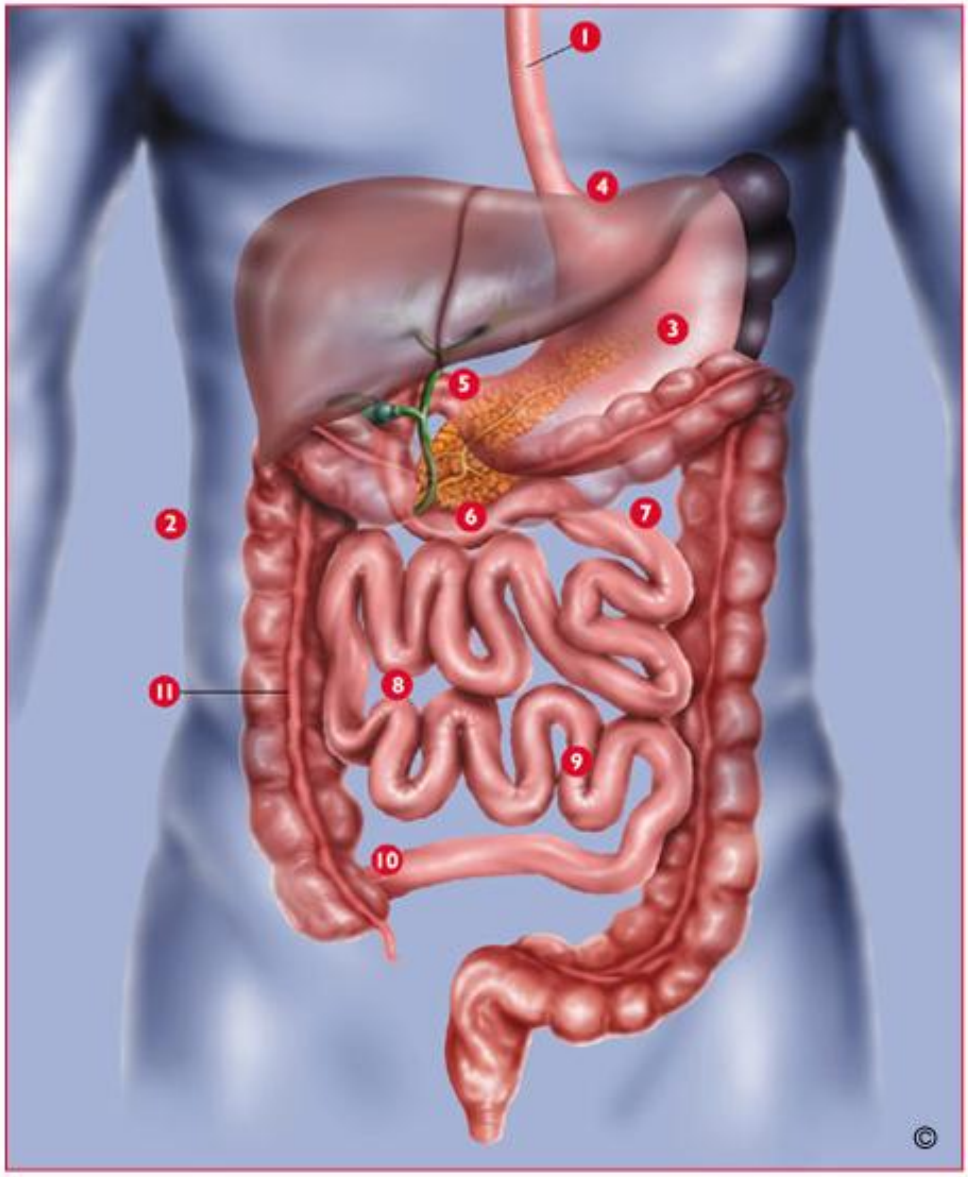
Pathophysiology of GIT

Oral cavity and salivary glands
Oesophagus
Stomach
Small intestine
Large intestine
Exocrine pancreas

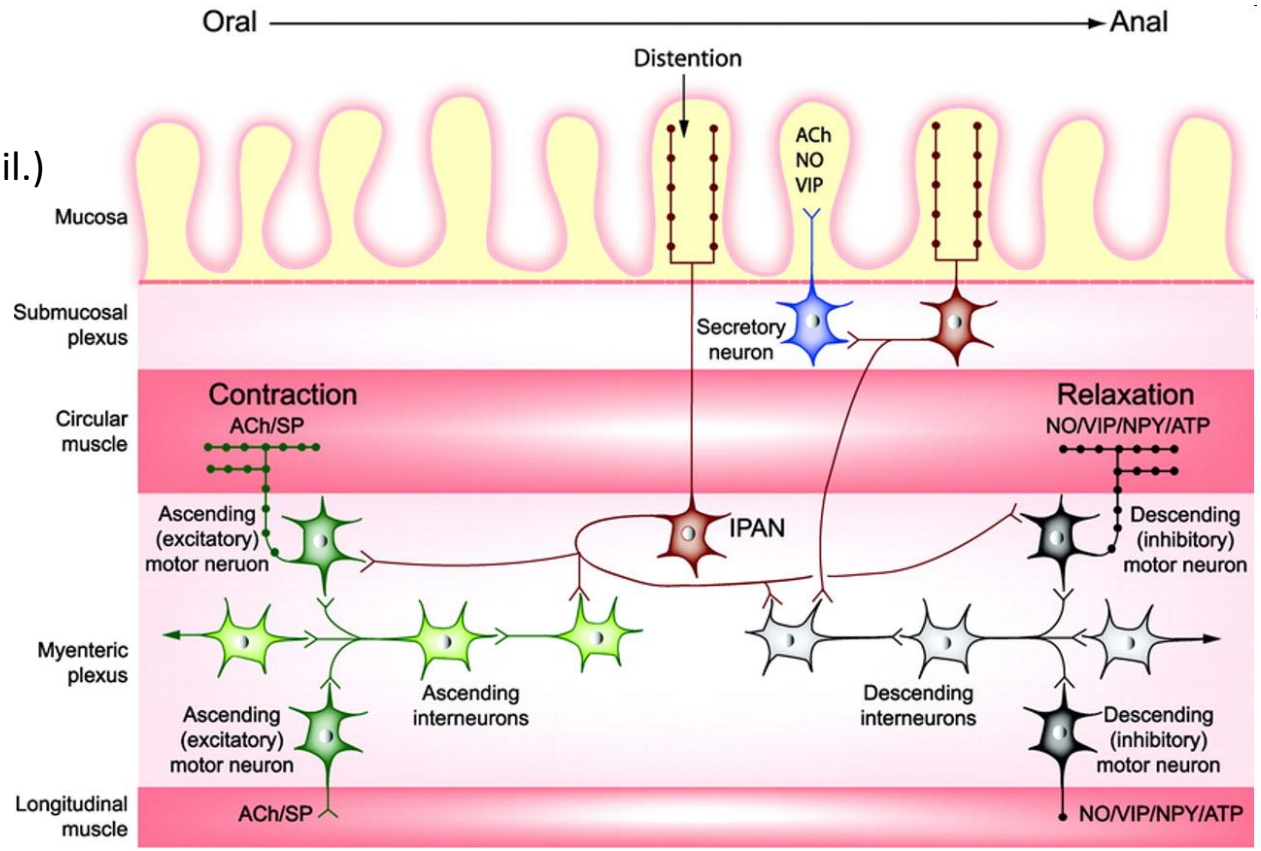
GIT



- 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

Enteric nervous system

- aprox. 500 mil. neurons
  - (brain aprox. 100 bil.)
  - (spinal cord aprox. 100 mil.)
- Plexus myentericus
- Plexus submucosus
- Sensory component
- Executive component
- Interneurons
- High level of autonomy
  - „brain in the gut“

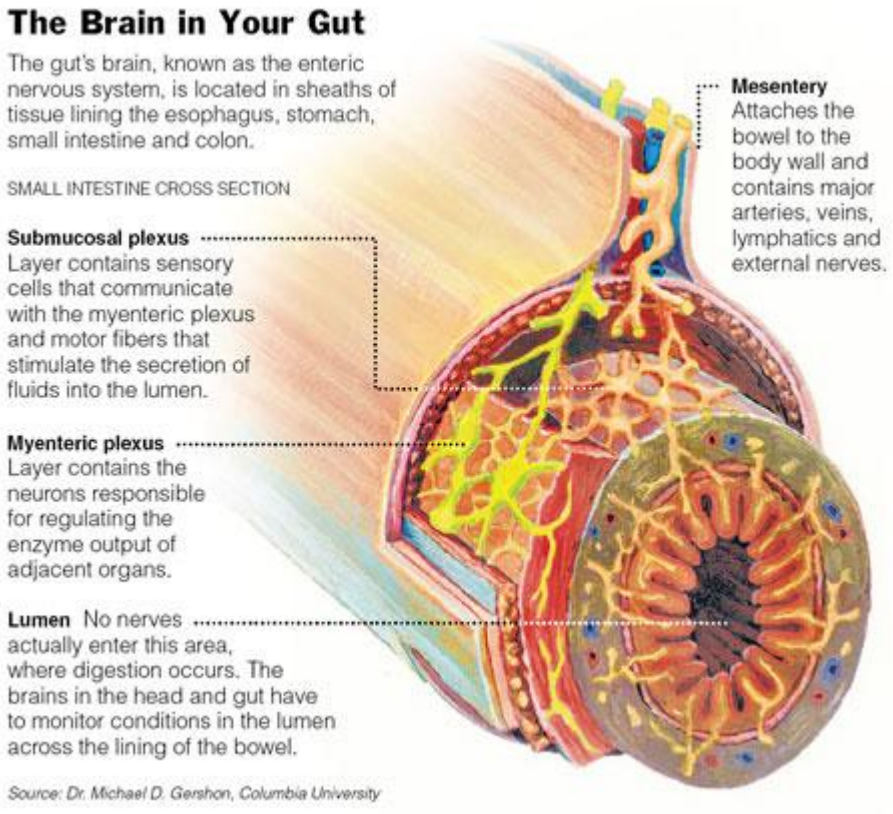


Furness JB (2006) The Enteric Nervous System. Blackwell, Oxford, pp 274

http://www.slideshare.net/carmencrivii/central-nervous-system-the-autonomic-nervous-system?qid=d1502190-93fe-4b05-9d92-6a42e3ca72fc&v=&b=&from_search=8

Enteric nervous system

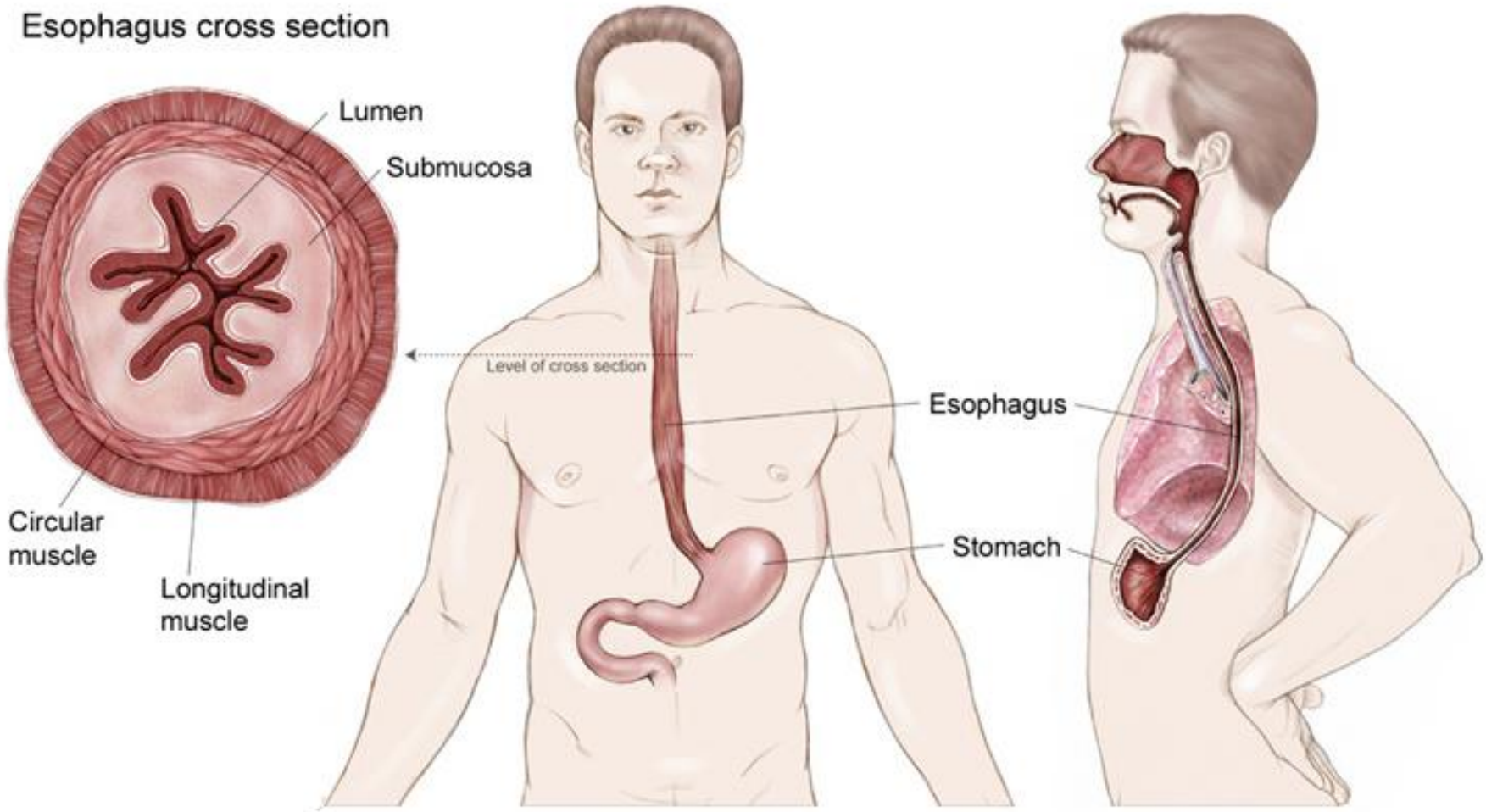
- Autonomy
  - Control of motility
  - Control of secretion
  - Control of blood flow
- Autonomic nervous system
  - Whole GIT regulation
  - Coordination of all organ systems activities



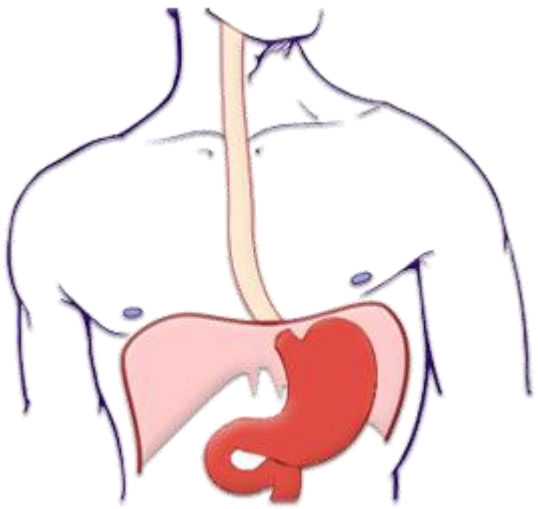
https://kin450-neurophysiology.wikispaces.com/file/view/gut.jpg/187924395/gut.jpg

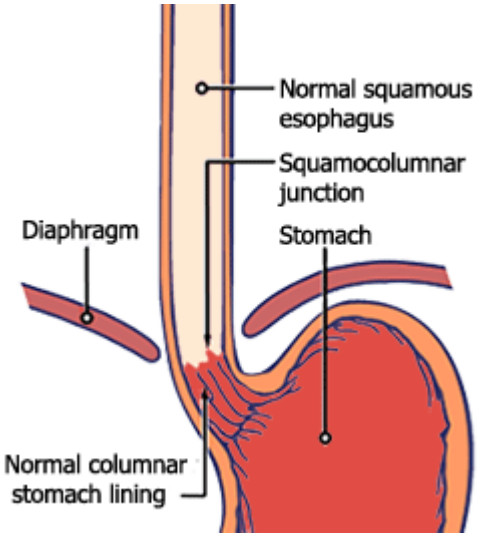
http://2.bp.blogspot.com/_MJ0CEYnSB4U/S99IJTUruOI/AAAAAAAAACs/NPzsh8ydzjQ/s1600/redistributionofbloodflow.jpg

Pathophysiology of oesophagus



Pathophysiology of oesophagus

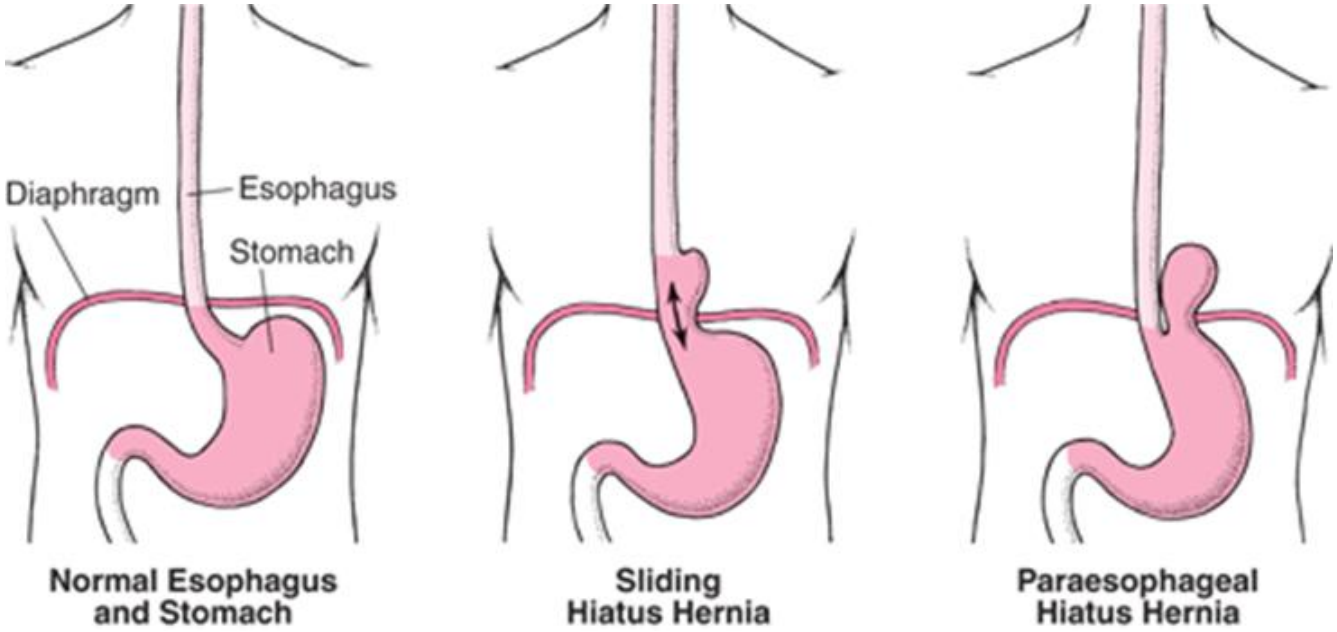




- anatomy and histology
  - upper 2/3 striated muscle + squamous epithelium
    - upper sphincter (m. cricopharyngeus)
  - bottom 1/3 smooth muscle
    - lower sphincter (smooth muscle)
    - in terminal part cylindrical epithelium
  - peristaltics
- disorders of motility and swallowing
  - dysphagia (oropharyngeal or oesophageal)
    - painful swallowing (odynophagia) + block of passage
    - 1) functional
      - e.g. scleroderma, amyotrophic lateral sclerosis or vegetative neuropathy in diabetes mellitus, achalasia, reflux. esophagitis, Chagas disease
    - 2) mechanical obstruction
      - strictures, peptic ulcer, tumours
  - achalasia
    - inability to relax lower oesoph. sphincter + lack of peristaltics
      - due to inborn or acquired impairment of myenteric nerve plexus (Meissneri) and production of NO by NO synthase

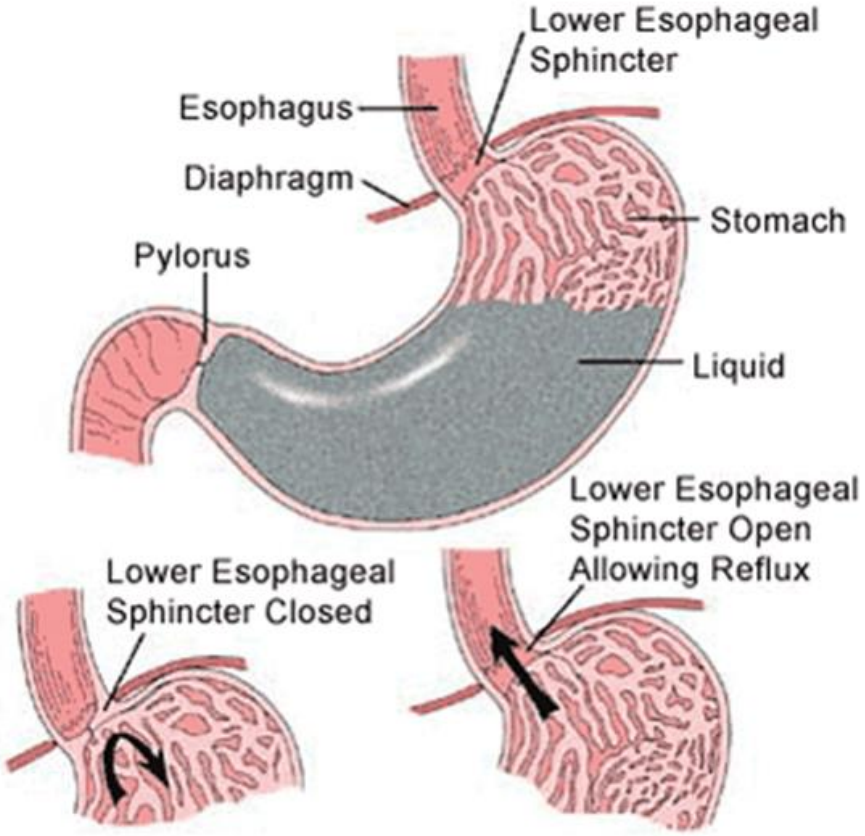
Hiatal hernias

- 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



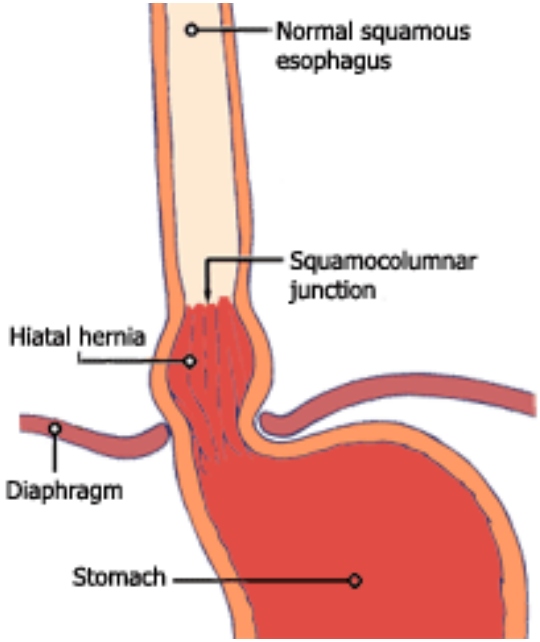
Gastroesophageal reflux (GER)

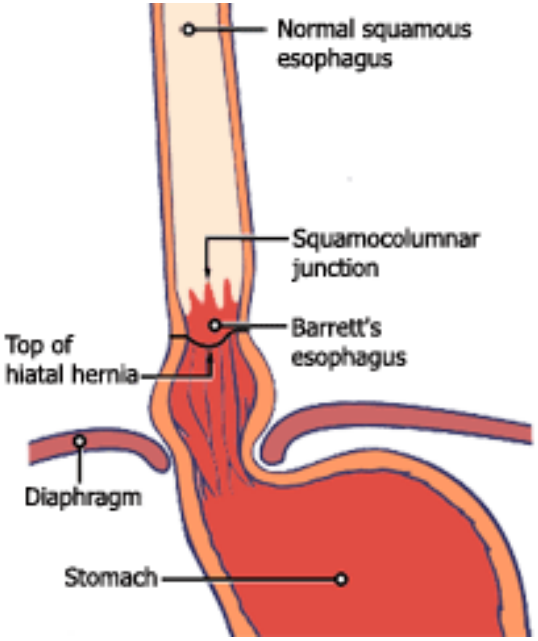
- retrograde passage of gastric content up to oesophagus where it acts aggressively
  - due to HCl, enzymes – proteases (pepsin) and event. bile (when dudodeno-gastric reflux also present)
- occasional reflux appears in healthy subjects
- risk is substantially higher in hiatal hernia
- anti-reflux barrier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

