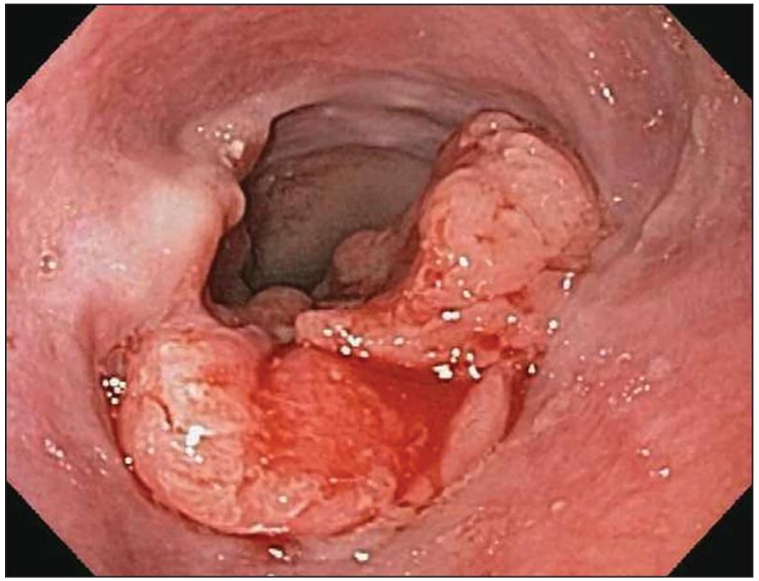
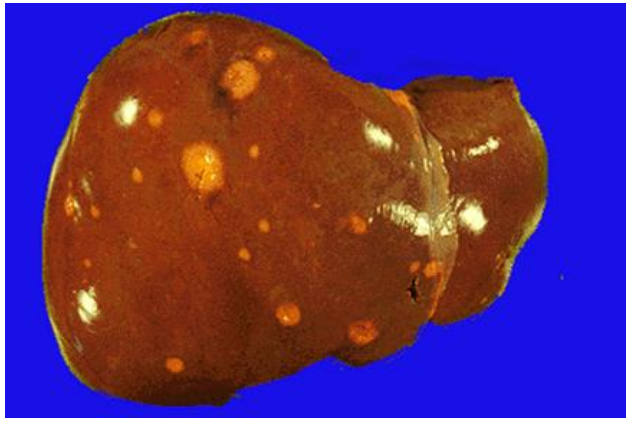
# Tumours of oesophagus

- benign
  - leiomyoma
  - fibroma
  - haemangioma
- malign
  - squamous cell carcinoma
  - adenocarcinoma
    - late complication of chron. GER!!!
    - males > females
    - only 10% of patients survives 5 yrs after diagnosis
    - TNM classification
      - T = tumour (size and depth of invasion)
      - N = lymph nodes (regional and distant)
      - M = metastases (most often liver)





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# STOMACH

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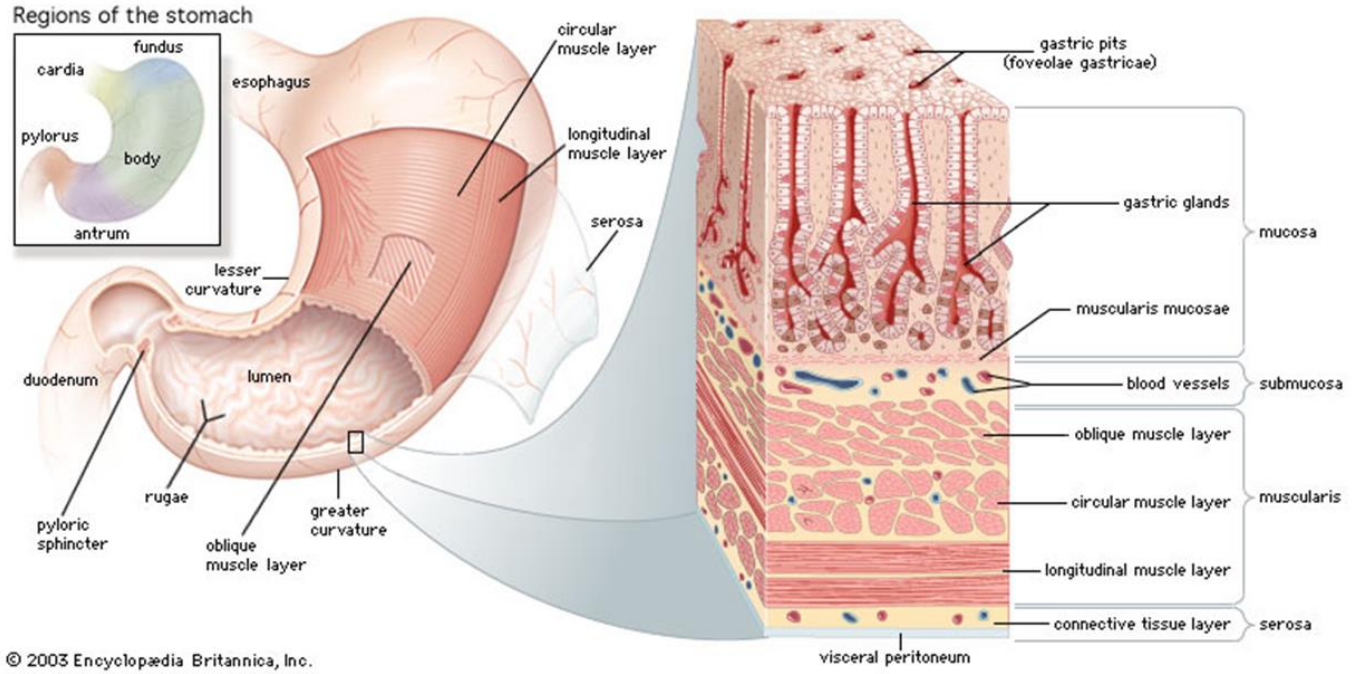
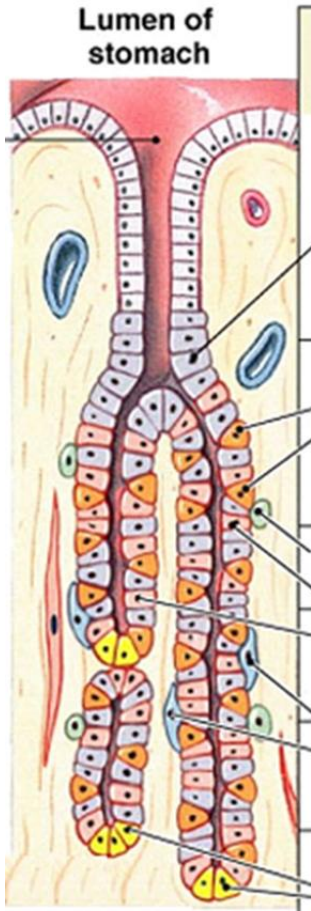
# Stomach anatomy, gastric pits and cells




| Cell Types | Substance Secreted |
|---|---|
| Mucous neck cell | Mucus (protects lining) |
| | Bicarbonate |
| Parietal cells | Gastric acid (HCl) |
| | Intrinsic factor (Ca++ absorption) |
| Enterochromaffin-like cell | Histamine (stimulates acid) |
| Chief cells | Pepsin(ogen) |
| | Gastric lipase |
| D cells | Somatostatin (inhibits acid) |
| G cells | Gastrin (stimulates acid) |

- motoric function
  - reservoir
  - mechanical crushing
  - emptying
- secretion
  - upper 2/3 of stomach contain mainly parietal and chief cells
  - antrum contains mucous and G cells

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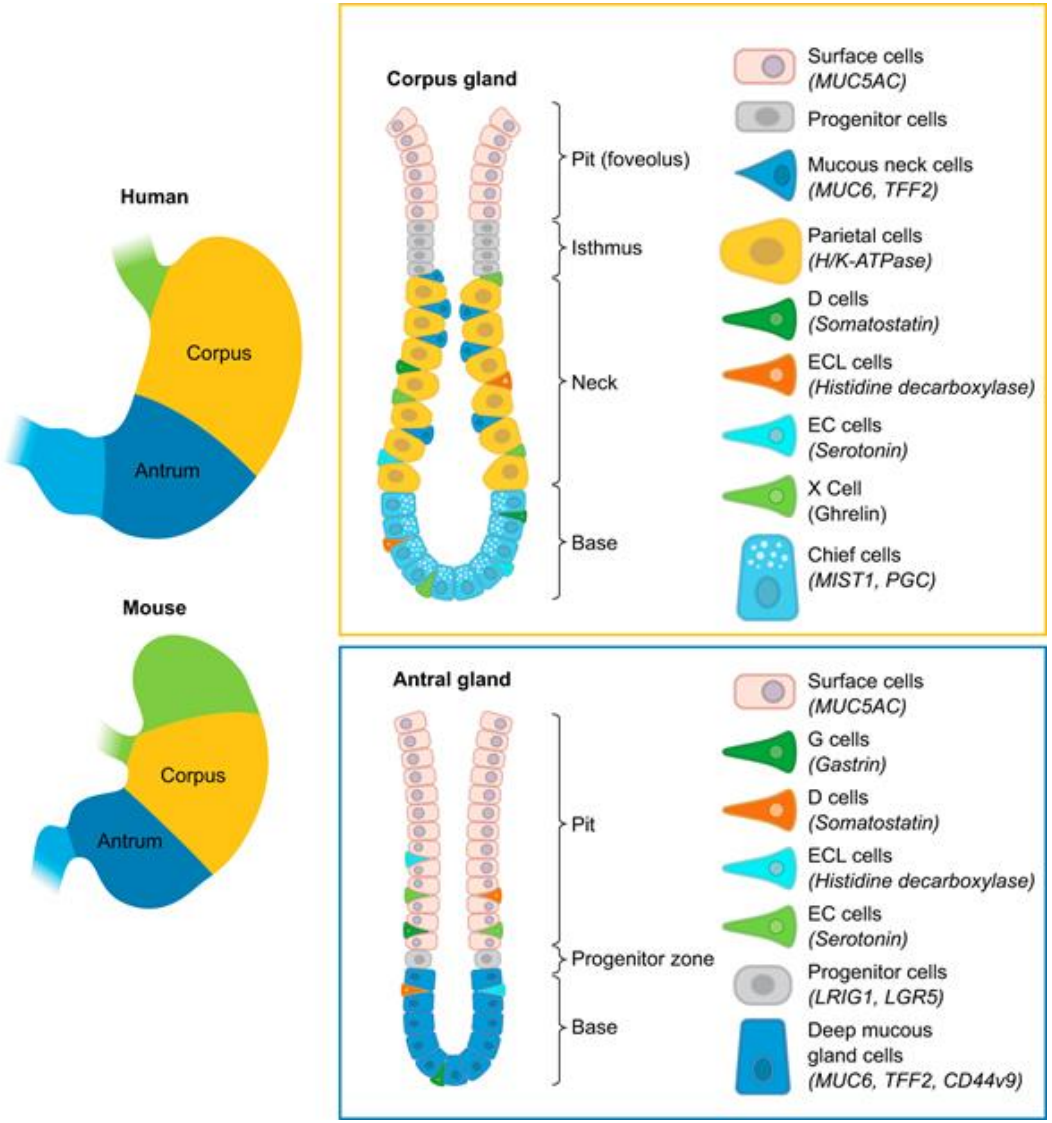
# Cellular anatomy of the stomach




