BIOMEDICÍNSKÉ CENTRUM

LÉKAŘSKÁ FAKULTA V PLZNI
UNIVERZITA KARLOVA V PRAZE

Patophysiology of gastrointestinal tract

EVROPSKÁ UNIE
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INVESTICE DO VAŠÍ BUDOUCNOSTI

OP Výzkum a vývoj pro inovace

PATOPHYSIOLOGY OF ORAL CAVITY

Oral cavity - biting food and mixing with saliva

chewing disorders - in pathological conditions, where chewing or chewing movements cause pain - direct affection of chewing muscles, trigeminal nerve, dental and gum disease, etc.). insufficiently homogenized food gets into the distal parts of digestive tract => digestive disorders (maldigestion).

saliva secretion disorders - the largest volume of saliva is produced by these three paired major salivary glands: *parotid, submandibular, and sublingual*
Salivary glands can be classified as:
- *serous*
- *mucous*
- *seromucous (mixed).*

In addition to mucin and amylase, the saliva contains also lingual lipase, lysozyme, IgA, R-proteins (B12 binding in the stomach), inorganic substances: K, Ca, Cl, Na, I, potassium rhodanide and HCO3 - saliva are de facto bicarbonate buffer = protection of dental enamel, neutralization of the gastric environment.
The water content is >99%.

PATOPHYSIOLOGY OF ORAL CAVITY

Saliva secretion disorders

Decreased saliva secretion

- dehydration (blood loss, diarrhea, uncompensated sweat loss during physical exertion or fever)

- the action of some drugs (antidepressants, antihistamines, sedatives, hypnotics, diuretics, anxiolytics, etc.)

- manifestation of systemic diseases, in particular Sjögren's syndrome:

PATOPHYSIOLOGY OF ORAL CAVITY

Saliva secretion disorders

Sjögren's syndrome

Autoimmune disease - occurs chronically, slowly progressing diffuse, chronic inflammation with destruction of exocrine glands (salivary glands, lacrimal glands, or exocrine pancreatic glands).

occurs by itself and **secondary** - when another connective tissue disease is present. (rheumatoid arthritis, systemic lupus erythematosus, mixed binder disease, systemic vasculitis).

The etiology is idiopathic, the influence of viruses (EBV, CMV), the association in the HLA system is assumed.

Damage to the salivary gland is irreversible. Patients are forced to use moisturizers and stimulants of exocrine secretion of salivary and lacrimal glands.

Salivary gland disorders - swelling, xerostomia (dry mouth) and dysphagia.

Gastrointestinal tract disorders - dysphagia, esophageal motility disorders, atrophic gastritis, decreased secretion of gut epithelium and external pancreas secretion => manifestations of malabsorption syndrome.

a frequent systemic manifestation is hepatitis

PATOPHYSIOLOGY OF ORAL CAVITY

Periodontal disease

- is a set of inflammatory conditions affecting the tissues surrounding the teeth.
- Deep pockets between the teeth and the gums
Loose teeth, in the later stages

The main cause is presence of periodontal pathogens along with the susceptible immune system of the individual

Porphyromonas gingivalis
Treponema denticola
Prevotella intermedia and P. nigrescens
Aggregatibacter actinomycetemcomitans
etc.

In the extreme causes, **a chronically infected wound** with a total area of up to 30 cm^2 is formed in the oral cavity - the risk of penetration of bacteria, their components (LPS), toxins and metabolites into the systém!

The relationship between periodontal disease and other illnesses is still poorly understood. For example, the presence of components of these pathogens in **atherosclerotic plaques**, or association with **endocarditis**, has been demonstrated. Recently, information on the possible association between beta-amyloid deposition and chronic bacterial parodontosis (Front Aging Neurosci 2017; 9: 336) has also been published.

PATOPHYSIOLOGY OF ORAL CAVITY

Gingivitis

- gum inflammation - redness, swelling, bleeding (typically when cleaning teeth).

Etiology: **dental plaque** but also **systemic factors** such as:

endocrine (pregnancy, diabetes),
general disorders (leukemia),
drug use (hormonal contraceptives, hydration, Cyclosporin A, calcium channel blockers).

It may have an acute and chronic form. Very common illness.

PATOPHYSIOLOGY OF ORAL CAVITY

Scurvy

-a manifestation of vitamin C deficiency. Vitamin C (ascorbic acid) is an important antioxidant factor that promotes iron resorption and affects beta-oxidation of fatty acids. It accelerates the detoxification, blocks the formation of carcinogens, promotes immune processes and CNS function.

Vitamin C has a specific role in collagen biosynthesis - a **hydroxylation cofactor when converting proline to hydroxyproline**. Deficiency of vitamin C is therefore manifested by a **functional and connective tissue biosynthesis disorder**, including gums and tooth suspension

As a result of vitamin C deficiency, it first appears in the oral cavity by swelling and gum bleeding.

Previously a typical sailor's disease, today cases of people receiving unbalanced diet, strong smokers, alcoholics, socially disadvantaged (especially homeless) are reported again.

PATOPHYSIOLOGY OF ESOPHAGUS

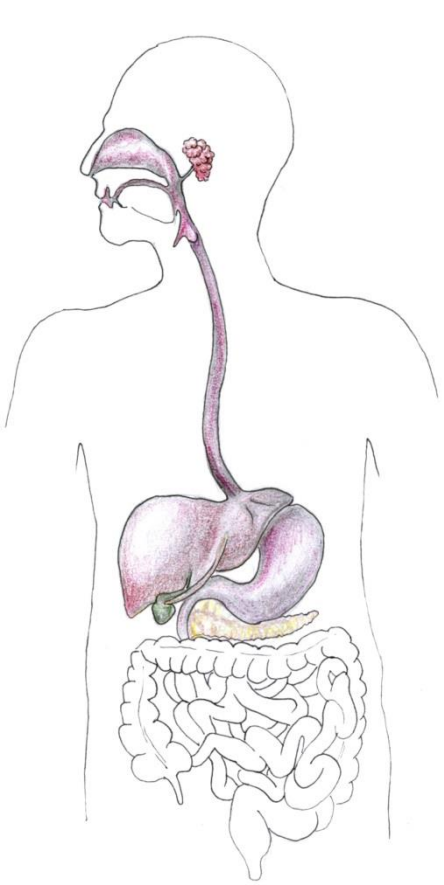
the fluid from the oral cavity passes directly into the oral part of the pharynx

Solid food is moved from the mouth by the tongue toward the pharynx (the **oral phase of swallowing**)

In the **pharyngeal phase of swallowing**, the nasopharyngeal joint is closed by lifting the soft palate and contractions of m. constrictor pharyngis superior. Closing the glottis and lifting the larynx will shortly stop breathing

In the esophageal paroxysmal part of the swallowing, the food is shifted through the peristalsis to the stomach, relaxing the lower esophageal sphincter, and the receptive relaxation of the stomach

Only the oral phase is controllable by will. The process is controlled from the swallowing center in reticular formation of the medulla oblongata



PATOPHYSIOLOGY OF ESOPHAGUS

Dysphagia is *a swallowing disorder*.

Odynophagia is *a painful swallowing*. It is a symptom of organic and functional disorders of the esophagus

Afagia is an *absolute impossibility of swallowing*. The patient is not able to swallow anything.

Dysphagia is classified into the following major types:

- Oropharyngeal dysphagia
- Esophageal and obstructive dysphagia

A. **Oropharyngeal dysphagia** occurs when the food passes from the mouth to the esophagus. Causes may be local (diseases of mouth, tongue, etc.) or mechanical pressure (tumor, foreign body). Others are functional, neuromuscular (myasthenia, thyrotoxicosis, etc.), or in case of poliomyelitis, multiple sclerosis, parkinsonism,

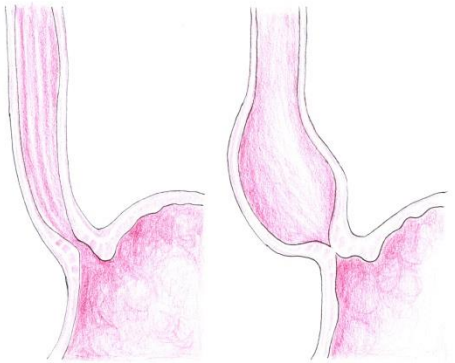
B. **Esophageal and obstructive dysphagia**: The patient swallows food that stops behind the sternum and pushes.

Causes of dysphagia: Neuromuscular, functional swallowing disorder (achalasia, diabetic neuropathy, scleroderma) or mechanical, either inside the esophagus - inflammation, tumor or pressure of the esophagus from outside (mediastinal tumor, lung cancer, aneurysm).
Functional dysphagia is caused by spasms and may be paroxysmal or paradoxical. *Organic dysphagia* is characterized by a constant swallowing disorder (striction, tumor).

PATOPHYSIOLOGY OF ESOPHAGUS

Disorders of the esophagus motility

A. Primary - in diseases directly affecting the esophagus:
Achalasia - loss of esophagus peristalsis, lack of relaxation of the lower sphincter when swallowing => stretching and prolongation of the entire esophagus; food is collected in the esophagus.



Normal Achalasia

etiology is unclear - apparently a failure of innervation and neuromuscular mechanism (demonstrated, for example on the effect of neurotoxins produced by Trypanozoma cruzi).

there are two types of esophageal spasm:
Diffuse esophageal spasm (DES), where there is uncoordinated esophageal contractions where several sections of the esophagus can contract at once.
Nutcracker esophagus (NE) also known as hypertensive peristalsis, where the contractions are coordinated but with an excessive amplitude.

Both conditions can be linked with Gastroesophageal reflux disease (GERD).

PATOPHYSIOLOGY OF ESOPHAGUS

B. Secondary disorders of the esophagus motility
are formed:

a) in systemic diseases of the connective tissue (scleroderma, lupus erythematosus, dermatomyositis, Raynaud's disease, etc.)

b) in neuromuscular diseases (myasthenia gravis)

c) nervous system disorders (Parkinson's disease)

d) metabolic diseases (diabetes mellitus)

e) endocrine disorders (especially thyroid gland)

PATOPHYSIOLOGY OF ESOPHAGUS

Esophageal diverticles

an outpouching of esophagus. It can be classified as:

- true (created by all the anatomical layers)

- false (created only by mucose and submucose outpouching through the muscle layer);

- tractional diverticulum

- pulse (due to increase of intraluminal pressure).