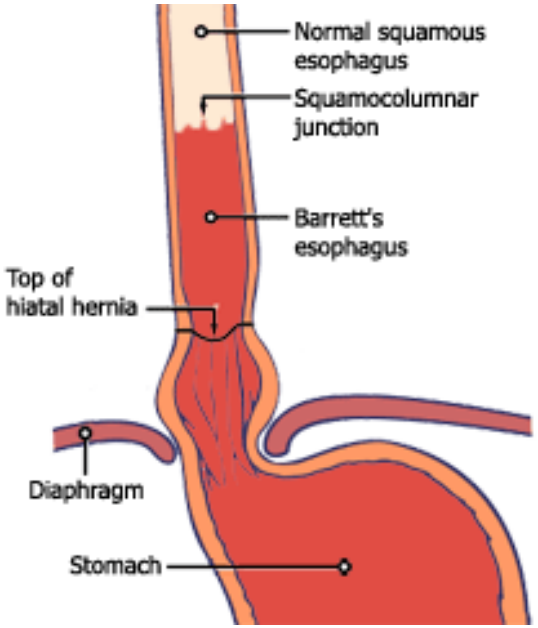


Barrett's oesophagus

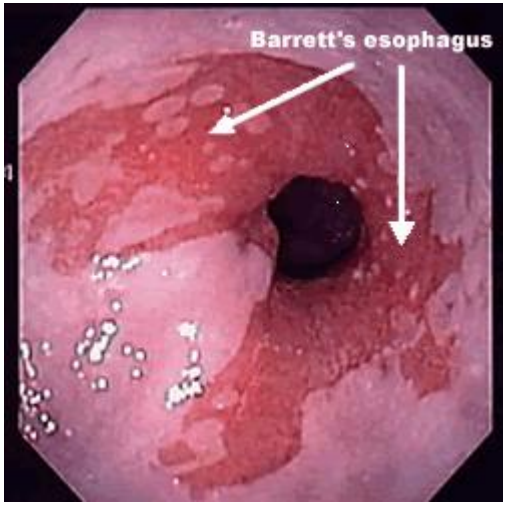
- metaplasia of mucosa in long term GER
  - squamous epithelium changes to cylindrical
- ↑ risk of adenocarcinoma
  - up to 40x higher than in healthy subjects
- pathogenesis not clear
  - suspected error of differentiation of pluripotent stem cells

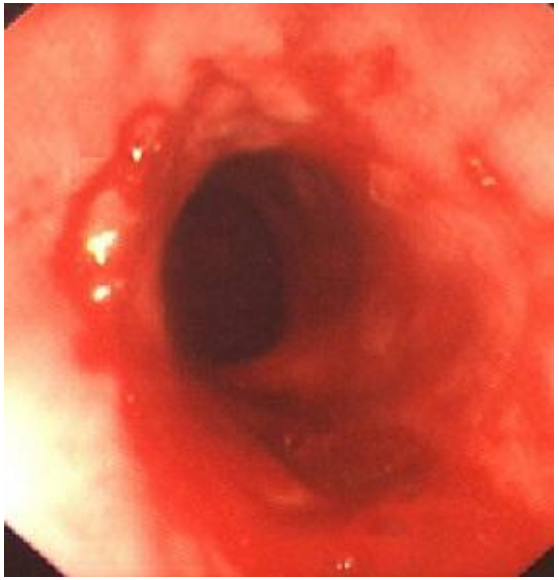


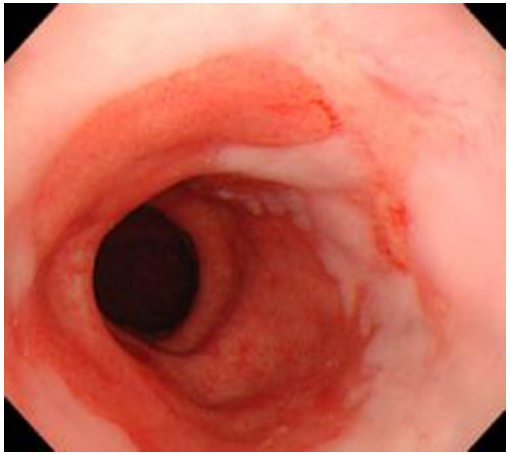


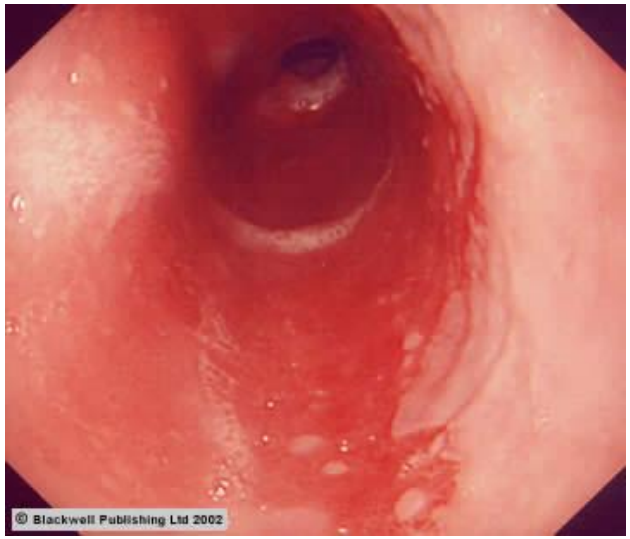


Barrett´s oesophagus



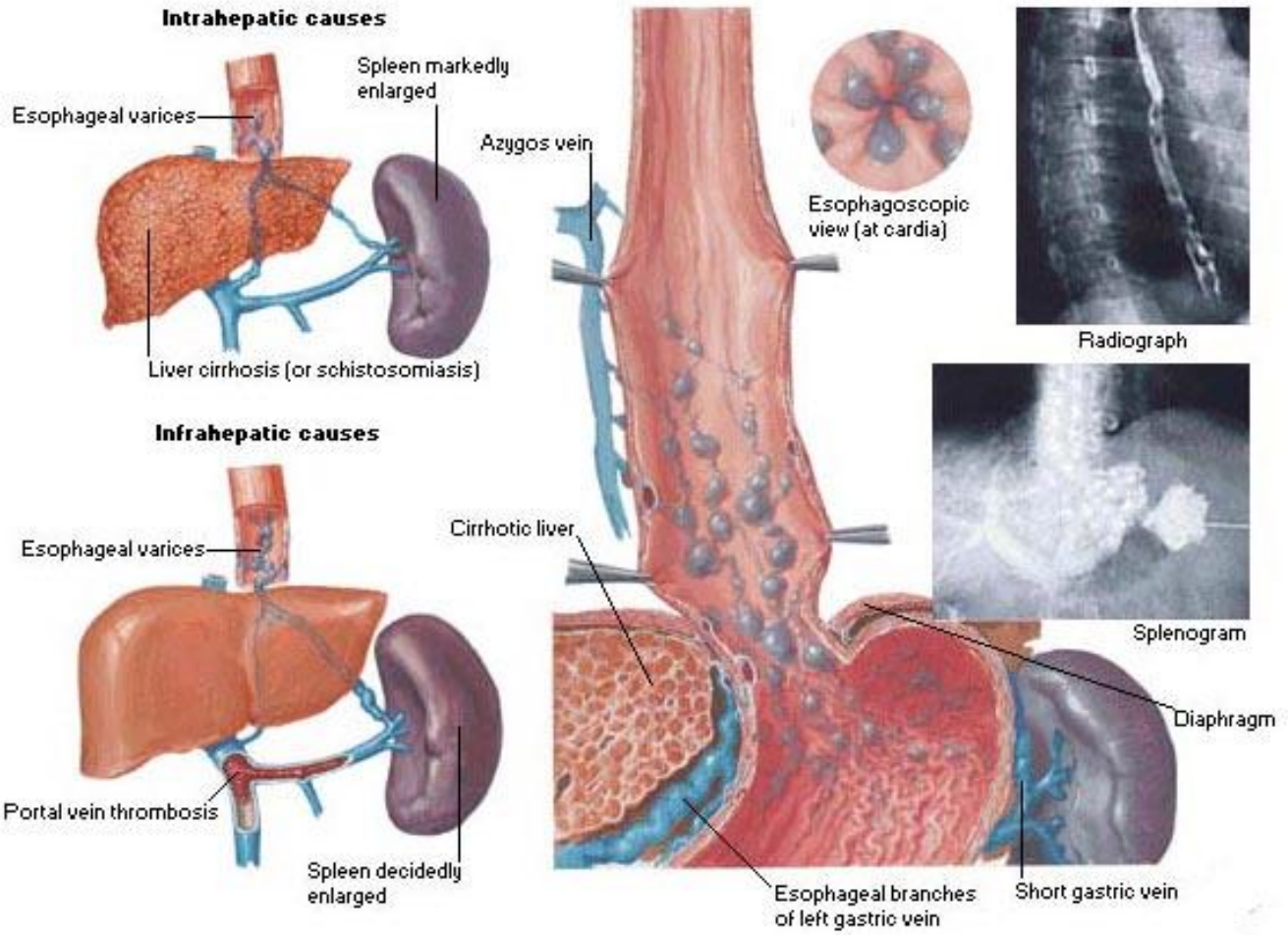






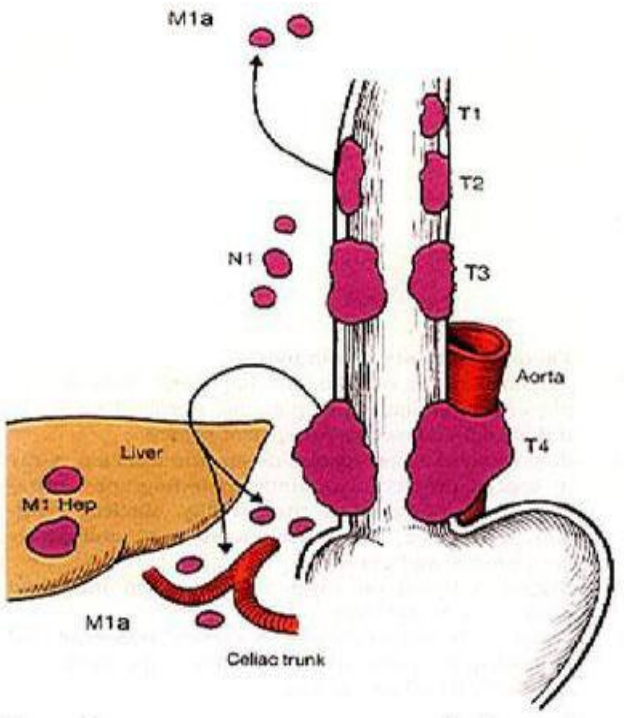
Oesophageal varices

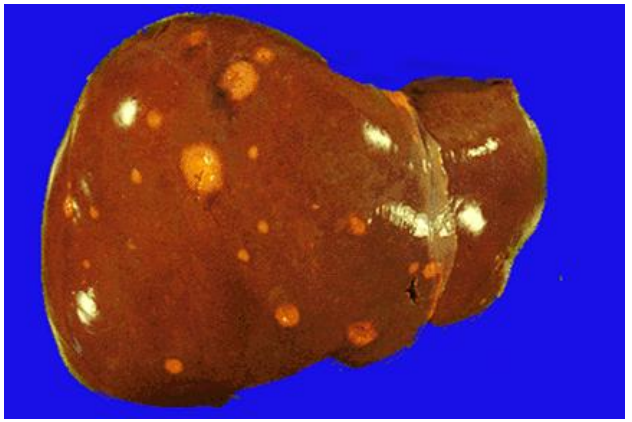
- due to portal hypertension (increased pressure in v. portae)
  - pre-hepatic (congestive heart failure)
  - hepatic (liver cirrhosis)
  - post-hepatic (thrombosis of v. portae)
- blood circumvents liver and enters the syst. circulation (lower v. cava) via
- portocaval anastomoses
- risk of bleeding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



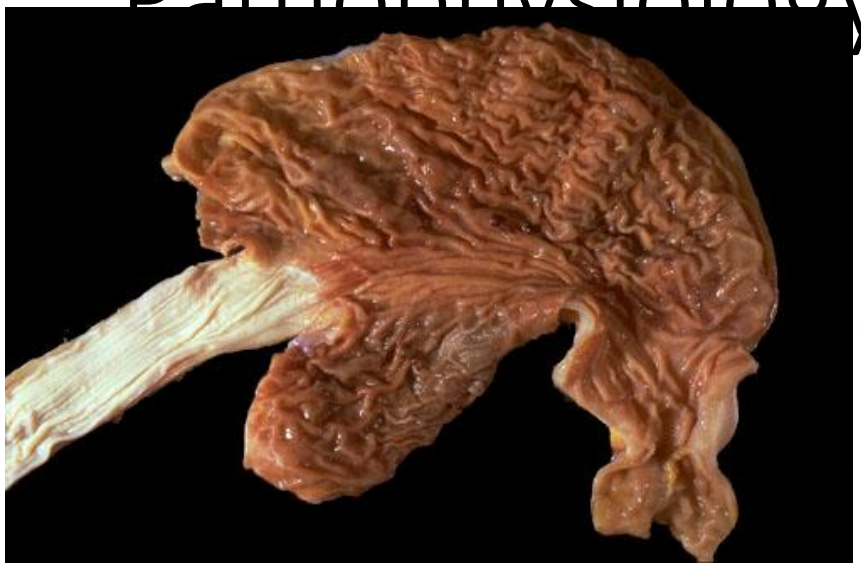
Tumours of oesophagus

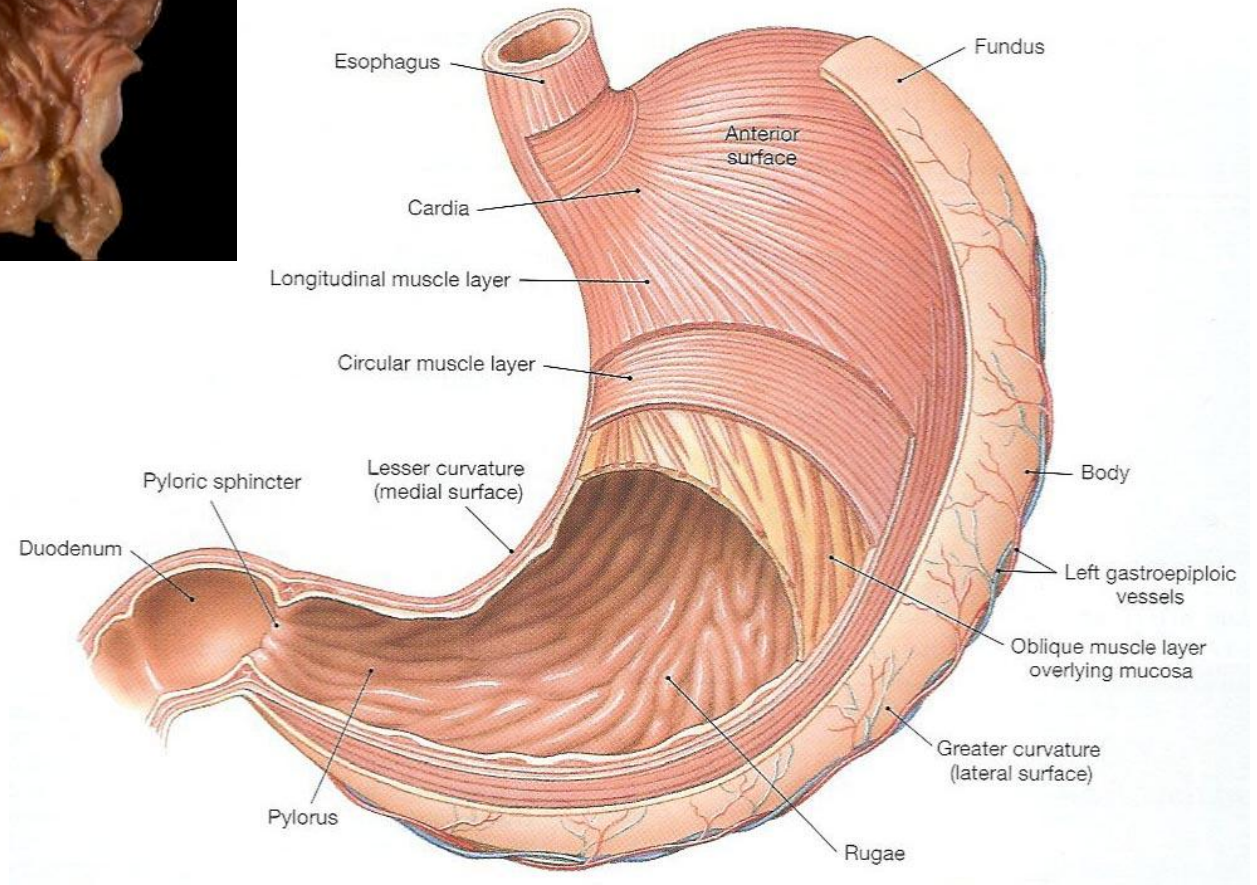
- benign
  - leiomyoma
  - fibroma
  - haemangioma
- malignant
  - adenocarcinoma
    - late complication of chron. GER!!!
    - males > females
    - only 10% of patients survives 5 yrs after diagnosis
  - Spinocellular carcinoma