- The human stomach is composed of three distinct regions:
  - the cardia, the corpus, and the antrum
  - (1) gastric cardia resides in the most proximal portion of the human stomach
  - (2) the corpus contains the oxyntic glands that harbor an isthmal progenitor region and contains the majority of acid-secreting parietal cells and pepsinogen-secreting chief cells
    - corpus glands uniquely contain ghrelin-secreting X cells
  - (3) the antrum with antral glands that are predominantly mucus secreting glands and uniquely harbor the gastrin expressing G cells
    - in the human stomach, the antrum contains a mix of oxyntic and antral glands; however, the oxyntic-type glands in the antrum have significantly fewer chief cells and parietal cells compared with corpus glands

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# Gastric juice secretion (and its composition)

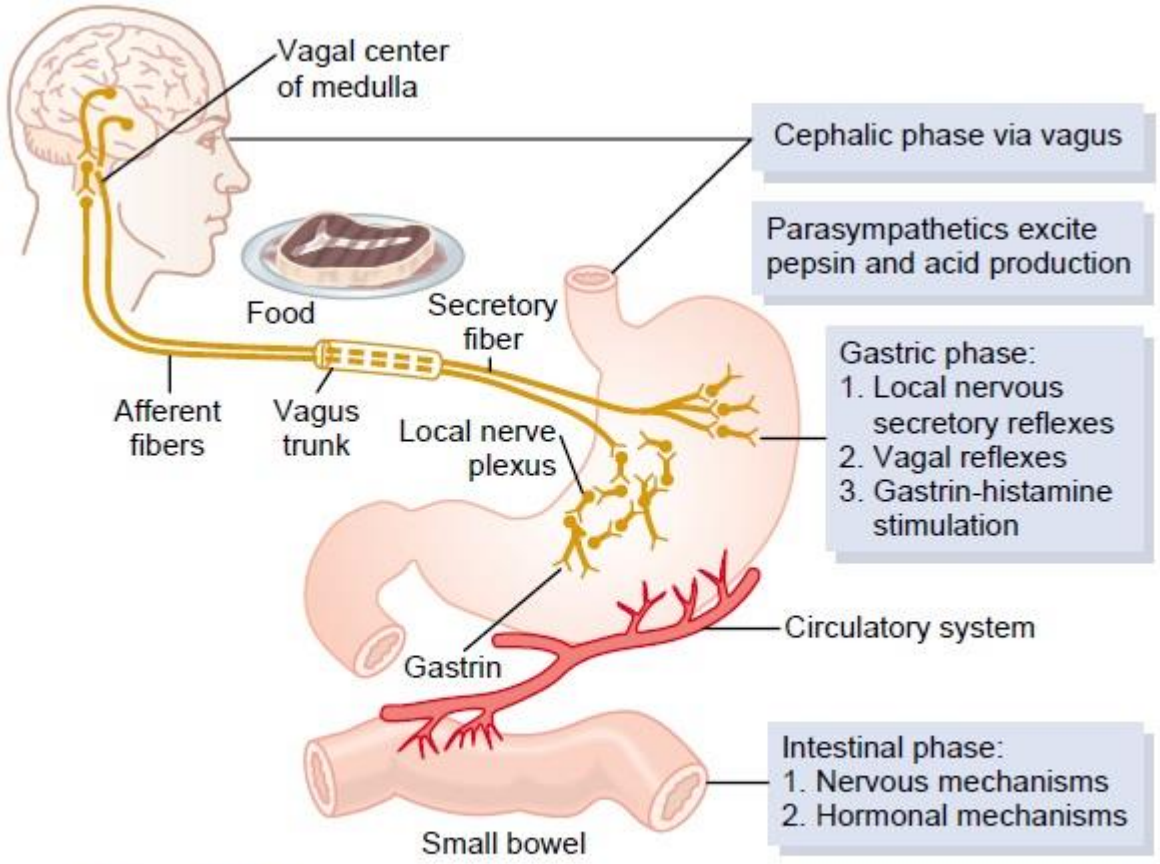
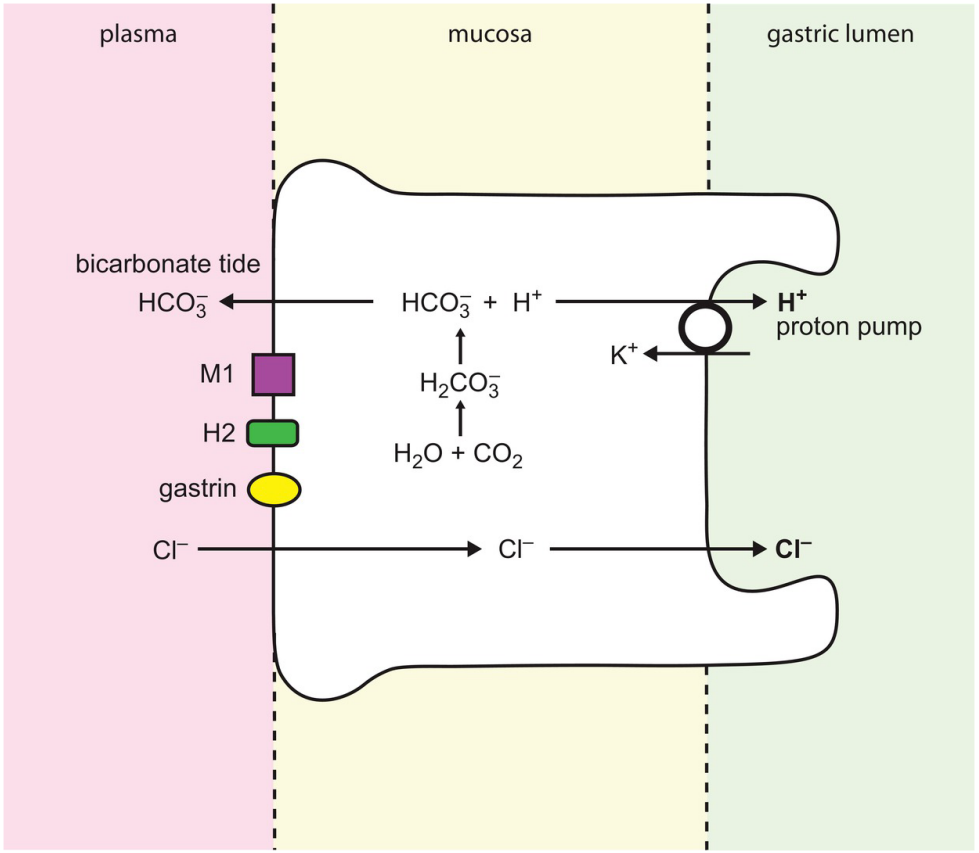
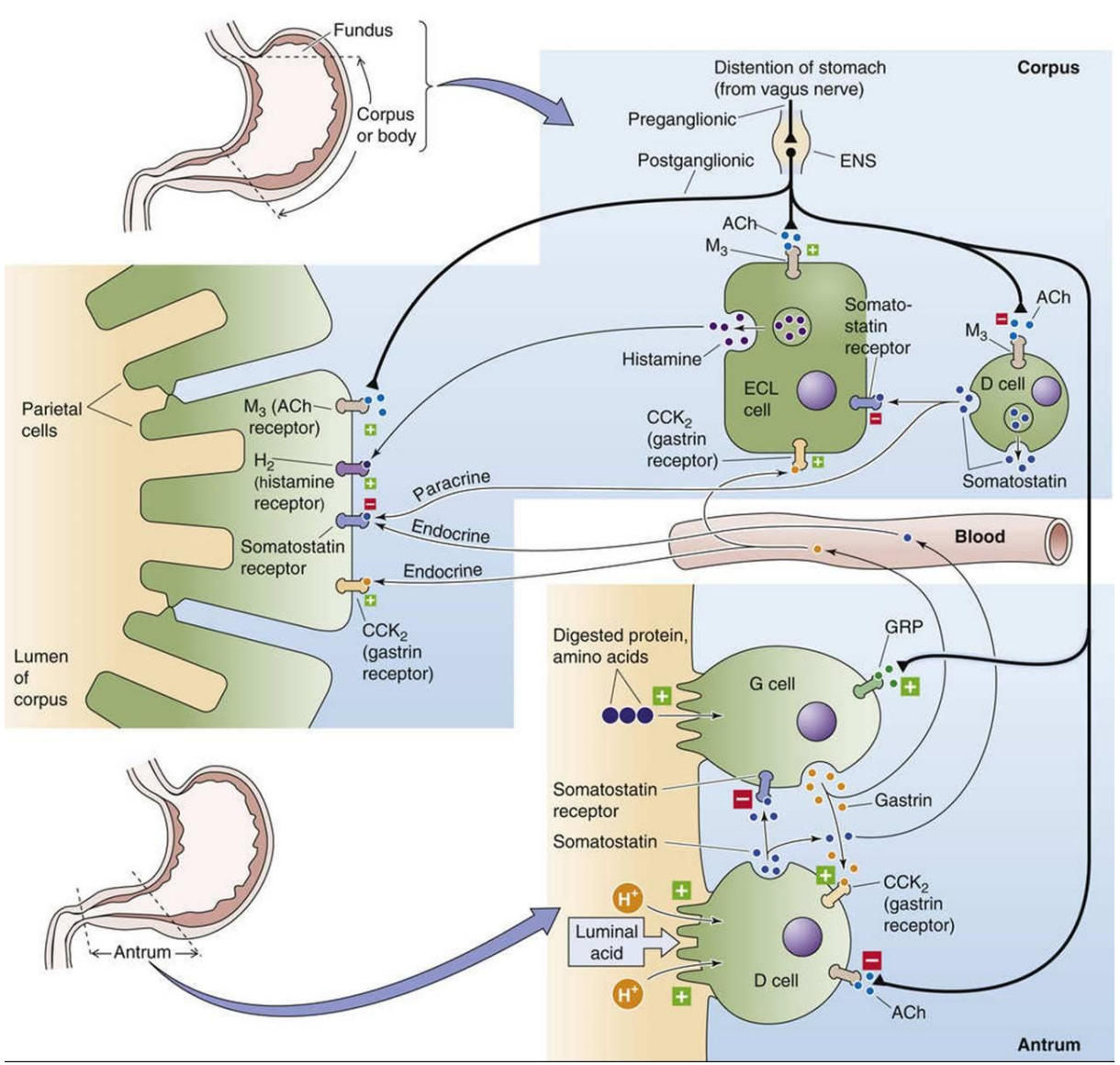



**Figure 64–7**

Phases of gastric secretion and their regulation.



