Pathophysiology of the GIT

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Common classes of signs and symptoms

- abdominal or chest **pain**
- altered ingestion of food due to **nausea, vomiting, dysphagia** (difficulty of swallowing), **odynophagia** (painful swallowing) or **anorexia** (lack of apetite)
- **altered bowel movements** ⟶ diarrhoea or constipation
- gastrointestinal **bleeding**
- not all cases of diseases present in the same way – e.g. peptic ulcer disease may be painless

Gastrointestinal diseases may be

- limited to the gastrointestinal tract, eg. reflux oesophagitis, peptic ulcer disease, diverticular disease
- manifested as a systemic disorder, eg. inflammatory bowel disease (Crohn´s disease, ulcerative colitis)
- manifested as a systemic disease resulting from a primary pathologic process in GIT, eg. vitamin deficiencies due to malabsorption

acute complications of GIT disorders:

dehydration
sepsis
bleeding

chronic complications:

malnutrition
deficiency states
partial or complete obstruction – due to adhesions and stenosis (from proliferation of connective tissue in response to inflammation)

Functions of GIT

- **motility** – depolarization of the cells occurs spontaneously and in response to a neural and hormonal stimuli
  myenteric plexus has two programmed responses – segmental and peristaltic; segmental – in postprandial period, peristaltic pattern during fasting
- **secretion** - daily fluid intake = app. 2 L of oral intake
  secretion = app. 7L (1.5 L saliva, 2.5 L gastric juice, 0.5 L bile, 1.5 L pancreatic juice, 1 L intestinal fluid); app. 100 mL / day is lost in stool
- **digestion** – process starts in the mouth (action of salivary amylase), in small intestine proceed 4 phases:
  hydrolysis in intestinal lumen
  hydrolysis at the enterocyte brush border
  transport of nutrients into enterocytes
  processing of nutrients within, export into the portal and lymphatic circulation

Mechanisms of defense of the GIT

- GIT = interface between external and internal environments
- **defense from acid**
  production of mucus
  bicarbonate
  prostaglandins
- **defense from infection**
  immune system in GIT – lymphoid tissue, Peyer´s patches
  normal colonic microflora
  stomach acid

Patophysiology of the oral cavity

- **saliva** – in oral cavity amount of salivary glands – maintenance of humidity
  three great salivary glands – release of saliva as response to secretion stimulus

- secreted saliva content
  120 mmol / liter of HCO_3 (protection of teeth against acid substantion)
  α-amylase – the begining of sacharides digestion
  lysozyme – hydrolysis of bacterial membranes
  antigenes in AB0 system,
  some viral antigenes

Disturbances of the mastication and saliva secretion

- main etiological factors: states followed by the pain (inflammation of the mandible joint, lesion of the tongue and mucose in oral cavity, gingivitis etc, trigeminal neuralgia etc.)

- enhanced saliva secretion
  food composition, mechanic irritation, inflammation, vagal stimulation, use of the parasympatomimetic drugs

- decreased saliva secretion
  isotonoc and pure water dehydration, fever, parasympatolytic drugs (atropin)

Manifestation of the some systemic diseases in oral cavity

- cardiovascular diseases – cyanosis
  incterus – yellow color of the skin and mucose membranes
  anemias – pale skin, mucose membranes
- protein malnutrition – gingivitis, ulcers,
- hypovitaminosis, avitaminosis
- inflammatory bowel diseases (Crohn´s disease, ulcerative colitis) – aphtae, mucosal oedema, ulcers
- hematology malignanties – ulcers, bleeding

Pathophysiology of the oesophagus

- only motor function - transport of meal into stomach

- primary contractions – follow pharyngeal phase of the swallowing
  secondary -"- - after oesophageal distention ⟹ emptying
  tertiary -"- - esp. in older persons, chaotic contractions

- in pathophysiology play role
  motility disturbances, diaphragmatic hernias, gastroesophageal reflux, inflammation, ulcers, erosion, varixices, diverticles, tumors

Motility derangment

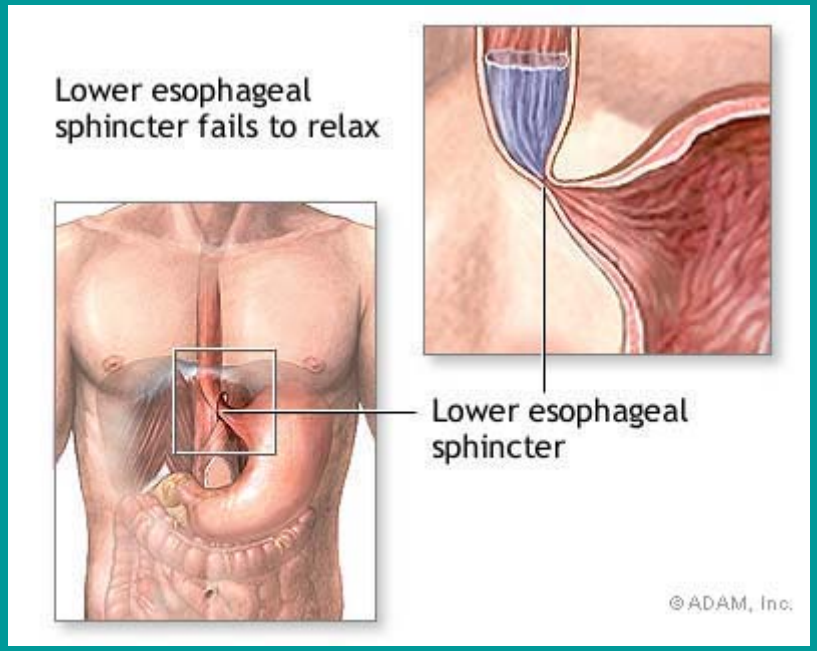
- mastication → primary and secondary contractions → transport of meal into stomach (fluid and firm meals are transported into stomach during 10 sec.)
- after failure of theese mechanisms → accumulation of the meal, oesophageal distention, nausea → **dysphagia**
- oropharyngeal dysphagia – due to disturbances of saliva secretion, disturbances of corticobulbar systeme
- oesophageal dysphagia – due to mechanical obstruction, e.g. tumor, stricture, scarring

Oesophageal achalasia

- motor disorder of oesophageal smooth muscles, increase of the sphincter tone
- cause: defective innervation of smooth muscles in oesophageal body and LES; loss of normal peristalsis (myenteric plexus degeneration?)
- etiology:
  1. idiopathic disorder
  2. malignancy – e.g. pancreatic cancer, prostatic cancer, lymphomas
  3. further diseases – e.g. amyloidosis, MEN, glucocorticoid deficiency syndrome
- clinical picture:
  chest pain, dysphagia, regurgitation
  LES dysfunction ⟹ tremendous enlargment of oesophagus (it can hold as much as 1 L putrid, infected material ⟹ high risk of aspiration pneumonia)

Secondary motility disorders

- connective tissue disorders (scleroderma, SLE)
- neuromuscular disorders (Parkinson´s disease, Huntington´s disease, myasthenia gravis)
- endocrinopathies (thyroid gland, diabetes mellitus)
- reflux


Lower esophageal sphincter fails to relax
Lower esophageal sphincter
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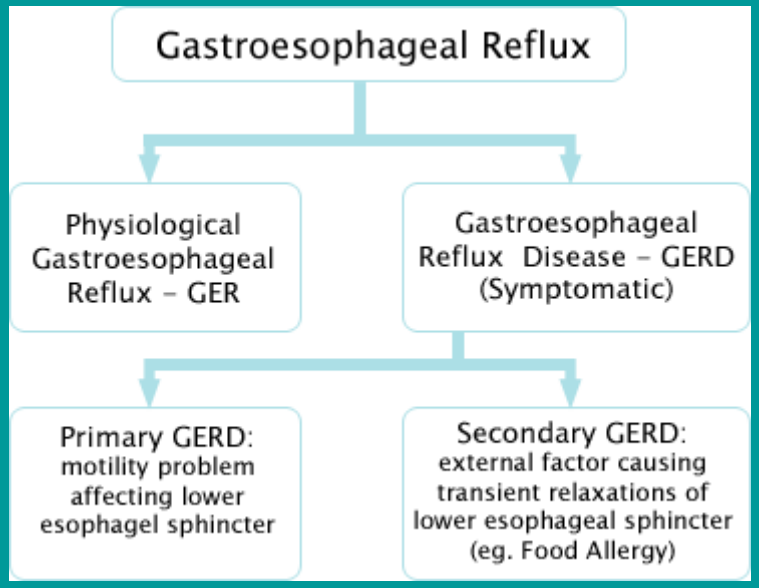
Gastrooesophageal reflux