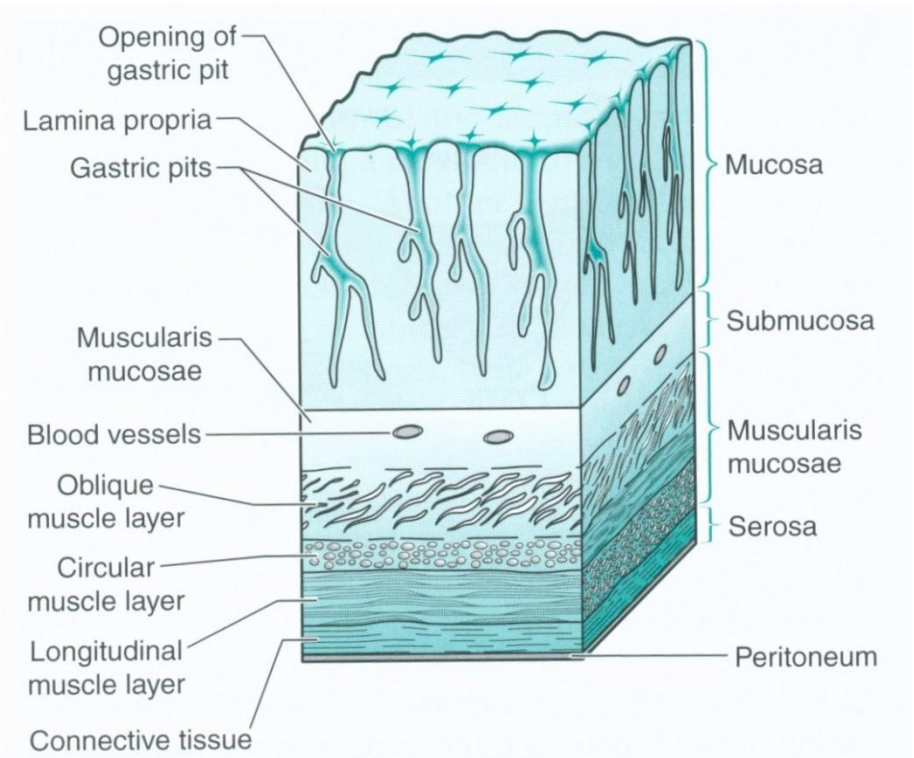


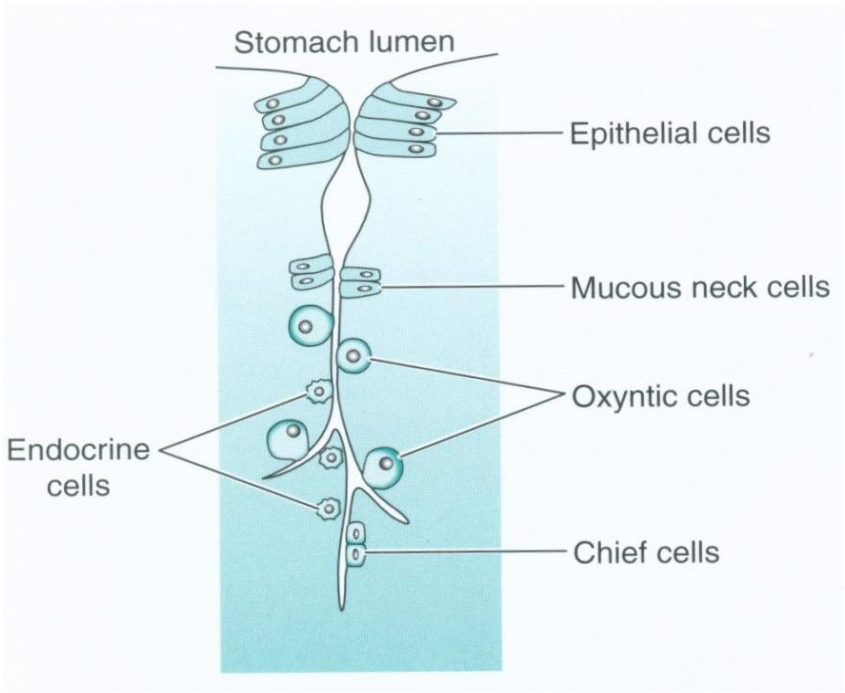
Pathophysiology of stomach

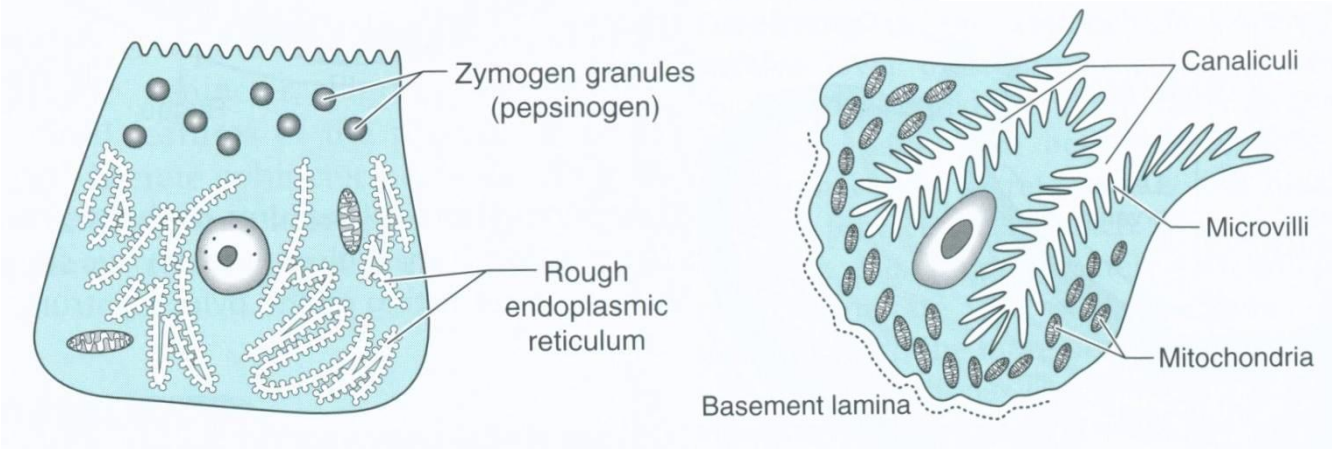


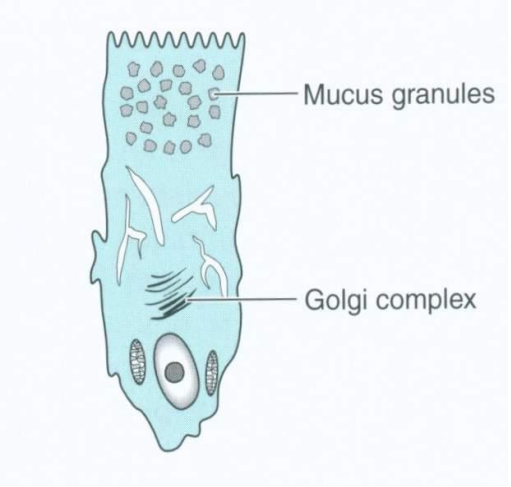


Gastric mucosa and glands



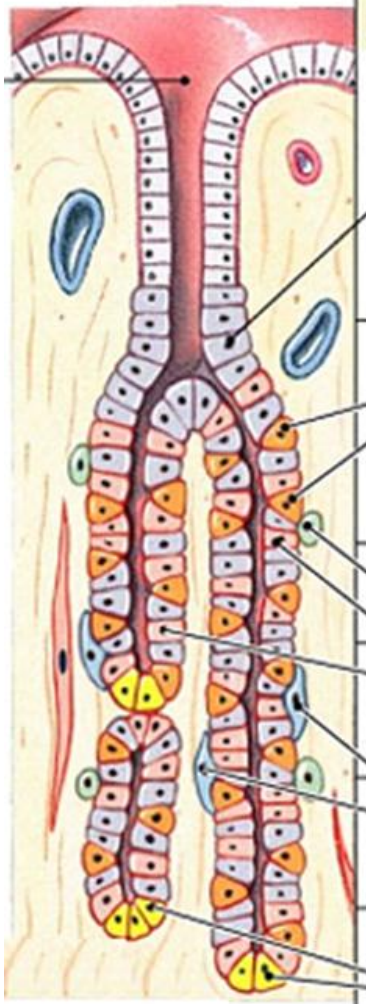






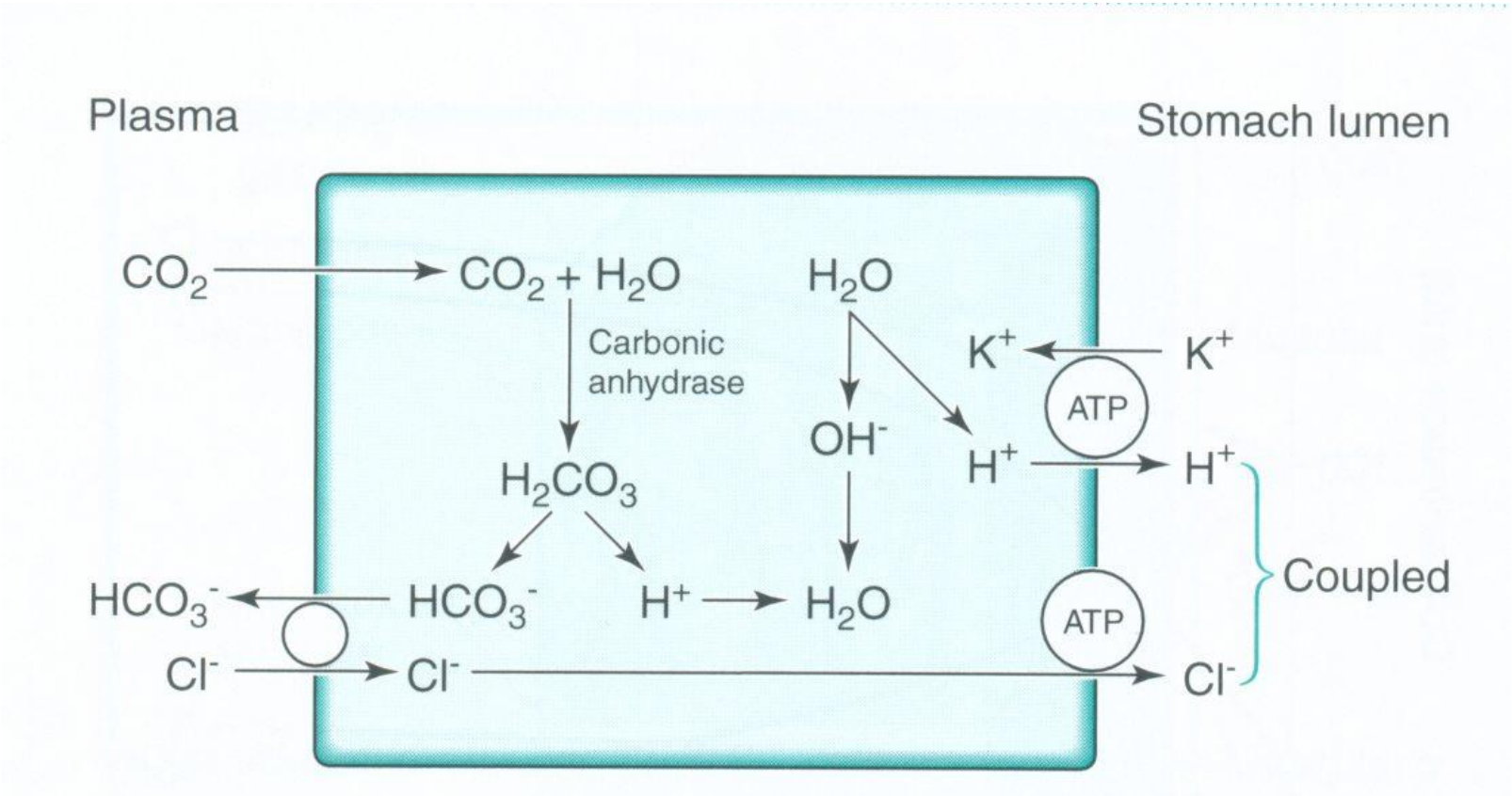
Function of stomach

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

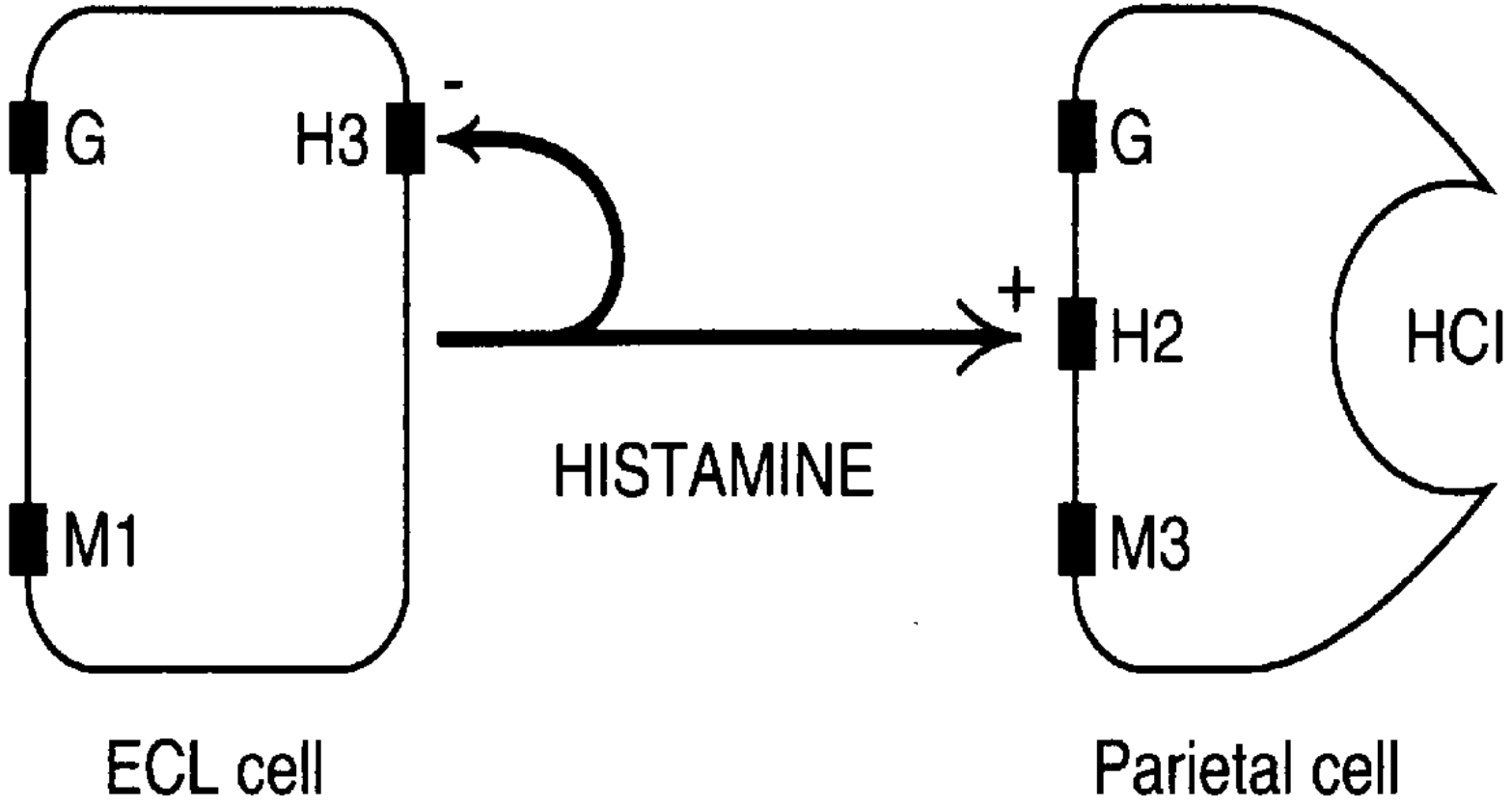


Cell Types	Substance Secreted
Mucous neck cell	Mucus (protects lining)
	Bicarbonate
Parietal cells	Gastric acid (HCl)
	Intrinsic factor (Ca++ absorption)
Enterochromaffin-like cell	Histamine (stimulates acid)
Chief cells	Pepsin(ogen)
	Gastric lipase
D cells	Somatostatin (inhibits acid)
G cells	Gastrin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

Principle of HCl secretion

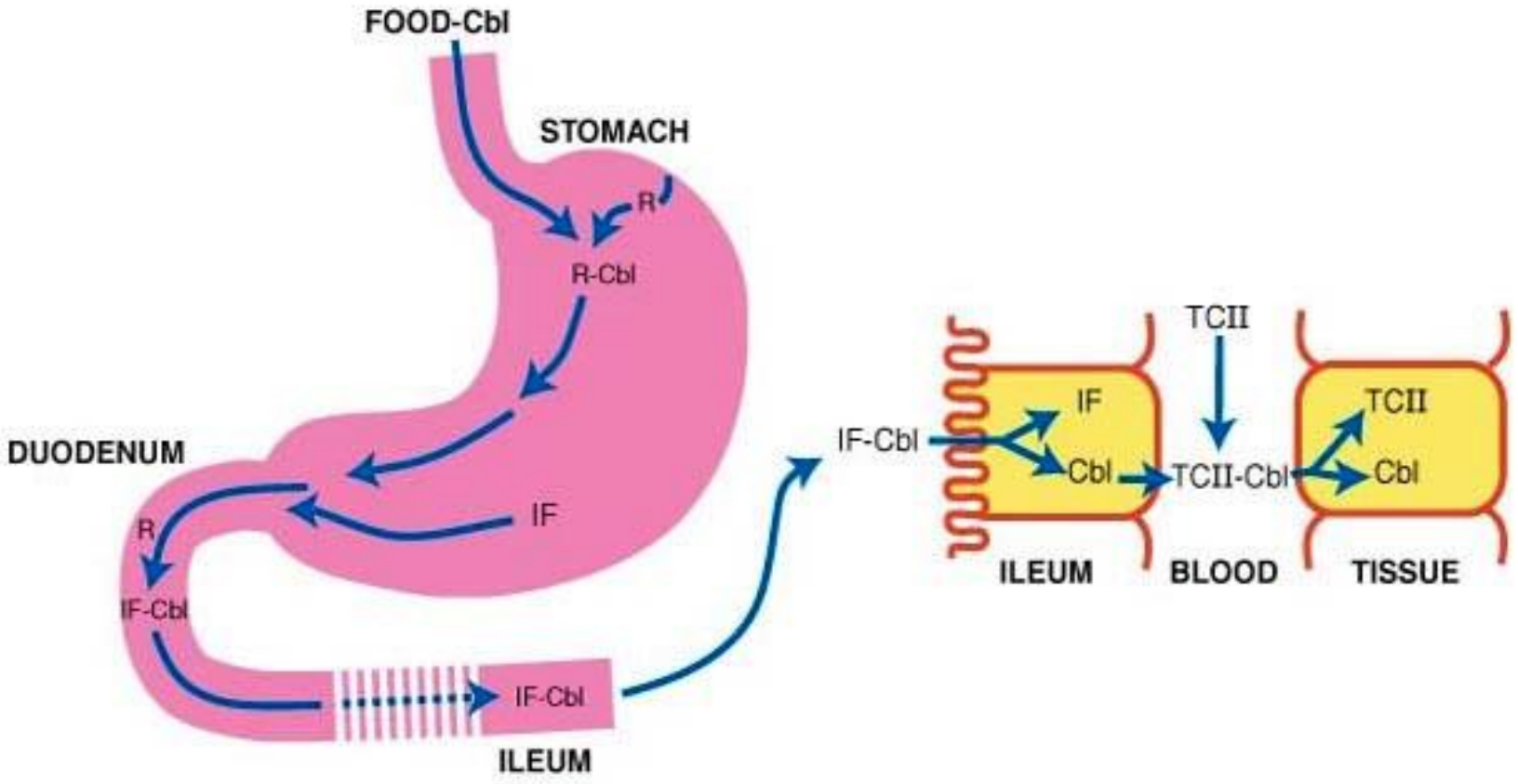


Regulation of HCl secretion



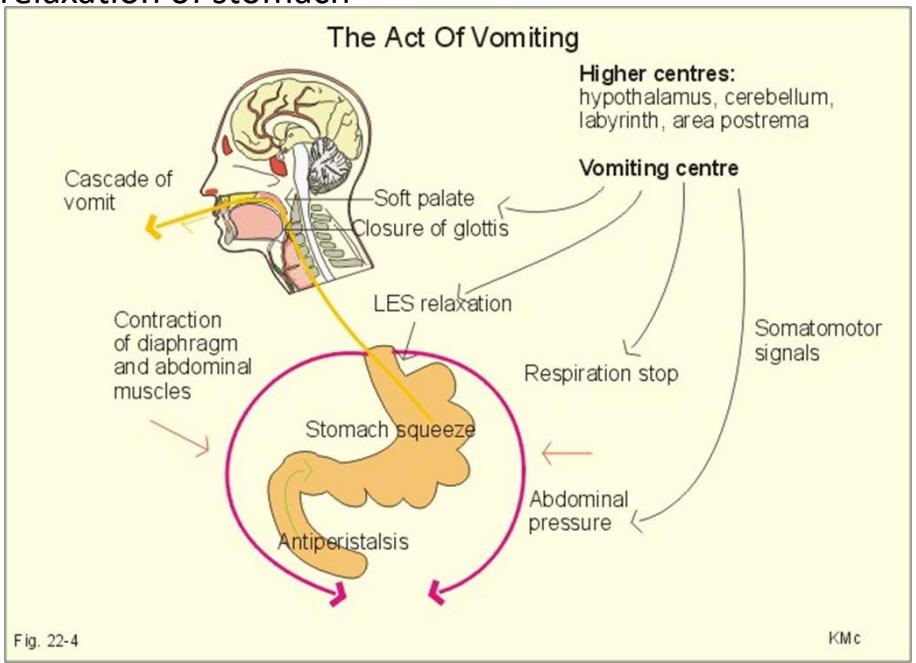
Resorption of B_{12}

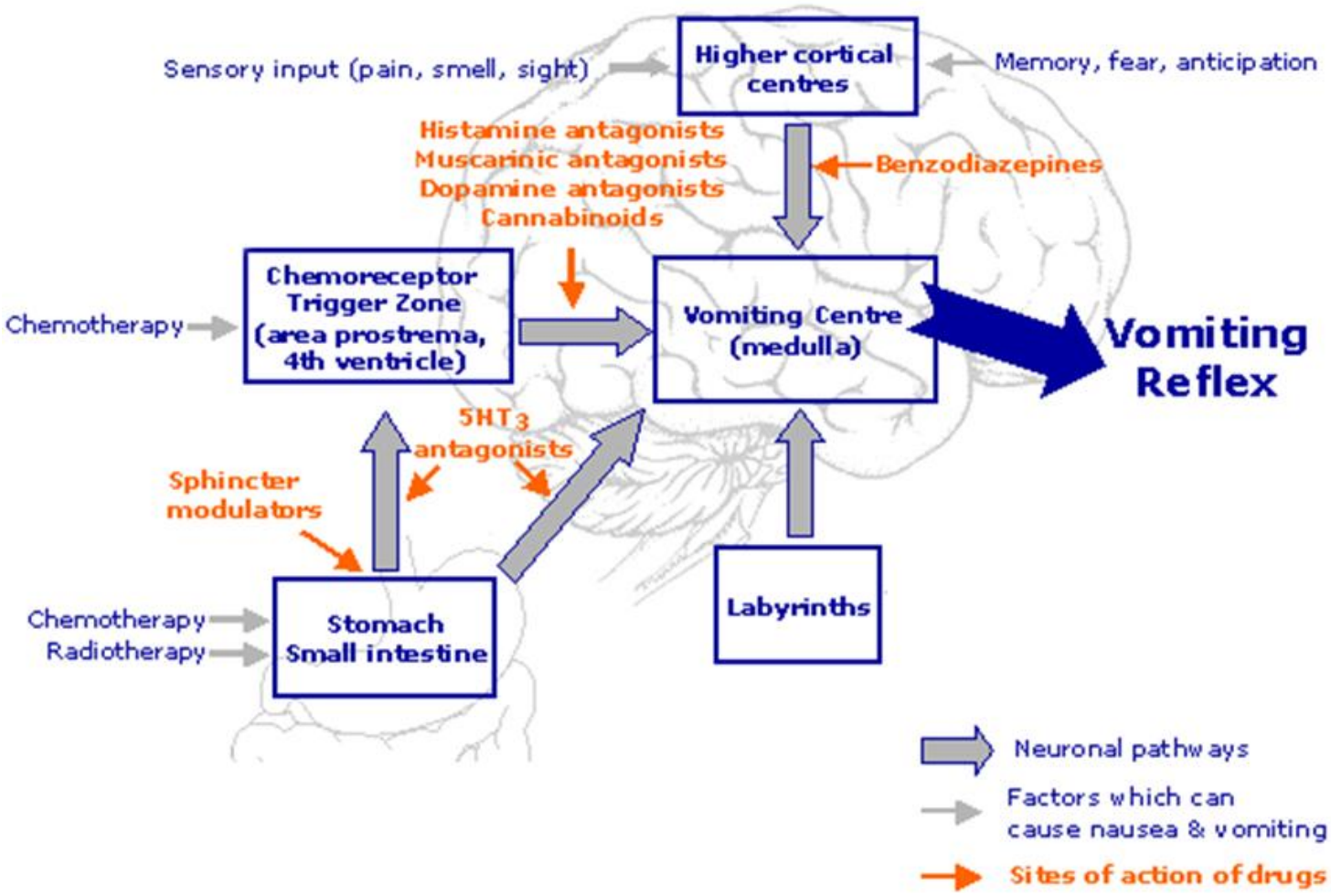
- stomach: binding to R factor (non-specific carrier protecting it from acid)
- duodenum: IF
- ileum (inside epithelia): transcobalamin (circulating)



Disorders of gastric motility

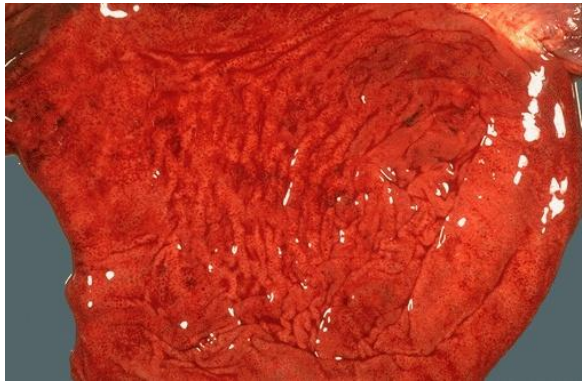
- vomiting reflex (emesis)
  - reflex act leading to expulsion of gastric content by mouth
- initiated from emetic centre in reticular formation in oblongate medulla
  - in proximity of respiratory and vasomotor and salivation centres
    - therefore increased heart frequency and salivation
- act of 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 naopak 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

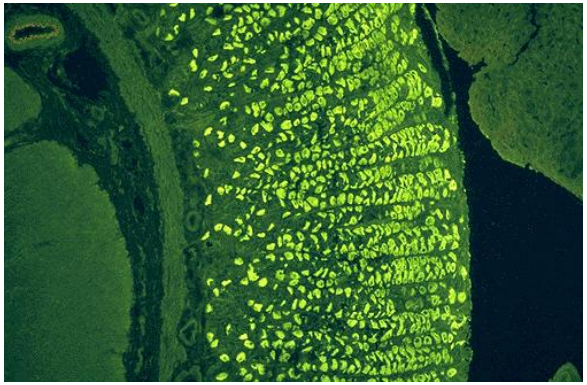


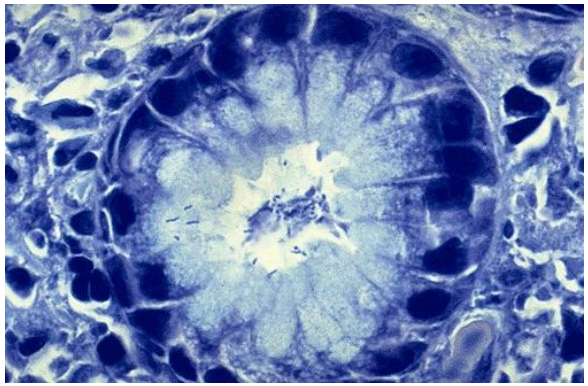

Sensory input (pain, smell, sight)
Higher cortical centres
Memory, fear, anticipation
Histamine antagonists
Muscarinic antagonists
Dopamine antagonists
Cannabinoids
Benzodiazepines
Chemoreceptor Trigger Zone (area prostrema, 4th ventricle)
Chemotherapy
Vomiting Centre (medulla)
Vomiting Reflex
5HT3 antagonists
Sphincter modulators
Chemotherapy
Radiotherapy
Stomach Small intestine
Labyrinths
Neuronal pathways
Factors which can cause nausea & vomiting
Sites of action of drugs

Gastritis

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

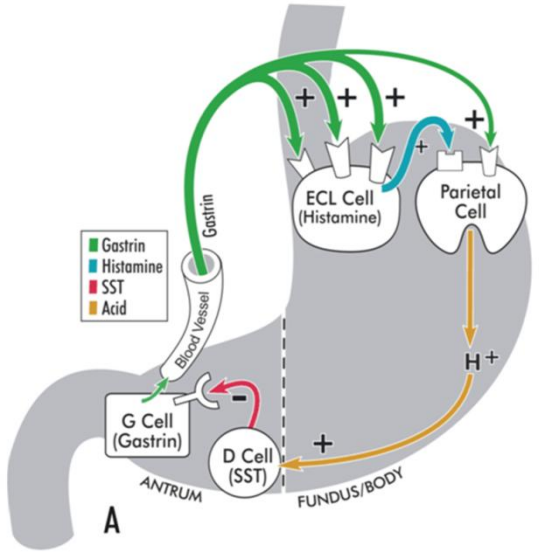


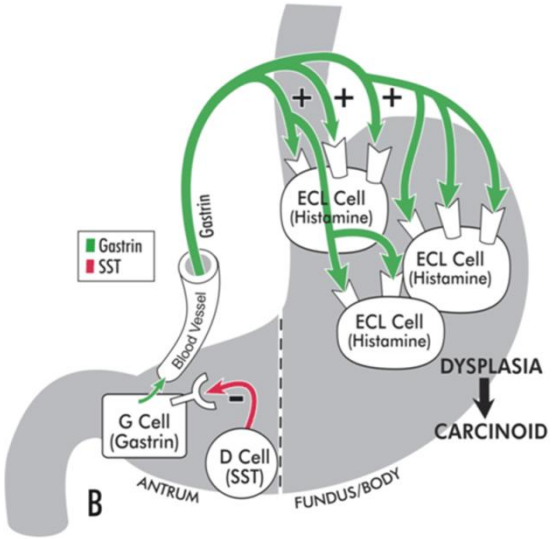




Atrophic gastritis prekancerosis

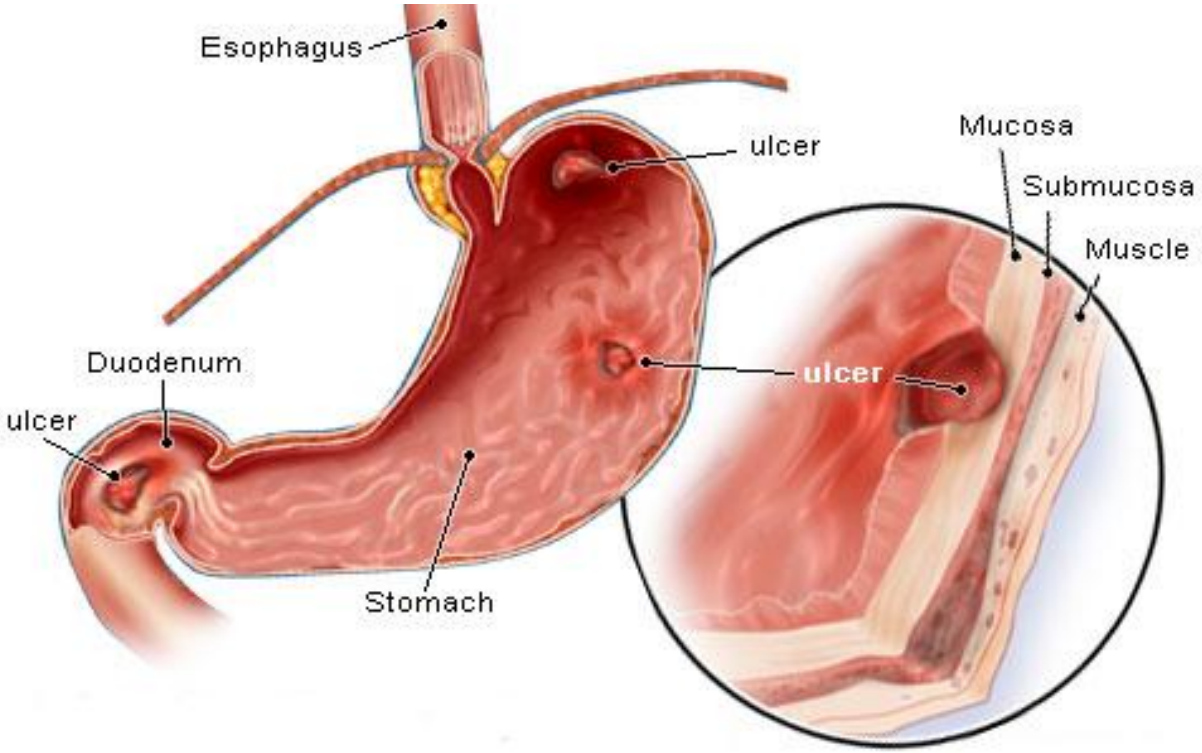
- destruction of mainly parietal cells by cytotoxic T-lymphocytes
  - compensatory ↑ gastrin
- antibodies against
  - intrinsic factor (IF) and complexes IF/B12
  - Na/K-ATPase
  - carbonic anhydrase
  - gastrin receptor
- consequences
  - achlorhydria leading to sideropenic anaemia
  - later megaloblastic (pernicious) anaemia
  - precancerosis