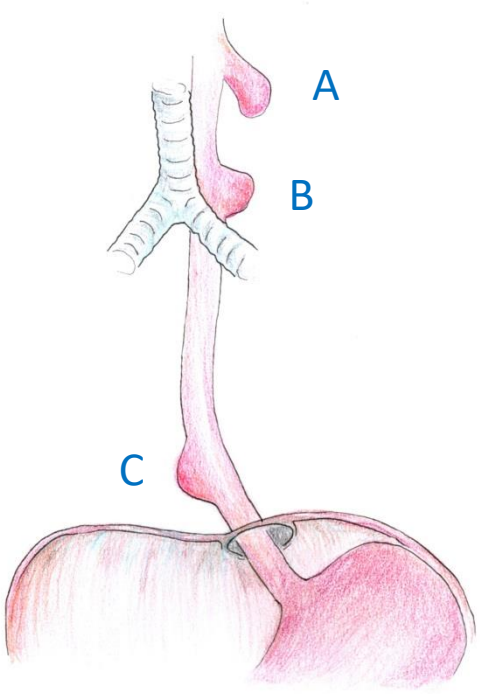
PATOPHYSIOLOGY OF ESOPHAGUS

Common types of diverticles:

Zenker's diverticulum (A) - also pharyngeal pouch, is a diverticulum of the mucosa of the esophagus, just above the cricopharyngeal muscle (i.e. above the upper sphincter of the esophagus).
can be manifested with the following symptoms:
- Dysphagia (difficulty swallowing), and sense of a lump in the throat
- Food might get trapped in the outpouching, leading to:
    Regurgitation, reappearance of ingested food in the mouth
    Cough, due to food regurgitated into the airway
    Halitosis, smelly breath, as stagnant food is digested by microorganisms
    Infection

parabronchial diverticulum (B) – true tractional diverticulum localized in the site of tracheal bifurcation – is formed by pulling on the esophagus wall with a scarred inflammatory process of the mediastinal lymph nodes, clinically it does not usually manifest. In extreme cases, it can be painful

epiphrenic esophageal diverticulum (C) - is an out pouching of esophageal lumen usually situated in the distal part of esophagus. It is typically seen within 10 cm of the cardia and usually originates from the right posterior wall . Clinically manifested as dysphagia



PATOPHYSIOLOGY OF ESOPHAGUS

Corrosive Esophagitis

characterized by caustic injury due to the **ingestion of chemical agents**, mainly alkaline substances or strong acids – attempted suicide, self-harm, accident
In case of acids – coagulation necrosis,
in alkalines - colliquative necrosis, more dangerous – risk of full thickness necrosis, escape of esophageal content and development of mediastinitis.
Can be caused also by some drugs – tablets of acetylsalycilic acid or alendronate

Perforation of the esophagus

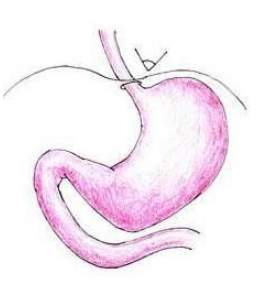
mechanical injuries - occur most often by the ingestion of a sharp body - typically toys in the case of small children, false teeth, fish bones, fruit stones, etc.
A specific problem in psychiatric patients !

Typical complications: bleeding, dysphagia, odynophagia, swelling. Perforation also includes emphysema, parafaryngeal or retropharyngeal abscess or mediastinitis
in a foreign body depends on its localization: often dysphagia or aphagia occurs. Small foreign bodies (fish bones) are often stuck in the pharynx - in tonsils, at the root of the tongue, etc. Larger bodies are stuck most often at the beginning of the esophagus.

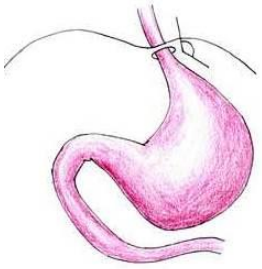
PATOPHYSIOLOGY OF ESOPHAGUS

Hiatal hernia
- moving the cardia and / or part of the stomach from the peritoneal cavity into the chest cavity. Gastroesophageal junction, stomach fundus, or fundus with gastroesophageal junction also get into the mediastinum. The extreme case is the dislocation of the stomach to the mediastinum (so-called upside-down stomach), when cardia and pylorus remain in the abdominal cavity.

False hernia - The stomach (or other intra-abdominal organs) are dislocated into the mediastinum or pleural cavity due to traumatic diaphragm rupture.
Traditional classification of herniae according to Ackerlund (1926):
Type I: Hiatus hernia with (congenital) short esophagus, making reposition impossible
Type II: the para-esophageal type, in which the esophagus is not too short but passes into the abdomen besides the hernia without forming part of the latter
Type III - Other hiatial herniae, in which the esophagus is not too short, but in which the distal portion of the gullet forms part of the hernia


normal


sliding hernia


pre-stage of hernia


paraesophageal hernia

PATOPHYSIOLOGY OF ESOPHAGUS

Reflux oesophageal disease

Gastroesophageal reflux (GER) = a reflux of gastric contents into the esophagus. It is rarely found in all individuals. However, if GER causes symptoms (prolonged exposure to acidic gastric contents in the lumen of the esophagus), it is already a **GERD (gastroesophageal reflux disease).**

Manifested as:
- pyrosis. Initially only after some meals and beverages (sweet cakes, coffee, alcohol ...). Later after each meal or during fasting - especially at night, when the gravitational effect disappears in the lying position. In the extreme case, the risk of inhalation of the stomach content => suffocation, aspiration pneumonia, the case of "only" damage to the larynx and the bronchus with acidic stomach contents.- regurgitation of gastric contents into the esophagus

The transient relaxation of the lower esophageal sphincter is considered the main etiopathogenetic mechanism.
The main causes include:
- lowering the tone of the lower esophageal sphincter,
- antral hypomotility,
- duodenogastric reflux.

the disease is due to the **imbalance of aggressive and protective mechanisms**. More commonly diagnosed in obese, physically inactive men over 55 years of age.
Protective factors include: antireflux barrier (lower esophageal sphincter), luminal oesophageal cleansing and tissue resistance (epithelial integrity).
Aggressive factors include: gastroesophageal and duodenogaster reflux, HCl, pepsin, bile salts, lysolecithin and pancreatic enzymes.
The severity of oesophagitis caused by reflux of acidic stomach contents ranges from the discovery of red mucosa to the finding of deep ulcers that lead to the formation of scarring, brachyezophagus or intestinal metaplasia (Barrett's esophagus)

PATOPHYSIOLOGY OF ESOPHAGUS

Barett's esophagus

- a condition where part of the normal esophageal mucosa is **replaced by a cylindrical epithelium** with intestinal metaplasia.

- This altered portion is visible endoscopically and must be confirmed by biopsy. It is the result of long-term and insufficiently treated gastroesophageal reflux. **Barett's esophagus is precancerosis** - in 10-15% develops in the esophagus adenocarcinoma.

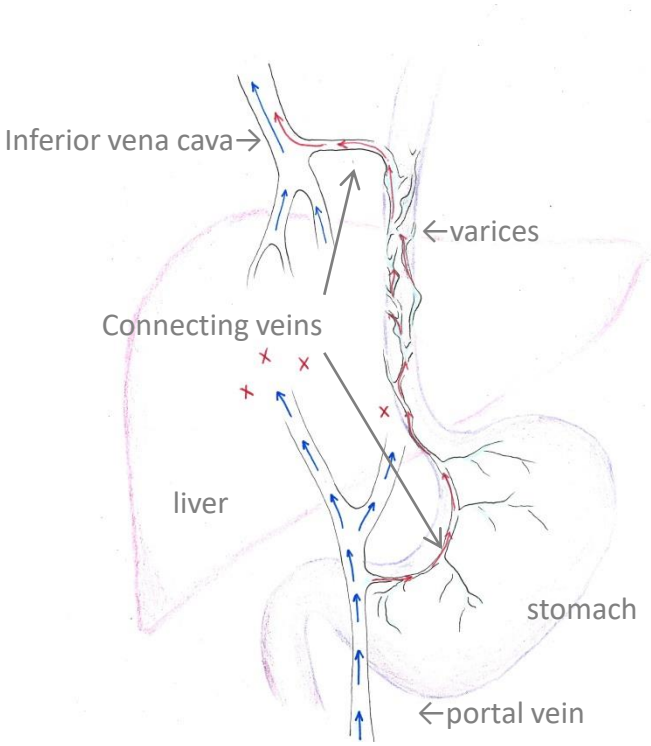
PATOPHYSIOLOGY OF ESOPHAGUS

Esophageal varices

are abnormal, enlarged veins in the esophagus. This condition occurs most often in people with **serious liver diseases.** Esophageal varices develop when normal blood flow to the liver is blocked by a clot or scar tissue in the liver. To go around the blockages, blood flows into smaller blood vessels that aren't designed to carry large volumes of blood. The vessels can leak blood or even rupture, causing life-threatening bleeding.

The pressure exerted on the walls of the esophageal veins deposited under the throat is too high. Consequently, varices are formed which can burst and bleed into the esophagus, which irritates the stomach and usually manifests a bright red haematemesis.

Bleeding from esophageal varices is a common complication of cirrhosis of the liver (30-60%) and bleeding from esophageal varices is the cause of death in half of patients with advanced liver cirrhosis.



↑- normal blood flow

↑ - pathologic blood flow

X - cirhosis

PATOPHYSIOLOGY OF ESOPHAGUS

Tumors of the esophagus

are **malignant** and **benign**

Most commonly, it is detected by **squamous cell carcinoma** (originating from the squamous cell lining the inner part of the esophagus)
followed by **adenocarcinoma** (arising from glands in the esophagus wall),
there are also mixed types.

Any part of the esophagus may be affected, but most often the middle and lower third.

PATOPHYSIOLOGY OF STOMACH

the stomach has 2 main functions:

- motoric

- secretory

The digestive process begins in the stomach. Resorption of basic food components is minimal.