- gastrooesophageal reflux
  reflux oesophagitis
  GERD – gastroesophageal reflux disease
- definition: retrograde shift of the stomach content into oesophagus
  main compounds: HCl, proteinases, bile (at contemporary existing duodenogastric reflux)
  in 7% of healthy persons – pyrosis
- etiology: conditions resulting in persistent/repetitive acid exposure (also proteinases and bile) to esophageal mucosa (any disorder that diminishes LES tone, increases gastric volume and pressure and acid production)
- clinical manifestation: heartburn - usual symptom → complications – strictures in the distal esophagus → dysphagia;
  hemorrhage, perforation, aspiration of the gastric content → risk of the aspiration pneumonia

Gastroesophageal reflux - complications

- reflux oesophagitis – ulceration, strictures, bleeding
- Barret´s oesophagus (in 14% of patients); metaplasia (squamous epithelium is substituted for columnar epithelium [higher resistance against HCl and proteases])
  metaplasia → dysplasia → adenocarcinoma (incidence 40x higher than in normal healthy population)
  clinical signs: pyrosis, dysphagia, regurgitation of gastric content → risk of aspiration
- GERD
  disturbance of the motility
  -"- -"- LES relaxation
  prolonged gastric emptying
  esophageal ulcers


Gastroesophageal Reflux
Physiological Gastroesophageal Reflux – GER
Gastroesophageal Reflux Disease – GERD (Symptomatic)
Primary GERD: motility problem affecting lower esophagel sphincter
Secondary GERD: external factor causing transient relaxations of lower esophageal sphincter (eg. Food Allergy)

- acute inflammation – GER
  bacterial toxins
  acids / lyes
- chronic inflammation – GER
  upon stenosis (scarring, achalasia, tumors)

- oesophageal ulcers – GER, ulcer disease, gastrinoma

- diverticuli – may content meal, consequently infection, risk of perforation

- varices
  pathogenesis: hypertension in *v. portae* (cirrhosis, trombus in *v. portae*
  important – **at the meal transport possibility of the bleeding (!!!)**

- tumors
  benign
  malignant – squamous cell carcinoma, adenocarcinoma

Review questions

- Which of the following substances increases LES pressure?

  A) Progesterone
  B) Nitric oxide (NO)
  C) Acetylcholine
  D) Vasoactive intestinal polypeptide (VIP)

- **Correct answer is C**
  Progesterone relaxes smooth muscle cells (from theese cells is composed LES), it produces LES relaxation
  Acetylcholine is released from postganglionic neurons, it stimulates or contracts smooth muscle cells, increases LES pressure
  The other postganglionic neuron releases noncholinergic nonadrenergic inhibitory neurotransmitters, which causes smooth muscle relaxation. VIP and NO are two of these neurotransmitters

Review questions

- The mechanism responsible for gastroesophageal reflux (GER) in most patients is:

  A) transient lower esophageal sphincter (LES) relaxation
  B) poor esophageal peristalsis
  C) delayed gastric emptying
  D) persistently weak LES pressure

- **Correct answer is A**
  All of these mechanisms listed contribute to or exacerbate GER. Transient LES rexations have be found to be the most important cause of GERD in healthy individuals and in those with esophagitis

Review questions

- The diagnostic test considered the gold standard for measuring GER is:

  A) endoskopy
  B) 24-hour ambulatory pH monitoring
  C) esophageal manometry
  D) barium esophagography

- **Correct answer is B**
  Endoskopy is a best test for detecting mucosal disease, including esophagitis and Barret´s esophagus. Mucosal disease is app. in 60% of the patients.
  Esophageal manometry evaluates the motility of the esophagus inc. LES pressure and esophageal peristalsis. However many patients have pressure normal LES and esophageal peristalsis
  Barium esophagography shows visual image for detection of structural lesions.
  Continual pH monitoring allows an assotiation to be made between the symptoms reported by the patients at a specific point in time with the pH at the same point in time.

Review questions

- Which of the following statesment concerning bleeding from esophageal varices is true?

  A) bleeding is often minimal and does not necessarily require blood transfusion
  B) variceal bleeding is not affected by the hepatic venous pressure
  C) treatment may include sclerotherapy, banding, transjugular intrahepatic portal systemic shunts, or surgery
  D) the mortality rate of a first variceal bleeding is 20% in patients with liver failure

- **Correct answer is C**
  Treatment may include all modalities mentioned in C, may also include agents to decrease portal pressure. Bleeding is usually massive, it is in relationship with portal hypertension.
  Mortality rate for first variceal bleeding in patients with normal liver function is 20% but 60% for those with liver failure

Stomach

- motor and secretory function

- motor function
  - gastric relaxation
  - contraction both of the gastric body and antrum
  - own peristalsis (slow waves – basic electric rhytm – 3 cycles / min

- secretory function
  - glands in cardia → mucus (it contains HCO_3^-)
  - parietal cells → HCL, intrinsic factor
  - chief cells → pepsinogen A and C, HCO_3^-, acid lipase,

Disturbance of the gastric motility

- **deceleration**
  organic causes — carcinoma, chronic peptic ulcer, pylorostenosis
  functional -"- — abdominal trauma, hypokalemia, disturbance of vagal innervation, hypothyroidism, diabetes mellitus
- **acceleration**
  less frequent, usually at hyperthyroidism

- **vomiting**
  control: from the centrum for vomiting in medulla
  activation of autonomic nerves (palpitations, tachypnoe, tachycardia, arrhytmias, mydriasis – sometimes bradycardia, hypotension)
  nausea – sometimes before vomiting
- at long-term vomiting: loss of H^+, ions and water
  metabolic alkalosis, dehydration

Disturbance of gastric secretion

- gastric secretion – decline in course of ageing; at diseases of stomach
- acc. to volume of released gastric juice hyper-, hyposecretion
- acc. to HCl production hyperacidity (hyperchlorhydria)
  hyp(o)acidity (hypochlorhydria)
  achylia gastrica ⟶ no HCl, no enzymes
- **increase** of secretion:
  short-term – acute inflammatory process, excitation of mucose – food, infection, Et-OH
  long-term + proteinases + hyperacidity – peptic ulcer, liver disease, hypercalcemia
- **decrease** of the secretion
  either volume, or HCl, proteinases, intrinsic factor or all
  achlorhydria and achylia – accompanied with atrophic gastritis

Peptic ulcer

- Davenport (1932): HCl in stomach = ulcer, no HCl = no ulcer
- discordance among protective and aggressive factors
- protective factors:
  mucose layer (mucus, HCO_3^-, phospholipids, water),HCO_3^-, prostaglandins (inhibition of H^+, creation of HCO_3^-), intact perfusion
- aggressive factors:
  HCl – activation of the proteinases
  pepsin, gastrixin
  decreased production of prostaglandins (!!! non-steroid antiinflammatory drugs)
  helicobacter pylori infection
  (releasing of proteases, gastrin overproduction, stop of granulocyte migration, arrest of phagocytosis)


Heliobacter pylori.