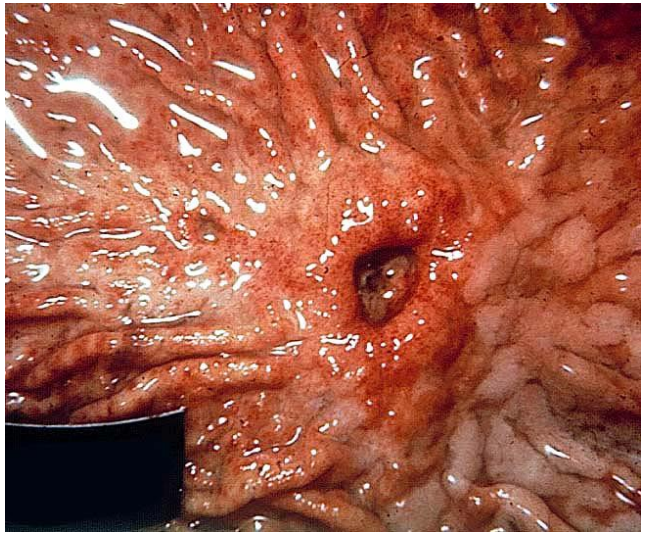
Peptic disease of gastroduodenum

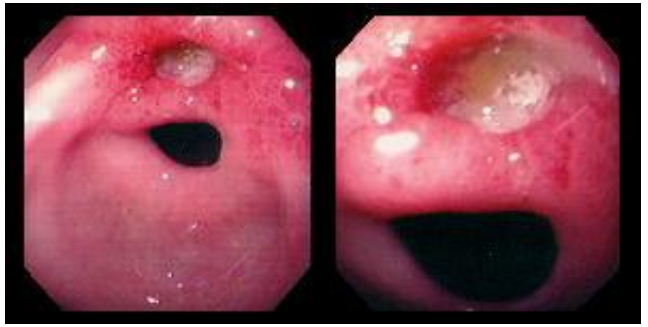
- historically hyperacidity was the main etiologic factor blamed
  - but the true hyperacidity is present only in few cases (stress ulcer and gastrinoma)
- disease is always a consequence of dysbalance between aggressive and protective factors
  - localization in dist. part of oesophagus, stomach, duodenum and prox. part of jejunum
- aggressive factors
  - HCl
  - pepsin
  - bile
  - alcohol, nicotine, caffeine
  - *Helicobacter pylori*
  - accelerated emptying of stomach
- protective factors
  - mucous
  - bicarbonate
  - adequate blood supply
  - prostaglandins
- extent/severity
  - ulcer = mucosal defect penetrating muscularis mucosae
  - erosion = defect limited only to mucous
- complications of pept. ulcer
  - bleeding
  - perforation
  - penetration
  - stricture

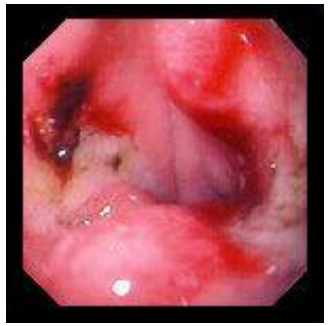


Ulcerogenic factors

- (A) hyperacidity
  - habitually increased secretion of parietal cells
    - ↑ basal secretion
    - ↑ number
    - ↑ sensitivity to histamine or gastrin
  - gastrinoma (Zollinger-Ellison syndrome)
    - tumour from D-cells of pancreas
      - secretion of gastrin by D-cells is normally minimal
  - chronic gastritis type B – infection by H. pylori
    - in ~75% patients with gastric ulcer
    - in ~ 90% patients with duodenal ulcer
    - in ~ 50% patients with dyspepsia
    - in ~ 20% healthy
- (B) loss of barrier function of stomach
  - ↑ pepsin (in ~50% cases) → increased permeability of mucosa → retrograde diffusion of H^+ ions
  - impaired trophic
  - stress – low perfusion
  - drugs
    - NSAID (eg aspirin)
      - inhibitors of cyklooxygenase
    - corticoids
      - inhibitors of phospholipase A

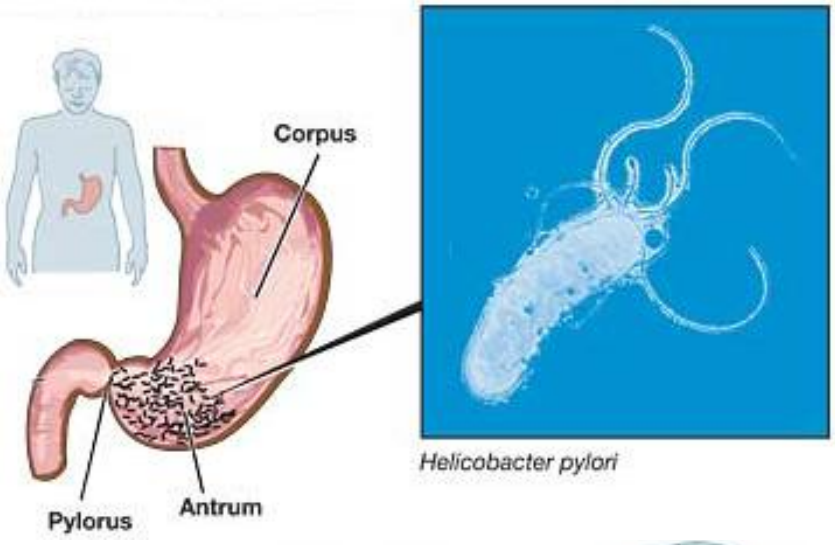


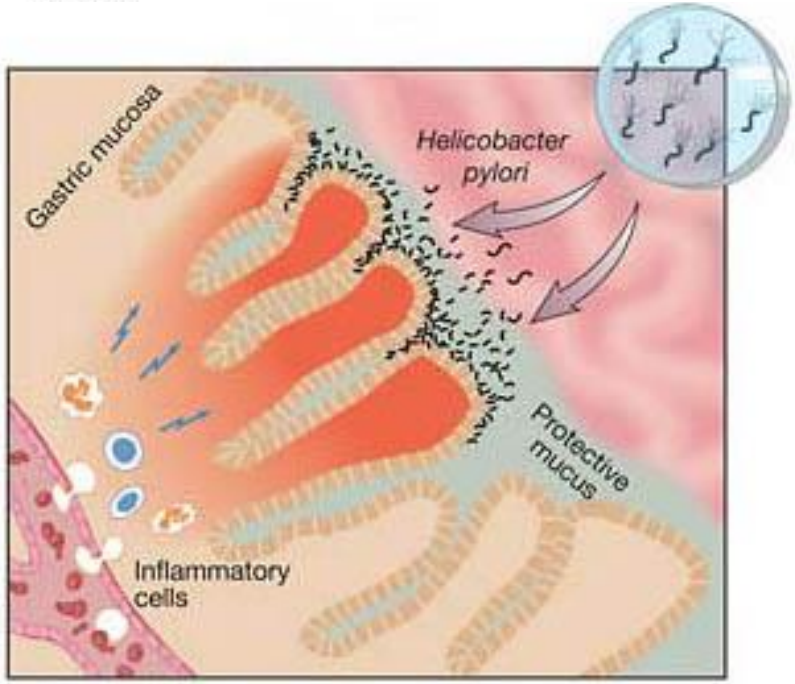




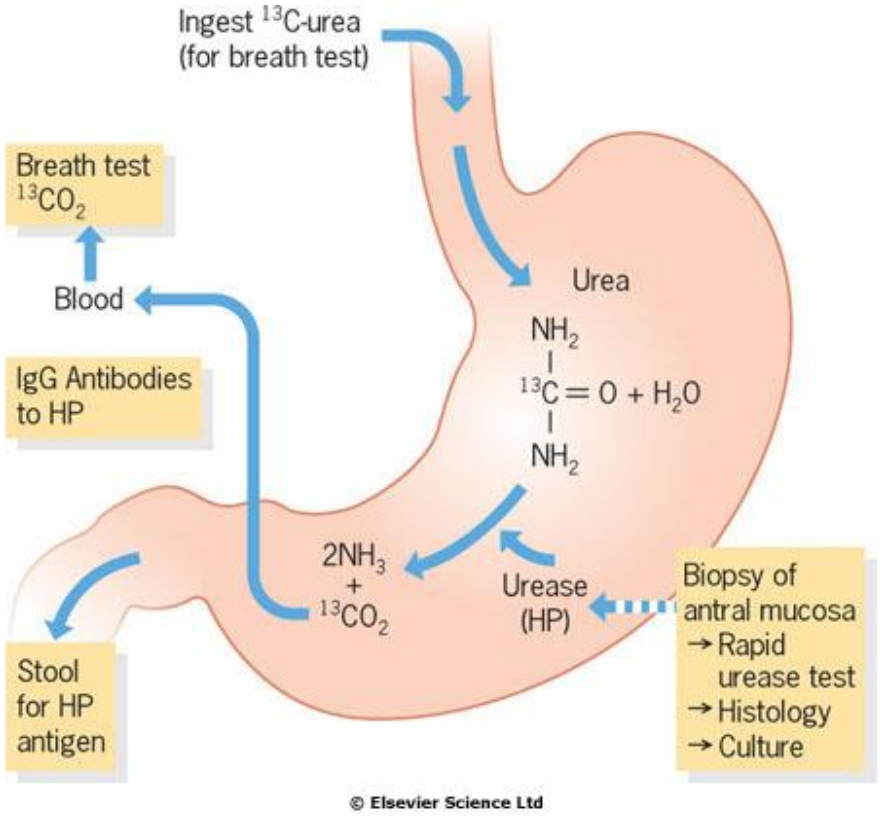
Helicobacter pylori

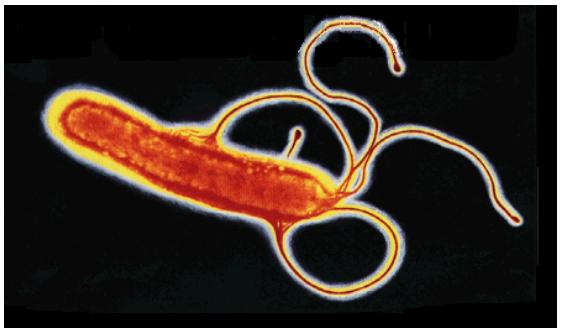
- successful human microbial pathogen
  - infects 50% of population
- induces chron. gastritis B-type, peptic ulcers and contributes likely to the development of gastric carcinoma
- localization mainly in antral part and duodenum
- mechanisms of action and resistance to acid environment
  - encapsulated flagellum enables *H. pylori* to move quickly in acidic surface and penetrate to the deeper layers (higher pH)
  - produces urease (and thus NH_3) = local neutralization of HCl
  - produces protein stimulating production of gastrin = ↑ HCl
  - activates proton pump
  - produces proteases and phospholipases = destruction of mucus
  - produces catalase = resistance to phagocytosis
- do not penetrate through epithelium → minimal or none systemic immune reaction
  - IgA antibodies
- infiltration by neutrophils





Detection of H. pylori





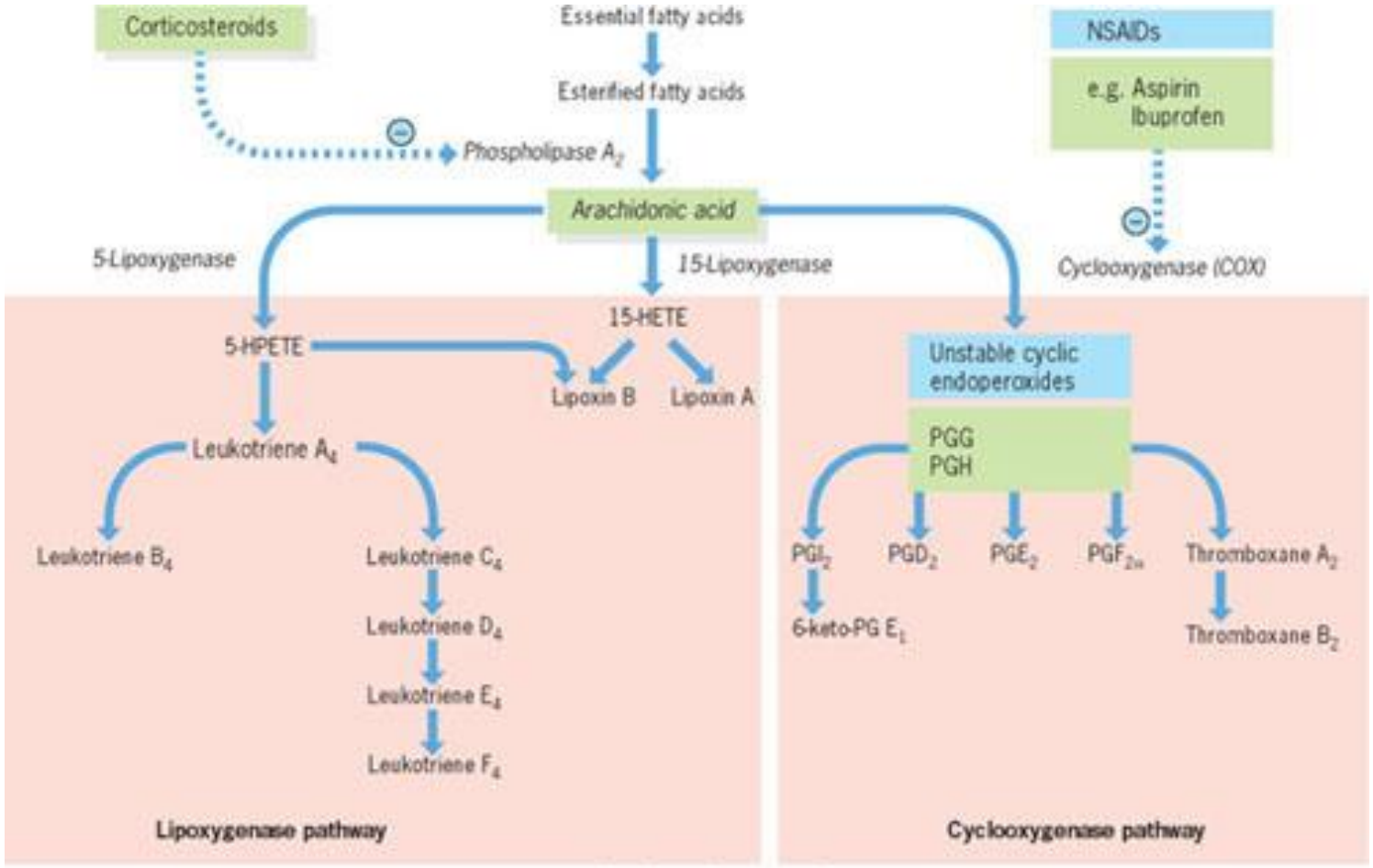
- invasive – by biopsy during gastroscopy
  - light microscopy
  - PCR
  - cultivation
  - intravital microscopy
- non-invasive
  - aspiration of gastric juice by nasogastric tube with subsequent PCR
  - PCR from stool
  - breath test

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 after meal

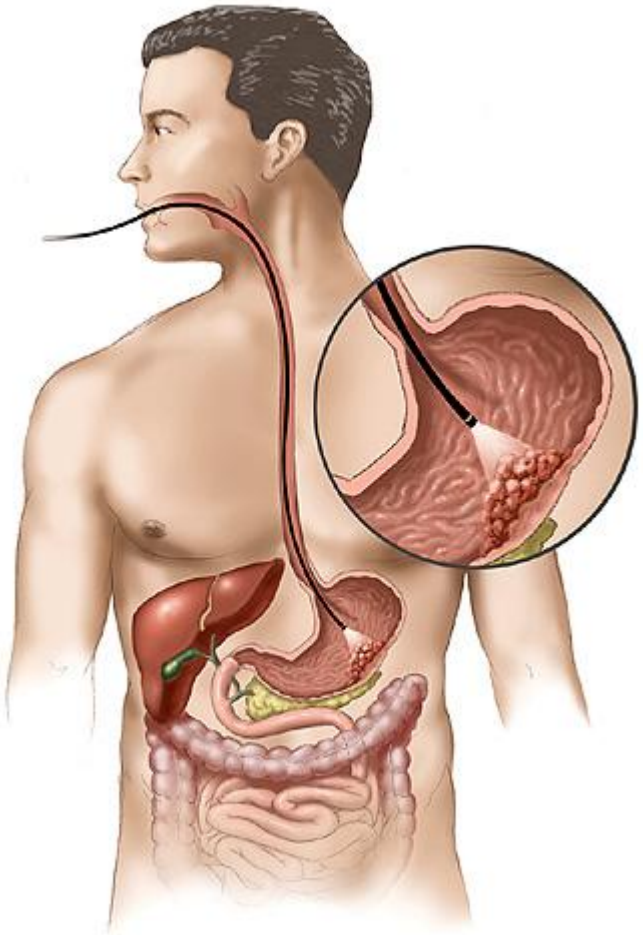
- duodenum
  - protection of duodenum weak
    - Brunner's glands secreting alkalic mucus
    - coordinated peristaltics mixing gastric content with pancreatic and biliary juices which then acidic content
  - etiologically more often hyperacidity and infection by H. pylori
  - genetic effects
    - often blood group 0
    - HLA-B5
  - younger people
  - painful in a fasting state, relieved by meal
    - patients often put on weight
  - neurotics (faster gastric motility)
  - seasonal manifestion

Ulcerogenic drugs

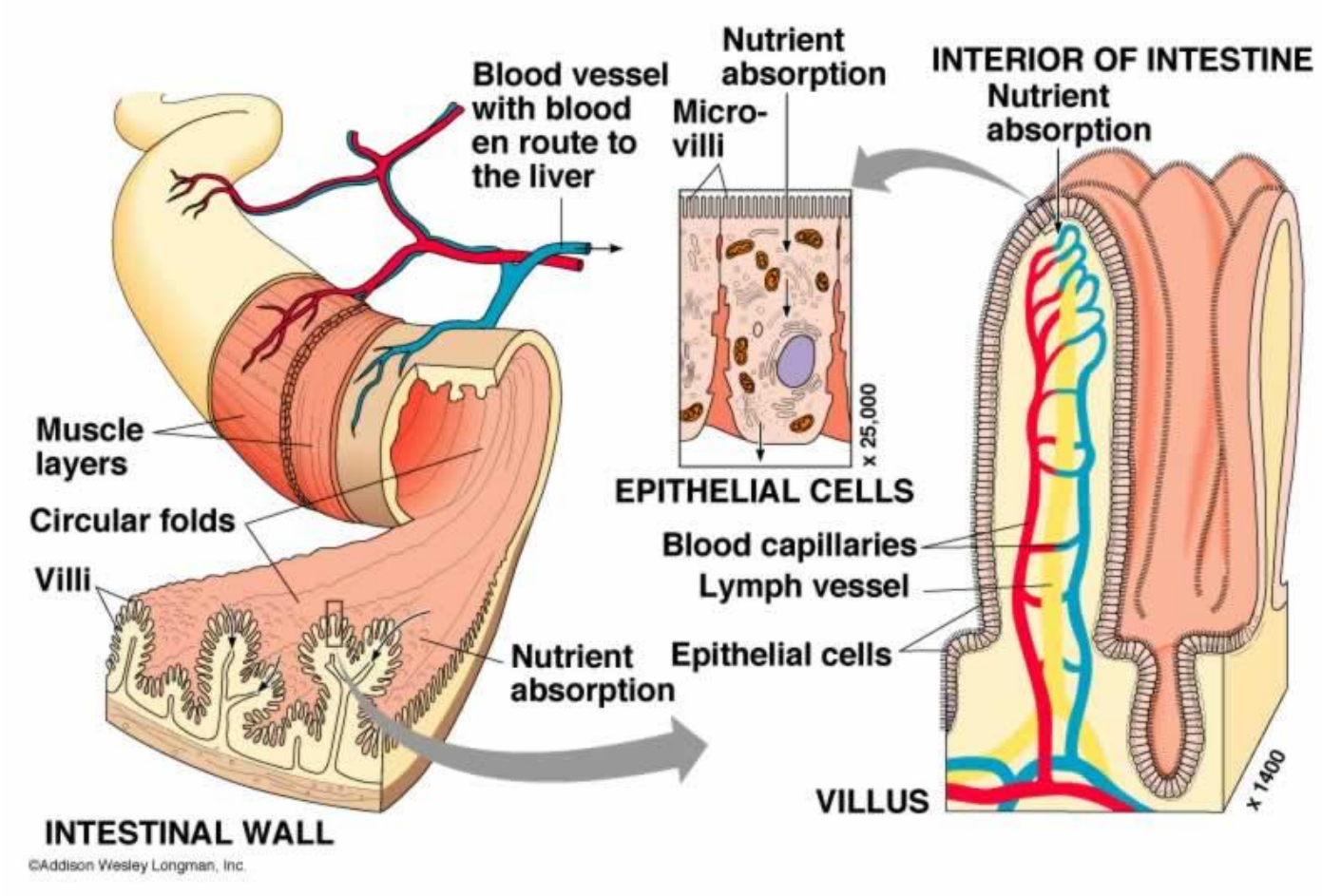


Tumours

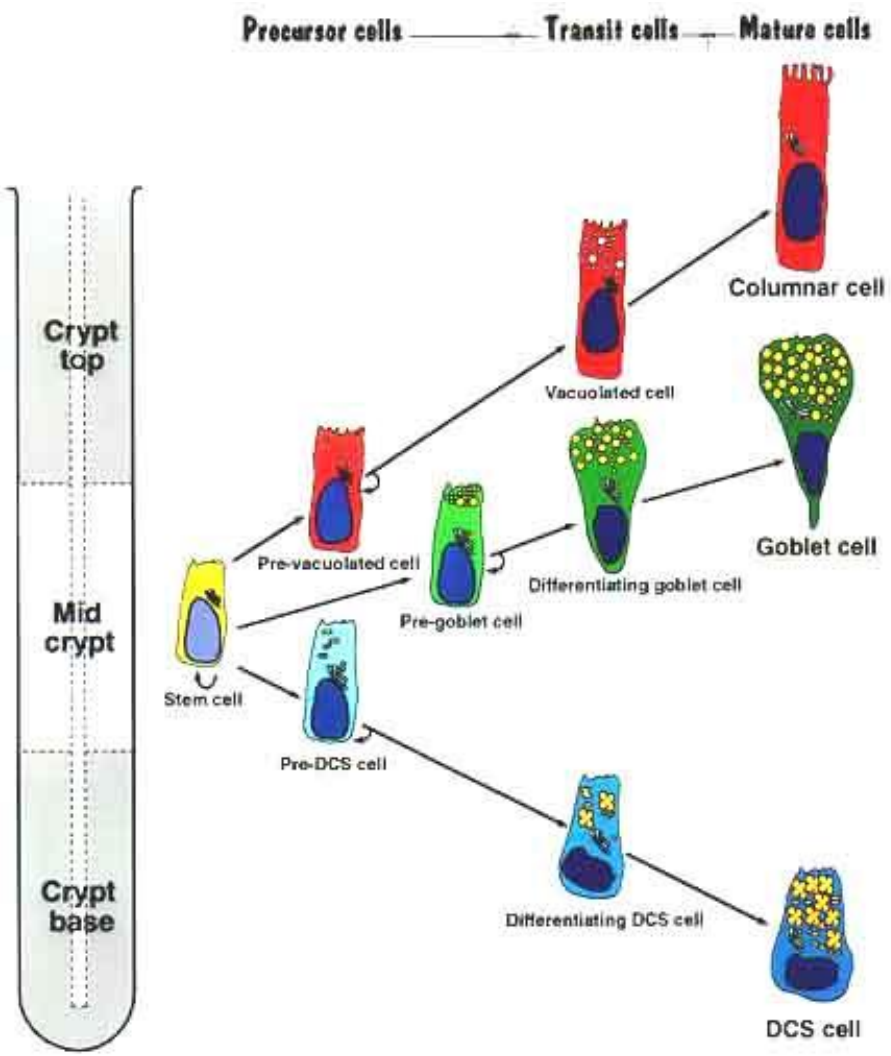
- benign
  - rare
- malign
  - lymphoma
    - also in small and large intestine
  - carcinoid
    - also in intestine, pancreas, bronchi and lungs
  - carcinoma
    - bordered × diffuse
    - aetiology
      - nutrition!
        - nitrates (conservation) → nitrits → nitrosamines (= mutagens)
        - carcinogens from smoked meat
        - lack of fiber (delayed emptying, longer contact of mutagens with gastric wall)
        - aphlatoxins
      - smoking
      - H. pylori/atrophic gastritis