Disorders of the motoric function of the stomach can be both **primary** and **secondary** (ie the manifestation of another disease)

Motility may be **slowed** or **accelerated**

PATOPHYSIOLOGY OF STOMACH

slowing of emptying

mechanical obstruction: most often a tumor, polyps, a chronic duodenal ulcer with pylorus stenosis, congenital pylori stenosis, or fibrotic changes of the duodenal bulb

malfunction:

- drugs (opiates, anticholinergic agents ...)
- neurological diseases (brain tumors, bulbar poliomyelitis, vagotomy, diabetic neuropathy ...)
- metabolic diseases (decompensated diabetes, hypokalaemia, hypo- or hypercalcaemia, hepatic encephalopathy ..)
- Inflammatory and infectious diseases in the abdominal cavity (appendix, pancreas ..)
- long-term immobility (paraplegia ..)
- abdominal pain (injuries, stomach ulcer disease ...)
- starvation
- tachygastry

PATOPHYSIOLOGY OF STOMACH

accelerated emptying

uncommon - is associated with duodenal ulcer disease, hyperthyroidism, gastrinomas, most often after surgery on the stomach (resection).

Food components, especially amino acids, protect the bulb from over-acidification. Accelerated gastric emptying of the amino acid from the duodenum leaves more rapidly and stimulates further acid secretion but is not neutralized by gastric content => when the stomach is rapidly emptied, more HCl is added to the duodenum => increased risk of duodenal ulcer.

PATOPHYSIOLOGY OF STOMACH

duodenogastric reflux

under normal circumstances, at higher antral pressure than in the duodenum, this reflux does not occur. It occurs during the **relaxation or surgical removal of the pyloric sphincter**. Psychosomatics can also participate!

The duodenal content irritates the gastric mucosa - the lecithin contained in the bile turns into a toxic lysolecitin that is hydrophilic and damages the gastric mucosa => **gastric ulcer**.

PATOPHYSIOLOGY OF STOMACH

Vomiting

is a neuronal controlled, coordinated reflex in which the contents of the stomach are forcibly evacuated through the mouth. Vomiting is controlled by the center of vomiting in the dorsal part of the reticular formation of the medulla oblongata. The neurons of this center receive signals from:

- gastrointestinal tract, abdominal organ inflammation, gastrointestinal wall enlargement and irritation;
- cerebral cortex;
- vestibula (statokinetic system) in kinetosis, vestibular system diseases (e.g., Meniere's disease);
- the chemoreceptors of the area postrema on the basis of IV. brain ventricle - these are activated by various drugs, toxins (endogenous and exogenous), hypoxia, neurotransmitters.

PATOPHYSIOLOGY OF STOMACH

Vomiting phases:

- nausea, salivation (enamel protection)
- reversal of peristalsis (transfer of digestion from the upper parts of the intestine back to the stomach),
- closure of glotis (prevents inhalation, aspiration, vomiting)
- keeping breath in a slight inspiration,
- contraction of abdominal wall muscles and increase of intraabdominal pressure, stomach relaxes
- relaxation of the lower esophageal sphincter,
- evacuation of stomach contents.

PATOPHYSIOLOGY OF STOMACH

The causes of vomiting

include a wide range of diseases. We can distinguish between **acute** and **chronic vomiting**. In most cases, it is accompanied by nausea.
- GI diseases

acute: gastroenteritis, pancreatitis, cholecystitis, appendicitis, small bowel obstruction, hepatitis,

chronic: reflux oesophageal disease, achalasia, esophageal diverticles, gastrointestinal tract stenosis, gastroduodenal ulcer, postoperative complications such as strictures, but also functional disorders:
- endocrinopathy - Addison's disease, thyroid disease (hyperfunction and hypofunction), complications of Diabetes mellitus (type I DM with ketoacidosis)
- malignancies - tumors of the GIT (pancreas) but also elsewhere - bronchogenic ca., brain tumors,
- neurological diseases - intracranial hypertension, migraine, head trauma (acute vomiting),
- psychiatric disorders - depression, anxiety, bulimia,
- infections outside the GIT - urinary tract infection,
- some drugs (anti-cancer chemotherapy, oral antidiabetic agents (metformin), antibiotics (erythromycin), opioids, anti-parkinson drugs, antiarrhythmics, digoxin);
- Alcohol.

Projective vomiting (severe vomiting without prior warning of nausea) is typical of intracranial hypertension and also in young children with hyperkalemia and pylorus stenosis.

A special type of vomiting - vomiting of the intestinal contents (usually during intestinal obstruction, acute condition!)

PATOPHYSIOLOGY OF STOMACH

Disorders of stomach secretion

Gastric secretion alterations are not a separate disease, but an accompanying symptom of stomach and other organ diseases

Short-term elevations - acute gastritis or irritation of the gastric mucosa (drugs, alcohol, toxic substances)

Hypersecretion and hyperacidity - Concomitantly with elevated pepsin content, duodenal ulceration is more common. Hypersecretion of HCl and pepsin may also induce hypercalcaemia (most often due to the calcium-containing infusion).

Reduced gastric secretion - may mean: a) only a reduction in the total production of gastric juice; b) reduction of gastric juice production with a decrease in secretion of HCl and / or pepsin; c) decrease in HCl production (hypochlorohydria) or complete disappearance of HCl production (achlorhydria).

may be:

false - after stimulation (eg pentagastrin) a limited amount of HCl is formed;

true - HCl does not form even after stimulation.

Some age-related decrease is natural: between 50 and 60 years of age number of parietal cells decreases.

Atrophic gastritis is the most common cause of a pathological decrease

Hyposecretion and subsequent hypoacidity to anacidity with disappearance of acidic gastric proteases affects gastric motility => slowing gastric emptying, changes in pancreatic secretion and digestive disorder.

In the case of atrophy of the mucous membrane, the secretion of other substances - certain proteases, in particular the intrinsic factor => the vitamin B12 deficiency and the risk of megaloblastic anemia.

PATOPHYSIOLOGY OF STOMACH

Gastritis

- inflammatory conditions of the gastric mucosa. It is divided into **acute** and **chronic**

The cause of **acute gastritis** is irritated mucosa, eg components of bad food, irritating food (spice), alcohol, infection (including Helicobacter pylori).
Changes in stomach mucosa variable from hyperemia to erosion and ulceration. Fast onset and rapid spontaneous recovery.

Haemorrhagic erosive gastritis - associated with respiratory failure, sepsis or trauma. Causes: changes in mucosal microcirculation and acidosis caused by extreme activation of vagal nuclei

Chronic gastritis lasts weeks to months, spontaneous withdrawal is rare. Mucosal damage can be both superficial and deep. Chronic inflammatory changes may lead to gastric mucosal hyperplasia or atrophy, often with intestinal metaplasia.

PATOPHYSIOLOGY OF STOMACH

Chronic gastritis

A - autoimmune gastritis - direct cytotoxic effect of lymphocytes on parietal cells. Antibodies against parietal cells, intrinsic factor and against its complex with B12 are formed. It affects the body of the stomach, often accompanied by achlorhydria, increased gastrin in serum, pernicious anemia

B - bacterial gastritis - *Helicobacter pylori* mainly colonizes the antrum mucosa, later other parts of stomach. Colonization is focal, not diffuse => a large number of endoscopic biopsies are required for diagnosis. Long-lasting chronic *H. pylor*i-induced gastritis can lead to mucosal atrophy and the development of intestinal metaplasia, the most common precursor of gastric adenocarcinoma of the intestinal type. H. pylori infection has a causal relationship to peptic gastroduodenal ulcer. Mucosal healing is conditional on the eradication of *H. pylori* (antibiotics).
The main pathogenetic mechanism is the breakdown of the defensive mechanisms of the mucosal barrier and the inflammatory reaction of the epithelial cells. *H. pylori* positivity is probably in 50% of the population. But only a small part of the positive people have clinical manifestations. The host-pathogen relationship is still very little known
some classifications also include type C:

C- chemical gastritis - the effect of chemicals on the gastric mucosa. Mostly alcohol, components of tobacco smoke in saliva, food components (nitrosamines) and, in particular, long-term use of NSAIDs with a high ratio of COX-1: COX-2 inhibition => decrease in cytoprotective prostaglandin production, bicarbonate.
The development of gastritis also occurs due to the long-term effects of duodenal contents at frequent duodenal gastric reflux (aggressive effects of bile and pancreatic enzymes).

The categorization A, B, C is still used but it is obsolete: at least 15% of cases of chronic gastritis are inappropriate according to this categorization. Other important factors include, for example, long-term stress

PATOPHYSIOLOGY OF STOMACH

Gastropathy

- a term for all diseases diffusely affecting the entire gastric mucosa accompanied by the proliferation of some cellular elements. **Inflammatory changes are not present**

This includes in particular:

Hypertrophic hypersecretory gastropathy - accompanied by significant mucosal thickening (macroscopically large and thick mucosal folds) Histologically: glandular hyperplasia - enlargement of the stomach glands by increasing number of parietal cells => increased production of HCl under basal conditions and after stimulation of stomach secretion - obviously trophic effect of gastrin on the stomach mucosa

Ménétrier's disease - also hypertrophic exudative gastropathy - is also accompanied by a marked gastric mucosal thickening. However, histologically, it is characterized by hyperplasia of the mucous cells of the gastric mucosa accompanied by cystic dilatation of the glands, which may extend to the submucosa.
Accompanied by large losses of plasma protein (major albumin) in gastric juice. In extreme cases, when albumin losses cannot be compensated by the liver synthesis, hypoalbuminemia and swelling of different extent occur. Other typical symptoms are hyposecretion and hypoacidity, or achlohydria

It is precancerosis!

PATOPHYSIOLOGY OF STOMACH

Peptic ulcers

General disease, where multiple etiological factors are involved. The main manifestation is always a mucosal lesion - gastric and duodenal ulcer, which is in direct contact with gastric juice or with content of duodenum.
Ulcer occurs as an imbalance between protective and aggressive factors

Protective factors:
- mucus layer (mucus, HCO3-, phospholipids...)
- production of prostaglandins (↑HCO3-↓H+). Negative effect of long-term use of NSAID (NSAID are also antiaggregants => ↑ risk of bleeding!)
- supplying mucous membranes with blood

Aggressive factors:
- HCl
- proteinases
- alcohol
- nikotin
- caffein

- *Helicobacter pylori* - production of bacterial enzymes disrupting mucosa and preventing phagocytosis, promoting gastrin and HCl production

Gastric ulcers are mostly found in the pyloric antrum and lesser curvature, the highest incidence after the age of 60, slightly more often in men, the pain in the epigastrium may come soon after eating.
If the mucosa is less perfused at some place, an ulcer is more easily formed. The smallest vascular supply has curvatura minor. The food taken dilates the curvatura major, but the lesser curvature is more or less fixed ("permanently contracted"), the vessels inside are also contracted => ↑ risk of microcirculation disorders => higher incidence of ulcers.