# Regulation of gastric acid secretion




- In the corpus of the stomach, the vagus nerve not only stimulates the parietal cell directly by releasing ACh, it also stimulates both ECL and D cells
  - vagal stimulation of the ECL cells enhances gastric acid secretion via increased histamine release
  - vagal stimulation of the D cells also promotes gastric acid secretion by inhibiting the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of histamine from ECL cells and the secretion of acid by parietal cells
- In the antrum of the stomach, the vagus nerve stimulates both G cells and D cells
  - vagus stimulates the G cells via GRP, promoting gastrin release
    - gastrin promotes gastric acid secretion by two endocrine mechanisms: directly via the parietal cell and indirectly via the ECL cell, which releases histamine
  - products of ongoing protein digestion (i.e., peptides and amino acids) directly stimulate the G cells to release gastrin, which stimulates gastric acid secretion (**positive feedback**)
  - vagal stimulation of D cells via ACh inhibits the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of gastrin from G cells and—by an endocrine mechanism—acid secretion by parietal cells
- decreasing pH (increasing luminal H+) directly stimulates the D cells to release somatostatin, which gradually inhibits gastrin release from the G cells, thereby reducing gastric acid secretion (**negative feedback**)

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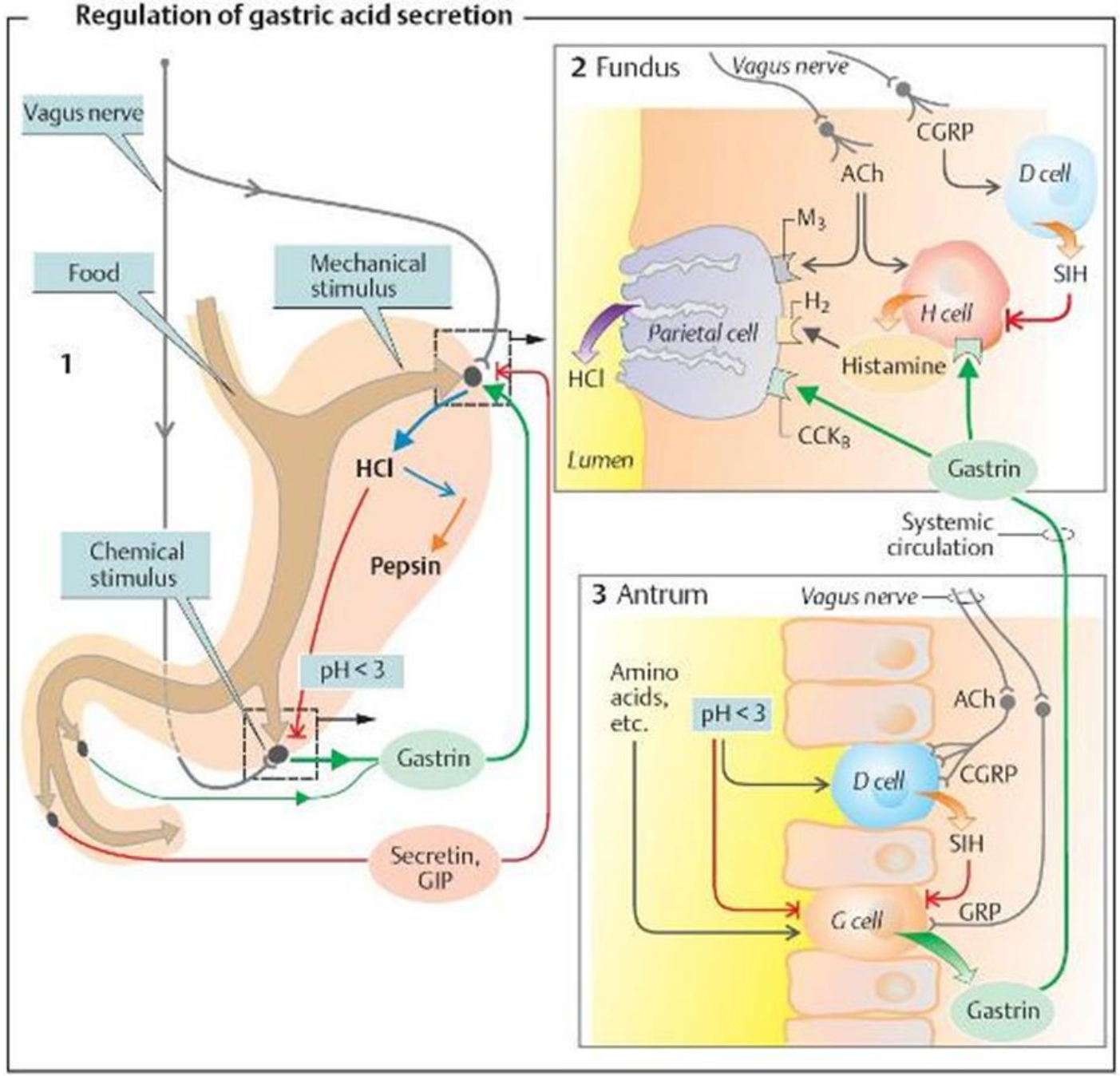
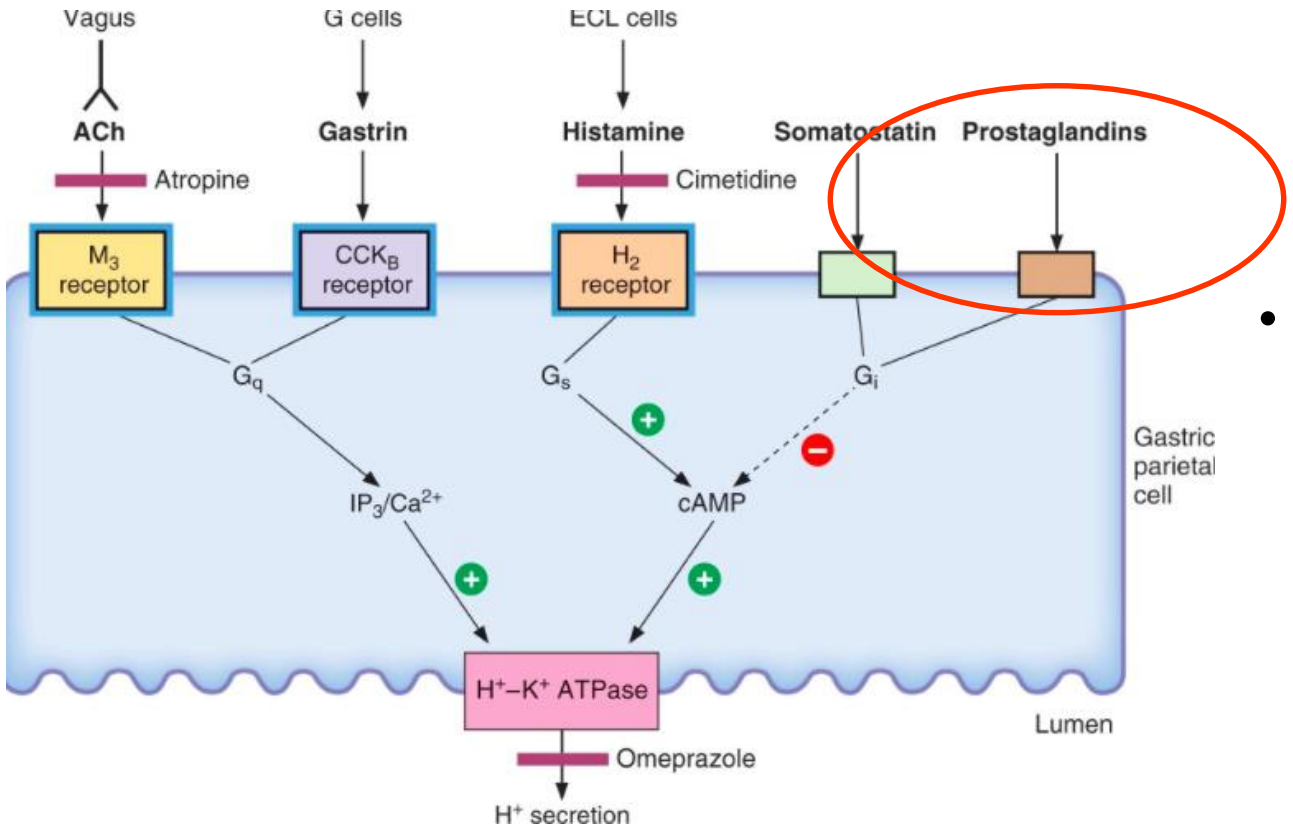
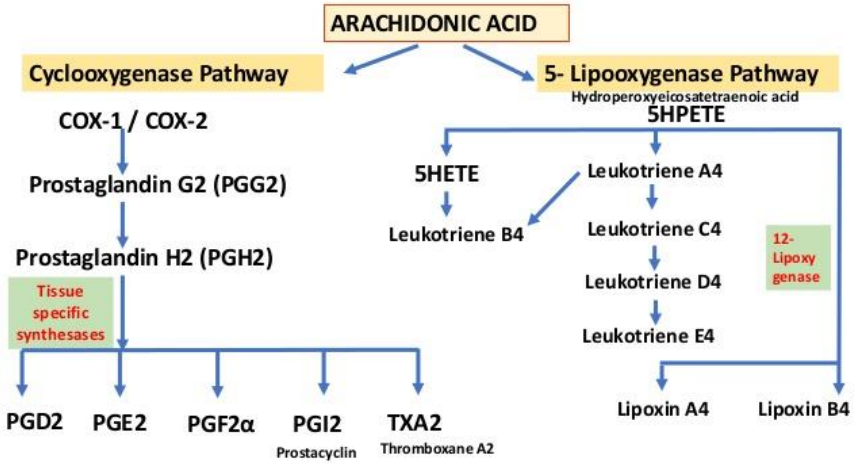

Regulation of gastric acid secretion
Vagus nerve
Food
Mechanical stimulus
1
HCl
Pepsin
Chemical stimulus
pH < 3
Gastrin
Secretin, GIP
2 Fundus
Vagus nerve
CGRP
ACh
D cell
M3
SIH
H2
H cell
Parietal cell
HCl
Histamine
CCK8
Lumen
Gastrin
Systemic circulation
3 Antrum
Vagus nerve
Amino acids, etc.
pH < 3
ACh
D cell
CGRP
SIH
G cell
GRP
Gastrin

# Important role of prostaglandins in the regulation of gastric juice production!!!




- Prostaglandins (PGE2 and PGI2) are found in high concentration in the gastric mucosa and gastric juice
  - prostaglandins inhibit acid secretion
  - stimulate mucus and bicarbonate secretion
  - maintain mucosal blood flow
  - and provide dramatic protection against a wide variety of agents which cause acute mucosal damage
- pharmacological inhibition of COX1 therefore affects gastric mucosa in a negative way