Small intestine

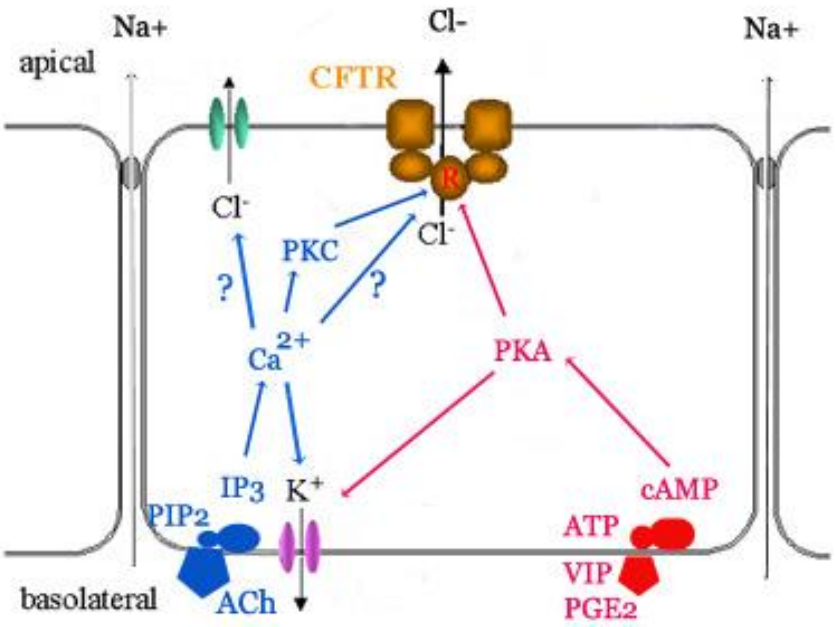


Physiology of small intestine



- cells of small intestine
  - enterocytes – enzyme digestion and resorption
  - goblet cells – production of mucus
  - Paneth (granular) cells – immune defense
  - APUD cells – production of hormones
- blood supply (~10% cardiac output) from a. mesenterica sup.
- functions
  - digestion and resorption – large area
    - total length 4.5–6m (large functional reserve - approx. 1/3 sufficient)
    - further increased by villi
  - immunity
    - by far the largest immune organ!!
    - Peyer's plaques + dispersed immune cells
    - non-specific: lysozyme, defensins, HCl, bile, mucous
    - specific: lymphocytes, IgA
  - motoric – peristaltics, segm. contractions
    - stimulated by: gastrin, CCK, motilin, serotonin, inzulin
    - inhibice: glukagon, sekretin, adrenalin
  - secretion
    - intestinal juice: water, NaCl, HCO_3^-, mucous, enzymes (carboxypeptidases, intest. lipase, disacharidases, maltase, lactase, izomaltase …)

Intestinal secretion and absorption



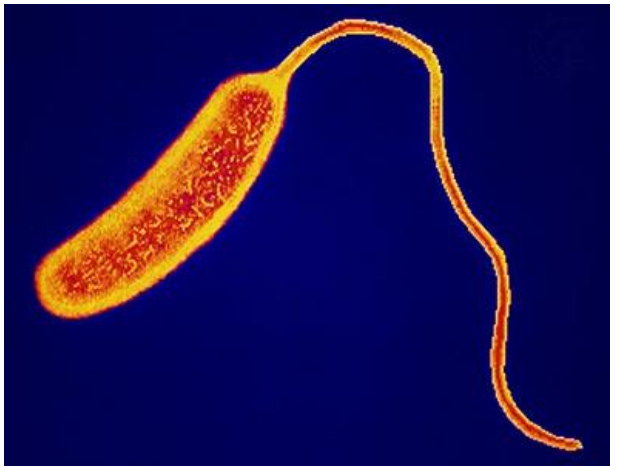
- enterocytes in in jejunum and ileum produce alkalic fluid
  - water
  - electrolytes
  - mucous
- control of secretion
  - hormones
  - drugs
  - toxins (e.g. cholera, dysentery, E. coli)
- types of intest. absorption
  - passive diffusion (conc. gradient)
    - aqueous pores (e.g. urea, some monosaccharides)
    - transmembrane (e.g. ethanol, FFA)
    - via tight junctions (e.g. ions, water)
  - carriers
    - ions, Glc, AA
  - active transport on the basolateral membrane
    - Na/K ATPase produces conc. gradients for secondary active transports

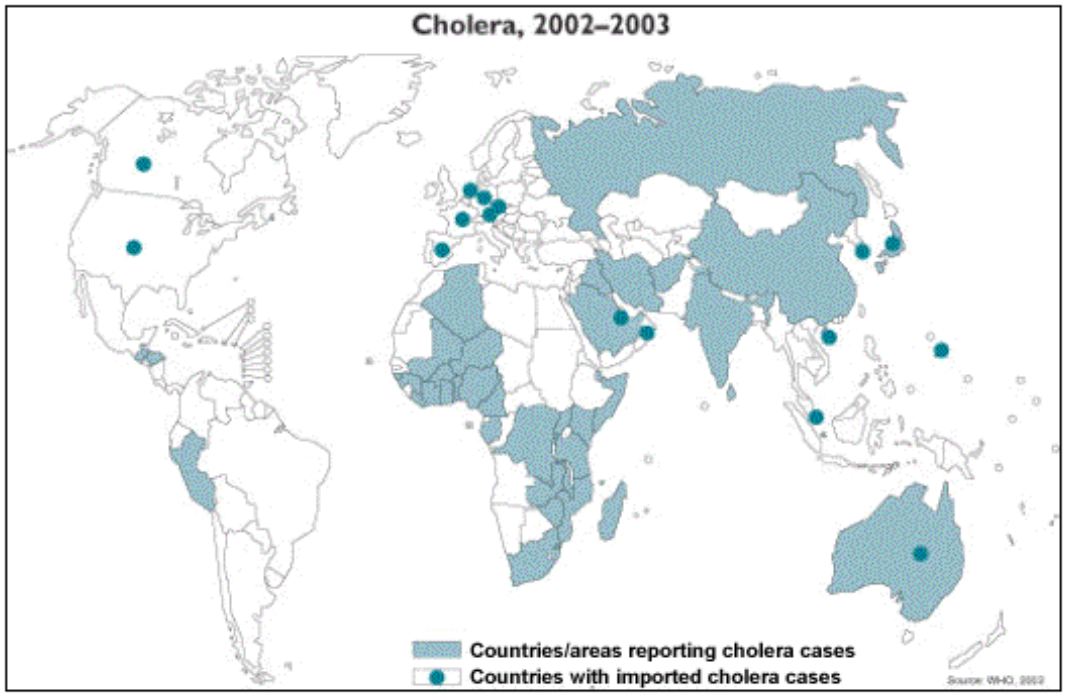
Disorders of intestinal secretion and absorption = diarrhea

- diarrhea = more frequent expulsion of stools (>3×/day), often more liquid consistence → loss of fluid
- due to imbalance between 3 main factors – secretion, resorption and motility
  - acute
    - infection
    - dietary error
    - alimentary intoxication
  - chronic
    - malabsorption (inflammatory bowel disease (Crohn disease, ulcerative colitis), chron. pancreatitis, liver and biliary diseases)
    - colorectal carcinoma
    - neurogenic
    - metabolic (uremia, hyperthyreosis, adrenal insufficiency)
- etiology
  - infection, toxins, diet, neuropsychological (anxiety)
- pathogeneses
  - ↑ osmotic pressure (and thus water) in intest. lumen = **osmotic**
    - typically when large amount of undigested nutrients stays in lumen
      - malabsorption syndrome (pancreatic insufficiency, biliary, disacharidaae deficiency – e.g. lactase)
      - ingestion (overdose) of salts (Mg, sulfates), antacids
      - bacterial overgrowth, resection, obstruction of lymphatics
  - ↑ secretion of Cl (and thus water) into lumen = **secretory**
      - bacterial enterotoxins (Vibrio cholerae, Shigella dysenteriae, E. coli, Clostridium difficile, Salmonella typhi)
      - inflammatory exudation (Crohn d., ulcerative colitis)
  - **hypemotility**
      - some regulatory peptides (VIP, serotonin, PGE)

Cholera

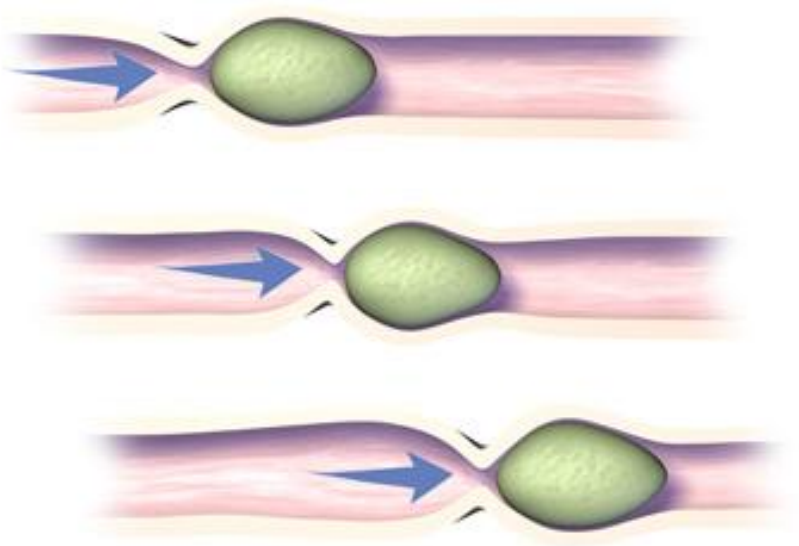
- Vibrio cholerae
  - produces toxin binding to monosialoganglioside receptor on the luminal membrane of enterocytes
  - activation of cAMP signaling cascade and CFTR channel
  - secretion of Cl and Na (and thus water) into the intest. lumen
    - production of up to 20l of fluid daily
- transmission by contaminated water (rivers, wells, lakes) and food
- V. cholerae carriers
  - in gallbladder
  - ~5% population in endemic areas





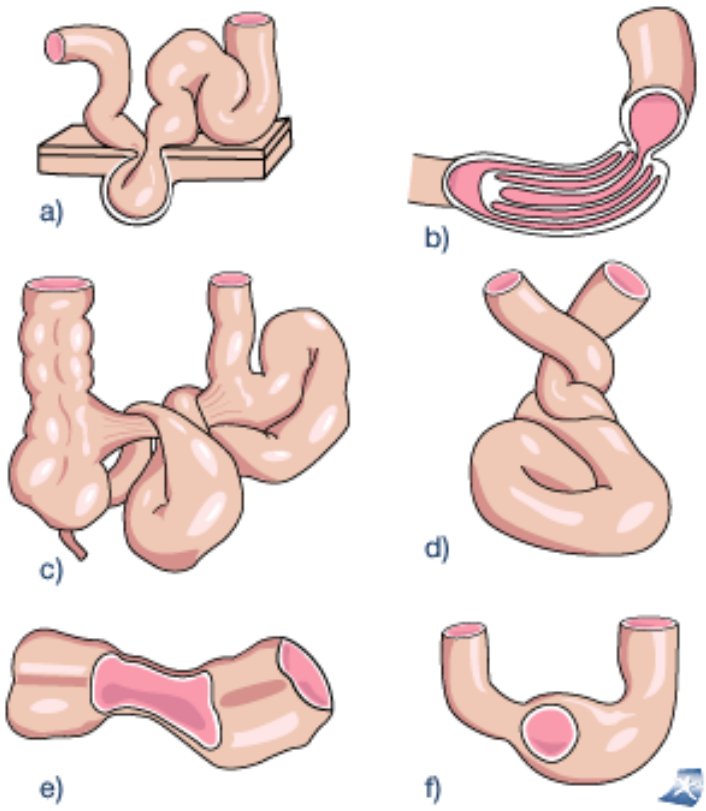
Intest. motility disorders

- **peristaltics =** coordinated contraction of muscular layers
  - necessary for mixing of lumen content with pancreatic juice and bile and aboral movement of digested content
- disorders
  - hypomotility (extreme form = ileus)
  - hypermotility
- drugs affecting intest. motility
  - purposefully – laxatives (secretory, osmotic, emolients, fiber) x prokinetics
  - side effects – opiates, sympatomimetics, anticholinergics, …

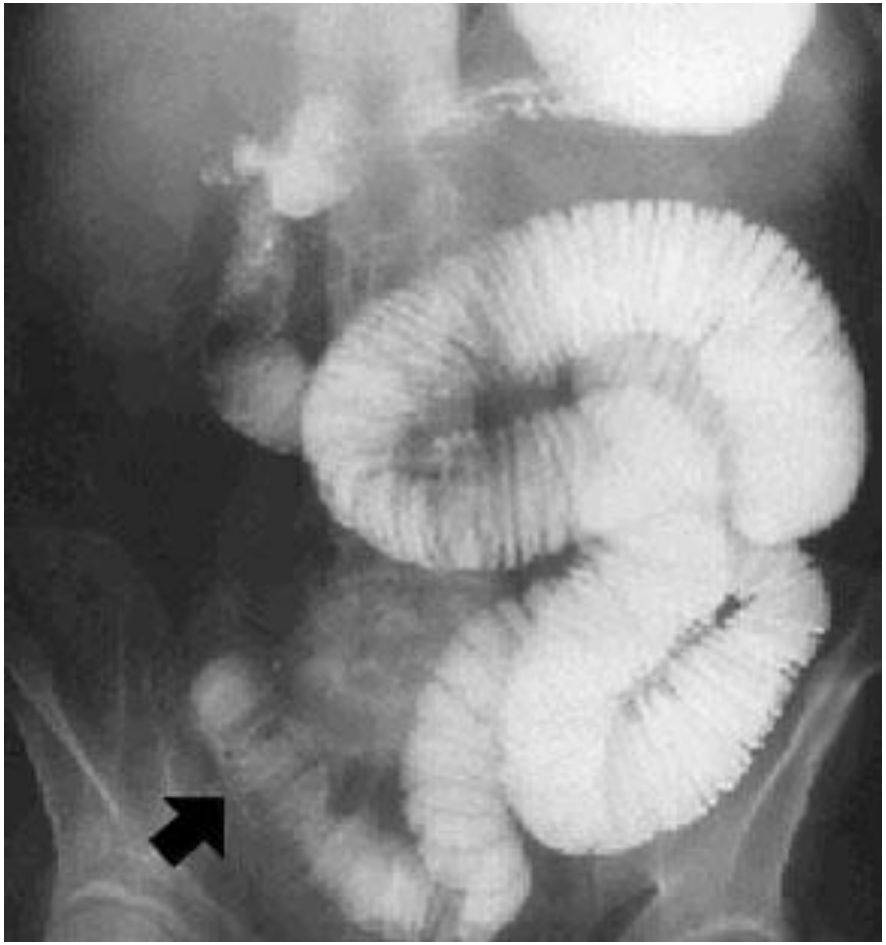


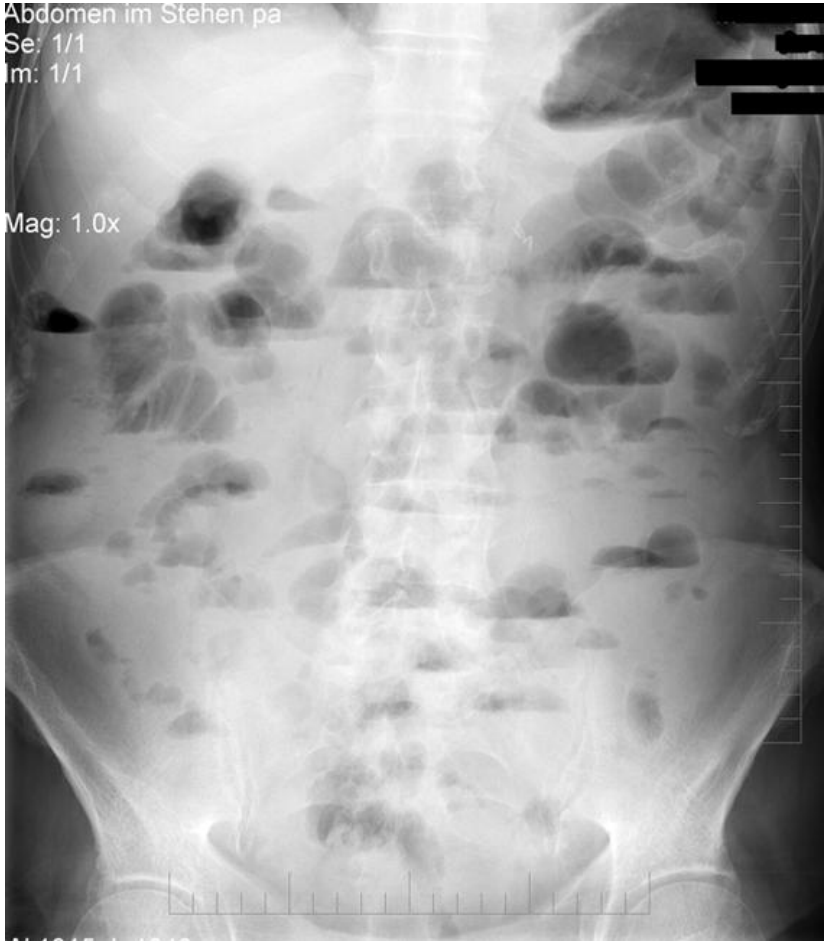
Ileus

- block of intestinal passage
  - **mechanic** = due to the external or internal obstruction
    - intraluminal: obstruction by tumor (e), bile stones (f), strictures, inflammation
    - extraluminal: adhesions, compression, herniation (a), invagination (b), strangulation (c), volvulus (d)
  - **paralytic** or **spastic** = ↓ motility
    - postoperative
    - acute pancreatitis
    - pain (colic, trauma, myocardial infarction)
    - peritonitis
    - hypokalemia
- at first peristaltics increased as an attempt to overcome the block
- water, gases and content stagnate above the block
- distension of intestine, hypoperfusion and later necrosis of the wall
- if not quickly surgically solved then lethal – dehydration, ion dysbalance and toxemia (bacteria from lumen into circulation)



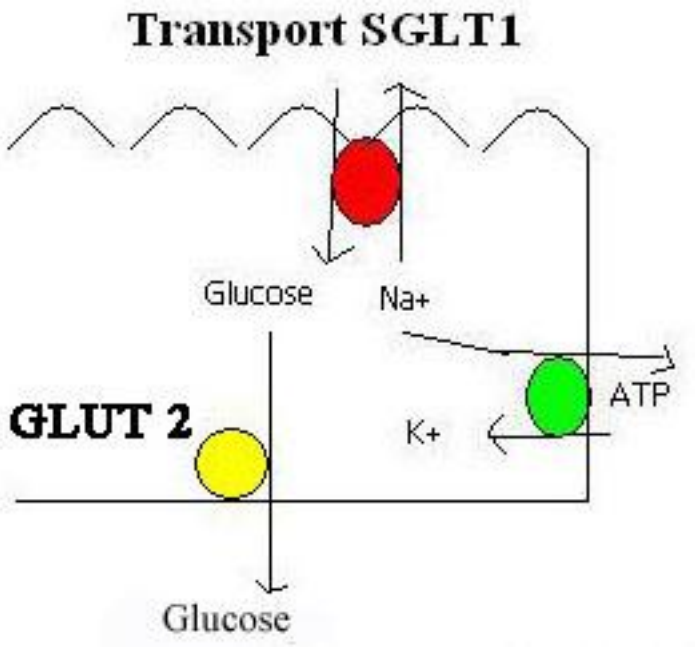
Obstructive and paralytic ileus





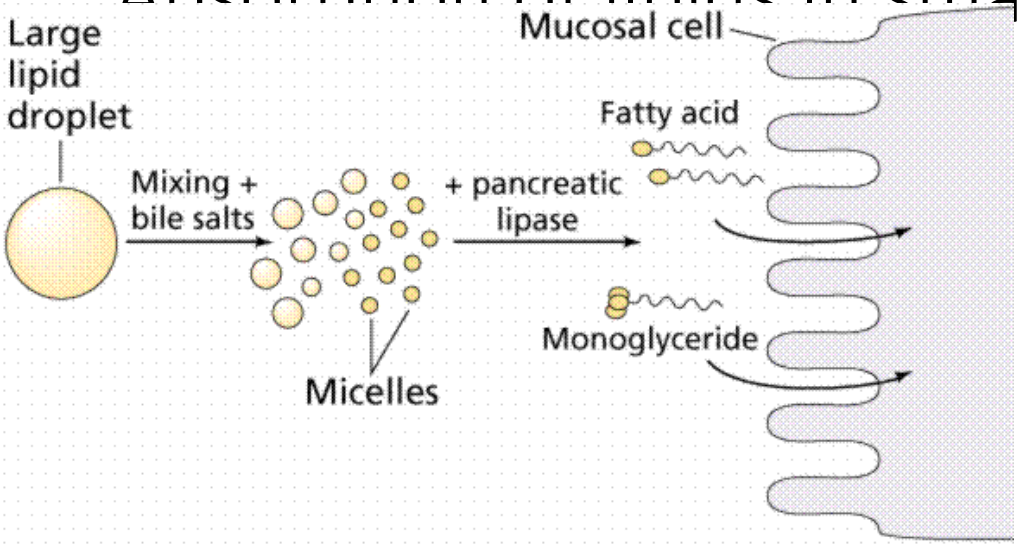
Digestion and absorption in small intestine

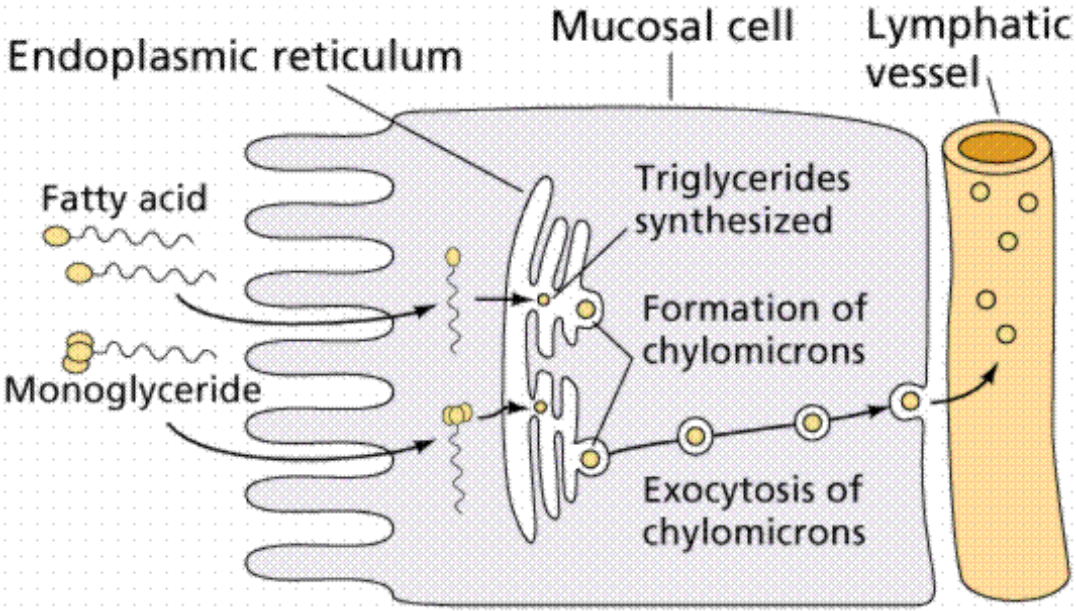
- mechanism
  - (1) slow by passive diffusion
  - (2) fast (but saturable) by facilitated transports
- localization
  - duodenum and jejunum
    - hexoses, AA, di- and tripeptides, vitamins, FA, water, ions
  - ileum
    - vit. C and B_{12}, bile acids, cholesterol, water, ions
- saccharides (mainly poly- and disaccharides)
  - saliva α-amylase $\rightarrow$ pancreatic α-amylase $\rightarrow$ disaccharides)
  - passivee absorption (pentoses), SGLT1 (glucose and fructose)



- proteins
  - endo- (pepsin, trypsin, chymotrypsin, elastase) and exopeptidases $\rightarrow$ pancreatic carboxy- and aminopeptidases $\rightarrow$ peptidases of enterocytes
  - passive absorption, facilitated (SLC, solute carriers – many types, Na-dependent or not) and actively
  - absorption of intact proteins (e.g. Ig of maternal breast milk, antigens, toxins, …) possible in limited extent
- lipids (TGA, cholesterol esters and phospholipids)
  - pancreatic lipase (min. salivary), cholesterolesterase, pospholipase A $\rightarrow$ emulsification (conj. bile acids!!) $\rightarrow$ absorption by diffusion $\rightarrow$ reesterification in enterocyte $\rightarrow$ chylomicrons

Absorption of lipids in small intestine





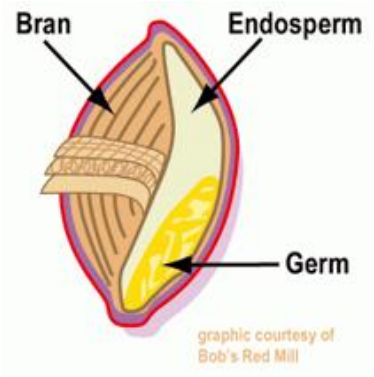
Malabsorption syndrome (MAS)

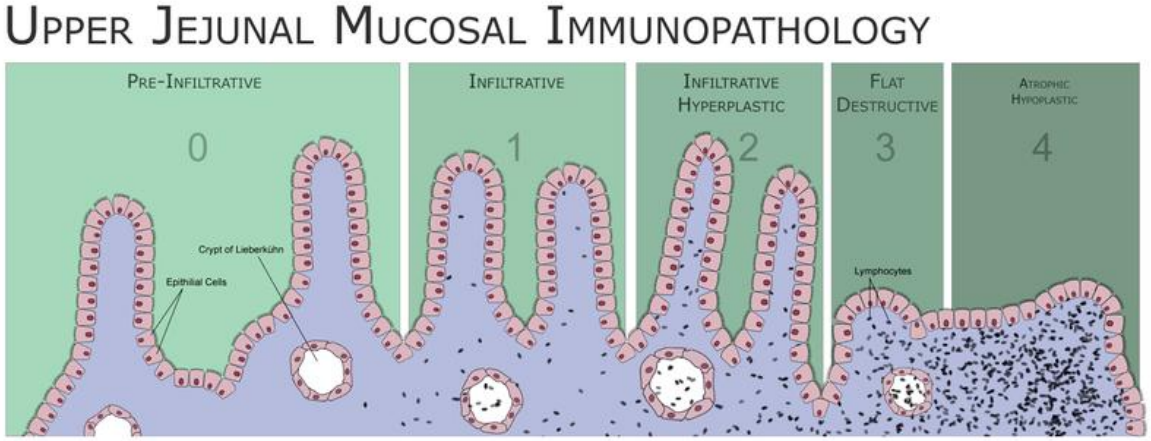
- **maldigestion** = impaired enzymatic digestion in stomach or intestine
- **malabsorption** = impaired absorption of digested compounds

- MAS impairs the normal sequence:
  - mechanical processing of food (chewing, gastric motorics) →
  - digestion in gastric and intest. lumen by secreted enzymes (gastric, pancreas, bile) →
  - digestion by membrane enzymes fo enterocytes →
  - absorption by intest. epithelium → processing in enterocyte →
  - transport by blood and lymph to livet and syst. circulation
- **practically every GIT disease** can lead in chronic duration to MAS
- MAS can be global or specifically affect
  - basic nutrients
    - saccharides –flatulence, osmot. diarrhea (e.g. lactase deficiency)
    - proteins – muscle atrophy, edemas (e.g. chron. pankreatitis)
    - lipids – steatorhea, vitamin A, D, E, K deficiency (e.g. chron. pankreatitis, m. Crohn, m. Whipple, celiac d.)
  - vitamins
  - elements (Fe, Ca, Mg)
  - bile acids (impairment of enterohepatal cycle)
  - any combination

MAS – selected examples – coeliac dis.