Peptic Ulcer Disease

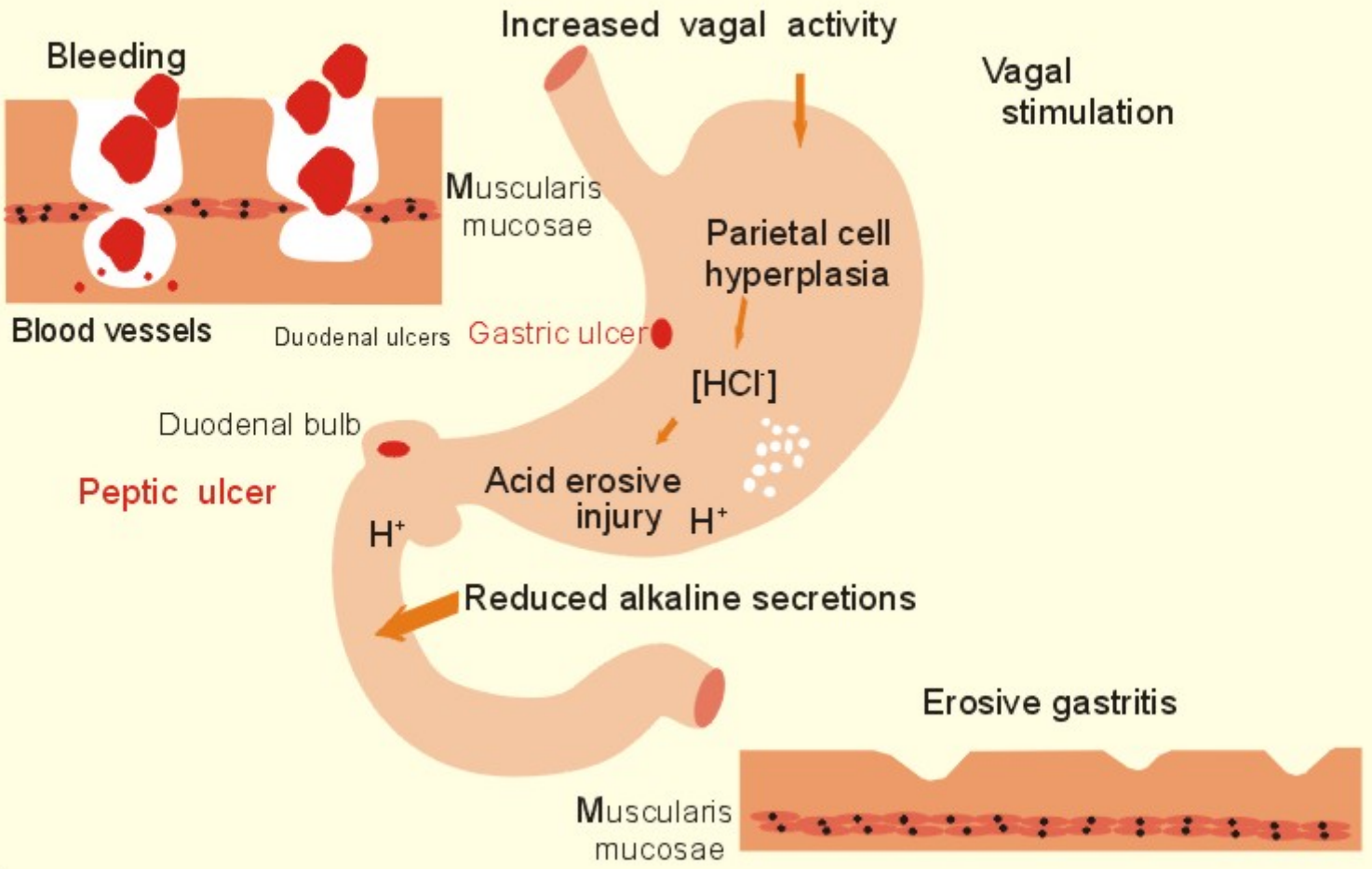


Fig. 22-18

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Gastric ulcer II.

some GU are related to impaired mucosal defense (acid and pepsin secretory capacity is normal or even below normal)

motility defects – duodeno-gastric reflux (esp. bile can lead to diminished mucosal barrier against acid and pepsin)

delayed gastric emptying (food retention) results in increse gastrin secretion and acid production

mucosal ischemia – prostaglandins increase mucosal blood flow, bicarbonate and mucus secretion → stimulation of mucosal cell repair and renewal

Gastric ulcer III.

Clinical signs:

abdominal and epigastric pain
nausea, vomiting

Review questions

- Which of the following mechanisms is involved in stimulation of acid secretion during **prandial** phase of gastric acid secretion

  1) bile reflux into stomach
  2) entrance of HCO_3^- into the gastric cavity
  3) entrance of food (chymus) into the colon activates HCl production
  4) sight, smell or taste of food can stimulate acid secretion

- **Correct answer is D**
  The only mechanism listed in the question that stimulates acid secretion in prandial phase of gastric acid secretion is thought, sight, smell or taste of food

Review questions

- The pathogenesis of peptic ulcer disease (PUD) is now felt to be an imbalance between aggressive and defensive factors in mucosal lining of the stomach and small intestine. Which of the following aggressive factors is most important in the production of gastric ulcer?

  A) pepsin
  B) bile
  C) *Helicobacter pylori*
  D) Alcohol, tobacco

- **Corect answer is C**
  All listed factors are aggressive. However, it has become clear that the most aggressive factor is *Helicobacter pylori*. This is most common infection of humans in the world today and has been clearly shown to play an important role of pathogenesi of peptic ulcer.

Review questions

- Which of the following questions about *H. pylori* is true?

  A) it is associated with 80% of gastric ulcers and 95% of duodenal ulcers in the absence of nonsteroidal anti-inflammatory drugs
  B) positive serology indicates the presence of ulcers
  C) residence in developing countries is not a risk factor for infection
  D) elimination of the organism has no effect on the reccurence of ulcers

- **Correct answer is A**
  Positive result of serologic testing indicates only that the patient has been exposed to the organism in the past, not the presence of ulcers.
  Residence in developing countries is a risk factor for ulcers, and treatment will reduce the reccurence.

Gastrinoma (Zollinger-Ellison´s syndrome)

- tumor derived from D(δ)-cells of Langerhans islets
  overproduction of gastrin ⟶ HCl
  local invasive tumor; mostly creation of metastases
  part of MEN I

- characterization: continual high secretion of gastric juice + high amount of HCl and proteinases; incidence of the ulcers in atypical location (oesophagus, proximal and distal part of duodenum, jejunum)

- source of overproduced gastrin may be in tissue surrounding pancreas and in duodenum

Gastritis

- acute gastritis (gastroenteritis) — bacterial, viral infection; alimentary origin

- chronic gastritis
  - superficial gastritis
  - gastritis in deeper layers of mucose and submucose
  - atrophic gastritis with loss of mucosal glands
  - atrophic gastritis with intestinal metaplasia

Acute erosive gastritis

includes
1. inflammation due to superficial mucosal injury
2. mucosal erosion

etiology – alcohol, smoking, drugs, stress

pathogenesis – acid hyperesecretion
gastric hypoxia
alteration of defense mechanisms, espec. diminished mucus secretion, prostaglandin production
reduced intramucosal pH

clinical signs abdominal or chest pain

hyperacidity and fail in defense mechanisms → gastric ulcer

Chronic athrophic gastritis

characterization:
inflammatory cell infiltration
gastric mucosal atrophy
loss of glands
reduced capacity to secrete gastric acid

Atrophic gastritis type A = autoimmune disease;
Ab against intrinsic factor (IFA=intrinsic factor antibody)
against complex intrinsic factor + vit. B_{12}
against parietal cells.
$CD8^+$ are activated
consequnces = achlorhydria (high level of gastrin in serum)
megaloblastic anemia, adenocarcinoma

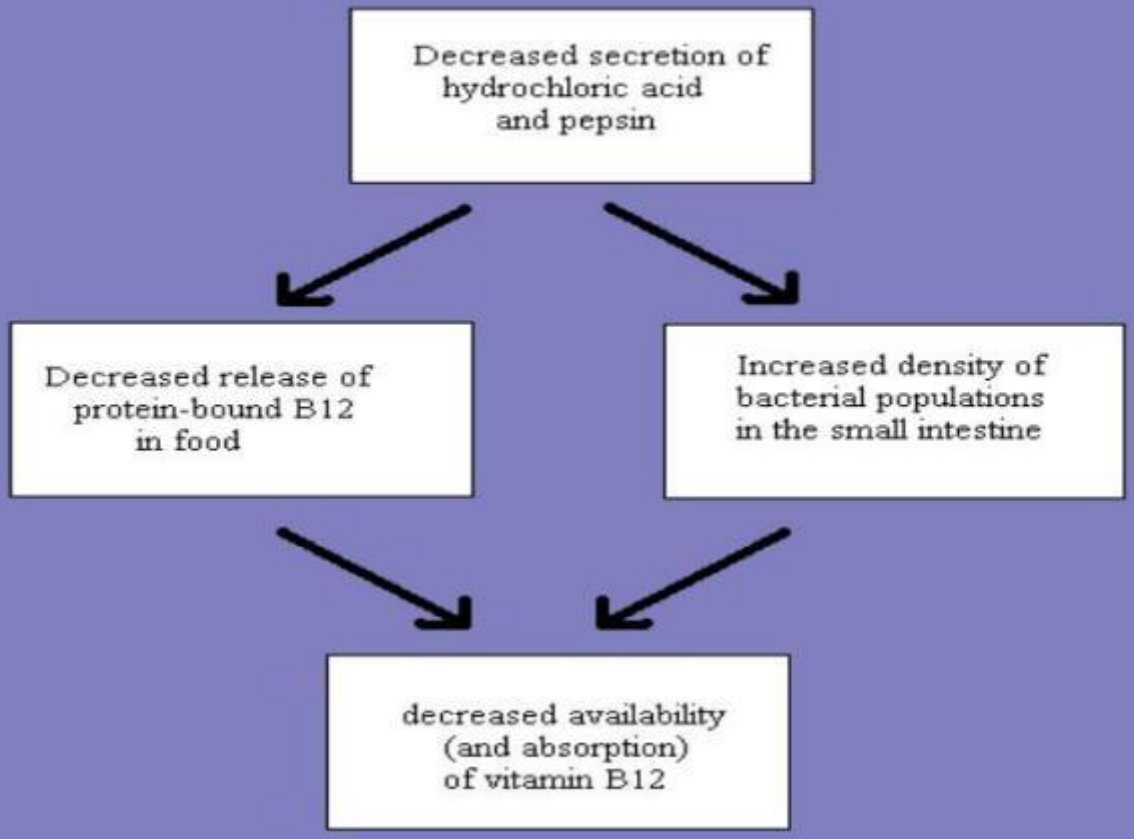
Chronic atrophic gastritis

- **chronic gastritis type B**
  in 90% of cases *Helicobacter pylori* infection
  after removing of *H. pylori* possibility of healing