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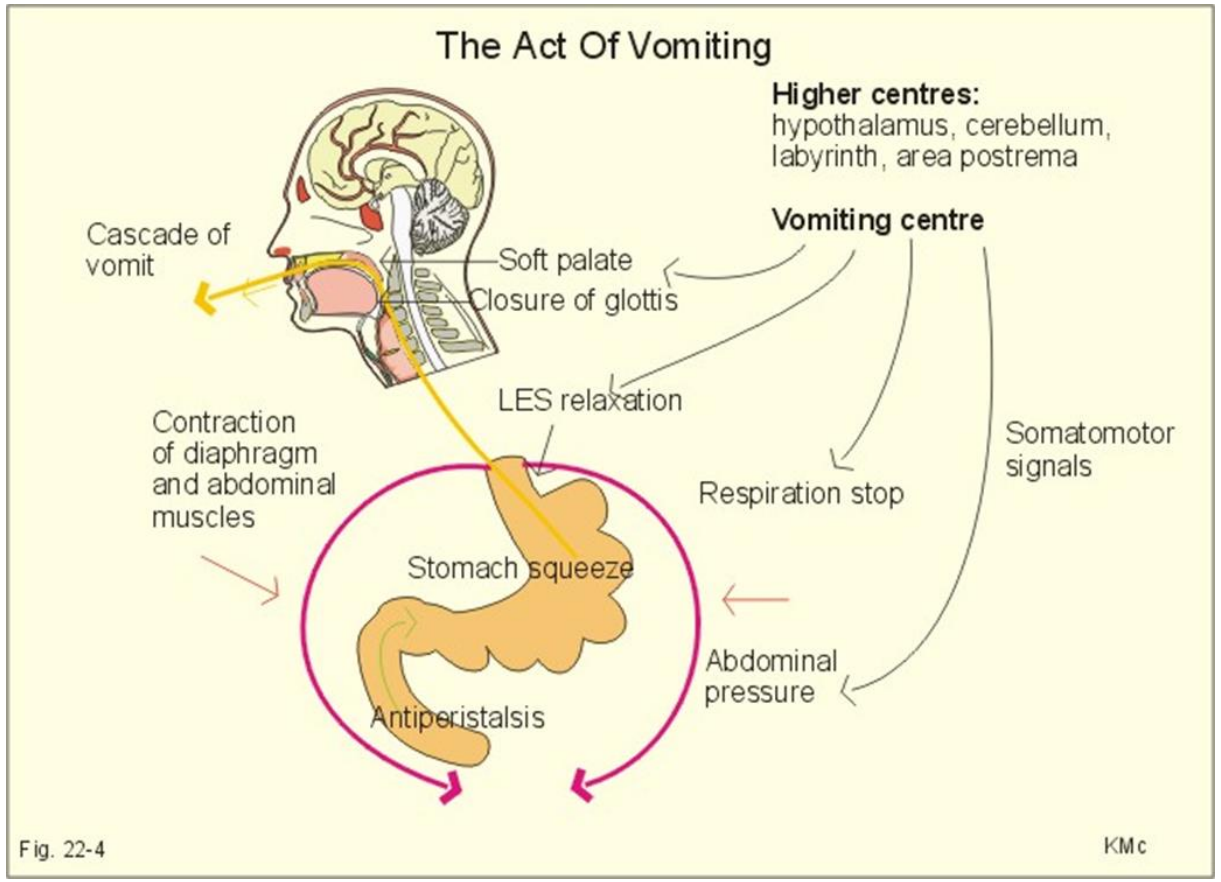
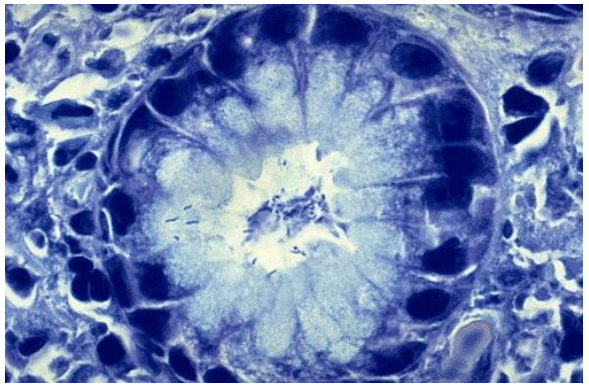
# Disorders of gastric motility

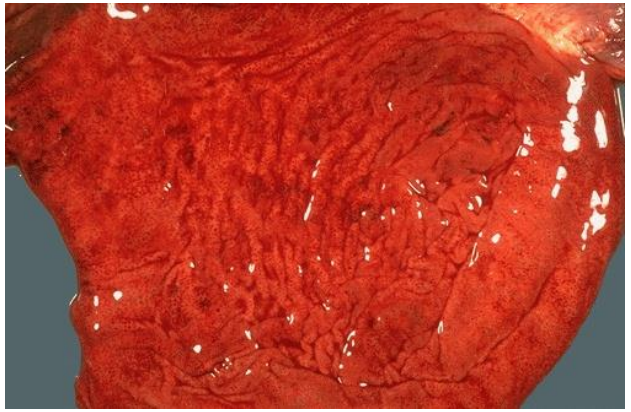
- vomiting reflex (emesis)
  - reflex act leading to expulsion of gastric content by mouth
- initiated from emetic centre in reticular formation in oblongate medulla
  - in proximity of respiratory and vasomotor and salivation centres
    - therefore increased  heart frequency and salivation
- act of vomiting
  - deep inspirium followed
  - closure of glottis
  - contraction of diaphragm, abdominal and chest muscles (i.e. increase of intra-abdominal and intra-thoracic pressure)
  - contraction of pylorus and duodenum and – vice versa - relaxation of stomach and lower oesoph. sphincter
    - stomach has obviously a passive role, everything is due to increased intraabdominal pressure
- vomiting is usually preceded by nausea
  - sensoric stimuli (sight, smell, taste)
  - distension of stomach, slow emptying, gastritis
  - irritation of vestibular apparatus
  - pain
- vomiting of central origin
  - meningitides, head trauma, tumours, epilepsy
  - usually without nausea

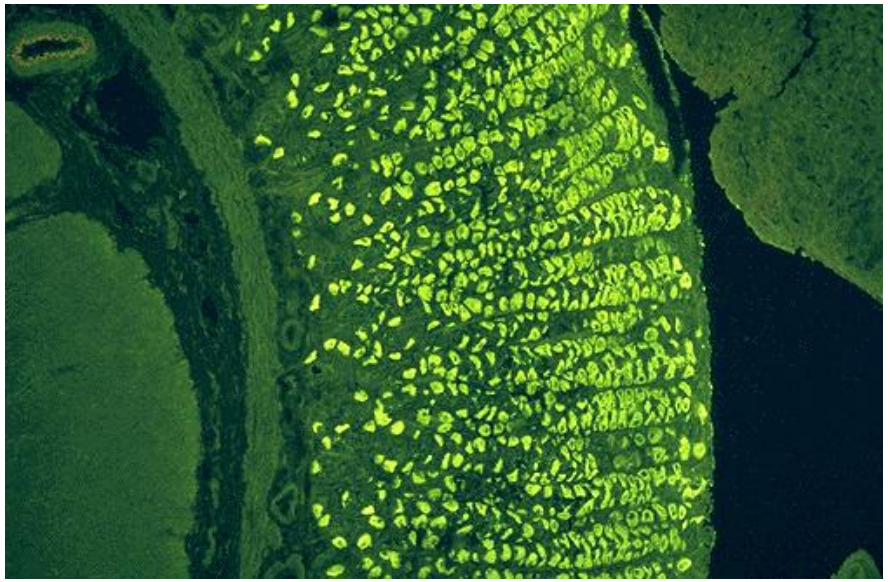


# Gastritis

- acute
  - stress (→ Cushing ulcer)
    - trauma, burns, after surgery
  - shock
  - infectious
  - post-radiation
  - alcohol
  - corrosive
  - systemic infection
    - bacterial and viral
  - uraemia
  - alimentary intoxication
- chronic
  - type A - autoimmune (→ atrophic gastritis)
  - type B – bacterial (infectious)
    - inflammation of antrum due to H. pylori infection (without achlorhydria and ↑ gastrin)







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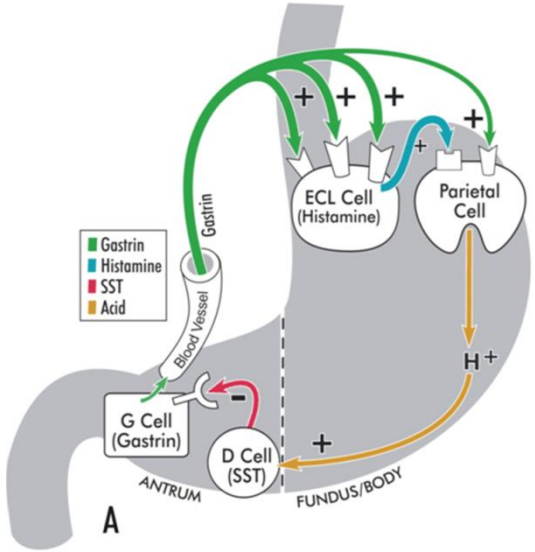
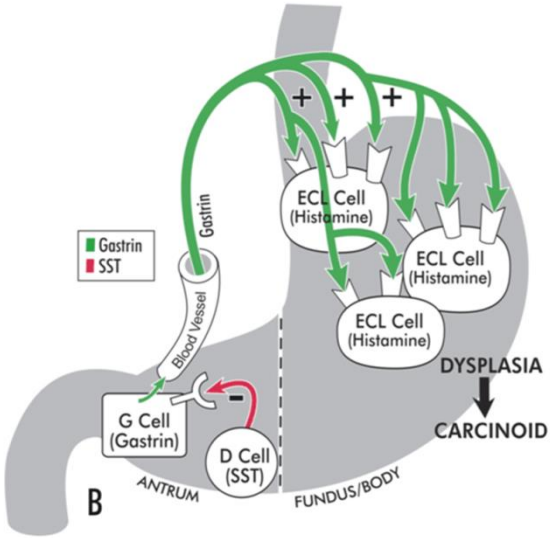
# Autoimmune/atrophic gastritis (A-type)

- destruction of mainly parietal cells by cytotoxic T-lymphocytes
  - compensatory ↑ gastrin
- antibodies against
  - intrinsic factor (IF) and complexes IF/B12
  - Na/K-ATPase
  - carbonic anhydrase
  - gastrin receptor
- consequences
  - achlorhydria leading to sideropenic anaemia
  - later megaloblastic (pernicious) anaemia
    - the liver stores of B12 are much larger than those of iron
  - pre-cancer state