- = gluten-sensitive enteropathy
- autoimmune reaction against intest. mucosa initiated by gluten and its products (gliadins)
  - gluten is a part of endosperm of cereals (wheat, rye, barley, oats)
- diseases starts in child after breast feeding when flour is introduced
- pathogenesis
  - gen. disposition – variants of MHC II genes (DQ2 and DQ8 haplotypes)
    - often associated with other autoimmunities, e.g. T1DM
  - external factors
    - gluten in diet
    - infection by adenoviruses (molecular mimicry)
- clinical course
  - immunization (antibodies against gliadin, reticulin and transglutaminase), infiltration by cytotox. T-lymph.) – injury of enterocytes of small intestine
  - malabsorption of main nutrients, vitamins, elements
    - hypo-/malnutrition, slow growth, anemia, neuromuscular disorders
  - in 20-40 years risk of intest. lymphoma (50%) or carcinoma (10%)
  - disorders of fertility

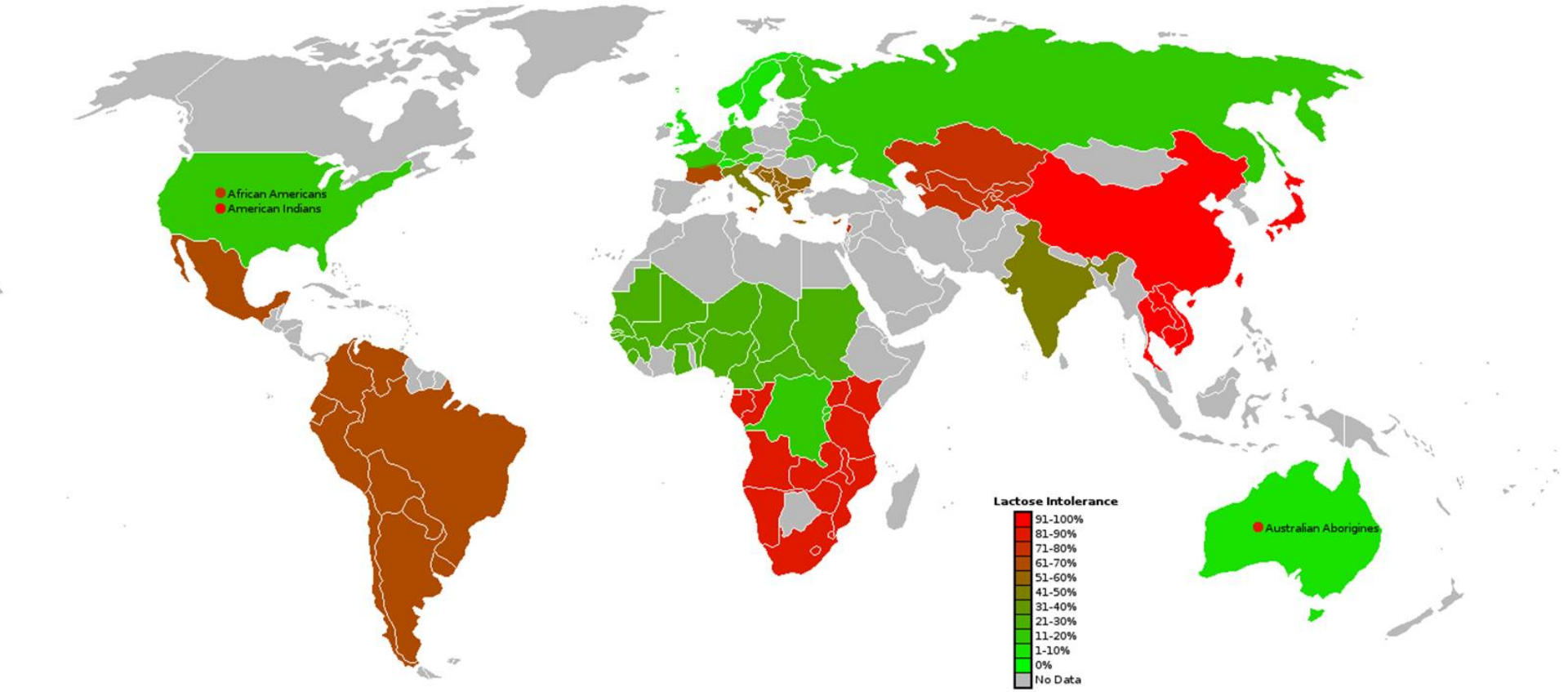




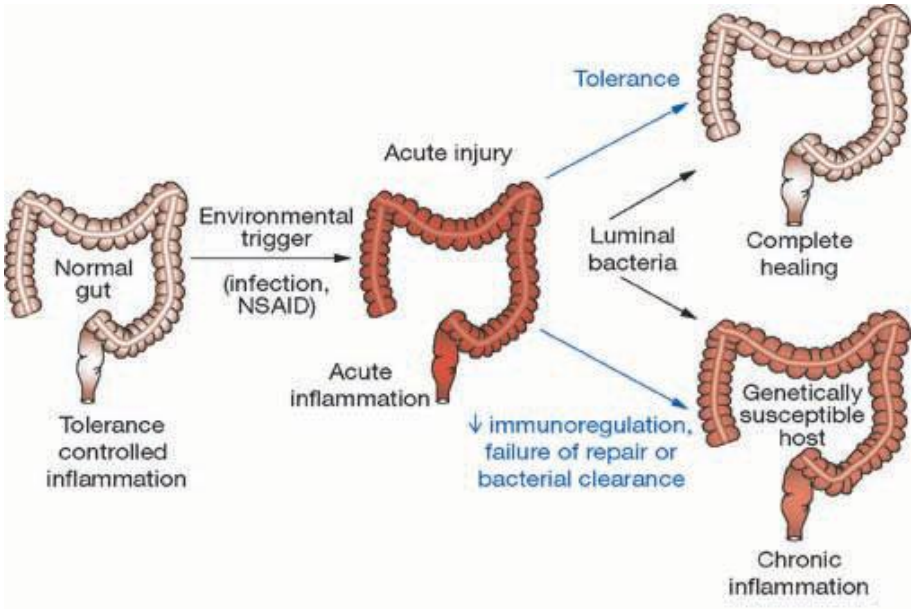
MAS - selected examples – lactase deficiency

- leads to **lactose intolerance**
- extremely frequent – mainly due to the fact that lifetime ability to digest milk (i.e. lactose) is considered a normal state
  - however, most mammals and part of human population loses the activity of lactase after weaning
  - the lifetime activity could be considered exceptional – **persistence of lactase**
    - genetic polymorphism (geographical distribution is evidently a consequence of genetic selection) in promoter of gene for lactase
      - highest prevalence of lactase persistence in Europe in Swedes a Danes (~90 %)
      - Czech population ~ 70 %
      - lowest in Turks (~ 20 %)
      - outside Europe high fervency of persistence e.g. in desert nomadic populations in North Africa
        - the reason for selection of persistence haplotype in northwest Europe could be the richer source of calcium in low vit. D generation climate
- manifestation
  - intestinal discomfort after fresh milk intake (not after diary fermented products such as cheese or yogurt)
  - diarrhea, flatulence, abdominal pain

Lactose intolerance prevalence



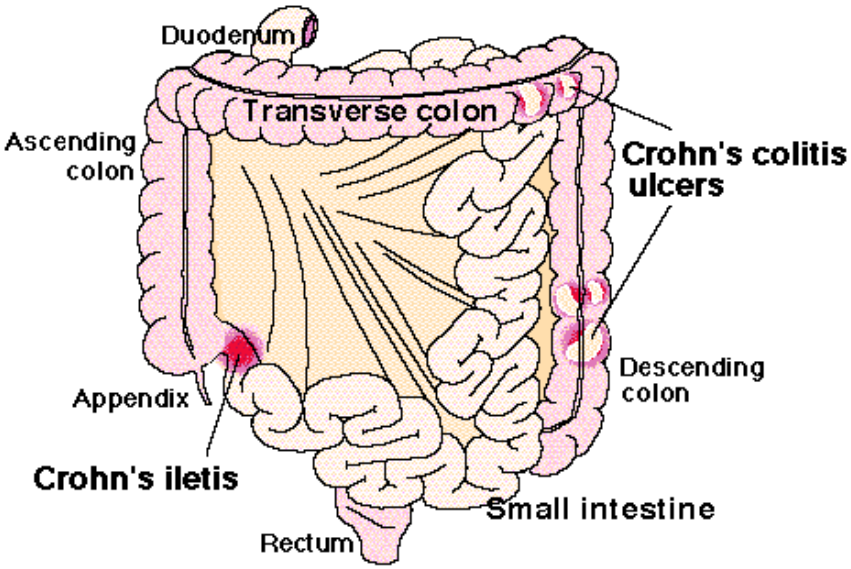
Inflammatory bowel diseases (IBD)

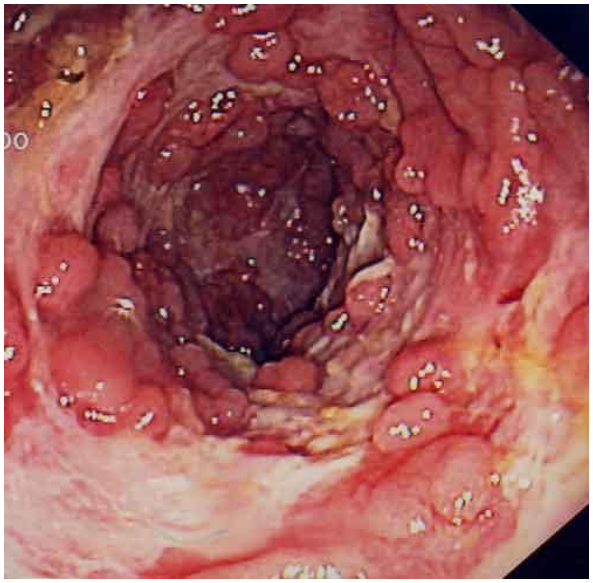


- Crohn's disease and ulcerative colitis
- both exhibit some similar features
  - manifestation in young adults
  - genetic predisposition
  - abnormal reactivity of immune system (T-lymph.) to intest. bacteria
  - impairment of intest. epithelial barrier
- localization
  - m. Crohn – any segment of GIT
  - ulcerative colitis – only colon
- incidence rises in Europe and N. America
  - environmental factors

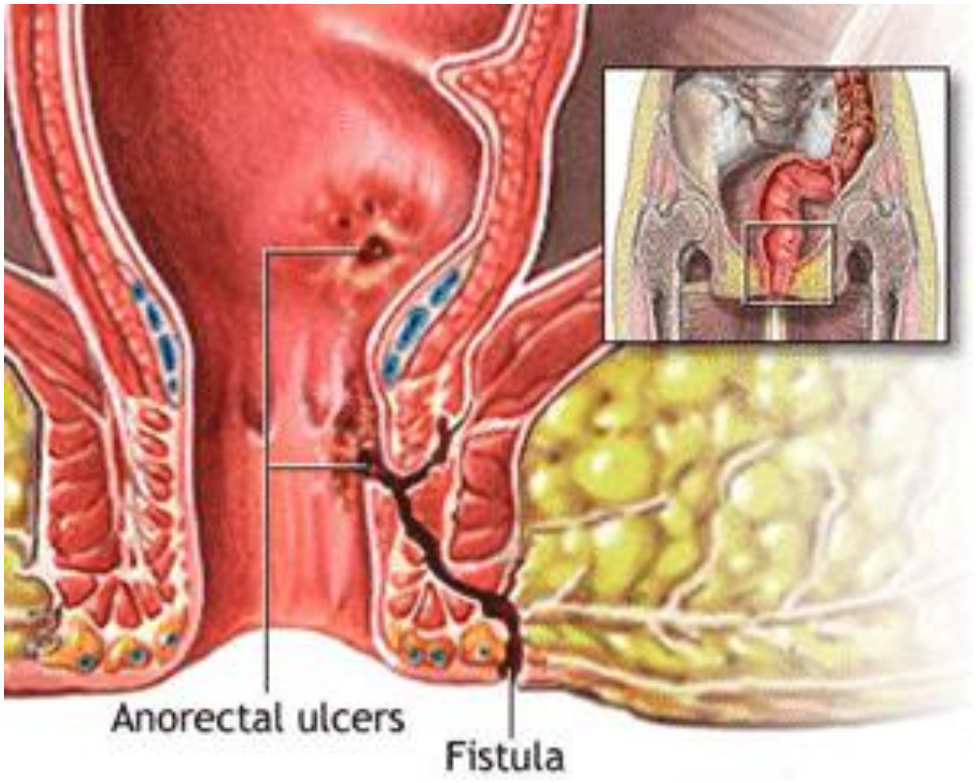
Crohn's disease

- = ileitis terminalis, enteritis regionalis
- chronic idiopathic inflammatory disease of commonly small intestine
  - but can affect any part of GIT beginning with oral cavity to anus
  - manifestation typically between 3. to 6. decade, more often women
- pathogeneses (multifactorial)
  - genetic factors (= disposition) lead to abnormal immune response of intest. mucosa to natural commensal bacterial antigens (>500 bact. strains)
    - normally opposed by production of defensins
    - mutation in gene for CARD15 in patients
  - triggering factors nor known (infection?) = sterile animals protected
    - lipopolysaccharide, peptidoglycan, flagellin, …
- clinical course – typically exacerbations (stomach pain, diarrhea, fever, seizures, blood in stools (enterororhagia)/remise
  - granulomatous type of inflammation affects all layers of intest. wall
  - ulcerations and bleeding
  - penetrated ulcers create fistulas (often perirectal)
  - affected areas interspersed by inaffected
- extraintestinal manifestations
  - arthritis
  - uveitis

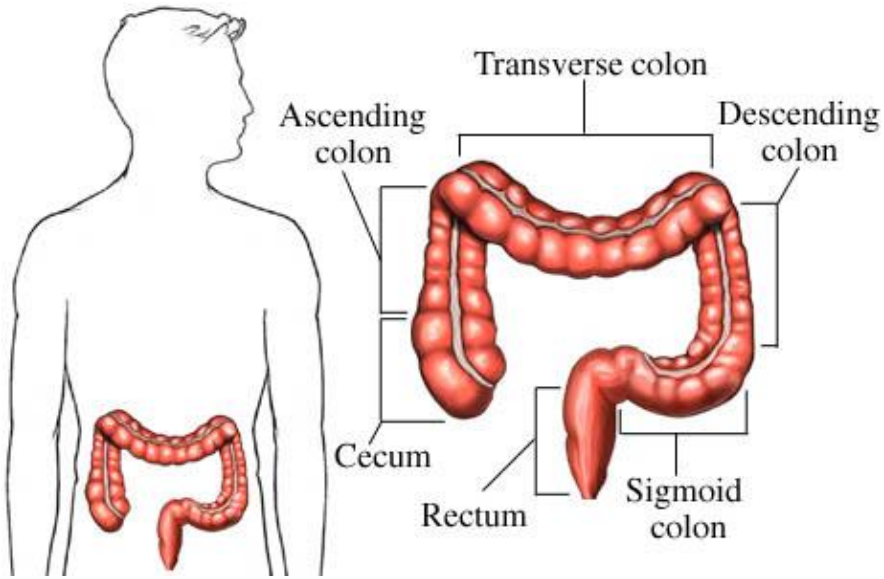


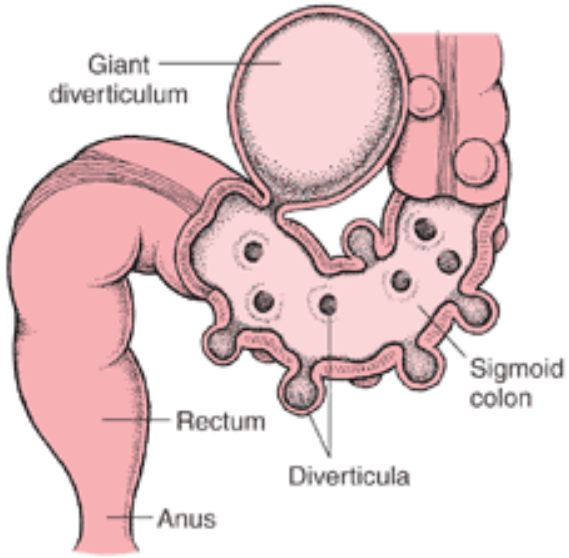


Complications of Crohn's disease



Pathophysiology of large intestine

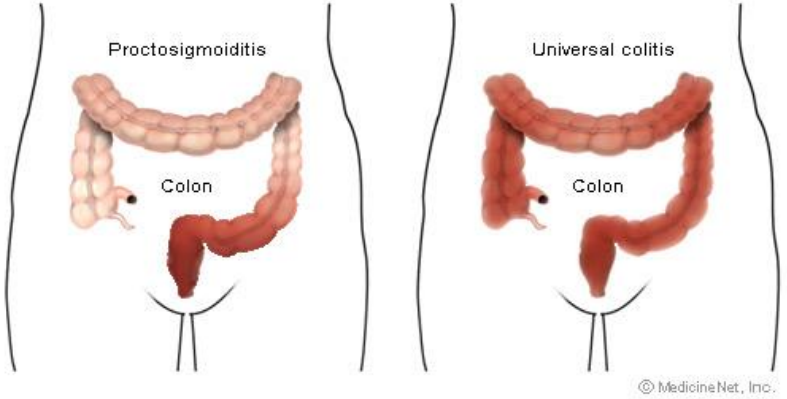


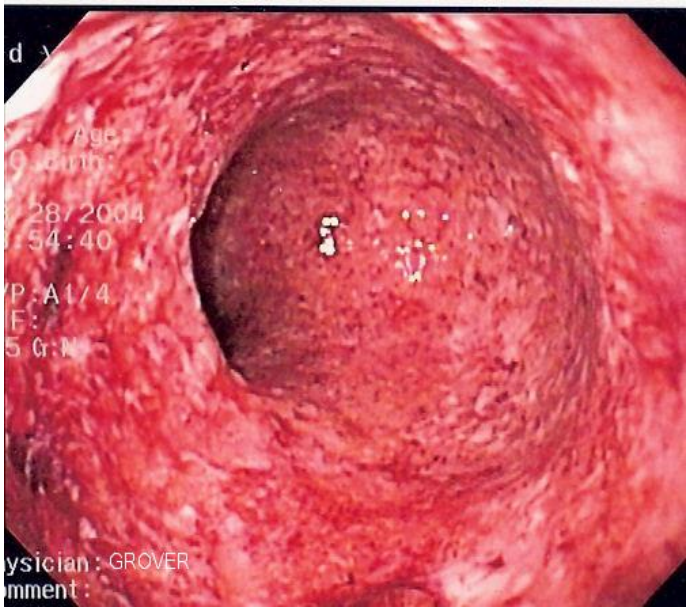


- functions
  - resorption of water (0.5-1l/24h)
    - along the whole length
  - motoric
- pathology
  - obstipation
  - diverticulosis
    - event. divertikulitis
  - polyposis
  - carcinoma
    - hereditary
      - polyposis
      - non-polypose
    - non-hereditary (sporadic)

Ulcerative colitis

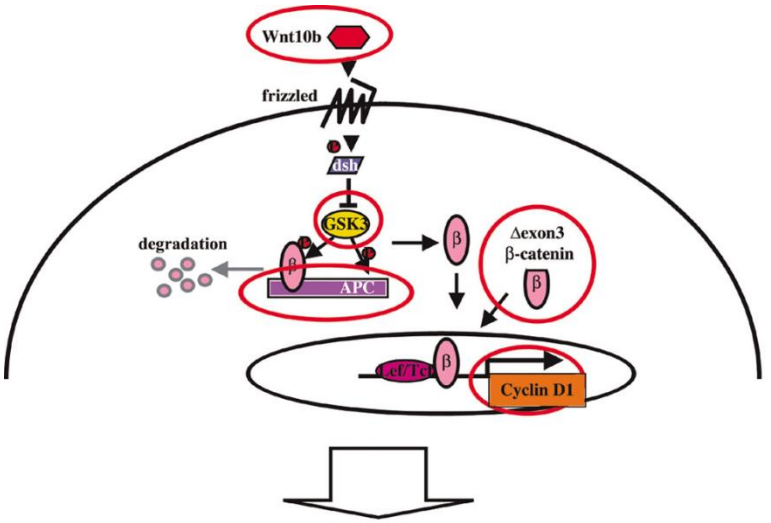
- max. incidence between 20 – 40. years of age
- typically Caucasian race, north-south gradient
- inflammation limited to mucosa
  - starts at the bottom of Lieberkuhn's crypts (infiltration by immune cells)
    - mainly rectum and sigmoideum
  - hyperemia, abscesses and ulcerations, bleeding, pseudopolyps, event. strictures
- clinical course
  - periodical = exacerbations x remissions (diarrhea, bleeding, abdominal pain, fever)
  - extraintestinal manifestations (5 – 15%): polyarthritis, osteoporosis, uveitis, cholangitis
  - chronic anemia, strictures, hemorrhoids, carcinoma