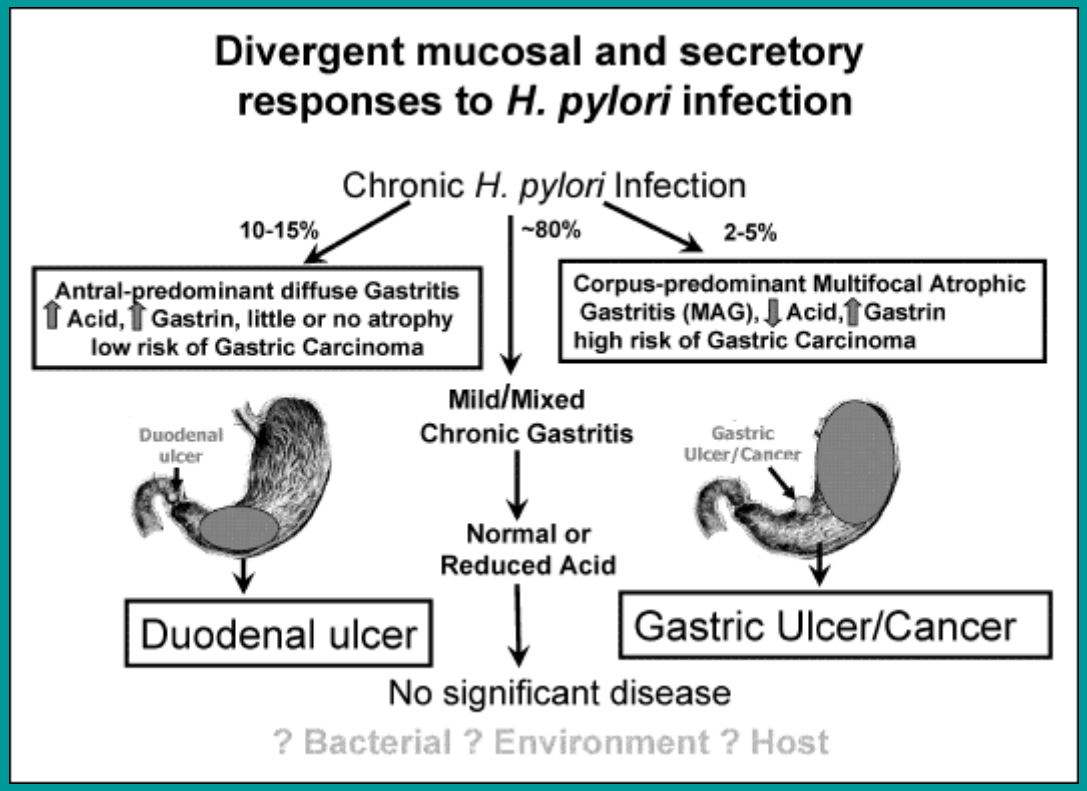
- close relationship with duodenal and gastric ulcers

- gastritis with intestinal metaplasia ⟹ risk for adenocarcinoma

Consequences of Atrophic Gastritis: Vit B_{12}



Divergent mucosal and secretory responses to *H. pylori* infection



Review questions

- Synthesis of gastrin is realized in
  A) A(α)-cells of Langerhans islets
  B) D(δ)-cells of Langerhans islets
  C) B(β)-cells of Langerhans islets
  D) F(PP)-cells of Langerhans islets

- **Correct answer is B**
  A-cells produce proglucagon, glucagon, GLP-1, GLP-2
  B-cells produce proinsulin, insulin, C-peptide, amylin, GABA
  F-cells produce pancreatic polypeptide
  D-cells produce somatostatin, gastrin. Physiological production of gastrin is insignificant. High production in seen at tumor from these cells (gastrinoma)

Review questions

- **Atrophic gastritis B** prevalently rises owing to
  A) cytotoxic effect of $CD8^+$ lymphocytes
  B) production of autoantibodies against intrinsic factor
  C) production of autoantibodies against complex intrinsic factor-vit. B_{12}
  D) *Helicobacter pylori* infection

- **Correct answer is D**
  Answers A, B and C are typical for atrophic gastritis A.
  Atrophic gastritis B is prevalently caused by *Helicobacter pylori* infection

Disturbances of duodenum

- function: gastric emptying
  alkalization of duodenal content
  stimulation of gastric, bile and pancreatic juice secretion,
  duodenal juice contents mucus and high amount of HCO_3^-

- diseases: inflammation (bulbitis)
  ulcus bulbi duodeni (UBD)
  tumors benign
  malignant (carcinoma, lyphoma etc.)

Duodenal ulcer

extends through the mucosa and muscularis mucosa into submucosa

occurs more frequently in men and in patients with blood group O

pathogenesis

1. increased acid and peptic secretory capacity
2. increased basal acid secretion
3. increased postprandial acid secretory response due to increased sensitivity parietal cells to gastrin
4. rapid gastric emptying

etiology – genetic factors, psychologic stress, diet, smoking, ethanol consumption, *Helicobacter pylori* infection (high production of gastrin) – eradication of *H.p.* reduces relaps in 70%, non-steroid inflammatory drugs

clinical signs – ulcer may erode into blood vessels → bleeding, through duodenum → perforation, peritonitis; it can penetrate into surrounding tissues and organs (pancreatic pain), abdominal pain

Small bowel

anatomic structure + physiologic functions (secretion + intestinal motility) → primary function = absorption
abnormalities → variety of syndromes (e.g. diarrhea, malabsorption, motility disorders)

intestinal immune system
intestinal mucosa represents effective defence mechanism against large amount of antigens from meal and external environment
throughout the small intestine and colon are nodules of lymphoid tissue, they are visible within the ileum as *Payer´s patches.*
The surface epithelium over noduli contains columnar absorptive cells + M (membranous) cells, theese M-cells transport antigens to underlying lymphocytes
T-lympho are scattered within the surface of epithelium (CD8). The lamina propria contains CD4 and activates B-lympho
The lymphoid nodules, mucosal lymphocytes + isolated lymphoid follicles and mesenteric lymph nodes constitute MALT (Mucosa-associated Lymphoid Tissue)

Review questions

- What of the folowing statements concerning intraepithelial lymphocytes is true?

  A) most intraepithelial lymphocytes are T-cells
  B) they function as helper cells in mucosal immunity
  C) their population size generally remains stable in most mucosal inflammatory states
  D) they are not specific to any one region

- **Correct answer is A**
  Intraepithelial lymphocytes are mostly T-lymphocytes which bear CD8 receptor. Their number greatly increases during disease states such as celiac sprue or GvHD. These cells are regionally specific and are thought to play a role in controlling mucosal abnormalities.

Absorption

small bowel mucosa = enormous surface area → efficient absorption

plasma membrane of enterocytes = barrier to the non specific movement of ions

crypt cells are responsible for secretory activity

villous cells are responsible for absorption

Absorption

- **iron and folic acid** – primarily absorbed in the duodenum
- **vit. B_{12}, bile salts**– absorption in the ileum
- **carbohydrates** – are ingested in the form starch, glycogen and varietry of disacharides. Starch and glycogen are hydrolyzed by pancreatic as well as salivary amylase → oligosacharides and disacharides. Disacharidases in enterocytes finish digestion
- **proteins** – pancreatic proteases (trypsin, chymotrypsin) convert peptide chains to di-, tripeptides and free AA. Aminopeptidases and carboxypeptidases → free AA
- **lipids** – digested in jejunum. Lipase → free FA + glycerol. Phospholipase converts lecithin to lysolecithin
- **water and electrolytes** – app. 9 L/day of fluid is produced, 90% is absorbed
  K^+ - passive transport, Na^+ , Cl^- - active transport

Diarrhoea

Definition: bowel movements, which are excessive in volume, frequency, liquidity (acc. clinicals: > 200g of the stool / day)

pseudodiarrhea – production frequent loss of stool (150 g/ day) without changes in consistency

small intestine – predominant site for fluid absorption – stool is voluminous

colonic pathology → small volume diarrhea

Diarhea II.