PATOPHYSIOLOGY OF STOMACH

Stress ulcers

- acute form of peptic ulcer - fast-forming ulcer under severe stress (severe injuries, sepsis, burns) and excessive blood loss. Often multiple lesions on the stomach and duodenum, bleeding into the GIT.

Cause: local vasospasm due to extreme activation of adrenergic stimulation => mucosal disruption, aggressive action of gastric juices. A common stress ulcer is **Cushing's ulcer** (especially in CNS injuries and increased intracranial pressure).

Duodenal ulcers

occur most frequently when more gastric juice is secreted to duodenum

Duodenal ulcer - 95% in duodenal bulb caused by *H. pylori*, highest incidence after 50 years, epigastric pain typically 90 or more minutes after a meal. Pain is usually after fasting, food provides pain relief.

At the beginning of the pathological process, inflammation of the mucosa (bulbitis) of the duodenum is followed by reflux and hypermotility of the stomach, with the formation of surface erosions, which are replaced by gastric mucosa more resistant to low pH => gastric epithelial metaplasia => creating suitable conditions for H. pylori colonization.

peptic ulcer complications:

- perforation - into the abdominal cavity followed by peritonitis
- penetration - most commonly in the head of the pancreas or in the liver
- bleeding - the most common complication
- scarring and stenosis - can cause stenosis, passage disorder (hourglass stomach)
- malignant gastric ulcer (->adenocarcinoma) - every gastric ulcer should be considered as precancerosis!

PATOPHYSIOLOGY OF STOMACH

Zollinger-Ellison syndrome

-a disease **caused by excess gastrin**, which is secreted by a tumor called **gastrinoma**. The nature of the tumor is benign to malignant, occurs most frequently in the pancreas, but can also occur in G-cells of the digestive tract.

High levels of gastrin stimulate HCl production by gastric parietal cells => hyperacidity => peptic ulcers (in duodenum, stomach, esophagus, or jejunum). Chymus is not sufficiently alkalized, its increased acidity causes reduced efficacy of digestive enzymes and damage to the small intestine mucosa, which can be manifested by diarrhea and steatosis (pancreatic lipase ineffective at low pH). Other manifestations of the disease are related to peptic ulcers - pain, gastrointestinal bleeding or anorexia. Ulcers are relatively resistant to H2 blockers

PATOPHYSIOLOGY OF STOMACH

Stomach tumors

they may be both **benign** and **malignant**.

Of the benign, **polyps** from the gastric glandular epithelium are most commonly detected
Malignant tumors of the stomach are most commonly carcinomas (distinguish between intestinal and diffuse types)

The key etiological factor is the **presence of nitrates in the diet** - these are reduced to nitrites in the stomach and subsequently react with amines due to the acidic environment to produce carcinogenic nitrosamines.
Another risk factor is the intake of **polyaromatic hydrocarbons** in smoked foods and in saliva when smoking tobacco. **Mycotoxins** (aflatoxin in moldy foods) are also at risk.

Especially in the case of diffuse gastric cancer, genetic factors and frequent familial occurrence are also involved. More often, individuals with blood type A are affected.

Precancerous conditions: polyps, chronic recurrent ulcers, chronic atrophic gastritis, duodenogastric reflux, etc.

PATOPHYSIOLOGY OF EXOCRINE PANKREAS

Pancreatic function:

endocrine and **exocrine** - secretory. The exocrine pancreas is the largest (84%) of the entire organ. The endocrine part accounts for only about 2%, 4% is for vascular cells and vessels and the remaining 10% is the extracellular matrix.

The external secretory function consists in the production and secretion of pancreatic juice (daily production of 1-2 liters, mean pH = 8.3).

Increased secretion disorders of pancreatic function are relatively rare.

Reduced secretion and pancreatic insufficiency are more common. It can be caused by inflammation, tumors, toxic effects (alcohol), malnutrition (especially protein deficiency). Pancreatic insufficiency results in **digestive disorders**

PATOPHYSIOLOGY OF EXOCRINE PANKREAS

Acute pancreatitis

is characterized by destruction of secretory cells by the action of active (!) pancreatic enzymes
Activation of pancreatic enzymes occurs in both intracellular and extracellular spaces.
Trypsinogen is activated in the intracellular space to trypsin => intracellular protein cleavage
Elastase is involved mainly in vascular destruction - elastin cleavage in the vascular wall => hemorrhage
Bradykinin => vasodilation and increased capillary permeability => increased granulocyte penetration into tissues
Lipolytic enzymes => necrosis are also involved in tissue destruction

The main etiological cause is:
- presence of cholelithiasis and obstruction of the pancreatic duct at the site of Oddi sphincter. The increased pressure in the bile duct causes that the bile gets into the pancreas through the Wirsung duct
- Alcoholism (especially intake of large amounts of spirits)
- viral infections
- abdominal injury
- metabolic disorders (hypolipoproteinemia with high concentration of triglycerides ..)

Acute pancreatitis is a **life-threatening condition** (acute abdomen, exudation - hypovolemia). If the patient survives, there is a high risk of lasting ill effects - pancreatic insufficiency => indigestion, damage to the endocrine part and development of diabetes.

PATOPHYSIOLOGY OF EXOCRINE PANKREAS

Chronic pancreatitis

is a long-term inflammation of the pancreas that leads to irreversible changes and to the gradual replacement of tissue with connective tissue. Exocrine and subsequently endocrine pancreatic insufficiency then develops in the advanced stages of the disease, ie insulin production decreases and diabetes develops.

Chronic pancreatitis is characterized by recurrent or persistent abdominal pain that accompanies the symptoms of **pancreatic insufficiency**.

The causes of chronic pancreatitis are multifactorial:

- long-term consumption of alcohol (in about 40-90% of patients)
- use of analgesics, corticoids, thiazides (diuretics)
- hypercholesterolemia and elevated TAG.

PATOPHYSIOLOGY OF EXOCRINE PANKREAS

Cystic pancreatic fibrosis

autosomal recessive disease (defective CFTR gene encoding chloride channel) affecting also the the pancreas.
Increased concentration of chloride anions leads to excessive sodium reabsorption. Sodium is passively followed by water, thereby reducing the water content of pancreatic juice, increasing its viscosity and loss of efficacy => maldigestion and malabsorption

Pancreatic cancer

severe pancreatic malignancy with very poor prognosis. Pancreatic juice secretion is reduced => maldigestion and malabsorption.
Of the etiological factors, chronic pancreatitis, alcoholism, and smoking are the most important.

PATOPHYSIOLOGY OF LIVER AND BILE DUCT

The liver is involved in the **formation of bile** to digest the ingested food in the digestive tract. Its main function is **emulsifying fat in the digestive tract**.

Bile is a yellow-brown liquid containing bile salts, bile pigments (bilirubin, biliverdin), fatty acids, fats, cholesterol and other substances. The daily bile production is 0.5-0.7 liters. It is collected in the gallbladder.

Bile is involved in the emulsification of the fatty components of the digestion. Fats are eaten in the form of triacylglycerols (up to 90%), to a lesser extent in the form of phospholipids and cholesterol esters.

Lipids are poorly soluble in water, so they must be emulsified. In the stomach, emulsification is achieved mechanically by the stomach motility. The gastric and lingual lipase is able to cleave about 25% of ingested fats here.
The remaining fats are cleaved in the duodenum by pancreatic lipase. For this it is necessary to emulsify fats with lecithin and bile acids! => increase of reaction surface => access for enzyme. Triglyceride cleavage results in glycerol, free fatty acids, monoacylglycerols and diacylglycerols, which are converted into micelles with bile acids = a form in which fats in the brush border are absorbed through the luminal membrane of enterocytes.

Most fats are absorbed in the duodenum and jejunum. The remaining bile acids are absorbed in the terminal ileum. They reach the liver through the portal circulation, where they are excreted in the bile with the newly formed bile acids.
Insufficient bile formation leads to **lipid malabsorption => steatorrhoea** and total digestion disruption, liposolubile vitamin uptake disorders (A, E, D, K)

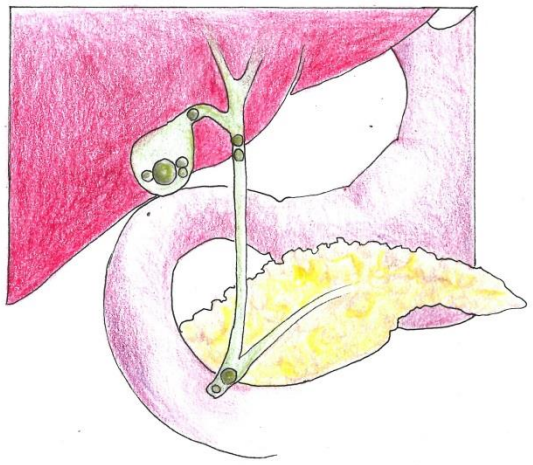
PATOPHYSIOLOGY OF LIVER AND BILE DUCT

Cholelithiasis

the most common biliary disease, one of the most common surgical indications. According to autopsy findings, up to 20-30% of the population is affected by cholelithiasis. It occurs four times more in women, more frequent in obese, diabetic and patients with pre-hepatic (hemolytic) icterus. - bile salts precipitate (concentration, pH)

gallstones may have different compositions (cholesterol, pigment, mixed)
In particular, a high fat diet leads to the formation of cholesterol stones.
Other reasons are:
cholestasis, inflammation, etc.

Bile duct obstruction causes billiary colic and can lead to acute cholecystitis.
Non-specific manifestations: pressure in the abdomen, nausea, vomiting, meteorism, belching and especially the feeling of tension after a fat meal.
Specific symptoms: colic pain, especially at night (horizontal position is more risky for bile duct obstruction).
Usually a consequence of some dietary error - fatty foods, eggs, nuts, chocolate.
Very important seems to be stress.
colic is usually self-limiting. In gallbladder inflammation, the pain is permanent
Risk factors: fatty diet, lack of exercise, obesity, haemolytic conditions, pregnancy, diabetes.