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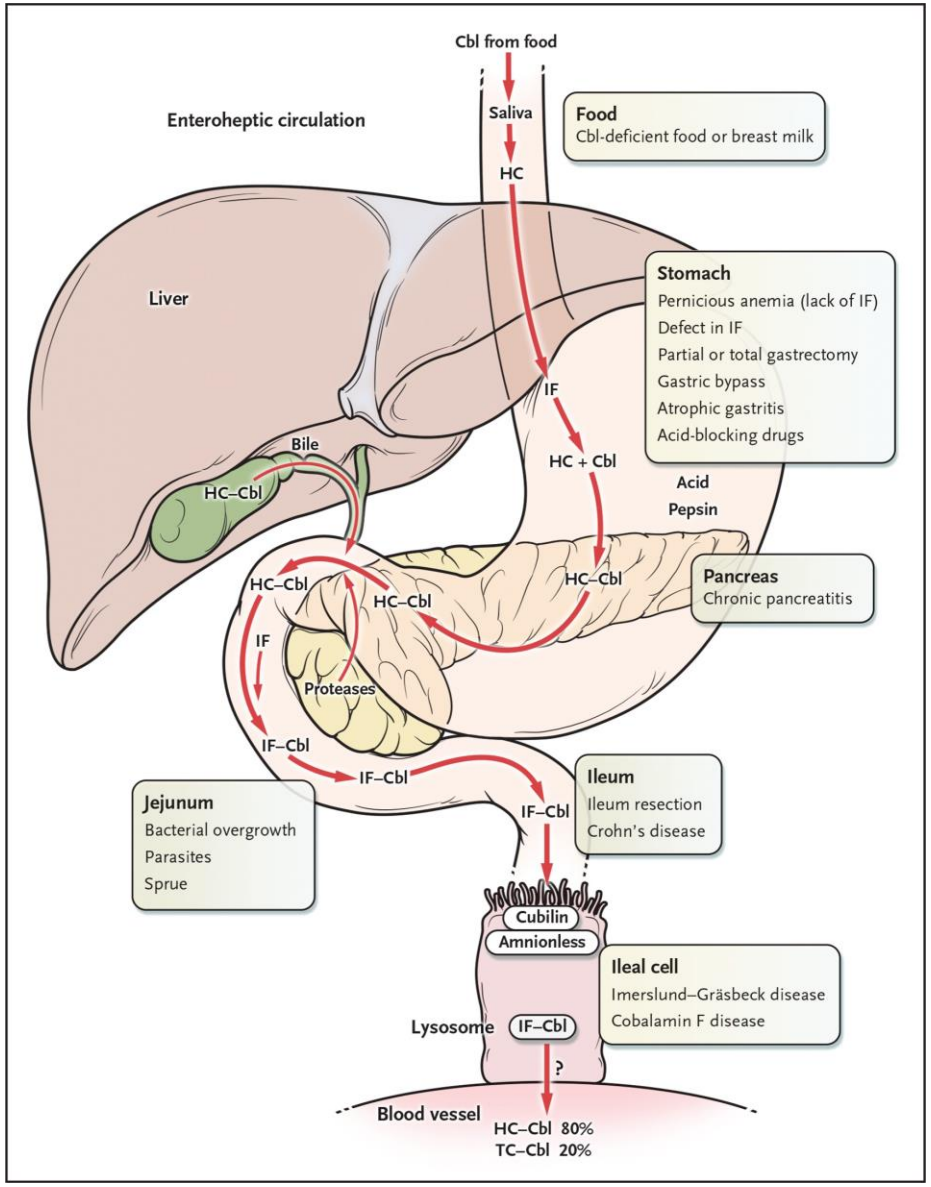
# Normal mechanisms and defects of $B_{12}$ absorption




- The vitamin $B_{12}$ (Cbl) released from food protein by peptic action is bound to haptocorrin (HC, also commonly known as the R-protein, or the R-factor) produced by the salivary glands of the oral cavity in response to ingestion of food
- Cbl-HC complexes are formed in the stomach and travel to the duodenum, where pancreatic proteases digest the HC, releasing Cbl to bind to intrinsic factor (IF)
  - !!! B12 is structurally very sensitive to the hydrochloric acid found in the stomach secretions, and easily denatures in that environment before it has a chance to be absorbed by the small intestine
- The IF-Cbl complex binds to a specific receptor in the distal ileum (the cubilin-megalin receptor) and is internalized, eventually released from lysosomes, and transported into the blood
- Both HC and transcobalamin (TC) bind Cbl in the circulation, although the latter is the cellular delivery protein

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# PEPTIC ULCER

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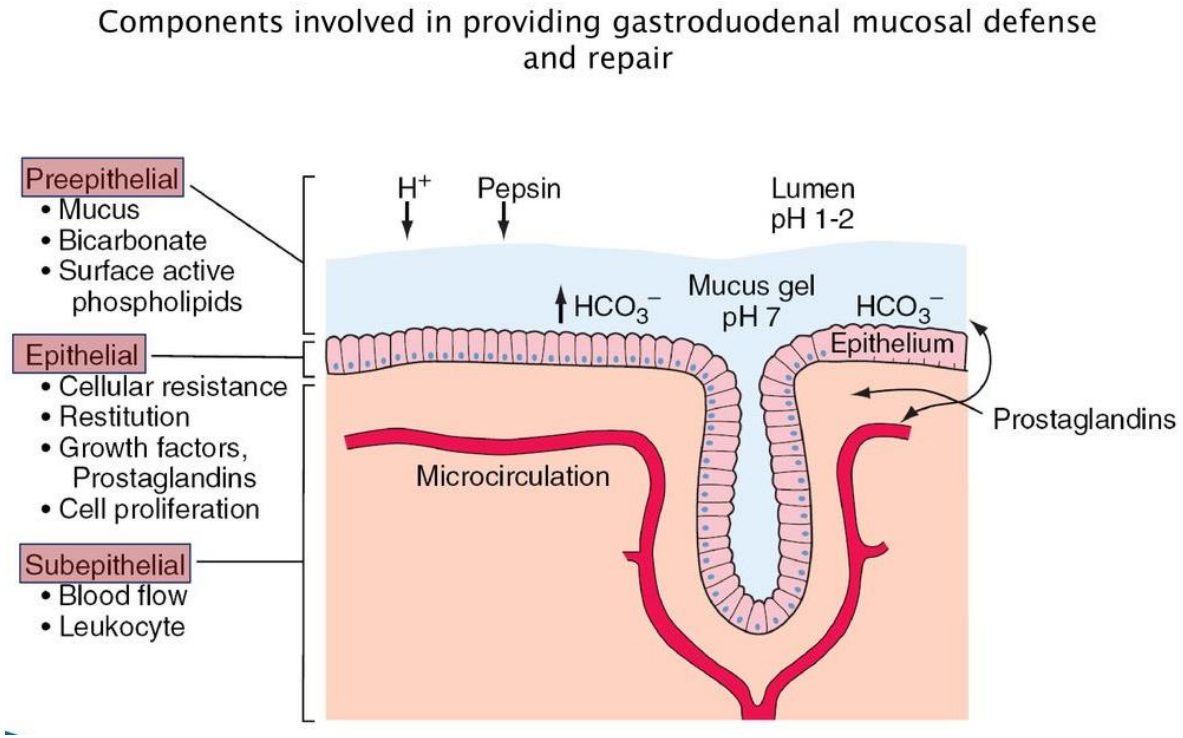
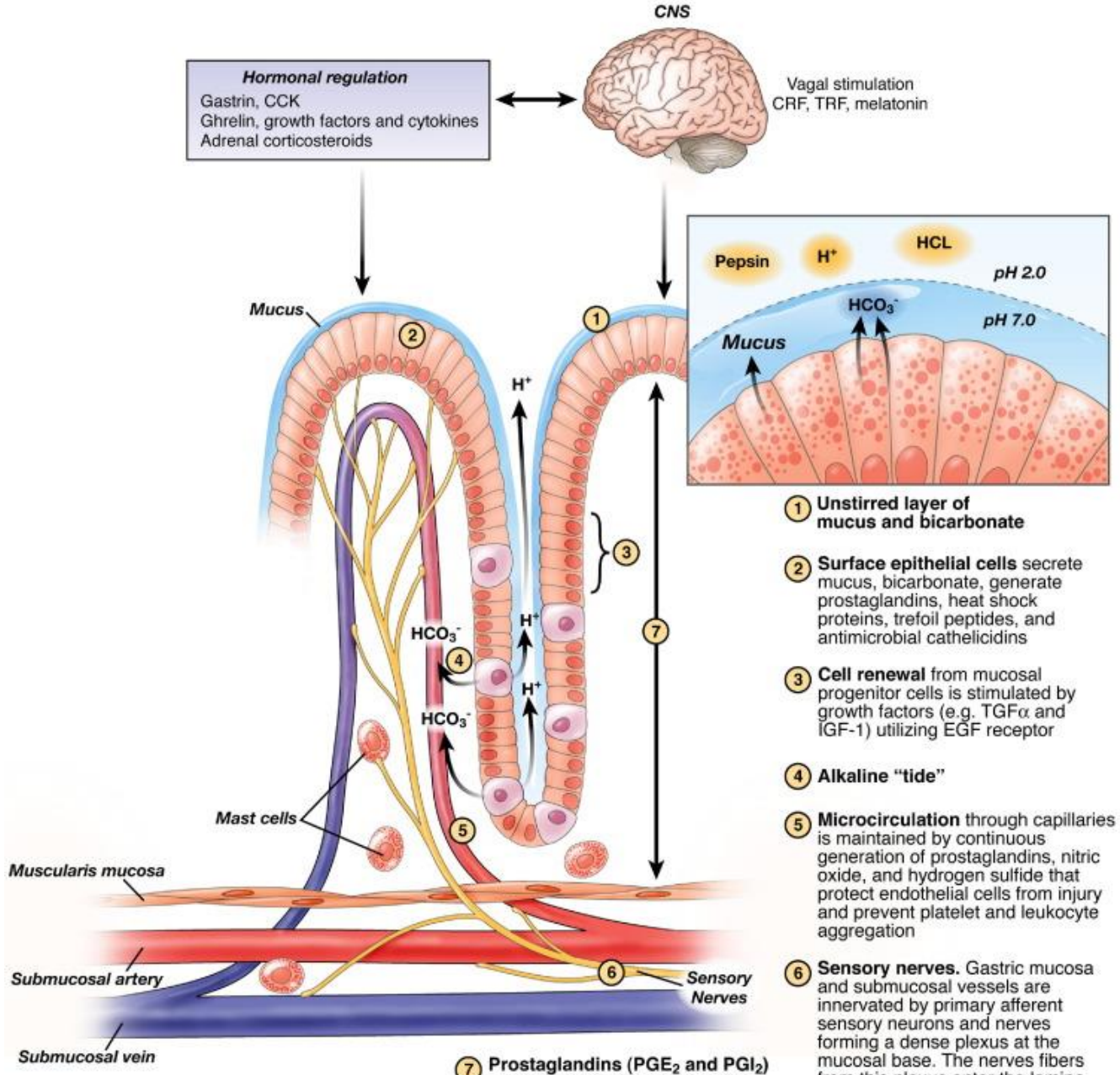
# The gastric mucosal barrier