- acute x chronic
- osmotic diarhea – nonabsorbable substrates cause increased osmotic load, draw water into the lumen
- secretory diarhea (large volum dia.) ← excessive mucosal secretion of fluid + electrolytes. Regulatory peptides (eg. VIP) stimulate chloride + water secretion.
- malabsorptive diarhea – ability of digest or absorb a particular nutrient is defective

- osmotic diarhea is dependent upon presence of osmotically active substances (eg. sugars), secretory diarhea is improved in a fasting state

Diarhea III.

- **inflammatory diarrhea** – associated with mucosal damage
  stool contains great number of granulocytes, may contain blood, systemic symptoms may be present

- **non-inflammatory diarrhea** – as a result of influence mainly toxicogenic *Escherichia coli,* viruses, cathartic, neuroendocrine tumors

Types + etiologic factors of the diarrhea

- **acute infectious diarrhea** – non-inflammatory (decreased fluid absorption + increased secretion) – rotaviri, Norwalk like virus
  inflammatory – variety bacterial, viral, parasitic, fungal agents
- **chronic infectious diarrhea**
  1. postenteric diarrhea – infection is resolved, residual effect is stil present
  2. chronic persistence of infection
- **cholera** – *Vibrio cholerae* – waterborne diarrheal ilness – mild to lifethreatening in severity. Most patients respond well to re-hydration consisting of glucose, electrolytes and water (glucose cotransport with sodium remains intact)
- **inflammatory diseases** → mucosal damage + altered cell permeability
  histamine, leukotriens, prostaglandins, some of neurotransmiters (subst. P) also lead to diarrhea
  healing by fibrosis and strictures → intestinal obstruction

Diarrhea - consequences

- **acute diarrhea**
  dehydration
  loss of electrolytes
  metabolic acidosis (due to loss of HCO_3^-)

- **chronic diarrhea**
  steatorrhea
  deficit of fatsoluble vitamins (disturbance in calcium and phosphate balance, bleeding etc)

Malabsorption

malabsorption may involve one or many substances; consequent patterns of nutritional deficiency are often similar regardless of the primary pathological lesion

excesive absorption
iron (in hemochromatosis)
copper (in hepatolenticular degeneration – Wilson´s disease)

carbohydrates, proteins, fat – can be malabsorbed, but term malabsorption commonly means fat malabsorption
fat malabsorption ← (1) maldigestion of intraluminal content owing to exocrine pancreas insuficiency (acute, chronic pancreatitis, cystic fibrosis), (2) malabsorption postmucosally – result of lymphatic obstruction, (3) malabsorption by the mucosa

Causes of malabsorption

- primary diseases of intestinal mucosa (disturbance in enterocyte enzymes)
- systemic diseases (involvement of mucosa or mesenteric lymphatic vessels)
- faulty digestion of food due to secretory disorders
- abbreviated contact between nutrients and mucosa
- inadequate mucosal surface available for absorption
- competition of bacteria and nutrients
- infective, toxic and nutritional factors

Some examples of malabsorption

celiac sprue – disease is activated by the ingestion of gluten (major disease activating component = α-gliadin) + similar proteins from rye, oats, barley) → damage of mucosa
genetic factors play role,as well as immunological factors (humoral + cell mediated immunity)
IgG and IgA antibodies to gliadin were estimated in patients with active disease, partially treated disease, asymptomatic disease
in mucosa = increeased number of intraepithelial lymphocytes bearing TCR
clinical picture: steatorrhea, weight loss, watery diarrhea
deficiency of iron, fatsoluble vitamins + other nutrients → anemia, osteoporosis, bleeding states, neurologic symptoms (parestesia, sensory abnormalities) Therapy: diet without gluten.

Tropical sprue
cause: persistent contamination of mucosa by coliform bacteria (*Klebsiella, Enterobacter cloacae, Escherichia coli*) – toxins make structural abnormality of mucosa
signs: megaloblastic anemia (folate deficiency), watery diarrhea, abdominal cramps, increased flatulence

Other malabsorptive conditions

Eosinophilic gastroenteritis – diffuse eosinophilic infiltration of the GIT (esophagus, colon, bladder, liver are oft infiltrated)
pathogenesis: food allergy (in children milk, in adults eggs, grains, beef, chicken)
mechanism of disease: genetic predisposition to form IgE antibody to specific food antigen. Many patients show systemic allergic reaction
signs: diarrhea, abdominal pain, weight loss, bleeding, edema

bacterial overgrowth – nutrients are consumed by bacteria in small bowel stasis (tumors, scarring)

common **immunodeficiency syndromes** → malabsorption

Small bowel malignanties

tumors make up less than 1% of all malignanties in GIT
malignant tumors = 50-60% of small bowel tumors, are usually fatal
in descending order adenocarcinoma, carcinoid, lymphoma, sarcoma
annual incidence: app. 2 cases / million, tumors are more prominent in male over age 60

The relative rarity may be explained:

1. small bowel has low bacterial counts, anaerobic bacteria (risk factor in colon cancer) are usually absent
2. rapid transit time, mostly liquid nature of the contents
3. phenomenon of apoptosis – body prevents itself

Carcinoid

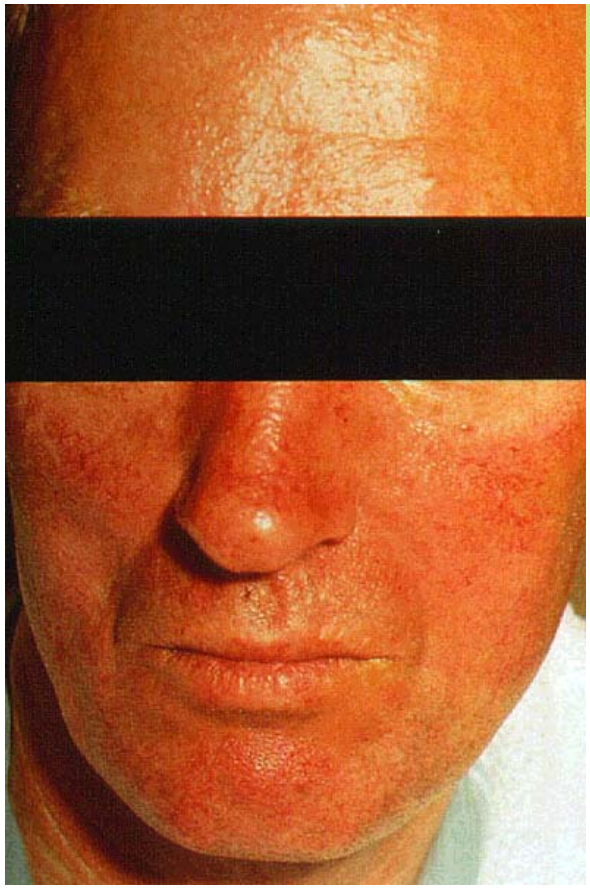
- malignant tumor with endocrine traits
- 70% of carcinoids are in appendix and ileum
- all carcinoids secrete serotonin (5-0H-tryptamin)
- further location: foregut, lung, pancreas, stomach, duodenum

- clinical features:

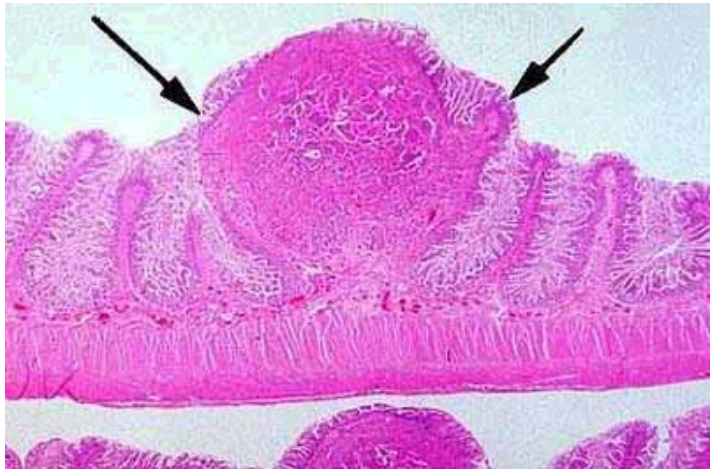
1. vasomotor disturbances – cutaneous flushes, cyanosis
2. intestinal hypermotility – diarrhea, cramps, nausea, vomiting
3. asthmatic bronchoconstrictive attack
4. hepatomegaly
5. systemic fibrosis