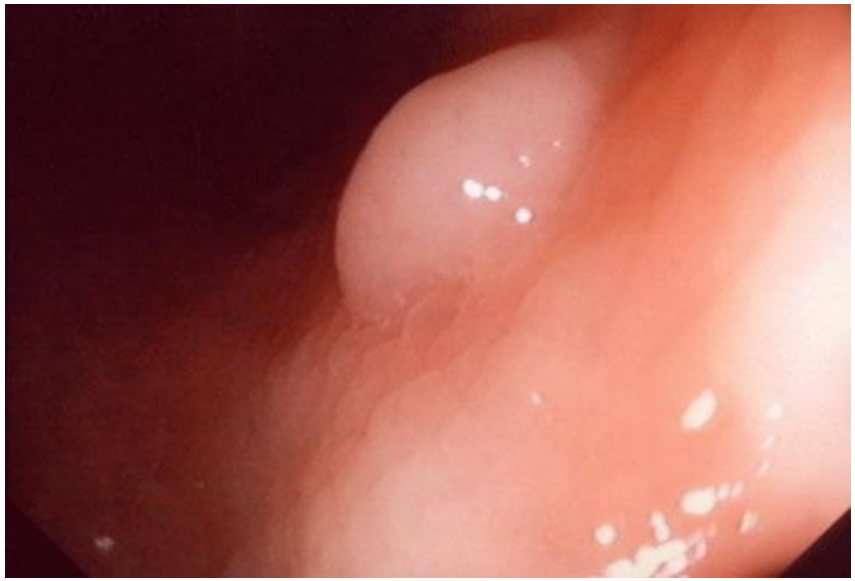




Polyps of large intestine

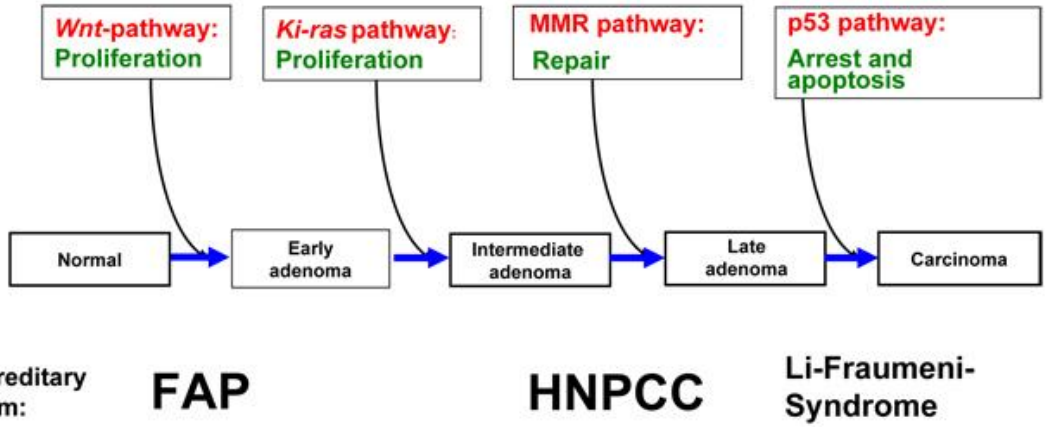
- polyp = any lesion/prominence into the lumen
- types
  - solitary
  - multiple
    - familiar polyposis, FAP)
      - autosomal dominant
      - precancerosis, polyps in puberty, carcinoma after 30th year of age
      - polyps more common in rectum but also in ileum
      - mutation in APC gene (Wnt pathway)
- etiology
  - hyperplasia in the inflammatory terrain
  - neoplastic
    - benign
    - malign



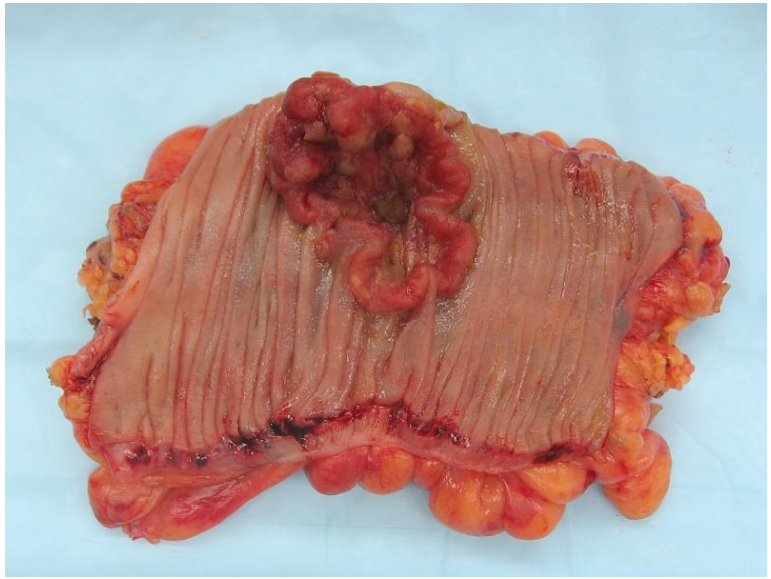


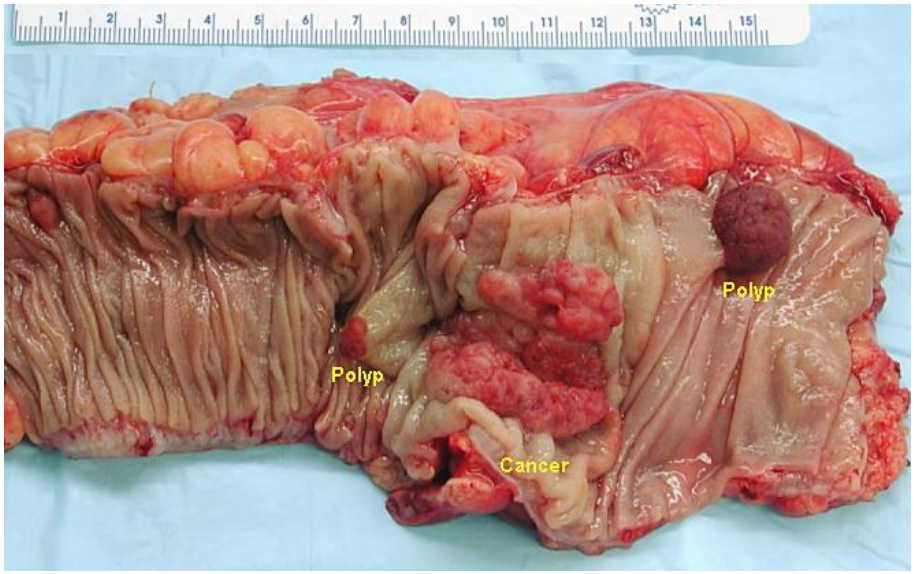
Tumors of large intestine

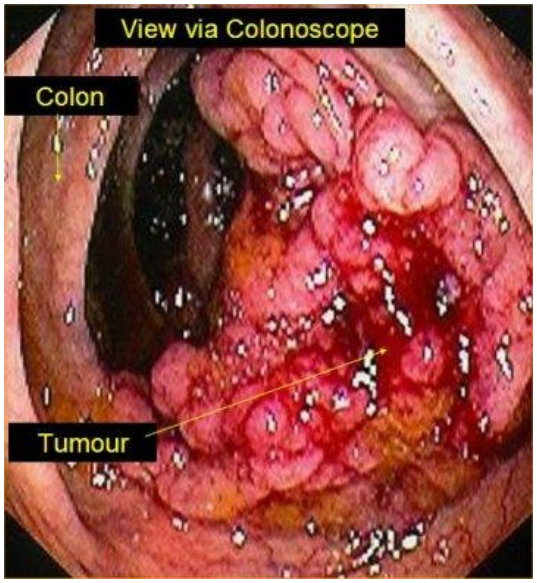
- benign
  - adenoma (adenomatous polyp)
  - fibroma
  - leiomyoma
  - hemangioma
- malign
  - lymphoma
  - carcinoid
  - carcinoma
    - hereditary
      - polypose
        - FAP (mutation in APC gene)
      - non-polypose
        - Li-Fraumeni syndrome (mutation in p53 gene)
    - non-hereditary (sporadic) – most common

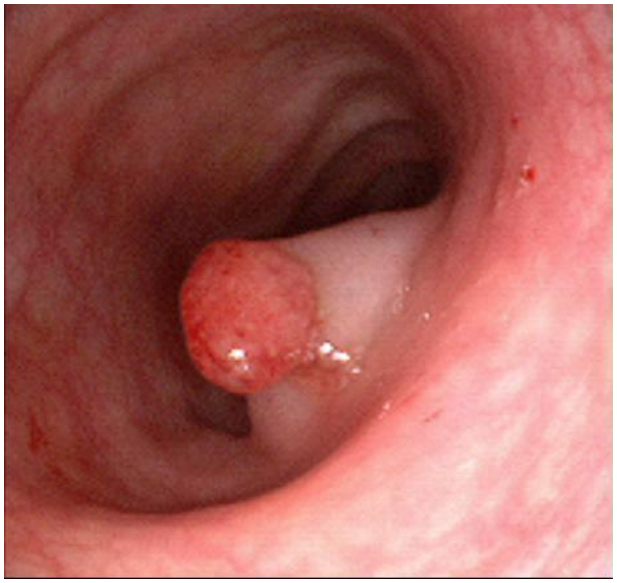


Colorectal carcinoma



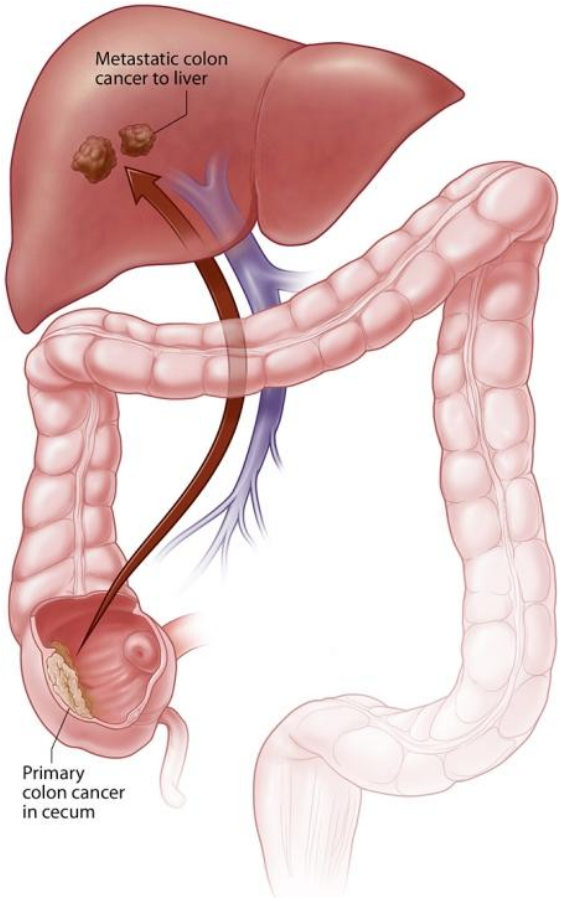






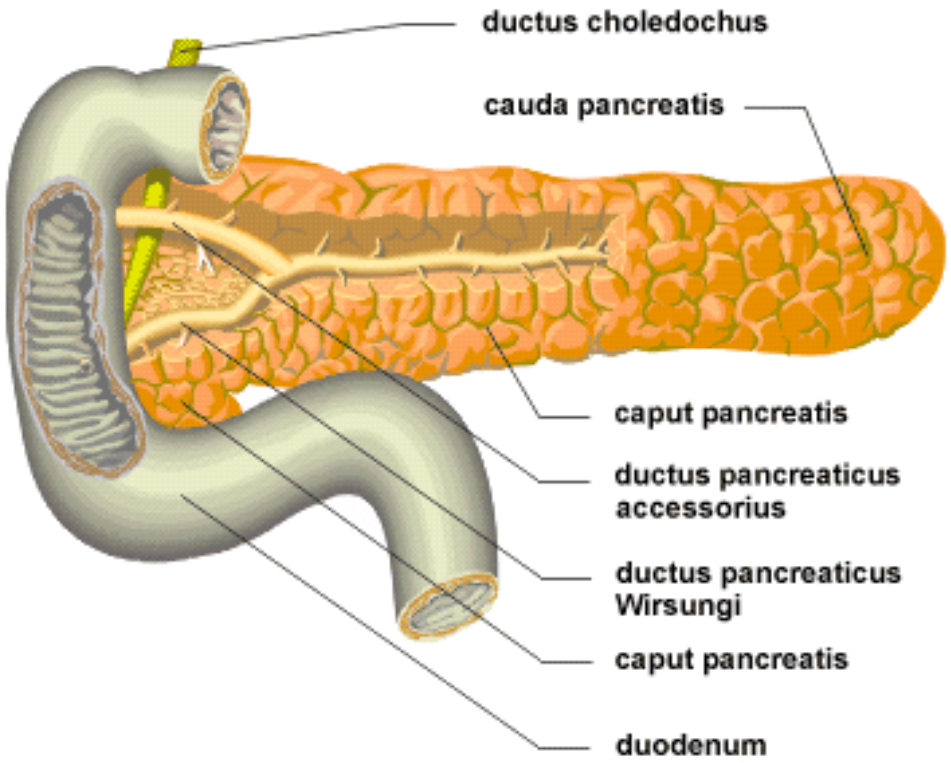
Colorectal carcinoma

- carcinogenesis in the intestine progresses slowly upon the exposure to dietary carcinogens and event. with contribution of genetic predisposition of the subject
- risk factors
  - age, genetics, polyps, bowel inflammation, obstipation, diet, smoking
- symptoms
  - bleeding, blood in stools
  - change of peristaltics
    - diarrhea
    - obstipation
    - tenesmus
  - intest. obstruction
  - pain
  - extraintestinal
    - liver metastases
      - icterus, pain, cholestasis = acholic stools
    - hematologic
      - sideropenic anemia, thrombosis
    - fatique
    - fever
    - anorexia, weight loss



- stadia
  - 0 in situ
  - I invasion into the wall
  - II
  - III presence in local lymph nodes
  - IV distant metastases

Pathophysiology of the exocrine pancreas



Cell types in the pancreas

- Endocrine – islets of Langerhans

α-cells – producing glucagon

β-cells – producing insulin and amylin

δ-cells – producing somatostatin

ε-cells – producing ghrelin

PP-cells – producing pancreatic polypeptide

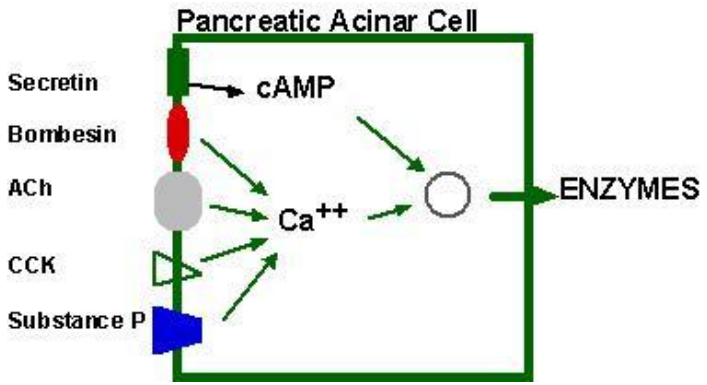
G-cells – producing gastrin

- **Exocrine – acini and ducts**

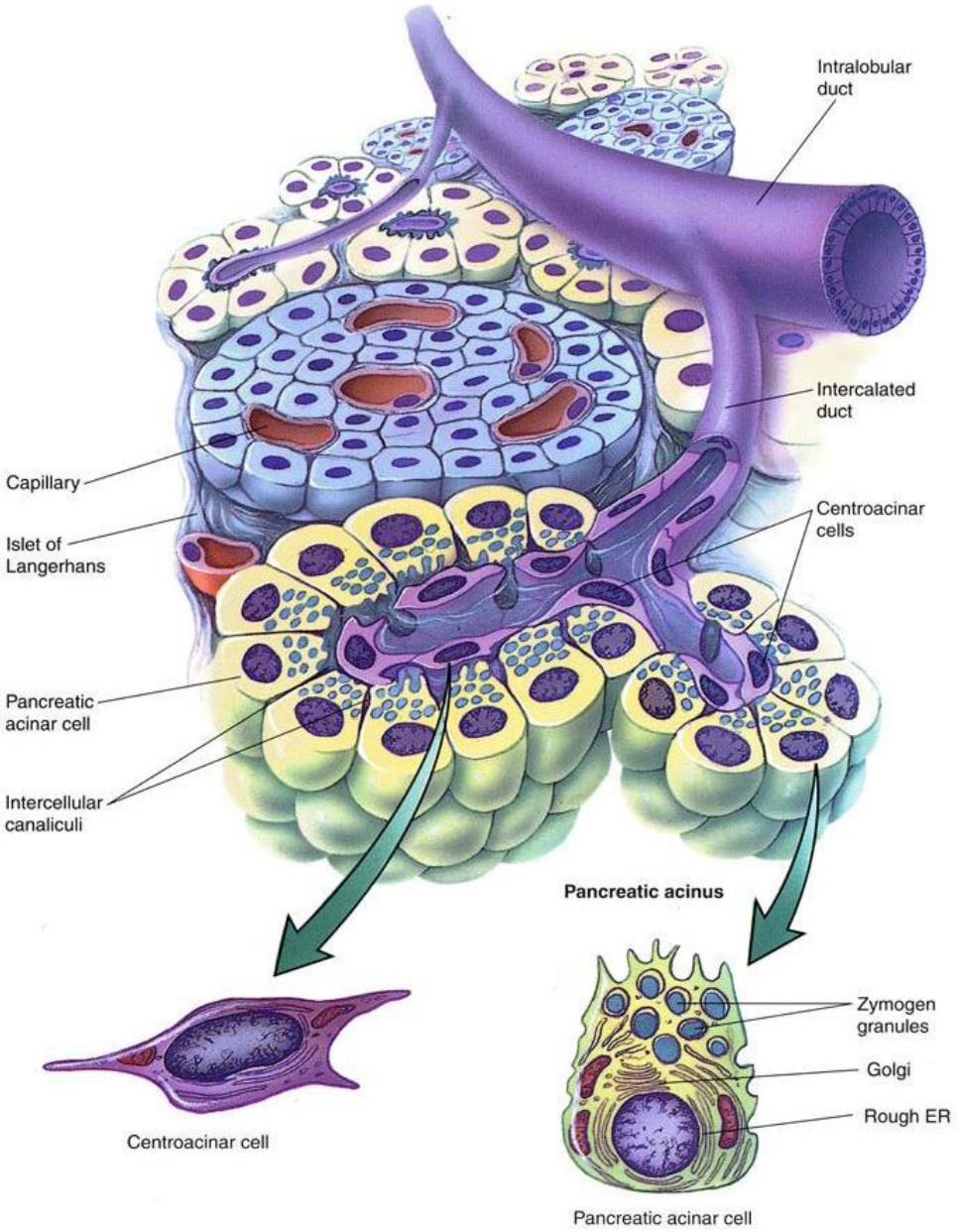
acinar (basophilic) cells – producing pancreatic enzymes (trypsin, amylase, lipase)

centroacinar cells – producing HCO_3^-

ductal cells – producing HCO_3^-

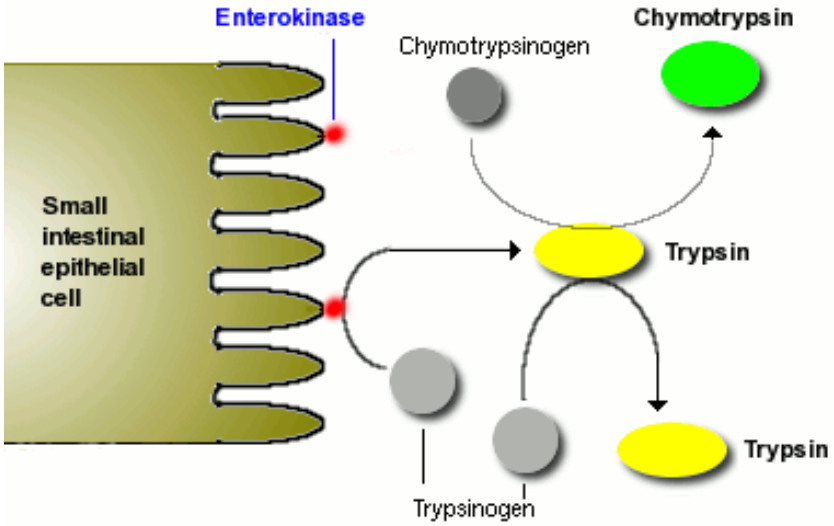


Anatomy of the pancreas



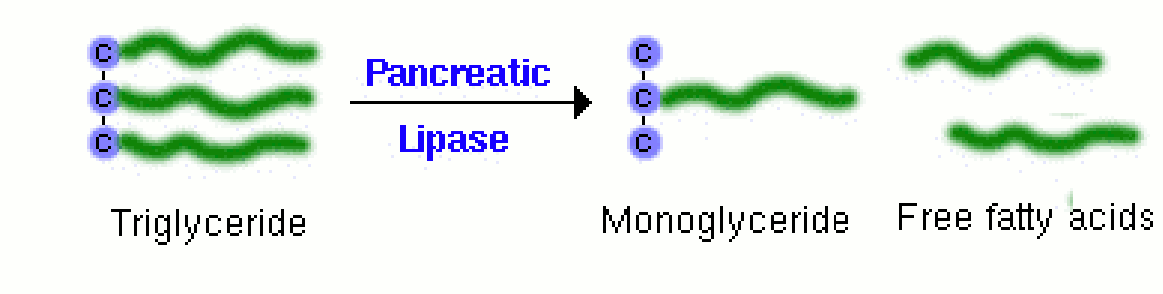
Exocrine pancreas in protein digestion

- Proteases – are secreted in inactive form: trypsinogen, chymotrypsinogen
- Trypsinogen is converted into trypsin by enterokinase in the small intestine
- Trypsin then converts chymotrypsinogen into chymotrypsin
- Each enzyme then cleaves peptidic bonds between different aminoacids
- Both act inside the protein - endopeptidases



Exocrine pancreas in lipid digestion

- Pancreatic lipase (LPS)
  - converts TAG into monoacylglycerol and FFA
  - acts together with bile acids, which emulsify lipids
- Lysophospholipase, Phospholipase A2
  - cleave phospholipids
- Cholesterol esterase
  - de-esterifies cholesterol and helps its transport into enterocytes



Exocrine pancreas and saccharide digestion

- Pancreatic amylase (AMS-pancr.)