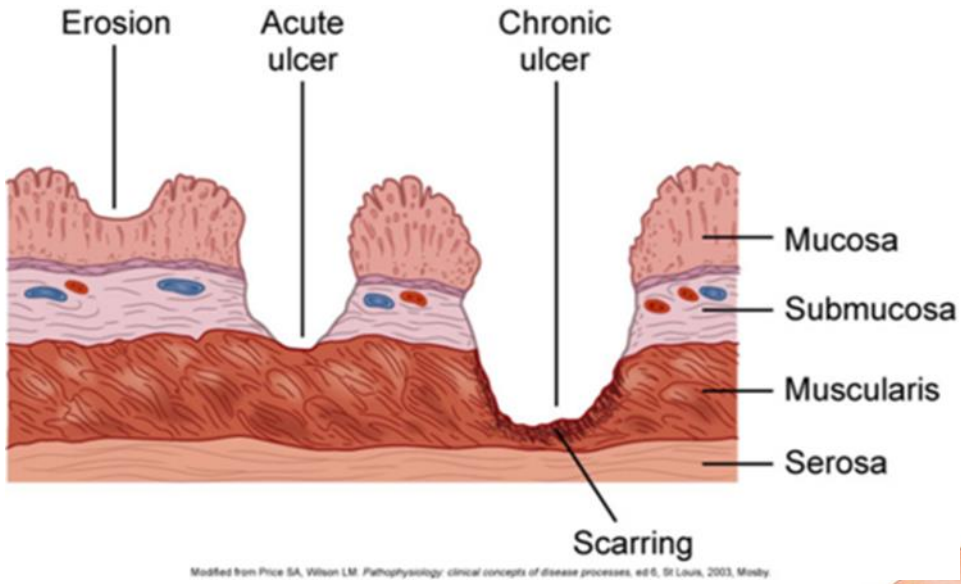
- property of the stomach that allows it to safely contain the gastric acid required for digestion
- the barrier consists of three protective components
  - (1) a **compact epithelial cell lining**
    - cells in the epithelium of the stomach are bound by **tight junctions** that repel harsh fluids that may injure the stomach lining
    - very **high regenerative capacity**
  - (2) a special **mucus** covering, derived from mucus secreted by surface epithelial cells and foveolar cells
    - this insoluble mucus forms a protective gel-like coating over the entire surface of the gastric mucosa
    - the mucus protects the gastric mucosa from autodigestion by e.g. pepsin and from erosion by acids and other caustic materials that are ingested
  - (3) **bicarbonate ions** secreted by the surface epithelial cells
    - the bicarbonate ions diffuse into the mucus (and gastric circulation) and act to neutralize harsh acids

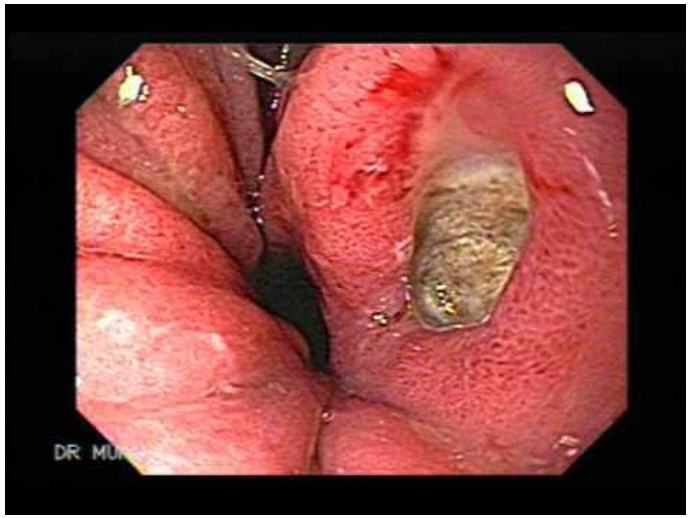


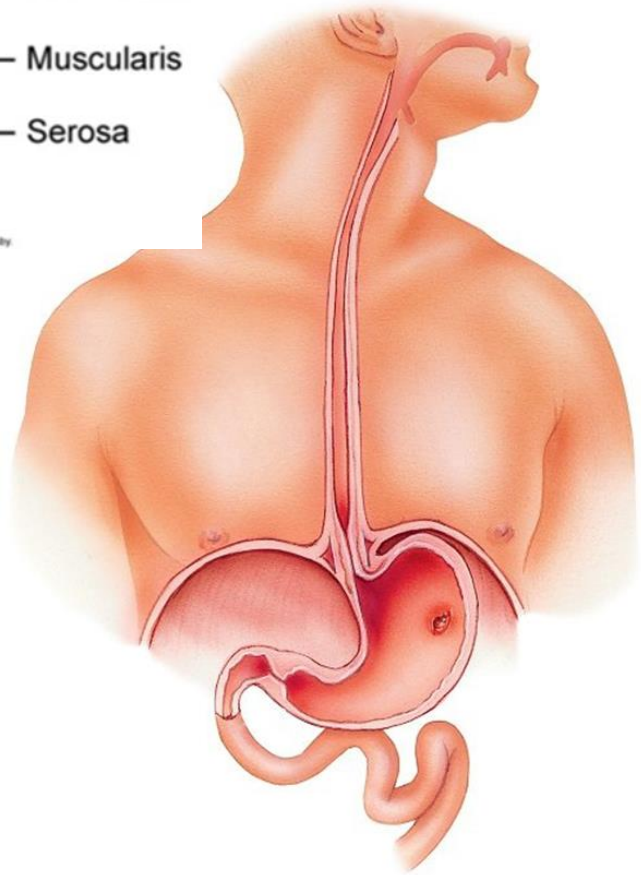

CNS
Hormonal regulation
Gastrin, CCK
Ghrelin, growth factors and cytokines
Adrenal corticosteroids
Vagal stimulation
CRF, TRF, melatonin
Pepsin
H+
HCL
pH 2.0
HCO3-
pH 7.0
Mucus
Mucus
H+
HCO3-
H+
H+
HCO3-
Mast cells
Muscularis mucosa
Submucosal artery
Submucosal vein
Sensory Nerves
1 Unstirred layer of mucus and bicarbonate
2 Surface epithelial cells secrete mucus, bicarbonate, generate prostaglandins, heat shock proteins, trefoil peptides, and antimicrobial cathelicidins
3 Cell renewal from mucosal progenitor cells is stimulated by growth factors (e.g. TGFα and IGF-1) utilizing EGF receptor
4 Alkaline "tide"
5 Microcirculation through capillaries is maintained by continuous generation of prostaglandins, nitric oxide, and hydrogen sulfide that protect endothelial cells from injury and prevent platelet and leukocyte aggregation
6 Sensory nerves. Gastric mucosa and submucosal vessels are innervated by primary afferent sensory neurons and nerves forming a dense plexus at the mucosal base. The nerves fibers from this plexus enter the lamina propria (accompanying capillary vessels) and end just beneath the surface epithelial cells
7 Prostaglandins (PGE2 and PGI2) maintain and enhance all mucosal defensive mechanisms working synergistically with nitric oxide

# Peptic ulcer

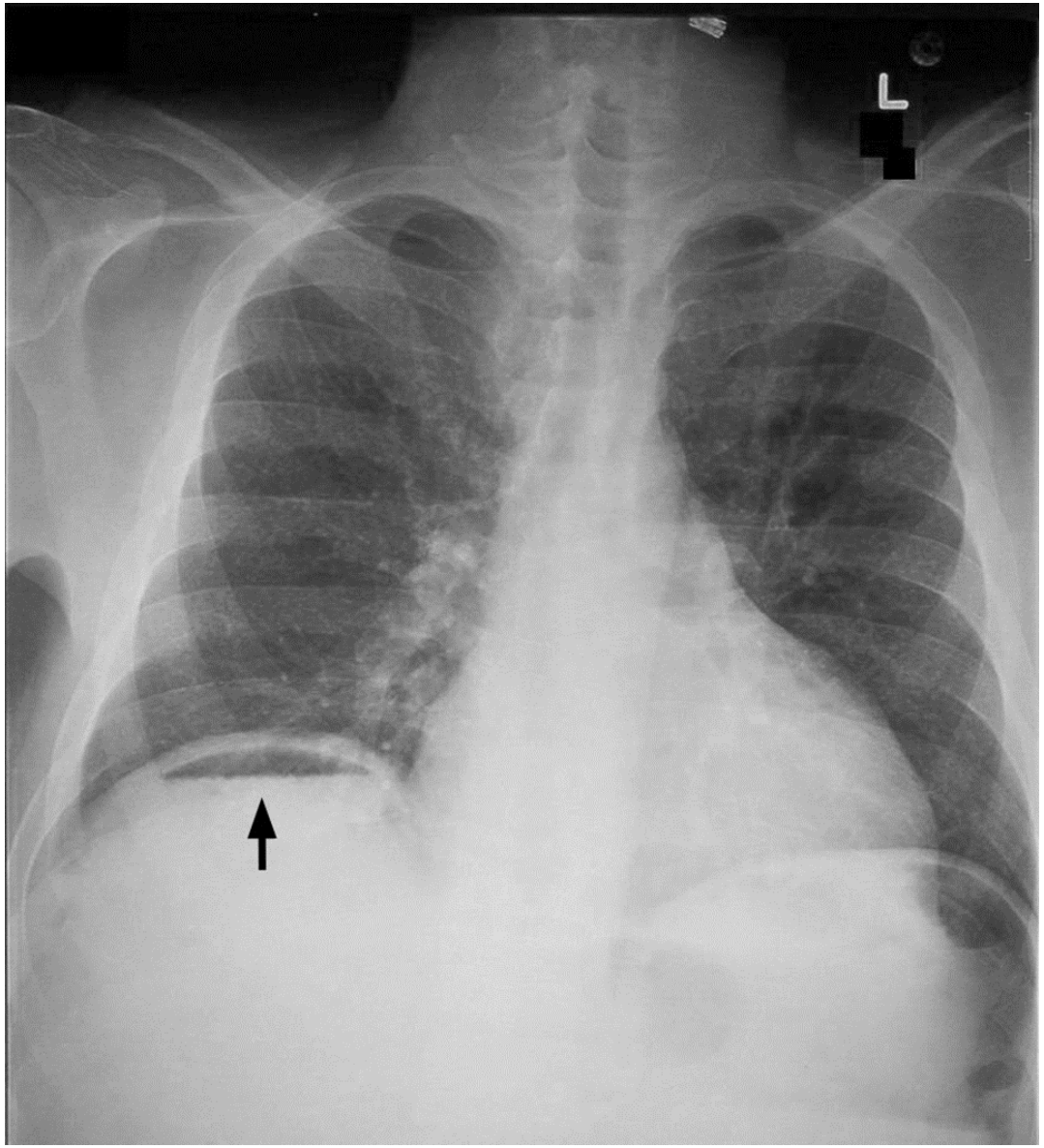
- historically hyperacidity was the main etiologic factor blamed
  - but the true hyperacidity is present only in few cases (gastrinoma – Zollinger-Ellison syndrome)
    - tumour arising from gastrin producing cells of pancreas
- localization in dist. part of oesophagus (in GERD), stomach, duodenum and event. prox. part of jejunum
- extent/severity
  - ulcer = mucosal defect penetrating muscularis mucosae
  - erosion = defect limited only to mucous
- complications of pept. ulcer
  - bleeding
  - perforation
    - air in the peritoneal cavity (pneumoperitoneum)
  - penetration
  - stricture