Charakteristické syndromy

Flash syndrom (součást syndromu karcinoidu)



Typický flush obličeje po paroxysmálním uvolnění hormonů z karcinoidu



Karcinoid ve sliznici ilea

Inflammatory bowel disease

there are two forms of the chronic noninfectious gastrointestinal inflammation – chronic relapsing disorders

1. Crohn´s disease
2. ulcerative colitis

both diseases result = from abberant host immune response to normal antigens in GIT

disruption of gene for IL-10 ---- Crohn´s disease
-"- of gene for TCR + IL-2 ---- ulcerative colitis

etiology: genetic predisposition, infectious causes

Crohn's disease

features: sharp demarcation of diseased bowel segment from adjacent uninvolved segments
traits: intestinal wall is rubbery and thick (result of edema, inflammation, fibrosis, hypertrophy of *muscularis propria)* – lumen is almost always narrowed
location: typically in distal ileum or the colon, anywhere in GIT (from mouth to anus)
complications: bleeding, anemia, fibrosis - constipation, perforation, marked loss of albumine (protein-losing enteropathy) malabsorption, specific malabsorption of vit. B_{12}, bile salts increased risk of cancer in GIT
extraintestinal manifestation: migratory polyarthritis, sacroiliitis primary sclerosing cholangoitis

Ulcerative colitis

-inflammatory disease limited to the colon, afecting only mucosa + submucosa

- extends proximally from the rectum

extraintestinal manifestation similar to Crohn´s disease

characterization – attacks of bloody mucoid diarrhea – serious bleeding, fluid and electrolyte imbalance

high risk of cancer of the colon

Review questions

- Which of the following is an extraintestinal manifestation of inflammatory bowel disease (IBD):

  A) primary biliary cirrhosis
  B) primary sclerosing cholangoitis
  C) rheumatoid arthritis
  D) erythema infectiosum

- **Correct answer is B**

  Primary sclerosing cholangoitis is characterized by fibrosing inflammation and may lead to bile duct obliteration, biliary cirrhosis and hepatic failure.
  There are four type of arthritides associated with IBD (peripheral arthritis, spondylitis, sacroiliitis, hypertrophic osteoarthropathy).
  Erythema nodosum and pyoderma gangrenosum are the main skin lesions associated with IBD

Colon

– in cooperation with small bowel – maintaining of the water + electrolyte homeostasis (daily fluid load to the gut = app. 9 liters, small intestine absorbs app. 7 liters, remainig 1500-2000 mL are delivered to the colon, app. 100-200 mL of water are passed in the stool / day

-colon absorbs water, sodium, chloride, secretes potassium + bicarbonate

-colon involves transcellular processes of
1. active transport by Na^+, K^+ ATPase
2. secondary active transport (co-transport of Na, K, Cl)
3. passive diffusion

Constipation

Pathophysiologic mechanisms most often involve poor colonic propulsive activity

It may be due to:

1. structural causes – benign or malignant tumors, strictures (due to fibrosis, inflammation, diverticular disease, irradiation, IBD)
2. anorectal causes – painful defecation (inflamed hemorrhoids, anal fissures, rectal inflammation, trauma
3. long term immobilization
4. metabolic causes – smooth-muscle disorders, collagen vascular disorders, drug-associated conditions, diabetic neuropathy, hypothyroidism
5. dehydration

Irritable bowel syndrome

motility disorder – absence of organic disease – diarrhea or constipation

sign and symptoms

1. abdominal pain associated with diarrhea or constipation, relieved by defecation or a change of the stool consistency
2. painless diarrhea (in minority of patients)
3. altered frequency of bowel movement
4. sensation of incomplete evacuation
5. passage of mucus upon defecation

psychologic factors exacerbate symptoms of IBS

patients have abnormal myoelectric and motor activity in GIT
(colonic slow wawes in healthy fasting subjects = 3 cycles / min
in patients = 6 cycles / min)

Review questions

- Which of the following factors is part of criteria for irritable bowel syndrome?

  A) negative endoscopy
  B) a negative test for lactose intolerance
  C) abdominal pain associated with a change in stool frequency
  D) abdominal pain associated with a change in stool color

- **Correct answer is C**
  Abdominal pain associated with a change in stool frequency is one of the main criteria for this state.

Review questions

- Fecal incontinence may be idiopathic in etiology but may also be seen in assotiation with:

  A) hypertension
  B) diabetes
  C) peptic ulcer disease
  D) hypothyroidism

- **Correct answer is B**
  Patients with with diabetes mellitus may have incontinence associated with sphincter abnormalities as well as sensory deficit. The other diseases are not associated with incontinence; in fact, hypothyroidism often results in constipation.

Diverticular disease

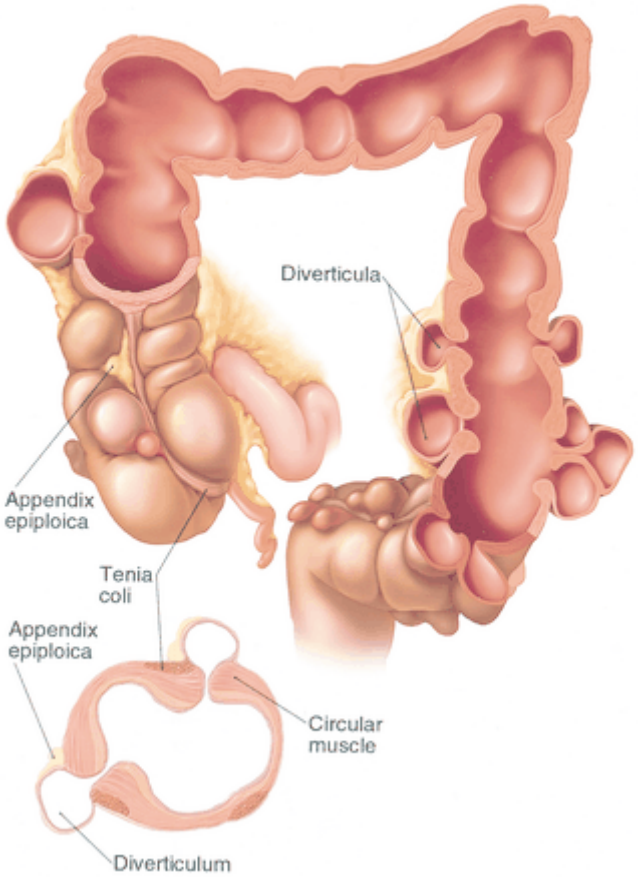
- acquired condition usually asymptomatic

- presence of diverticuli in the colonic wall (it is caused by herniation of mucosa and submucosa through *muscularis propria* into „sites of weaknes“ in the wall (enter of blood vessels into submucosa)

- DD in industrial countries affects 1/3 of persons aged 45 years and 2/3 of patients aged 80 and older. DD is rarity in Africa and Asia

Clinical manifestation:

1. abdominal pain – usually without inflammation
2. inflammation – diverticulitis; localized inflammation = perforation
3. bleeding – usually acute and brisk


Diverticula
Appendix epiploica
Tenia coli
Appendix epiploica
Circular muscle
Diverticulum

Colon polyps

Definition: polyp is an elevation of the colonic mucosa with tissue proliferation that protrudes from the colonic wall into the lumen

Classification: non-neoplastic polyps = hyperplastic
inflammatory polyps
neoplastic polyps = benign (adenoma)
malignant (carcinoma)

Adenoma – carcinoma sequence

Cellular dysplasia = histologic feature common to both types of neoplastic polyps

adenomatous epithelium is characterized by abnormal cell diferentiation resulting in hypercelularity of colonic crypts

adenomatous polyps → malignant potential

adenoma- carcinoma sequence typically raises over decade, proceeds from normal mucosa with cellular proliferation, oncogene activation, mutation of tumor-suppressor genes and chromosomal deletion to adenoma formation increasing of dysplasia in the adenomatous polyp → development of adenocarcinoma