  - catalyses cleavage of starch or glycogen into oligosaccharides (dextrin, maltotriose, maltose)

  - cleavage by both salivary and pancreatic AMS represents the initial stage in saccharide digestion

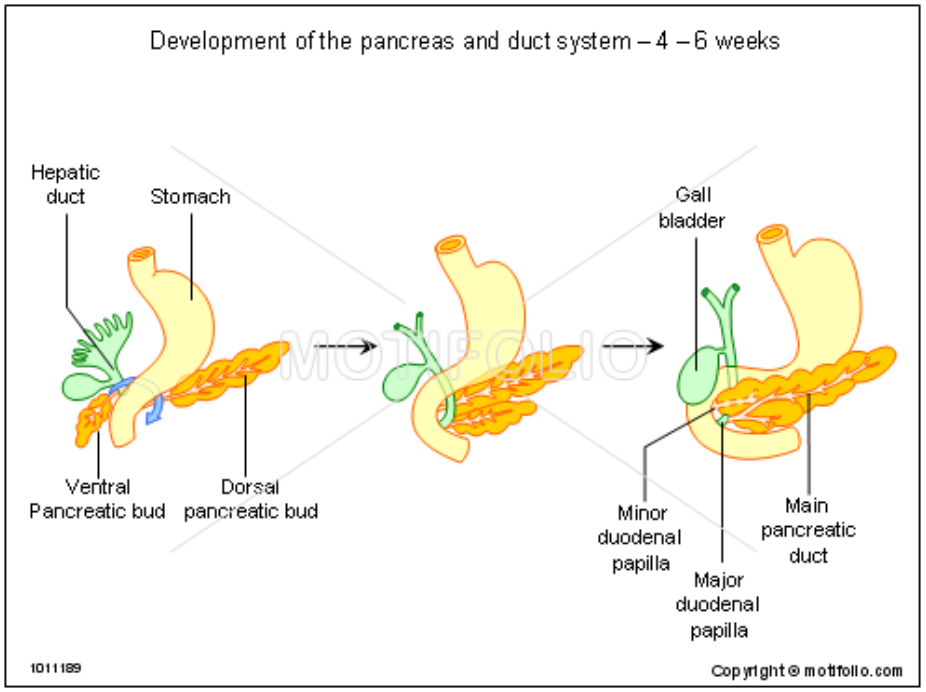
  - Its products are further cleaved by intestinal enzymes (glucosidases, maltase) into monosaccharides, which are transported into blood

Diseases of exocrine pancreas

- Congenital malformations
- Acute pancreatitis
- Chronic pancreatitis
- Cystic fibrosis
- Tumours

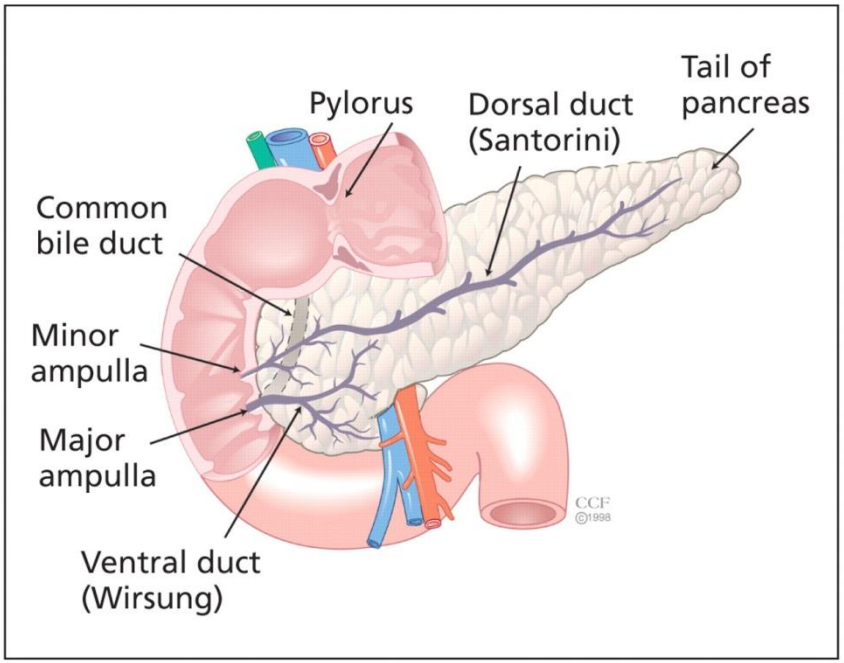
Congenital malformations

- During development, pancreas is formed through the fusion of ventral and dorsal bud
- Ventral bud turns into most of the head of pancreas, while dorsal bud turns into its body and tail
- Initially, they both have separate ducts, in most cases, the ducts are joint together during development. Ventral duct (duct of Wirsung) drains most of pancreas.
- Usually, it has common orifice with biliary duct



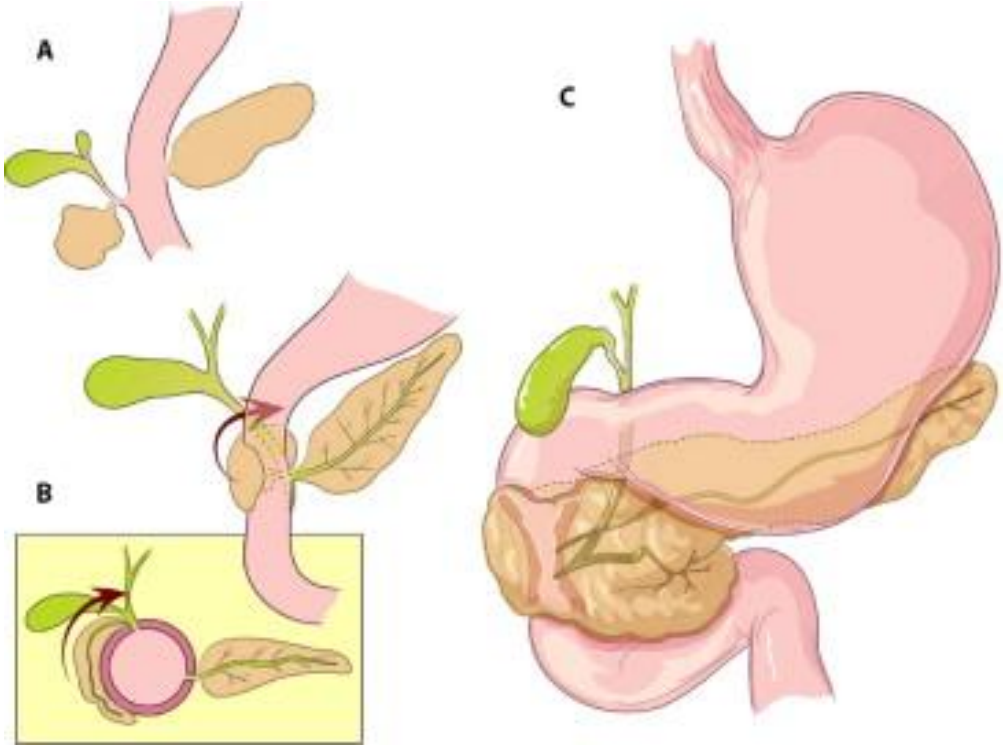
Pancreas divisum

- In some cases, the fusion of both buds is incomplete
- Smaller dorsal duct is sometimes incapable to drain pancreatic juice effectively
- The condition can lead into repeated acute pancreatitis



Annular pancreas

- In other cases, ventral bud can pinch the duodenum during its abnormal rotation and fusion, causing vomiting and duodenal ulcers



Acute pancreatitis

- Various factors lead into the damage of acinar cells
- Granules with trypsinogen are overpresented in cells and trypsinogen can react with lysosomal enzymes
- The reaction can lead into conversion of a small amount of trypsinogen into trypsin
- Trypsin can activate other enzymes (as chymotrypsin or phospholipase A)
- This leads into the autodigestion of the pancreas and consequent complications

Causes of acute pancreatitis

- Obstruction of pancreatic ducts (most often)
  - obstruction of common biliary and pancreatic orifice (ampulla Vateri) – usually together with icterus
  - tumours
  - pancreas divisum
- Alcoholic excess
- Metabolic causes (e.g.hypertriglyceridemia)
- Idiopatic

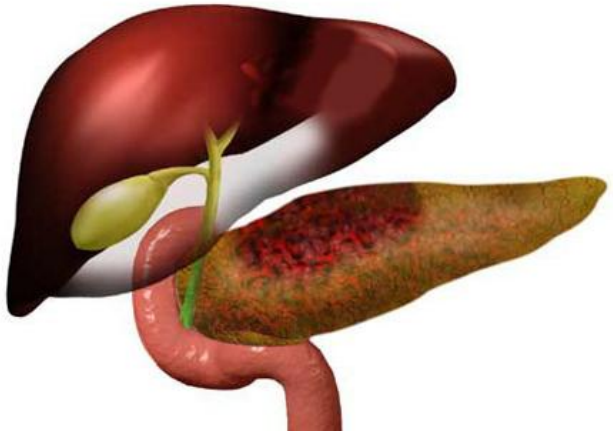
Manifestation of acute pancreatitis

Mild form (80%)

- interstitial oedema
- inflammation of interstitium

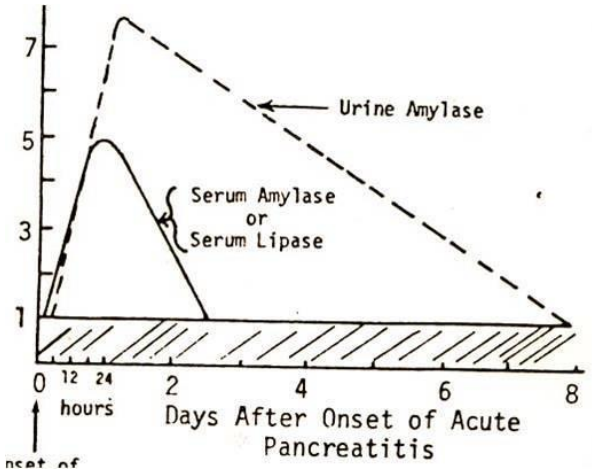
Severe form (20%)

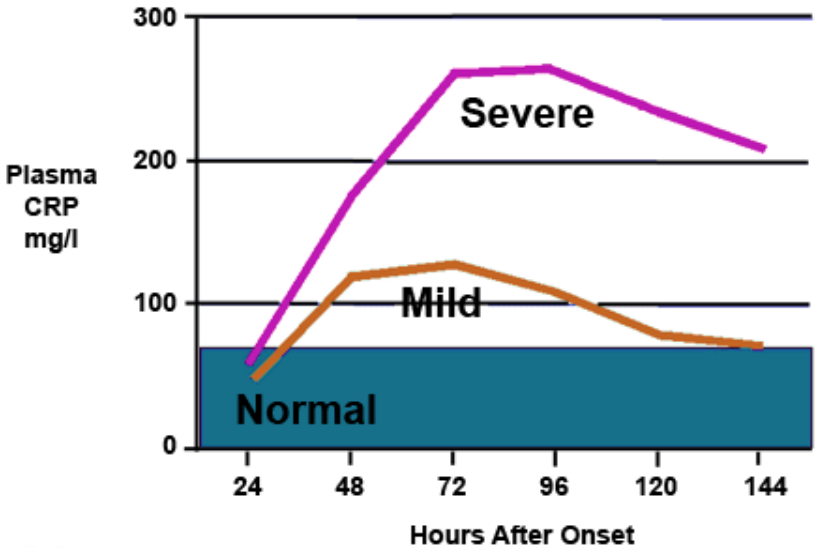
- necrosis
- haemorrhage
- necrosis of surrounding tissue
- sepsis
- circulatory shock
- DIC



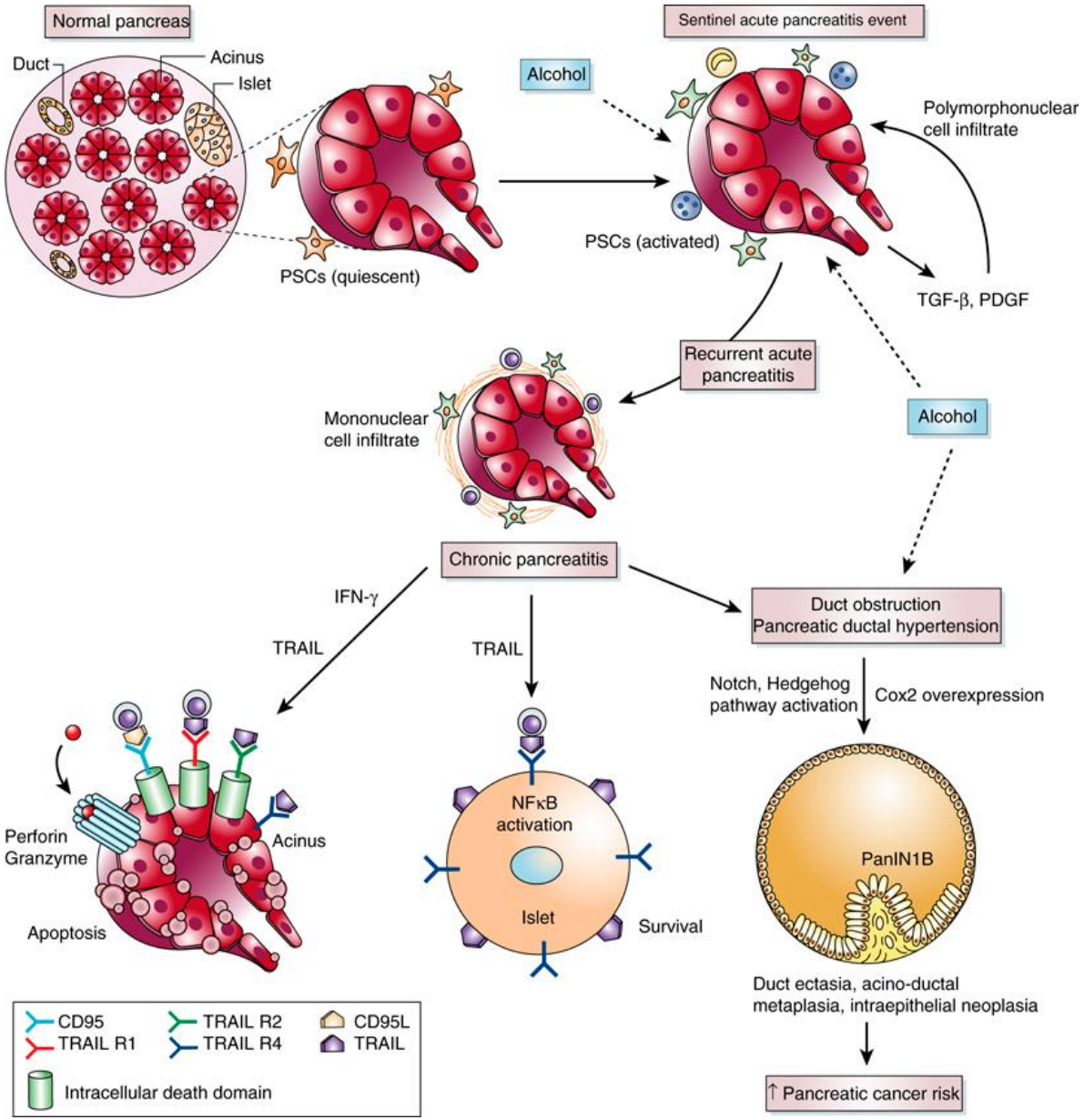
Clinical and laboratory findings

- Severe stomach ache (usually after alcohol intake or fatty meal)
- Fever, CRP and leukocytes elevation
- Elevation of LPS, pancreatic AMS (within several hours after onset





Late complications



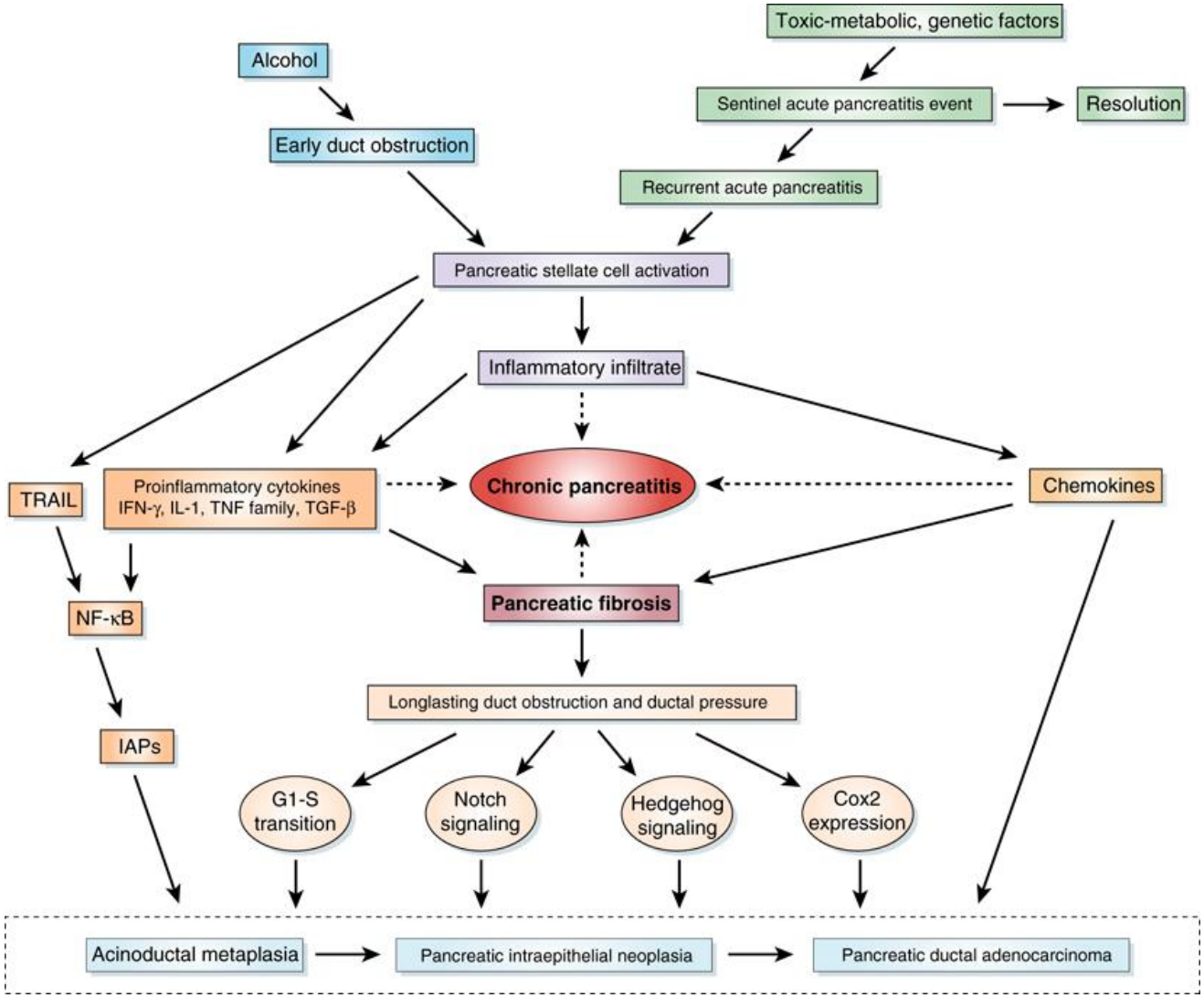
Chronic pancreatitis

- Various causes, exact pathophysiology is not always clear
- Chronic irritation of pancreas by alcohol or other causes leads into chronic monocyte and lymfocyte infiltration
- Occassional reaction of pancrteatic proenzymes with lysosome hydrolases (as in acute pancr.)
- Necrosis of acinar cells and subsequent fibrosis is present
- In final stage, endocrine pancreas is also affected

Causes of chronic pancreatitis

- Abuse of alcohol (most often)
- Idiopatic
- Toxic or radiation damage
- Hereditary
  - congenital anomalies (e.g. pancreas divisum)
  - cystic fibrosis
  - α-1 antitrypsin deficiency
- Acute pancreatitis

Development of chronic pancreatitis

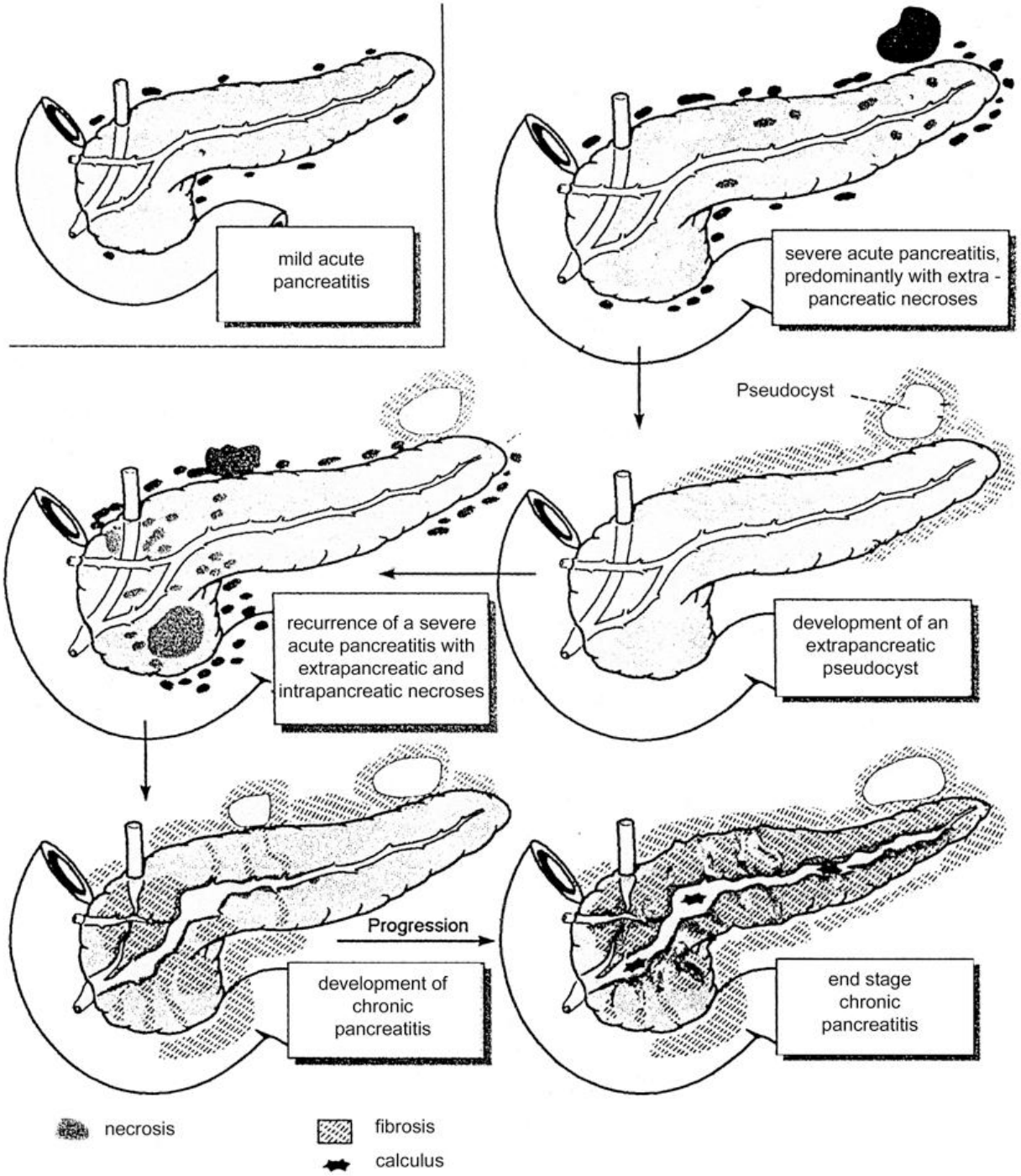


Clinical findings

- Stomach ache (very variable)
- Diarrhoea, steatorrhoea
- Malabsorption
  - vitamin carence
  - hypoproteinemia with oedemas
- Secondary diabetes
- Obstruction of biliary duct with icterus
- Ascites (rare)

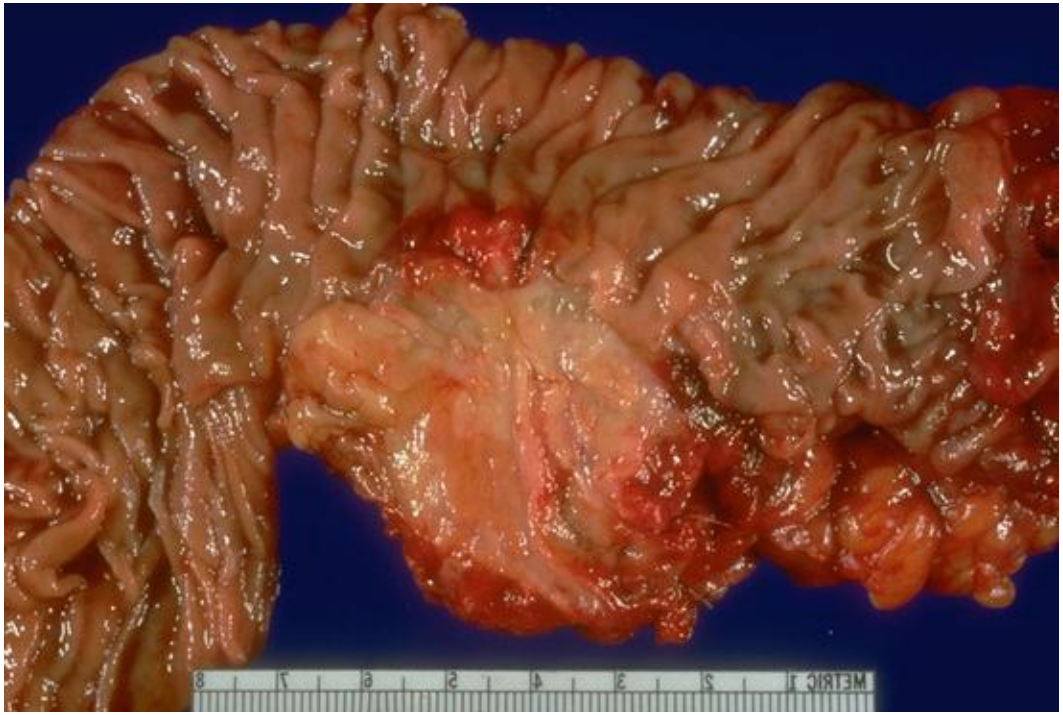
Chronic pancreatitis - diagnosis

- Pancreatic AMS or LPS are useless (elevated just in acute exacerbations)
- Imaging methods: ultrasonography, CT, MR
- Secretin-CCK test (invasive, measures amylase, trypsin and acidity in the duodenum)
- Secretin and CCK can be replaced by lipid-saccharide-protein solution (but with lower sensitivity and specifity)


mild acute pancreatitis
severe acute pancreatitis, predominantly with extra - pancreatic necroses
Pseudocyst
recurrence of a severe acute pancreatitis with extrapancreatic and intrapancreatic necroses
development of an extrapancreatic pseudocyst
Progression
development of chronic pancreatitis
end stage chronic pancreatitis
necrosis
fibrosis
calculus

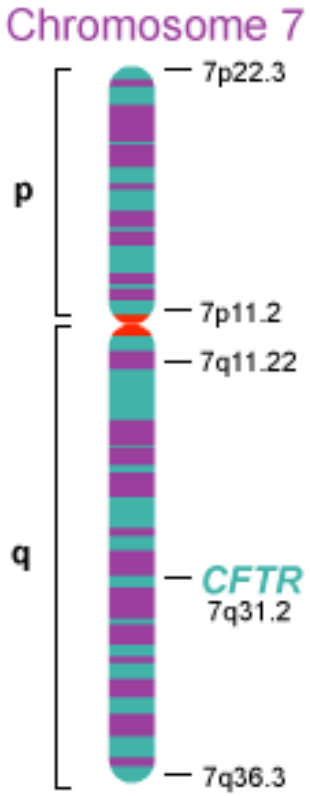
Tumours of pancreas

- Exocrine: adenocarcinoma
  - bad prognosis (5-years survival <10%)
  - 90% of tumours are practically untreatable due to late diagnosis
- Endocrine: both benign or malign
  - usually with endocrine activity



Cystic fibrosis (mucoviscidosis)

- Monogenic disease with autosomal recessive inheritance
- Mutation in the gene for CFTR (Cystic Fibrosis Transmembrane conductance Regulator)
- Its product is a chloride channel, present in mosttissues
- Gene for CFTR is located in 7q31.2. locus
- In Czech and most other European populations, approximately 4% of population are carriers of mutated allele



Various manifestations of CF

- The retention of chlorides leads into increased viscosity of secretions
- In the sweat glands, chloride (and sodium) re-uptake is blocked