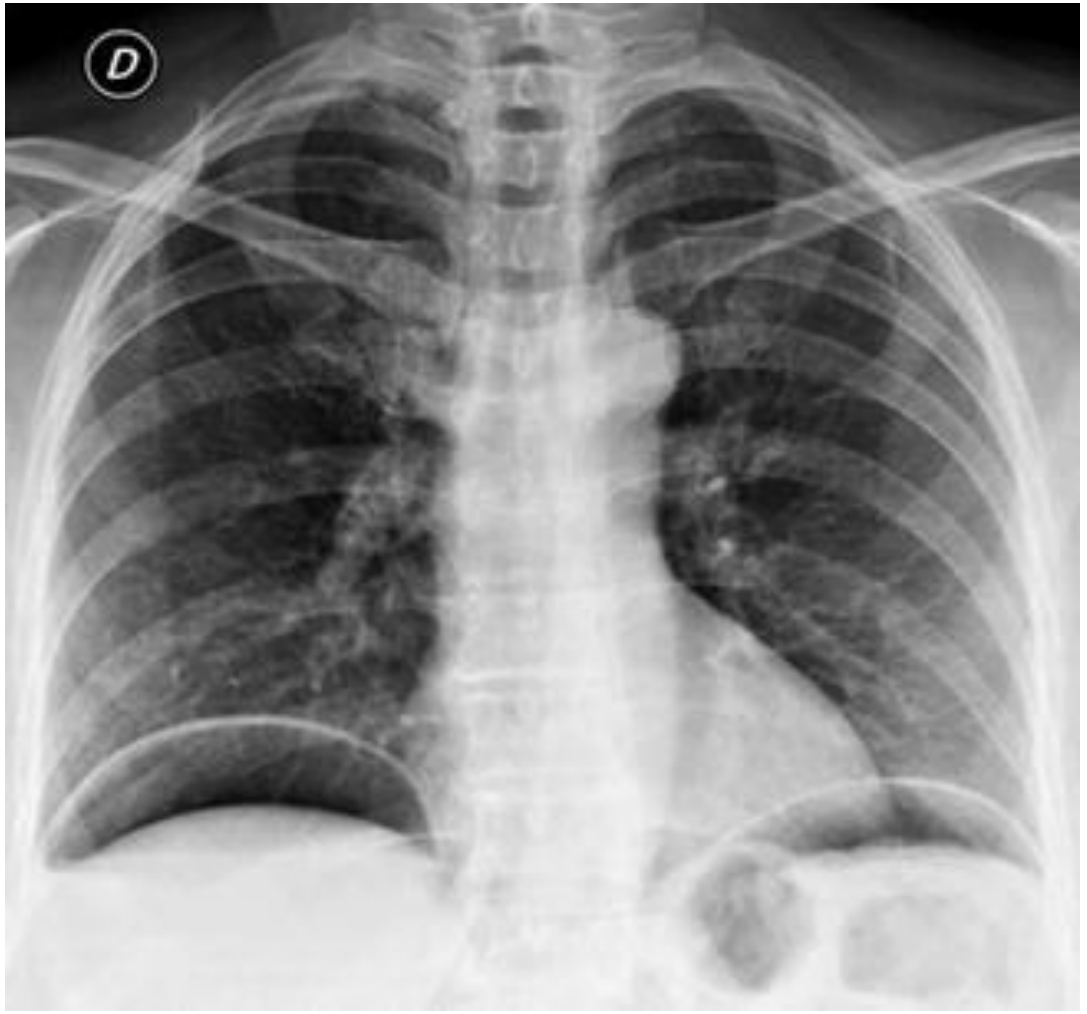




# Pneumoperitoneum

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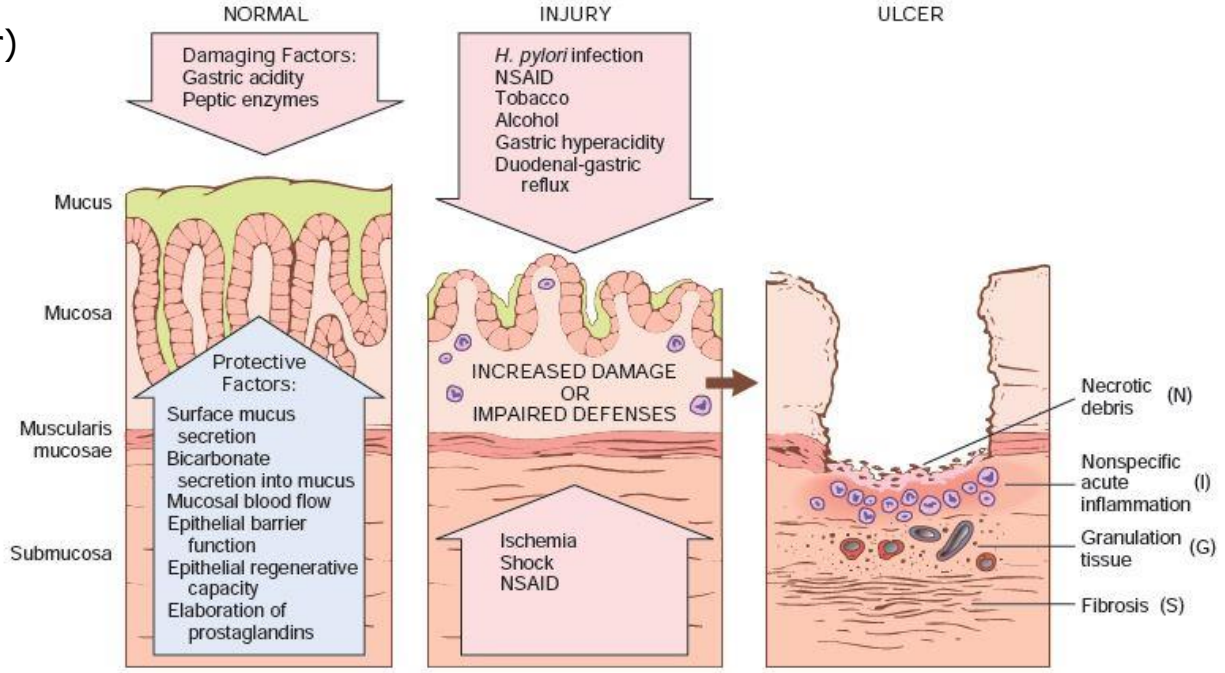
# Pathophysiology of peptic ulcer

- disease is always a consequence of dysbalance between aggressive and protective factors (i.e. fall in mucosal defence)
- fall in mucosal protection/defence
  - decreased mucosal blood flow
    - e.g. stress or shock (burns!), high ICP (Cushing ulcer)
    - drugs – COX1 or phospholipase A inhibitors
      - NSAIDs
      - corticosteroids
  - dysmotility
    - delayed gastric emptying for gastric ulcer
    - accelerated emptying of stomach fro duodenal ulcer
  - impaired epithelial restitution
  - impaired prostaglandin synthesis
- aggressive factors
  - hyperacidity (↑HCl)
    - habitually increased secretion of parietal cells - interindividual variability in
      - basal secretion
      - number
      - sensitivity to histamine or gastrin
  - ↑ pepsin
  - bile (in duodenal-gastric reflux)
  - alcohol, nicotine, caffeine
  - Helicobacter pylori

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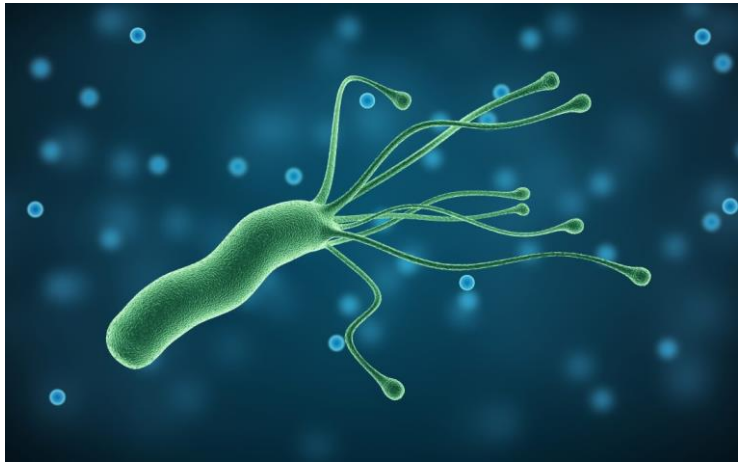
# Helicobacter pylori



- successful human microbial pathogen
  - infects >20% of population (some estimate >50%)
- pathogenicity is determined by
  - host factors as well as
  - variation among H. pylori strains
  - clinical outcomes
    - chronic gastritis type B – dyspepsia (~ 50% patients positive for H. pylori)
    - gastric ulcer (~75% patients positive for H. pylori)
    - duodenal ulcer (~ 90% patients positive for H. pylori)
    - asymptomatic (~ 20% healthy positive for H. pylori)
    - its contribution to the development of gastric carcinoma is debated
- H. pylori is G-negative, nonsporing curvilinear bacillus
  - its genome encodes 1500 proteins incl. enzymes (e.g. urease, phospholipase), adhesive proteins, exotoxins (e.g. VacA), pro-inflammatory mediators (e.g. CagA)
    - the genome of *H. pylori* changes continuously during chronic colonization of an individual host by importing small pieces of foreign DNA from other *H. pylori* strains during persistent or transient mixed infections
- H. pylori causes gastritis by 2 ways :
  - direct injury of gastric epithelial cells
    - encapsulated flagellum enables H. pylori to move quickly in acidic surface and penetrate to the deeper layers (higher pH)
    - produces urease (and thus NH3) = local neutralization of HCl
    - produces proteases and phospholipases = destruction of mucus
    - produces catalase = resistance to phagocytosis
  - stimulating production of
    - HCl (by the action on G-cells in the antrum) and activation of proton pump
    - exotoxins (such as VacA → cytochrome C release from mitochondria → apoprotsis)
    - pro-inflammatory mediadotrs (CagA) inducing proinflammatory cytokines (IL – 1β and TNF)
- mechanisms of action and resistance to acid environment
- H. pylori does not penetrate through epithelium → minimal or none systemic immune reaction
  - IgA antibodies