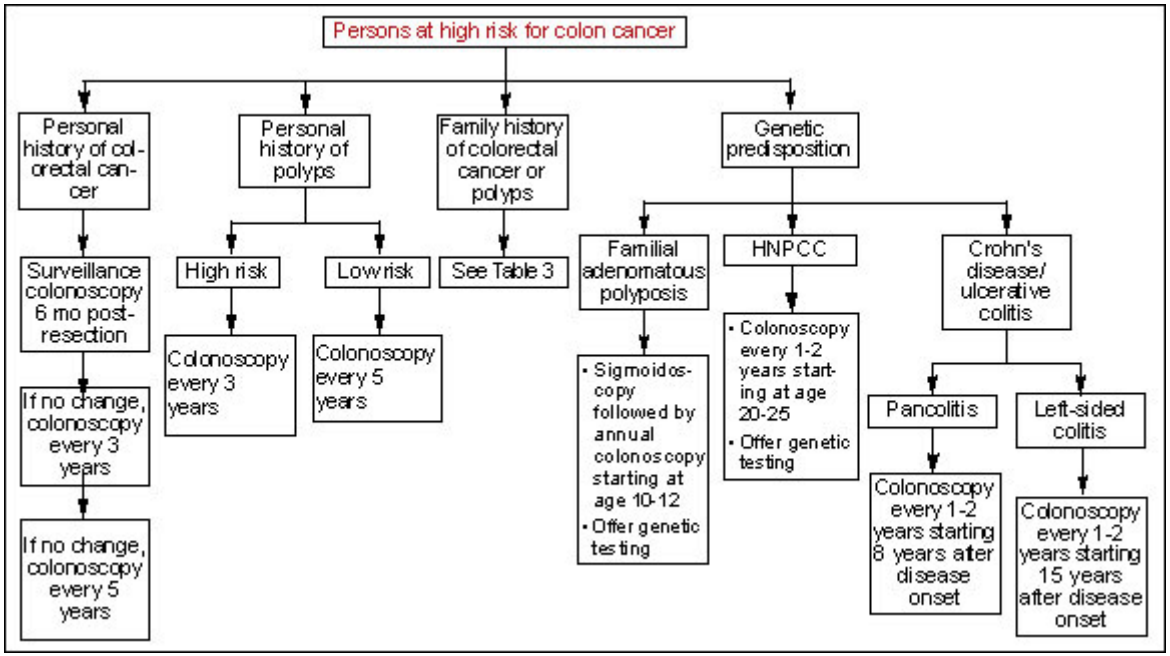
Colorectal cancer

most frequent neoplasm of the GIT, most common cause of the cancer mortality

etiology:
genetic predisposition: Gardner´syndrome, familial polyposis = ass. with adenomatous polyps (100 and more)
ulcerative colitis
age – incidence is very low before age 40
increased fat intake + decreased fiber in diet

pathogenesis: adenoma-cancer sequence, mutation of tumor-supressor genes (APC, DCC)

clinical features:
CC=usually asymptomatic; rectal bleeding → iron deficiency anemia
lower abdominal pain, constipation


Persons at high risk for colon cancer
Personal history of colorectal cancer
Surveillance colonoscopy 6 mo post-resection
If no change, colonoscopy every 3 years
If no change, colonoscopy every 5 years
Personal history of polyps
High risk
Colonoscopy every 3 years
Low risk
Colonoscopy every 5 years
Family history of colorectal cancer or polyps
See Table 3
Genetic predisposition
Familial adenomatous polyposis
• Sigmoidoscopy followed by annual colonoscopy starting at age 10-12
• Offer genetic testing
HNPCC
• Colonoscopy every 1-2 years starting at age 20-25
• Offer genetic testing
Crohn's disease/ ulcerative colitis
Pancolitis
Colonoscopy every 1-2 years starting 8 years after disease onset
Left-sided colitis
Colonoscopy every 1-2 years starting 15 years after disease onset

Disturbance of the exocrine pancreas

- exocrine part = 84 %, endocrine part = 2 %, remain = vessels, ducti etc.
- pancreatic juice: H_2O, Na^+, K^+, HCO_3^-
  enzymes in active form: lipase, amylase, ribo-, deoxyribonuclease
  proenzymes: trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, prophospholipase A_2
  another proteins: plasma proteins, mucoproteins,α_1-antitrypsin
- HCO_3 in juice 140 mmol / L (plasma level 24 mmo / L), pH = 8,3
- enterokinase ⟶ trypsinogen ⟶ trypsin + conversion proenzymes
- secretion control:
  secretin (stimulation by gastric juice, peptides, AAs) ⟶ H_2O, HCO_3^-
  cholecystokinin (stim. by FA + peptides) ⟶ enzymes, little of HCO_3^-
- diurnal secretion: 1000 – 1500 m / day

Changes in pancreatic juice secretion

- increased — rarely
  decreased — in pancreatic insuficiency

- achylia pancreatica (arrest of the secretion) – in heavy diffuse damage of the pancreatic tissue – pancreatic insufficiency – (pancreatitis, tumor, protein malnutrition)

Acute pancreatitis

- **pathogenesis** – in ICF and ECF activation of trypsinogen ⟶ trypsin ⟶ activation of further proenzymes (proelastase, prophospholipase A_2) which then take part in process autodigestion
- elastase ⟶ destruction of blood vessels with interstitial hemorhage
- necrosis of fat by lipolytic enzymes (pancreatic lipase, phospholipase A_2) ⟶ creation of lyzo- compounds ⟶ damage of cell membranes

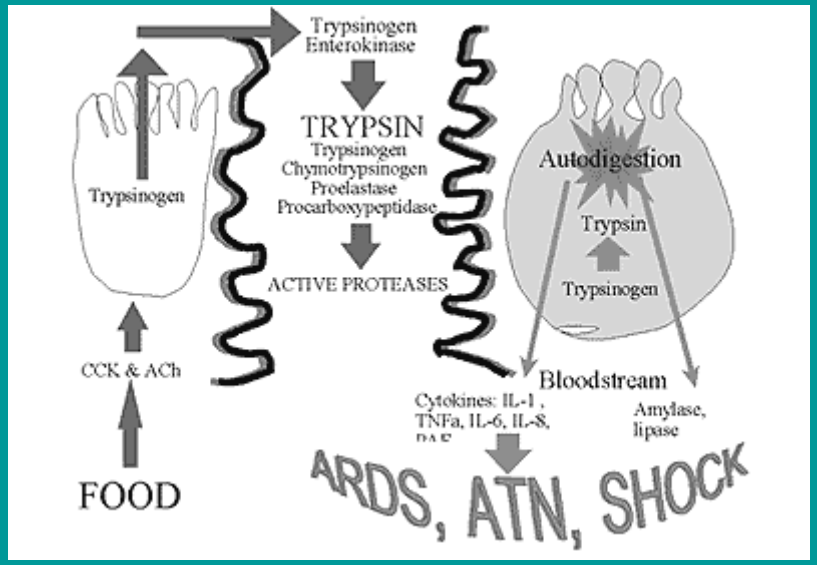
  damage of lung and kidney function
- proteolytic destruction of pancreatic cells
- kalikreinogen ⟶ kalikrein ⟶ **vasodilation + increased permeability** of cell wall ⟶ shock
- enzymes in interstitium ⟶ inflammatory reaction (release of inflammatory cytokines – IL-1,2,6,8, TNF, PAF)
- acute phase proteins – α_1-antitrypsin, α_2- microglobulin – create irreversible complexes with trypsin, chymotrypsin and elastase

Acute pancreatitis - etiology

- most often: alcohol abuse, occlusion of pancreatic ducts by gallstones
- **alcohol** – toxic influence on cells, inflammation of Oddi´s sphincter alcohol-induced oxidative stress generates free radicals in acinar cells → abnormality of protein secretion, acinar cell necrosis, inflammation
- **biliary tract** – occlusion (stricture, gallstones) → crossing passage of infection as well as bile acids into pancreatic tissue
- **trauma of abdomen (pancreas), surgery in peritoneal cavity**
- **shock, hypovolemia**
- **viral/bacterial diseases**
- **hypercalcemia** → stone precipitation in ducts; trypsinogen activation
- **hyperlipidemia, hyperlipoproteinemia** → initiation of inflammatory response (free FA)
- **drugs:** cytostatics, corticoids, immuno-suppressive drugs

normal state

acute pancreatitis



Acute pancreatitis – laboratory and clinical findings

- high activity of amylase, lipase
- leukocytosis, hemolysis, DIC, fluid sequestration, systemic organ failure (shock, ARDS, acute renal failure), pancreatic abscess, pancreatic pseudocyst, duodenal obstruction
- abdominal pain – cardinal manifestation