PATOPHYSIOLOGY OF LIVER AND BILE DUCT

Cholecystitis

- inflammation of the gallbladder. Very common cause of the acute abdomen. It may take both chronic and acute forms: it may occur as a primary inflammation, but more frequently is an acute epizode of chronic cholecystitis. In> 90% of cases, there is a history of cholecystolithiasis. In this case, the stone or biliary sediment acts as a reservoir of infection and as an obstruction in bile duct.
If bacterial infection occurs, septicemia may develop, which significantly increases mortality.

PATOPHYSIOLOGY OF SMALL INTESTINE

- small intestine - nutrients are finally digested and the nutrients are resorbed. The total resorption area of the small intestine is about 300 m^2.

The epithelium rapidly proliferates from the center of the Lieberkühn crypt and enterocytes functionally differentiate to the top of the villi during the procedure. The most intense digestive and absorption processes take place at the top of the villi. The entire surface of the small intestine is restored every 24 - 72 hours.

The key conditions for proper functioning of the intestine:

- villi are normally developed, unatrophied
- the enterocytes are morphologically and functionally mature, with a fully developed microvilous zone
- the digested food is sufficiently exposed to the intestinal mucosa surface to allow resorption (intestinal motility!)
- intestinal secretion and intestinal absorption are at the desired equilibrium

Disruption of any of the above conditions results in impaired absorption associated with diarrhea, flatulence, dyspepsia, changes in microflora composition in the distal GIT, or even manifestations of nutrient deficiency and other food components.

PATOPHYSIOLOGY OF SMALL INTESTINE

Maldigestion and malabsorption

Maldigestion - disorder of food digestion caused by a disturbance of various digestive organs (stomach, pancreas, liver, intestine). It is characterized by a large volume of stool

Digestive disorders can have various causes:
- insufficiency of digestive enzymes in gastric juice
- insufficiency of digestive enzymes in pancreatic juice
- insufficiency of the enzymes in the microvillous zone of enterocytes
- bile production disorders (insufficient emulsification of the digestion)

Malabsorption is a disorder of absorption of nutrients and other food ingredients

PATOPHYSIOLOGY OF SMALL INTESTINE

Disorders of carbohydrate digestion and absorption

Carbohydrate Digestion:
1. in the mouth - **salivary amylase** - very effective. Due to rapid food intake, it has only limited effect. Amylase cleaves starches into dextrins or maltose
2. in the stomach – still **salivary amylase**. Optimal activity at pH 6.5. Active in the stomach (about 30 minutes, then deactivated with HCl).
3. in the duodenum - **pancreatic amylase**
Cleavage of starch is completed by maltase in the small intestine, in the brush border of enterocytes - it cleaves maltose into glucose units.

Only monosaccharides are absorbed from the intestine.

Disaccharides can get from the intestine only paracellularly - the space between tight junctions of enterocytes. This route of absorption is strongly influenced by the integrity of intestinal epithelium!
Disaccharidase deficiency - relatively common, especially lactase deficiency. Less frequently, the deficiency of saccharase-isomaltase or maltase. Uncleaved disaccharides = osmotic laxatives! (Lactulose)
Monosaccharides are absorbed transcellularly by several mechanisms:
- diffusion (eg rhamnose, mannitol and other sugar alcohols)
- facilitated by diffusion (fructose by the GLUT-5 membrane transporter)
- active Na + sync (glucose and galactose with SGLT-1 transporter)

SGLT-1 deficiency is manifested by osmotic watery diarrhea and hypertonic dehydration shortly after birth. tretament = elimination of glucose and galactose from the diet (mainly replaced by fructose). It is a relatively rare autosomal recessive disorder.

PATOPHYSIOLOGY OF SMALL INTESTINE

Lactose intolerance

Lactose is the major energy component of all mammalian milk. Human milk has a very high content (7.1 g / L) compared to cow's milk (4.7 g / L). Key importance for infants who have very high lactase activity

Lactose is cleaved by lactase in a brush border. Lactase is produced by enterocytes, but also by intestinal microflora (Streptococcus, Bifidobacterium, Lactobacillus ...)

The most common cause of lactose intolerance in older children and adults is the genetically determined **reduction in lactase production**. To some extent, it is a physiological process, significant differences within each ethnic group - For European aborigines (especially from the north), the incidence of lactose intolerance is low (eg 4% in Denmark and Ireland), gradually rising to the south of Europe (56% in Italy)). In SE Asia, South Africa and South America, it is over 90% of the population.

Secondary lactose intolerance - temporary, related to some diseases (eg celiac disease, Crohn's disease, gastrointestinal infections). Once recovered, lactase activity may be restored.
The consequence of impaired lactose cleavage in the intestine is **osmotic diarrhea**; during fast intestinal passage, lactose in the distal intestine sections is cleaved by microflora => fermentation dyspepsia, flatulence

PATOPHYSIOLOGY OF SMALL INTESTINE

Digestive disorders and protein absorption

Protein digestion consists in cleaving them into amino acids, dipeptides or tripeptides. In particular, gastric pepsin, pancreatic peptidases (trypsin and chymotrysin) and intestinal enterokinase and dipeptidases serve this purpose. Exopeptidases (carboxypeptidases and aminopeptidases) are also present in pancreatic juice and intestinal juice.

Congenital disorder of protein digestion is **lack of enterokinase**. It is manifested by diarrhea, hypoproteinemia, and growth retardation.

Congenital disorders of protein (amino acid) absorption are Hartnup's disease and cystinuria.

Hartnup's disease = consequence of an isolated defect in the transport of neutral amino acids in the intestine and in the kidneys. It is manifested by inflammatory changes to the skin, neutral aminoaciduria and neurological and psychiatric symptoms.
Cystinuria is the result of a defect in the transport system for dibasic amino acids, which also transports cystine. In addition to cystinuria, kidney stones and chronic pancreatitis are present.

The most common acquired disorders of protein digestion and absorption are associated with pancreatic diseases:
- acute pancreatitis
- chronic pancreatitis and cystic fibrosis
- diseases of the whole intestine, eg their surgical withdrawal

PATOPHYSIOLOGY OF SMALL INTESTINE

Digestive disorders and lipid absorption

Lipid digestion:
1. lingual lipase
2. gastric lipase
The optimal pH for gastric lipase is 4.5 - 6.0. In particular, milk lipids (being emulsified) are particularly well digested.
3. pancreatic lipase - active as a complex with colipase. The complex is active only in alkaline environments. In a pH <7 environment, the complex is inactivated. This makes pancreatic lipase sensitive:
In **chronic pancreatitis**, with less lipase production, less HCO3- => ineffective neutralization of acidic gastric juice in the duodenum. Pancreatic lipase cannot act in an acidic environment = >**steatorrhea**
Also, overproduction of gastric acidic acid at gastrinoma may highly exceed the HCO3- neutralization capacity.
The effect of lipase is optimal when lipids are in micelles with bile salts. Micelles also allow easy absorption by enterocyte membranes.
lipid absorption disorders
Lipids are absorbed as fatty acids or other monomers (e.g. cholesterol), such as monoacylglycerols or as diacylglycerols.
In enterocytes: re-esterification of lipids, incorporation into lipoproteins => chylomicrons into intercellular fluid => into lymph and lymphatic pathways into large central veins => bypass portal vein and liver
The major apolipoprotein of chylomicrons is apolipoprotein B-48.

PATOPHYSIOLOGY OF SMALL INTESTINE

Digestive disorders and lipid absorption

Abetaliproteinemia

= Inability of enterocytes to form chylomicrons. Often congenital. It exhibits characteristic symptoms:
- steatorea;
Enterocytes in biopsy samples from the intestinal mucosa are filled with lipids;
Erythrocytes have an abnormal shape (acanthocytosis);
- There are signs of neurological disability

PATOPHYSIOLOGY OF SMALL INTESTINE

Secretion disorders

In addition to fluids taken with food, the gastrointestinal tract recirculates 8-10 liters of extracellular fluid daily. water is in the form of glandular secretions and is resorbed by mucous membranes.
Physiological losses of electrolytes and water are negligible compared to kidney activity. The situation may be quite different in pathological situations associated with diarrhea or disruption of intestinal barrier integrity.
Intestinal secretion may be reduced (less frequently) or increased - clinically more significant.
Even a minimal disturbance between secretion and absorption can lead to diarrhea. In extreme cases - secretory diarrhea caused by bacterial toxins.

PATOPHYSIOLOGY OF SMALL INTESTINE

Small intestine motility

The contraction of the muscle layers in the small intestine is of two types:
1) Segmentation movements
2) Propulsion movements

Segmentation movements- segmentation is a manifestation of electrical slow waves - action potentials that arise from the smooth muscle automation. The slow wave frequency is 3-12 / min.

Propulsive movements - In the small intestine, the contractile ring moves aborally at about 0.5-2 cm / min. Faster in the proximal sections, distally slows down. One contraction ring travels a maximum of 10 cm, then extinguishes and begins to move when the new = total chyme passage speed of about 1 cm / min.

Control of small intestine motility- propulsion motions in the small intestine stimulated by food intake (by entering chyme into the small intestine itself), but also by gastroenteric reflex - motility of the intestine (not only the stomach) is activated by stretching the stomach wall. The components of this reflex are completely in the myenteric plexus. In addition, hormones - CCK, gastrin, insulin and motilin act to increase the frequency of both propulsion and mixing movements. Conversely, secretin and glucagon inhibit the motility of the small intestine.

Ileocecal valve - The function of this valve is to prevent the reflux of chyme from the large intestine to the small intestine. In fact, it is not a valve, but the mouth of the terminal ileum, which enters the caecum. But thanks to muscle it works as a valve. Similar to the pyloric sphincter, its function depends on the tone or resistance of the ileocaecal orifice. About 1500-2000 ml of digestion passes through this mouth daily.

PATOPHYSIOLOGY OF SMALL INTESTINE

Colon Motility

Colon has 2 main functions:
- absorbs electrolyte and water residues
- stores indigestible food residues.

Both of these functions require no extensive motor activity. Therefore, the longitudinal muscle layer in the colon was reduced to so-called taenie (= three muscle stripes that extend along the entire length of the intestine). Motility-slower than the small intestine.

Colon haustration

mixing (basically modified segmentation) movement:
1. contraction of circular muscle.
2. contraction of taeniae => colon haustra.
3. Increasing the pressure inside haustra => facilitates displacement of water with electrolytes. After about 30 seconds, the pressure reaches its maximum and then the haustrum disappears. In a few minutes, the process is repeated elsewhere.