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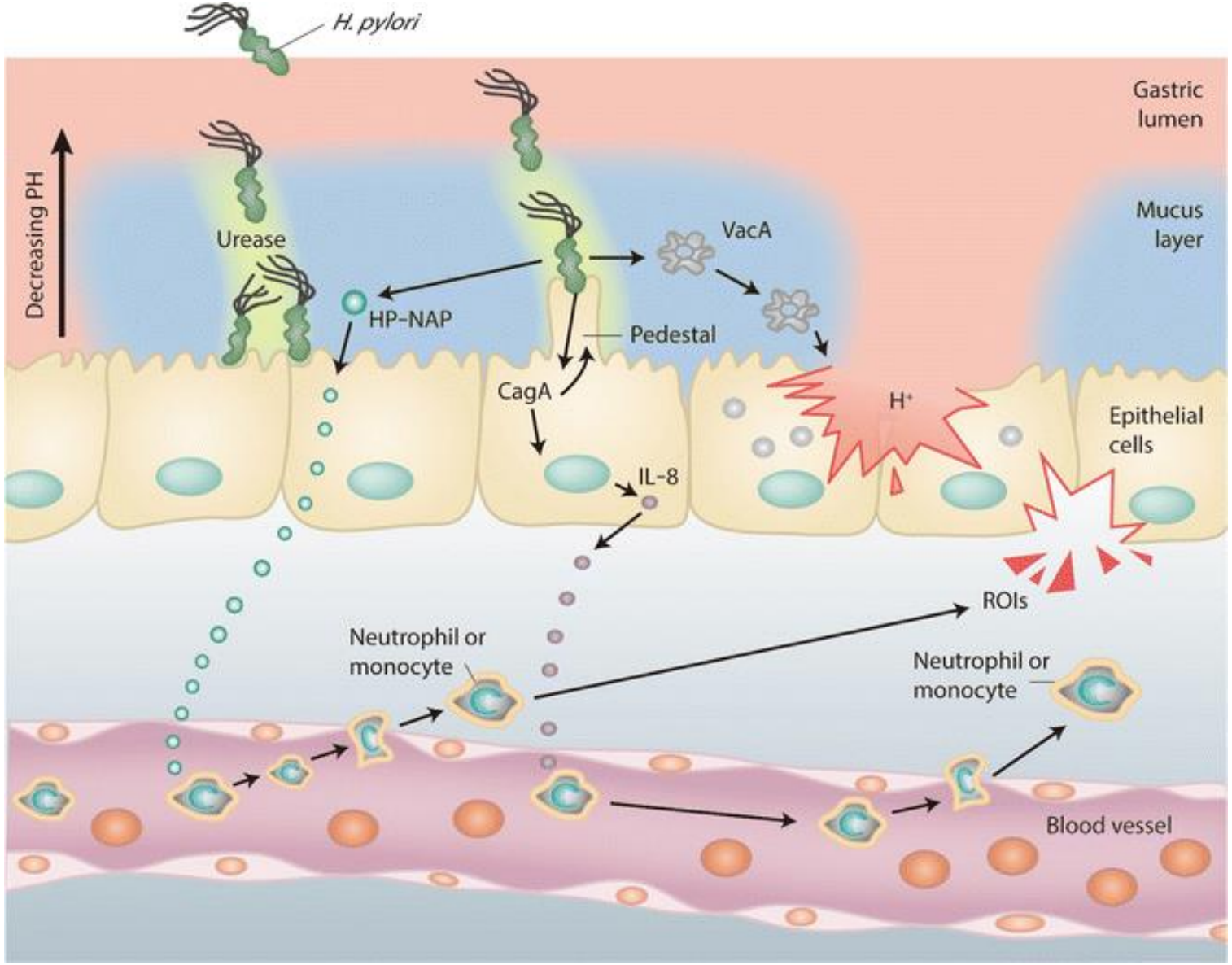
# Pathogenesis of H. pylori




- H. pylori moves in the viscous mucin layer via flagella
- the urease activity enables production of ammonia from endogenous urea that buffers gastric acid in the immediate vicinity of organism
- expresses of bacterial adhesins that enhances the bacterial adherence to foveolar cells
- expression of bacterial toxins
  - Cag A (Cytotoxin associated gene A protein)
    - alters signalling pathway, alters the cytoskeletal rearrangement and alters the tight junctions between the cells
  - Vac A (Vacuolating cytotoxin gene A protein)
    - causes formation of vacuoles in the cells, induces apoptosis, causes disruption of epithelial junctions and blocks the T cells response

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# Symptoms of gastric vs. duodenal ulcer

- stomach
  - etiologically more often contribution of loss of barrier function rather than true hyperacidity
    - chron. gastritis type B
    - duodenogastric reflux
    - drugs
  - older people
  - painful soon after the onset of eating
    - avoiding eating, patients often put on weight
- duodenum
  - protection of duodenum weak
    - Brunner's glands secreting alkalic mucus
    - coordinated peristaltics mixing gastric content with pancreatic and biliary juices which then acidic content
  - etiologically more often hyperacidity and infection by H. pylori
  - genetic effects
    - often blood group 0
    - HLA-B5
  - younger people
  - neurotics (faster gastric motility)
  - painful later after meal
    - relieved by food
  - seasonal manifestation

**Clinical comparison of Gastric ulcer and Duodenal ulcer**

| Gastric Ulcer | Duodenal Ulcer |
|---|---|
| • Occur in the stomach | • Occur in the duodenum |
| • Epigastric pain 1-2 hours after eating | • Epigastric pain 2-5 hours after eating |
| • Can cause hematemesis or melena | • Can cause melena or hematochezia |
| • Heart burn, chest discomfort and early satiety are commonly seen | • Heart burn, chest discomfort are less common but may be seen |
| • Can cause gastric carcinoma (mostly in the elderly) | • Pain may awaken patient during the night |

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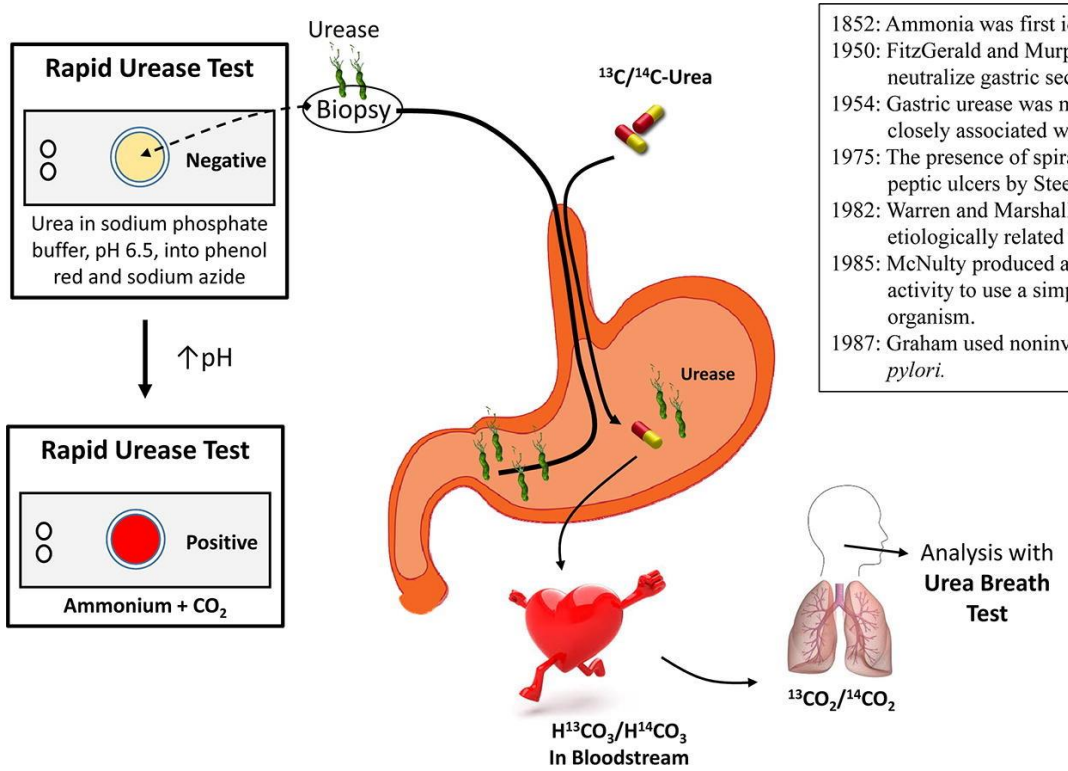
# Detection of H. pylori

- invasive – by biopsy during gastroscopy
  - light microscopy
  - PCR
  - cultivation
  - intravital microscopy
  - urea test
- non-invasive
  - aspiration of gastric juice by nasogastric tube with subsequent PCR
  - PCR from stool
  - urea breath test




1852: Ammonia was first identified in the stomach.
1950: FitzGerald and Murphy showed urea was possible to neutralize gastric secretion and heal a duodenal ulcer.
1954: Gastric urease was microbiological in origin and was closely associated with the epithelium in by Kornberg.
1975: The presence of spiral bacteria associated with gastritis and peptic ulcers by Steer.
1982: Warren and Marshall culture *H. pylori* and prove it was etiologically related to gastritis and peptic ulcer
1985: McNulty produced a clinical test for gastric biopsy urease activity to use a simple test to diagnose the presence of the organism.
1987: Graham used noninvasive $^{13}C$-urea breath test to detect *H. pylori.*

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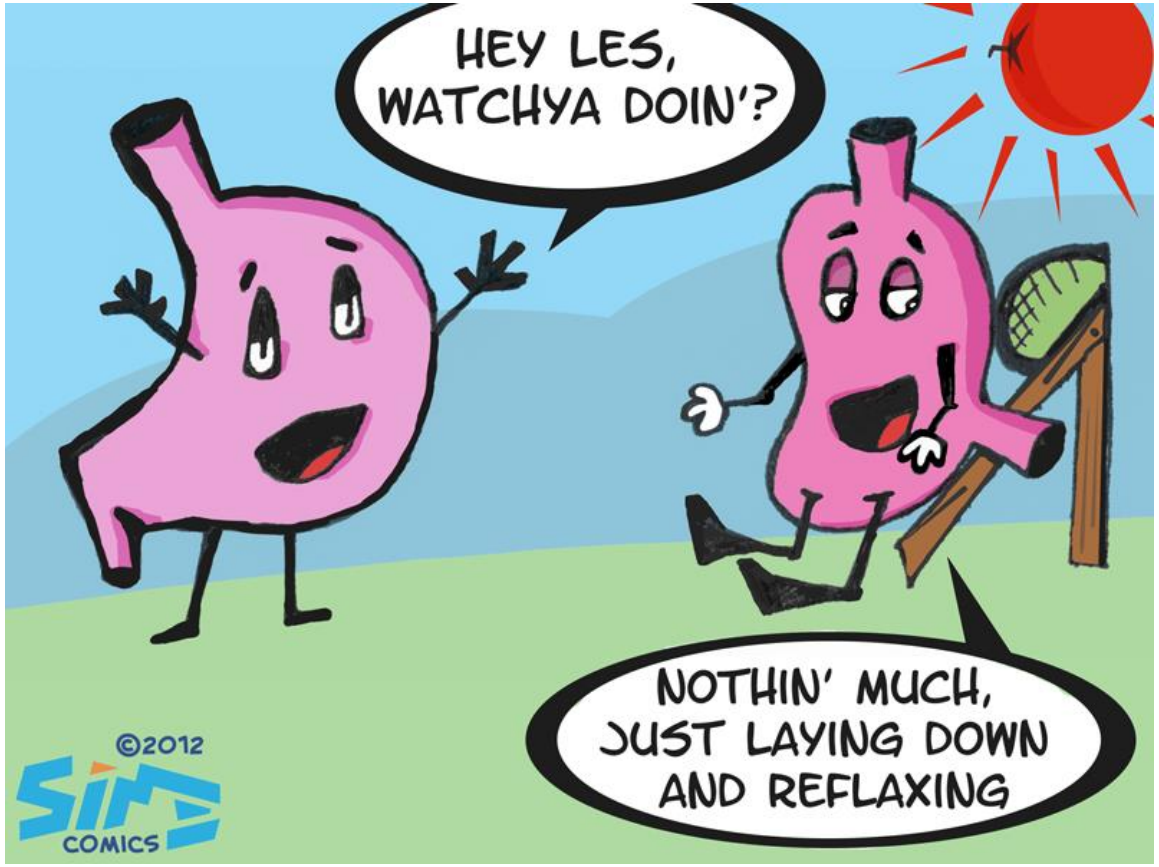
HEY LES, WATCHYA DOIN'?
NOTHIN' MUCH, JUST LAYING DOWN AND REFLAXING
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