Chronic pancreatitis

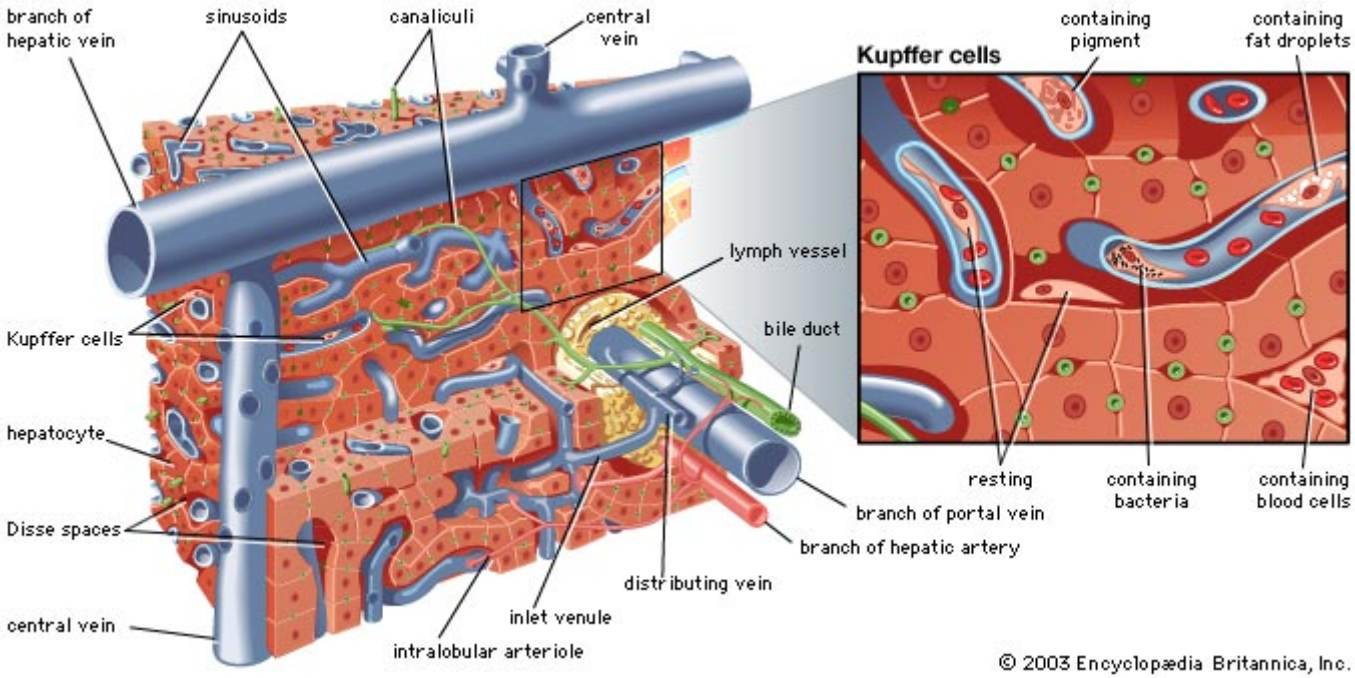
- characterization: chronic inflammation ⟶ destruction of acinar cells, dilation of ducts, calcifications, loss of gland parenchyma and fibrosis
- etiologic factors: **alcohol,** ductal obstruction by concretions (low molecular weight protein *lithostathine* normally inhibits intraluminar precipitation of calcium carbonate – its secretion is disturbed), **protein malnutrition** (acinar cells are extremely sensitive to lack of AA – hypoproteinemia, cirrhosis)
- consequences: pancreatic insufficiency, malabsorption of lipids and vitamins soluble in fats
- complications: cysts (epithelium from dilated ducts), pseudocysts (fibrous wall, pancreatic juice, necrotic debris), from cysts and pseudocysts ⟶ crossing passage of pancreatic juice into peritoneal and chest cavity (lung oedema, ARDS)
  the most severe: hypovolemic shock (ascites, bleeding into peritoneal cavity)

Insufficiency of the pancreas

- disturbance of enzyme production ⟶ maldigestion
  disturbance of lipid cleaving ⟶ steatorhoea
- the most often cause: chronic pancreatitis, cystis fibrosis, tumor, gastrinoma
- signs:
  steatorrhoea, diarrhoea
  hypocalcemia + hypophosphatemia ⟶ disturbance of vit. D_3 resorption
  + Ca^{2+} binding to FA ⟶ non-soluble soaps (prevention of bond Ca^{2+} with oxalate) ⟶ oxaluria – stones
  hypocalcemia ⟶ neurologic signs (tetany), hyperparathyroidism
  vitamin B_{12} deficiency (due to lack of proteases) – from this reason low release of vitamin from transport protein

Liver

- central organ of metabolism
- metabolism of sacharides (glycogenelysis, gluconeogenesis)
- metabolism of lipids – synthesis, β-oxidation, peroxidation of FA, cholesterol, triacylglycerol, phospholipid synthesis, synthesis of keton-bodies (acetico-acetic acid, β-OH-butyric acid, acetone)
- metabolism of AA:
- detoxication: NH_3 (AA desamination: a) ornithin cycle
  b) glutamin synthesis-glutamate+NH_3
  bilirubin-glucuronide etc. – incurred molecules → urine
- hormone degradation, inactivation
- plasma protein synthesis except immunoglobulins, vWf
- store of lipids, glycogene, Fe (ferritin), vit. A,D,K and B_{12}
- hemopoiesis - during embryonal development
  in adult age after bone marrow damage → extramedullary hemopoiesis



Main factors leading to liver damage

- viral hepatitis
- alcohol
- some of toxic substances, some of the drugs
- disturbances of circulation
- hepatic tumors, metastases of tumors into parenchyma
- inborn and acquired metabolic derrangement

Reaction of liver parenchyma on damage

- the changes are independent on the character of etiologic factor
- mild injury ⟶ increasing of cell permeability, deterioration of metabolism in hepatocytes, storage of lipids in the cells ⟶ steatosis
- major injury ⟶ cell death
- long-term or forcible damage ⟶ fibrosis ⟶ **cirrhosis**

Cirrhosis

- irreversible restructuring of the liver – lobuli, vessels, fibrous tissue
  increased creation of fibrous tissue – geniculated rearangement of parenchyma
- disturbance of liver architecture, reduction of blood stream, worsening of liver perfusion
- most often causes:
  chronic hepatitis
  alcohol abuse
  metabolic disturbances
  biliary cirrhosis
- sequelae:
  failure of liver functions
  portal hypertension (ascites, esophageal varixices)
  higher frequention of carcinoma

Hepatitis

- comonly they are mentioned situations evoked by viral infect
  further etiologic factors: alcohol, intoxications, EBV infections, leptospirosis
- course
  acute – mainly without consequences X superacute course → failure
  chronic – relatively benign X aggressive course ⟹ cirrhosis
- hepatitis A – benign course oral-phoecal mode of infection
- hepatitis B – transmision by blood, syringes, sex, transmission mother ⟹ foetus
- hepatitis C – mode of transfer is the same; frequent pass into chronic phase

- hepatitis B and C ⟹ frequent pass into chronic phase
  infection = risk factor for carcinoma

Conseguences of liver damage

- **steatosis** – fat storage in the hepatocytes – sometimes may be reversible (after elimination of the cause)
  causes: alcohol abuse, obesity, DM, gravidity (!)
- **toxic damage**
  causes: intoxication by several toxins and substances (phaloidin, afla – toxin, tetrachlormethane etc.
- **Rey´s syndrome** – in children ⟶ acute liver failure and steatosis
  cause: treatment of the fever by salicylates (no salicylates in children age, only paracetamolum !!!)
- **cholestasis**
  long-term cholestasis ⟶ cirrhosis
- **hepatal tumors**
  primary – hepatoma
  secondary – metastasis
- **metabolic malfunction**
  storage of several substances in hepatocytes
  glycogene ⟶ glycogenosis
  Cu ⟶ Wilson´s disease
  Fe ⟶ hemochromatosis

- **hypertension in v. portae**
  evoked by a) increasing of blood flow resistance
  b) increasing of blood flow in v. portae (late stage of cirrhosis)
  sequelae: splenomegaly, congestion of organs and mucose membranes in GIT; creation of collaterals – portocaval shifts – caput medusae
  esophageal varices
  internal hemorrhoids

- **jaundice (icterus)**
  prehepatal (hemolysis)
  hepatal (inflammation, viral infections)
  posthepatal (gallstones)

- **encephalopathy**
  at advanced stages of liver failure – infiltration of brain tissue by toxic substances (namely NH_3) – creation of false neurotransmitters
  clinicaly: disturbance of consciousness, coma

- **hypalbuminemia, oedema, ascites**

- **bleeding**
  synthesis of coagulating factors in the liver
  bleeding from esophageal varixices

- **disturbances of metabolism**