Propulsive movements

- mainly caused by haustration, which progressively and slowly progresses from caecum to sigmoideum. The passage of the digestion material through the colon takes about 12 hours and the liquid chyme becomes a solid faeces.

However, there is also a faster propulsive movement of the colon:
- about three times a day approximately one hour after a meal,
- it lasts for a short time (about 15 minutes) and reminds of peristalsis

there is a contraction ring that gradually moves in aboral direction. Usually, it originates in the colon transversum and the normal haustral activity disappears for 15 minutes.

PATOPHYSIOLOGY OF SMALL INTESTINE

How the motility is controlled

All movements that perform the colon are controlled by reflexes:
1) **Gastrocolic reflex**
2) **Duodenocolic reflex**
The gastrocolic reflex - triggered after the stomach wall is tightened with food. Then, through the myenteric plexus, this signal reaches the large intestine, where it increases the frequency of haustra formation.
The duodenocolic reflex is triggered by the tension of the duodenal wall. The signal spreads through the myenteric plexus to the colon and also increases the frequency of action potentials in smooth muscle cells. This will increase the speed of the propulsion movement.

Intestinal motility disorders
2 main causes:
- *abnormalities in the intestinal muscle layer (myopathy)*
- *abnormalities in innervation of the intestinal muscle layer (neuropathy*)
These disorders may be primary, congenital - very rare
Much more common - secondary to systemic diseases (lupus erythematosus, Parkinson's disease, diabetes, scleroderma, thyroid disorders, muscular dystrophy, etc.). Significant and inflammatory conditions (celiac disease, effects of radiation ..), influence of drugs

Manifestations: diarrhea, constipation, maldigestion, malabsorption, malnutrition. If the ileocecal valve function fails, excessive colonization of the distal sections of the small intestine by the large intestinal microflora.
The manifestation of motility disorders may be internal diarrhea - due to accelerated small bowel motility, poorly digested and unresorbed food enters the distal sections and stagnates there. It is clinically manifested as constipation, but food remains undigested in the stool
false diarrhea - especially in old immobile patients. The digestive process is normal, but chyme stagnates in the colon, which is hypomobile => constipation, where the contents irritate the colon mucosa to secretion. The diluted stool is then extrected as diarrhea.

PATOPHYSIOLOGY OF SMALL INTESTINE

Disruption of the immune and barrier function of the intestine

The intestinal mucosa represents a large interface between the internal environment of the organism and the external environment consisting of intestinal contents and microflora.
The mucosa is covered by a specialized monolayer epithelium, the entire surface of which is covered with a protective layer of adherent mucus (major component of glycoproteins, secreted from Lieberkühn crypts). Mucus also contains antibiotic defensins and IgA

The GIT immune system must:
- to protect against pathogens and toxins
- and at the same time be able to distinguish them from harmless commensals and food ingredients

MALT (mucous associated lymphoid tissue) - is a specialized lymphatic tissue of all mucosal surfaces dominated by IgA on the mucosa and mucosal secretions
GALT (gut associated lymphatic tissue) is one of the largest components of MALT in the human body - the intestinal mucosa is about 200-300 m2 and up to 5 g of IgA is transported daily to the intestinal lumen. GALT consists of several functionally separated compartments:

Peyer‘s patches and mesenteric lymph nodes - macroscopic structure of mucosa and ileum submucosa. Dominant cells: dendritic cells, B-lymphocytes, macrophages and T-lymphocytes. The main function is to recognize antigens using specialized M-cells. Peyer's patches are one of the places where tolerance to non-harmful food antigens is established.
Lamina propria - is located under the intestinal epithelium as a compartment of T and B lymphocytes, plasma cells, macrophages, NK cells, dendritic and mast cells. The prominent portion of T cells is memory cells. T-helper lymphocytes (CD4 +) are also significantly represented.
Intraepithelial lymphocytes - localized between enterocytes, mostly CD8 + T lymphocytes. About half of these cells in the small intestine and most in the colon recognize MHC class I surface molecules and have cytotoxic properties on damaged or altered epithelial cells.

PATOPHYSIOLOGY OF SMALL INTESTINE

Main mechanisms of barrier and defense function of intestinal mucosa

1) intestinal mucosal surface covered with mucus containing antibiotic defensins (innate immunity) and IgA (specific immunity). Defensins and chemokines attract neutrophil granulocytes
2) Intestinal epithelial integrity is ensured by tight enterocyte connections, tight junctions
3) Toll-like enterocyte receptors recognize bacterial antigens
4) NOD-like receptors recognize those antigens that have penetrated the cytoplasm (eg, muramyl dipeptides from bacterial walls)
5) Dendritic cells of macrophage origin capture antigens with their protrusions into intestinal lumina
5) M-cells make bacteria available to macrophages
Collected antigens present in lymphoid tissue => specific immune response - helper T cells and B cells

Oral tolerance = suppression of potentially unwanted systemic immune response to food allergens escaping from intestinal lumina in immunogenic form.

GIT Diseases Caused by Immune Disorders:

- celiac sprue
- Non-specific bowel inflammation (ulcerative colitis, Crohn's disease)
- autoimmune gastritis
- Helicobacter pylori ulcer disease
- autoimmune pancreatitis
- eosinophilic esophagitis

PATOPHYSIOLOGY OF SMALL INTESTINE

Disorders of microbial colonization of the intestinal tract

There are about 10^{14} microorganisms in the human gut - mostly bacteria (estimated at about 500 species). Also protozoa, fungi .. Mainly in the colon

The relationship between human and microbes is **symbotic**: microorganisms ferment undigested organic matter from food (eg cellulose to fatty acids => as a source of energy), help digest lactose, **interact with the immune system**

The intestine is sterile after birth, the newborn is colonized by the mother. Lactic acid producing bifidobacteria predominate in the infant's gut => protection against colonization by pathogenic bacteria. The composition of the intestinal microflora during ontogeny in the next life is significantly influenced by food (= substrate for microorganisms). **Antibiotic use** is a major intervention in the microbiome composition!

PATOPHYSIOLOGY OF SMALL INTESTINE

Disorders of microbial colonization of the intestinal tract

Bacterial overgrowth syndrome

- as a result of colonization of the small intestine by the colon bacteria. It accompanies numerous diseases. It is manifested by diarrhea, steatorrhea, signs of malnutrition (growth disorders, anemia, etc.). There is a risk of spreading bacteria into tissues outside the intestine or into the blood with subsequent bacteremia and sepsis.

Most often, the syndrome is caused by slowed bowel passage or accumulation of intestinal contents. Very common causes are local inflammatory changes in the intestinal mucosa that cause hypomotility or even constipation or ileus. Deceleration of the passage promotes overgrowth of bacteria from large to small intestine. The predisposing circumstances are:

Malfunction:
- *S*econdary disorders in the affection of the stomach, pancreas, liver, after administration of some drugs, etc.

Anatomical obturation:
- Diverticles, strictures, tumors, etc.
- Direct connections between colon and small intestine (fistulae, surgical connections).

prevention of overgrowth of bacteria is the maintenance of a balanced intestinal microbiome.

PATOPHYSIOLOGY OF SMALL INTESTINE

Disorders of microbial colonization of the intestinal tract

Short bowel syndrome

usually as a result of radical surgery where less than 2 m of the small intestine remains (with the removal of the colon as well), or <0.7 m of the small intestine remains and the colon remains intact.
It is also important whether the intact **ileocaecal valve** has remained. At its loss, the risk of colonization of the small intestine by the microflora of the colon increases = the disruption of digestive processes by bacteria.

The syndrome is accompanied by maldigestion, malabsorption => malnutrition, incl. deficiency of vitamins (especially B12), minerals, disturbance of the bile acid cycle. A special diet is needed, excluding milk and dairy products, flatulent vegetables, legumes and crude fiber. On the contrary, digestible fiber retarding the intestinal passage is desirable.

Parenteral nutrition and permanent catheterization are often necessary

PATOPHYSIOLOGY OF SMALL INTESTINE

Crohn's disease

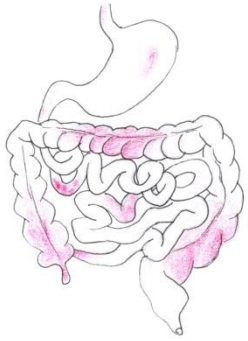
less common type of inflammation of the digestive tract: chronic non-specific inflammation (up to granulomatous) affecting the entire thickness of the intestine wall, inflammatory changes are segmental or plurisegmental.
Any part of the digestive tract (from the esophagus to the rectum) may be affected, but most often it is the terminal ileum. The disease affects rather young individuals (25-30% of patients are diagnosed before 20 years of age).

The **cause of the disease is still unknown**. Probably dysregulation of immune response to common bacterial antigens. Transmural inflammation then develops during the autoimmune reaction. Epithelioid granulomas, ulcerations and fissures form in the intestinal wall. Often intramural and intraperitoneal abscesses or fistulae (especially in the anal region). Typically, the affected sections alternate with non-affected (different from ulcerative colitis!).

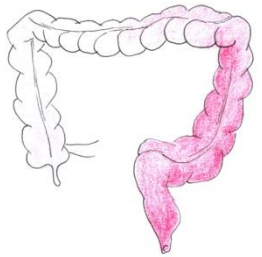
Due to long-term inflammation, the bowel may become narrower by scarring the tissue (scarring stricture).

Gastrointestinal symptoms are in particular:

- diarrhea with blood;
- abdominal pain associated with defecation;
- rectal tenesmus



Crohn‘s disease



Ulcerative colitis

PATOPHYSIOLOGY OF SMALL INTESTINE

Ulcerative colitis

-a rare autoimmune type of inflammation in the digestive tract. It is a **haemorrhagic-suppurative ulcerative inflammation of the mucosa and submucosa of the rectum and the adjacent part of the colon**.
- there are never changes in the small intestine!
- 20% of patients are diagnosed before the age of 20.

The cause is unknown. The most likely theories include dysregulation of the immune response to common bacterial antigens. Inflammation affects, to varying degrees, only rectum and colon. Pancolitis is common in children. Inflammation is continuous, distal colon segments are mostly affected more.
Lesions are, unlike Crohn's disease, continuous. Macroscopically, the contraction of the affected section, the mucosa is hypertrophic and edematous with numerous ulcers, the serosa is shiny, the mesocolon is not thickened. Microscopically crypt abscesses (dilated crypts filled with polymorphonuclear cells, their disintegration leads to separation of mucosa and ulceration)
Gastrointestinal symptoms
- diarrhea with blood;
- abdominal pain associated with defecation;
- rectal tenesmus

According to localization we distinguish two basic syndromes:
- rectal syndrome
- colitis syndrome

Other complications include: iridocyclitis, glaucoma and cataract due to corticosteroid treatment, primary sclerosing cholangitis - may precede manifestations of ulcerative colitis, overlap syndrome with autoimmune hepatitis, primary sclerosing cholangitis and ulcerative colitis, thromboembolic complications, toxic megacolon, colorectal cancer

PATOPHYSIOLOGY OF SMALL INTESTINE

Irritable bowel syndrome

- is a functional disorder. It affects up to 20% of the population, especially in developed countries. Accompanied by abdominal pain, meteorism, changes in defecation stereotypes.

According to the stool character, the disease can be divided into:

- *Irritable bowel with predominant diarrhea*
- *irritable bowel with predominant constipation*
- *mixed type*

Causes of the disease are unknown, probably due to: stress, visceral hypersensitivity, gastrointestinal infections or genetic factors

PATOPHYSIOLOGY OF SMALL INTESTINE

Food allergies

Allergic symptoms occur within one hour of food intake. The most common symptoms include skin reactions, tongue edema and oropharyngeal edema, dyspnea, asthma, vomiting, diarrhea, abdominal pain and cramps. Hypotension and loss of consciousness occur in severe cases. Severe conditions can result in death.

Food responses are very varied and are caused by various causes. They are generally divided into:

Immunologically conditioned reactions:
- IgE-mediated immediate hypersensitivity reaction;
- immunocomplex reactions;
- T-cell mediated cell type.

Non-immunological mechanisms:
- enzyme deficits;
- reaction to additives;
- reaction to histamine or tyramine in the diet (mackerel, banana, cheese, citruses, strawberry, chocolate, spinach);
- plant, bacterial, animal toxins.

The most dangerous food allergens are:
- Protein of cereal grasses – gluten
- Milk protein - especially cow casein
- Peanut proteins - a whole group of allergens, the most dangerous proteins Ara h2 and Ara h6
- Soy proteins - glycinins and β-conglycinins (structural similarity to peanut allergens - botanical relationship of both plants)

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PATOPHYSIOLOGY OF SMALL INTESTINE

Gluten- sensitive enteropathy

chronic disease - inflammatory changes of the small intestine mucosa => absorption of nutrients, minerals, vitamins and water is negatively affected.

Precancerosis!

The mucosa exerts **abnormal immune response to gliadin segments of gluten**

Anti-gliadin antibodies are produced in the mucosa and an inflammatory process is triggered => accompanied by structural and functional alterations of the intestinal mucosa
Probable triggers are some viruses (eg adenovirus type 12) - serologically proven in many GE patients. The adenovirus protein is structurally similar to α-gliadin and the anti-virus protein cross-reacts with some part of the gliadin molecule. Adenovirus infection can thus sensitize disposable individuals!

Clinically, GE is a classic pyramid - only a minority of patients have clinically active, fully developed disease. The greater part are patients with latent and silent forms of the disease.

Main symptoms: diarrhea, weight loss, dyspepsia, anorexia, flatulence. Furthermore, disorders of resorption of Fe and B12, metabolic osteopathy from deficiency of vitamin D and Ca.
Gluten enteropathy can also manifest as a skin disease - **dermatitis herpetiformis Duhring**!

The only effective treatment - a diet excluding gluten-containing cereals.

PATOPHYSIOLOGY OF SMALL INTESTINE

Cow milk protein allergy

Typically found in infants and young children. The basis is the allergic reaction of the small intestine mucosa to casein, sometimes to other cow's milk proteins. The allergic reaction may or may not be IgE-mediated
I
gE-mediated form is characterized by a higher risk of earlier allergic response when contacted with allergen (urticaria, angioedema, vomiting, laryngeal edema, eyelid edema, eventually anaphylactic reaction)

Most affected is:

- gastrointestinal tract (50-60%) - frequent regurgitation, vomiting - diarrhea, constipation - blood in stool with sideropenic anemia. A link between milk allergy and the development of gastroesophageal reflux is also likely!
- skin (50-60%) - atopic dermatitis - urticaria, edema of the eyelids, angioedema
- airways (20-30%) - chronic rhinitis, cough ..

It is necessary to exclude milk from cattle (and also from goats, sheeps..) and to switch to nutrition containing hydrolysed proteins (without allergenic potential)

PATOPHYSIOLOGY OF SMALL INTESTINE

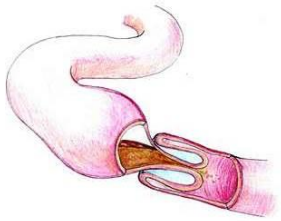
Ileus

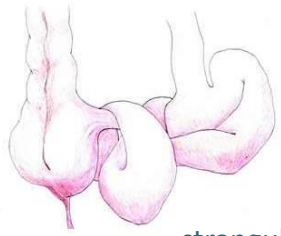
= obstruction of the intestine. It belongs to acute abdomen.
Based on etiopathogenesis we distinguish 3 main types of ileum:

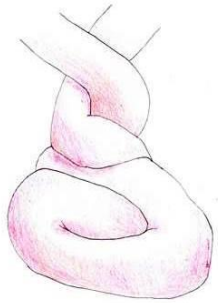
Mechanical - the mechanical cause can be intraluminary, in the intestinal wall, but also extraluminal - the intestinal cavity is compressed externally.
The most common cause of intraluminal is obstruction by tumor, gallstone, inflammation, swallowed object, etc.
Extraluminal causes are: herniation, adhesions, invagination, strangulation, volvulus, etc. (these events lead not only to obstruction, but also to ischemia and necrosis of the intestine)

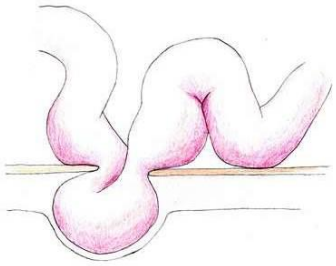
Functional
- Neurogenic (paralytic, spastic and mixed). Most often after surgery, acute pancreatitis, peritonitis, hypokalaemia, myocardial infarction, etc.
- Vascular (due to arterial embolism or venous thrombosis).

Mechanical ileus is first manifested by increased peristalsis (an attempt to overcome a mechanical barrier). Chyme accumulates above the obstacle, water and gases => intestine expands => disrupts its blood supply, ischemia, necrosis
Acute, life-threatening condition (dehydration, ionic imbalance and toxemia due to bacterial penetration)


invagination


strangulation


volvulus


herniation

PATOPHYSIOLOGY OF SMALL INTESTINE

Bleeding in the digestive tract

Bleeding may occur in any part of the GIT, localization may be difficult.

Generally:
- upper GIT bleeding (above Treitz's ligament) is manifested by hematemesis and melena
- Lower GIT bleeding is manifested by enterorrhagia.

upper gastrointestinal bleeding:

Hematemesis = as vomiting blood. Clear red content = most frequently oesophageal variceal bleeding or peptic ulcer arterial bleeding. The dark content of the upset stomach content ("coffee grounds") = digested blood, while being accompanied by melena.
Melena = black, tar-like stool caused by bleeding orally from cecum. Bleeding may also cause hemorrhagic shock.

Most common causes:
- Peptic ulcer of stomach and duodenum - responsible for 50% of all bleeding
- Erosive gastropathy
- Reflux esophagitis: bleeding is often diffuse.
- Mallory-Weiss syndrome: a consequence of hard and repeated vomiting.
- Esophageal varices (loss of often more than 500 ml of blood!)
- Stomach cancer.

PATOPHYSIOLOGY OF LARGE INTESTINE

Bleeding in the digestive tract

Lower GIT bleeding

= distal to duodenal-jejunal flexure. Massive bleeding can lead to circulatory instability or even hemorrhagic shock. Occult bleeding manifests as anemic syndrome.

Enterorrhagia is defecation of fresh blood - it means bleeding from the distal part of the IT (most often from or just above the anal canal).
Hematochezia indicates the presence of darker blood clots or darker blood coming from the proximal colon sections.

Most common causes:
- colon diverticulum (40%);
- angiodysplasia (20%);
- mesenteric colitis (10-15%);
- NSAID-associated colopathies and enteropathy
- Infectious inflammations of the colon (Salmonella, EHEC, Cryptosporidium)
- Other causes include bleeding after endoscopic interventions (especially polypectomy) and bleeding from tumors.

PATOPHYSIOLOGY OF LARGE INTESTINE

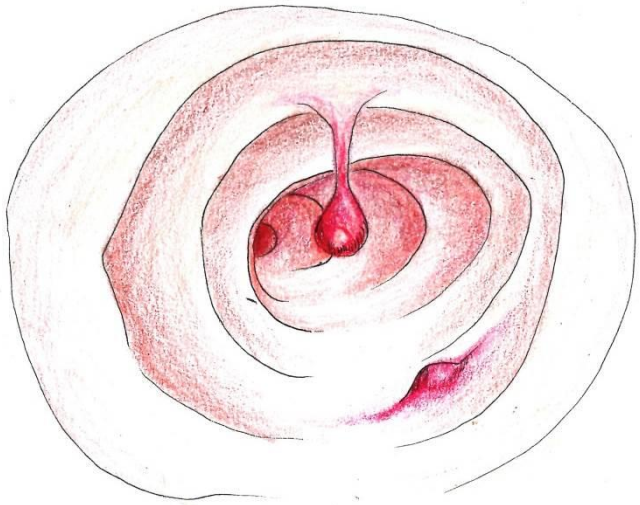
Colon polyps

Very common clinical finding. Mucosal protrusions can be only in one place or multiple. Histologically, many categories are distinguished from completely benign to precancerous.

Different types of polyps may differ in clinical behavior.

Polyps can be divided into three groups:
- sporadic epithelial polyps (Colorectal adenoma)
- sporadic mesenchymal polyps (Ganglioneuroma, Fibroblastic polyp.)
- polyps associated with syndromes (Juvenile polyp, Peutz-Jeghers syndrome…)

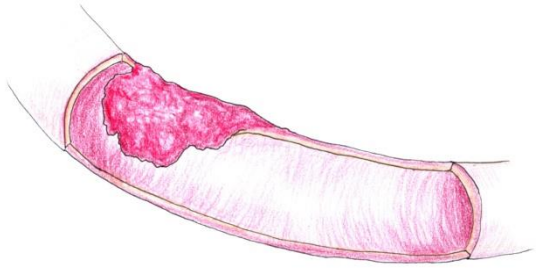
Mostly they do not manifest clinically, they are found accidentally during colonoscopy. Sometimes they can bleed



PATOPHYSIOLOGY OF LARGE INTESTINE

Colon tumors

- colorectal cancer - the most common colon cancer and one of the most commonly diagnosed tumors. Very high incidence in developed countries
it depends on the location and the way of growth - the clinical picture can be varied.



Complications: bleeding into the colon, obturation, subileus to ileus

Risk factors:
- *other colon diseases* - history of intestinal adenomas and chronic intestinal inflammation, especially ulcerative colitis; hyperinsulinemia;
- *obesity*;
- *smoking*;
- *eating habits* - especially frequent consumption of red meat, excessive intake of animal fats and insufficient fiber intake in the diet are at risk.

Protective factors: dietary fiber, omega-3 polyunsaturated fatty acids, folic acid
Diagnosis: occult blood tests, colonoscopy

PATOPHYSIOLOGY OF LARGE INTESTINE

Diarrhea

a condition in which stool volume and fluidity increase as well as the frequency of emptying more than three unformed stools per day. Stool weight greater than 300 g per day.

Diarrhea may have acute (2-3 days) and chronic form (> 2 weeks)

From the etiological point of view, diarrhea can be divided into infectious and non-infectious.

Examples of **infectious diarrhea**:
- viral - rotaviruses, coronaviruses, adenoviruses ..
- bacterial - Campylobacter jejuni, Salmonella, Shigella dysenteriae, Vibrio cholerae, E. coli
- Parasitic - Cryptosporidium parvum, Giardia lamblia, Entamoeba histolytica, Ascaris, Strongyloides, Taenia ..
- enterotoxicosis - caused by enterotoxins

Non-infectious diarrhea has a number of causes, including:
- Drugs
- the presence of osmotically active substances
- toxic substances (eg fungi, plants ..)
- inflammatory diseases
- bowel disorders (motility, secretion ..)
- stress

PATOPHYSIOLOGY OF INTESTINE

The categorization of diarrhea is not entirely uniform; the individual categories overlap. From a **pathophysiological** point of view, diarrhea can be divided into:

1. **Osmotic diarrhea**: occurs when unabsorbable, water-soluble substances appear in the gut and retain water there. Most often: magnesium sulfate, lactulose, sugar alcohols (sorbitol, mannitol), glycerol, etc.

2. **Secretory diarrhea**. Both the small and large intestine normally absorb ions and water from food or from the secretions produced by the digestive tract. Diarrhea may occur if the small and large intestines secrete water and electrolytes more than they absorb.

Drug-induced secretory diarrhea: laxatives (bisacodyl, sennosides), bile stones dissolving drugs (chenodeoxycholic acid), prostaglandins (misoprostol), aminosalicylates.
Also some toxins (amanitin from toadstools)

A specific group is infectious **secretory diarrhea caused by bacterial toxins**, eg cholera toxin (Vibrio cholerae): the toxin in the apical membrane of enterocytes activates the cAMP signaling cascade and subsequently the CFTR channel => massive secretion of Cl- into intestinal lumina accompanied by Na + and water. Water loss can be life-threatening. Secretory diarrhea - also some other bacterial toxins (Clostridium difficile, Salmonella..)

PATOPHYSIOLOGY OF INTESTINE

The categorization of diarrhea is not entirely uniform; the individual categories overlap. From a **pathophysiological** point of view, diarrhea can be divided into:

3. **Diarrhea due to structural alterations of the small intestinal mucosa** - intestinal absorption is impaired by inflammatory processes - in ulcerative colitis, lymphoma, eventually carcinoma. This Diarrhea is usually exudative.

Diarrhea accompanying intestinal inflammation often combines osmotic and secretory components with increased motility: activated immune cells produce a number of factors that affect mucosa and its blood supply and disrupt both secretion and reabsorption of ions and water in the intestine. Their effects are often potentiated with other agents (eg toxins) in the intestinal lumen.

4. **Diarrhea at increased filtration** - Increased pressure in the capillaries of the villi with simultaneous obstruction of lymph flow in the mesenterium. Excessive loss of protein and lymphocytes into the lumen occurs.
Causes: intestinal obstruction increasing intraluminal pressure and further portal hypertension.

PATOPHYSIOLOGY OF INTESTINE

The categorization of diarrhea is not entirely uniform; the individual categories overlap. From a **pathophysiological** point of view, diarrhea can be divided into:

5. Diarrhea from increased motility. Normal absorption requires the intestinal contents to be in contact with a sufficiently large GIT absorption surface for a sufficient period of time.

Factors that reduce this time are:

- resection of the small or large intestine,
- gastric resection
- Pyloroplasty
- vagotomy,
- surgical bypass of intestinal segments
- Irritable colon
- some drugs (prokinetics, acetyl choline esterase inhibitors, central muscle relaxants, psychopharmacs, colchicine ..)
- stress

PATOPHYSIOLOGY OF INTESTINE

Complications of diarrhea:

loss of electrolytes (Na, K, Mg and Cl) and water => dehydration and collapse. Increased risk in elderly and weak individuals and children

Metabolic acidosis may develop as a result of HCO_3^- losses.

Serum Na^+ concentrations are variable depending on the relative composition of diarrhea losses relative to plasma.

Hypokalaemia may occur with severe or chronic diarrhea if the stool contains excessive mucus. There may also be a tetany caused by both hypokalemia and hypomagnesaemia.

Oral rehydration therapy required, possibly compensating for water and electrolyte losses by infusion.

PATOPHYSIOLOGY OF LARGE INTESTINE

Constipation

perception of difficulties can be very subjective

can be defined as **difficult defecation** (less than 3 times a week)

From the pathophysiological point of view, the water content of the stool is critical. If it drops below 70%, the stool is too stiff and its passage through the colon is poor

constipation is in most cases caused by a **slow digestion passage**. The most common cause is **low dietary fiber**.

Furthermore, the cause of constipation may be a **disrupted pelvic floor mechanics** => disruption of the stool evacuation mechanisms

PATOPHYSIOLOGY OF LARGE INTESTINE

In practice, it is necessary to distinguish between **acute** and **chronic** constipation

Acute constipation

- can be defined as sudden difficulty in emptying, lasting for a shorter period (in days).

the cause may be:

- change of defecation regime (change of environment, inappropriate hygienic conditions, social circumstances ..)
- change of diet (mainly lack of fiber)
- decrease in hydration (insufficient fluid intake, increased urine output and sweat)
- change of medication - constipation is an adverse effect of a number of drugs: anticholinergics, antacids, antidepressants, opiates, diuretics, etc.

The cause of acute constipation may be an ileous condition - acute intestinal obstruction.

Chronic constipation

1. *Organic constipation*

Causes: structural changes in the gastrointestinal tract, especially in the colon and in the recto-anal region. An extreme example is obturation by colorectal cancer.

2*. Secondary Constipation*

accompanies many diseases of other organs and systems (endocrine disorders, neurological and psychiatric diseases, gynecological diseases)

3. *Constipation as a separate disease*

a) habitual constipation

Cause: suppression of defecation reflex

the extinction of the unconditioned reflex component is due to a lack of natural stimulation - ie a low-volume diet with a lack of fiber, lack of fluid, low physical activity

extinction of the conditioned component - by suppressing spontaneous defecation, mainly because unsatisfactory hygienic conditions, feeling shy etc.

b) spastic constipation

abdominal pain during or shortly after defecation. One of the forms of functional colopathies.

PATOPHYSIOLOGY OF LARGE INTESTINE

Less common causes of constipation

a) **inert colon (Lane's syndrome)**
characterized by marked hypomobility. It affects only young women and all common causes of constipation are absent or play an insignificant role. The probable cause is a disorder of intestinal muscle innervation - changes in the Auerbach plexus, as well as a significant reduction in interstitial Cajal cells in the entire colon segment

b) **disorders of defecation mechanics** - constipation from disturbance of evacuation in recto-anal area (outlet obstruction)
the defecation reflex is maintained, but the stool must be forced out. The cause is a mechanical obstacle consisting of anatomical or functional failure of the terminal section of the digestive tract:
- rectal prolapse, rectocele, intususception
- dyssynergy of pelvic floor muscles
- painful anal affections - fissure or stenosis, hemorrhoid

c) **fekalom** - mechanical obstruction caused by the a stone made of feces.

PATOPHYSIOLOGY OF LARGE INTESTINE

Hemorrhoids

nodal vascular plexus in the area of the rectum and anal canal. According to localization they can be **internal and external**
Very common disease (up to 50% of the population), the incidence increases with age.

Their formation is conditioned by an **increase in the pressure in the haemorrhoidal venous plexuses**, which can react by enlargement, swelling, bleeding or mucosal prolapse.

The causes of hemorrhoids are not fully understood. They are usually formed by prolonged pressure increases in haemorrhoid venous plexuses for various reasons:

- increased sphincter tone - makes it difficult to drain the plexus.
- from intra-abdominal pressure - defecation disorders - constipation, diarrhea, small stool volume for lack of fiber, pregnancy, obesity, sedentary work, lack of exercise.
- Small pelvis tumors.
- AV anastomosis hyperplasia.
- genetic disposition(?)

hemorrhoids are related to human lifestyle:
Risk factors: obesity, stress, smoking, alcoholism, sedentary life, low movement, bad eating habits, fluid deficiency, low fiber Intake.

PATOPHYSIOLOGY OF LARGE INTESTINE

Hemorrhoids

Two theories describe the mechanisms of origin:

1) **Mechanical theory** (more likely) - There is a gradual degeneration of the connective tissue surrounding the venous plexus, which is then not well fixed, expanding and weakening at higher pressure.

2) **Haemodynamic theory** - Due to the increased tone of the internal sphincter, drainage fails with blood stasis, decreases oxygen saturation and increases CO_2 with subsequent vascular wall involvement resulting in thrombosis with local inflammatory response.

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