Chronic gastritis

Methodic materials for international students (IV-VI year)

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Definition:

Chronic gastritis is a chronic progressive stomach disease, pathological base of which are dystrophy, inflammation, disregeneration of gastric mucosa with atrophia as the outcome of these events. These conditions are accompanied by secretion, motoric and incretory functions disturbances. The disease is manifested by following syndromes: pain, dyspepsia, regurgitation as well as by extra-organ disturbances.

Prevalence: By biopsy, revealed in more than 50% of population in developed countries with atrophic variants prevalence increasing with age; autoimmune variant is revealed less than in 1% of population. No gender differences exist. Due to high rate of asymptomatic course chronic gastritis can be first diagnosed by biopsy or autopsy.

H pylori–associated chronic gastritis appears to be more common among Asian and Hispanic people than in people of other races; in the United States:more common among black, Native American, and Hispanic people than among white people, a difference that has been attributed to socioeconomic factors; the infection is usually acquired during childhood with complications developing later

Autoimmune gastritis: more frequent in individuals of northern European descent and in African American people, and it is less frequent in southern European and Asian people; female-to-male ratio is 3:1. The disease is typically diagnosed in age approximately 60 years.

Special types of gastritis

Lymphocytic gastritis (1.4% of all gastrites), more common in Europe: can occur in children but is usually patients are aged 50 years.
Eosinophilic gastritis mostly affects people younger than 50 years.

Aethiology:

Exogenous			**Infectious**	**Endogenous**
Food	**Mechanic, termal, professional etc**	**Chemicals and drugs consumption**		
Changes of quality and	- heat - acids and bases	- alcohol - its surrogates	1. H.Pylori infection	- metabolic and endocrine disorders

amount	steams - dusts: coal, cotton, silicate - cocain use (granulomatous gastritis) - foreign bodies	- smoking - NSAIDs - Potassium preparations - some antibiotics - digitalis	Other infections: A. mycobacteriosis, syphilis, histoplasmosis, mucormycosis, South American blastomycosis, anisakiasis, or anisakidosis (granulomatous gastritis) B. Parasites: *Strongyloides* species, schistosomiasis, *Diphyllobothrium latum* C. Viral infections: cytomegalovirus, herpes virus	(incl.uraemia) - tissue hypoxia (heart and respiratory failure; anaemia; portal hypertension); ishemia - food allery - systemic granulomatous diseases (non-infectious granulomatous gastritis, associated with Crohn disease, Sarcoidosis, Wegener granulomatosis, Rheumatoid nodules, granulomas associated with gastric carcinoma, Langerhans cell histiocytosis) Other systemic diseases: Tumoral amyloidosis and Gastric diseases: Gastric lymphoma etc

- Uremic gastropathy
- Chronic noninfectious granulomatous gastritis, associated with the following:

Crohn disease
Sarcoidosis
Wegener granulomatosis

  - Foreign bodies
  - Cocaine use
  - Isolated granulomatous gastritis
  - Chronic granulomatous disease of childhood
  - Eosinophilic granuloma
  - Allergic granulomatosis and vasculitis
  - Plasma cell granulomas
  - Rheumatoid nodules
  - Tumoral amyloidosis and granulomas associated with gastric carcinoma
  - Gastric lymphoma
  - Langerhans cell histiocytosis
- Lymphocytic gastritis, including gastritis associated with celiac disease
- Eosinophilic gastritis
- Radiation injury to the stomach
- GVHD
- Ischemic gastritis
- Gastritis secondary to drug therapy

- Chronic gastritis of undetermined etiology or gastritis of undetermined type

Pathogenesis:

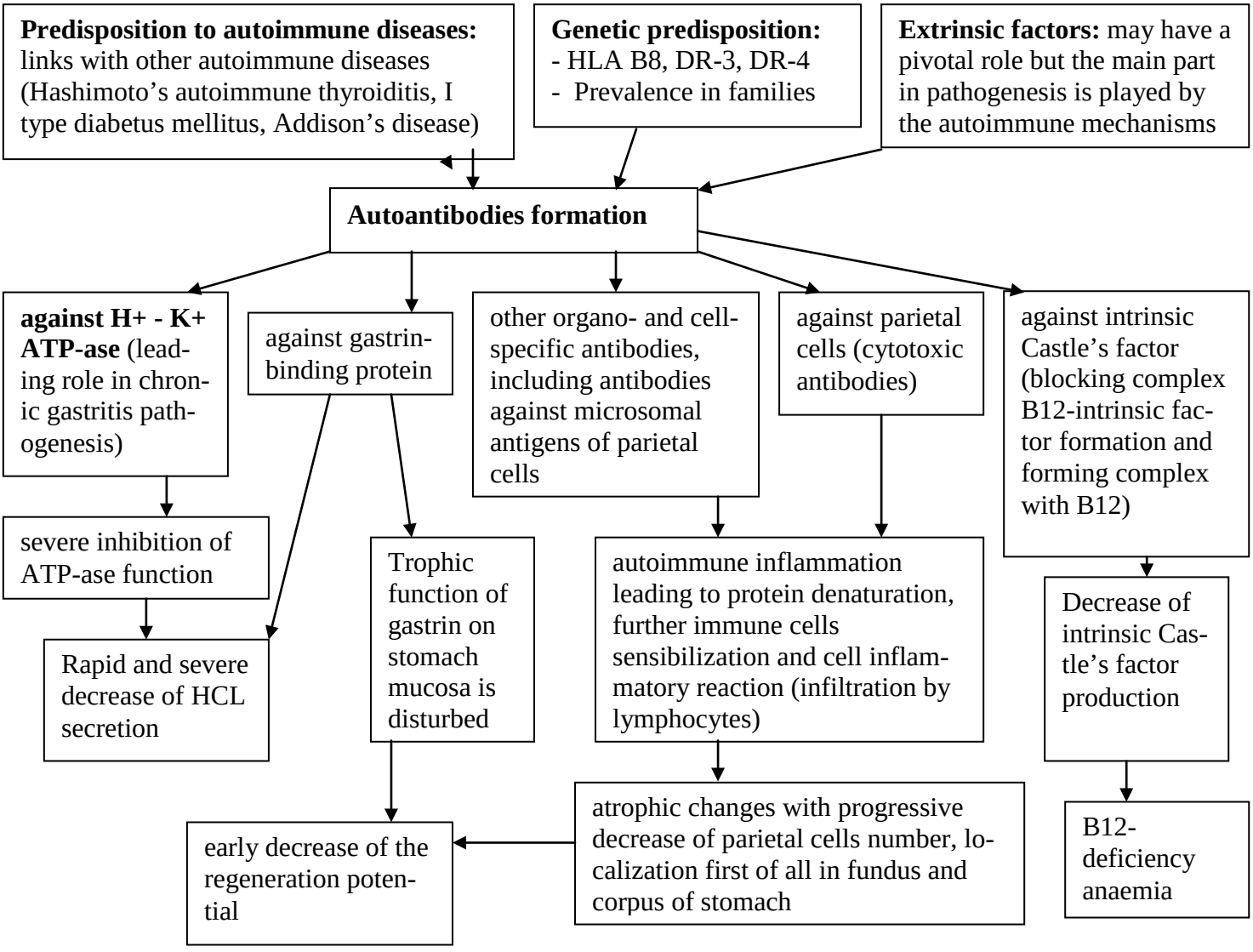
Normal reparation of gastric mucosa with renewing of the cells is genetically determined and takes about 3-6 days. Regeneration phases include cellular proliferation and specialization, when the cells become specialized for certain functions (main, parietal cells etc).

Above mentioned exo- and endogenous factors influence on the second phase, causing its suppression, while the first one – proliferation – remains unaffected. Thus, developing young cells become defected and sensitive to pathological influences, so that they soon die with atrophic changes progression (especially in the body part), which causes gradual decrease of glandular apparatus secretory activity up to achlorhydria and achylia development.

Pathogenetic types of chronic gastritis (R.G.Strickland and J.R.Mackay):

A-type: Autoimmune

Prevalence: less than in 1% of population

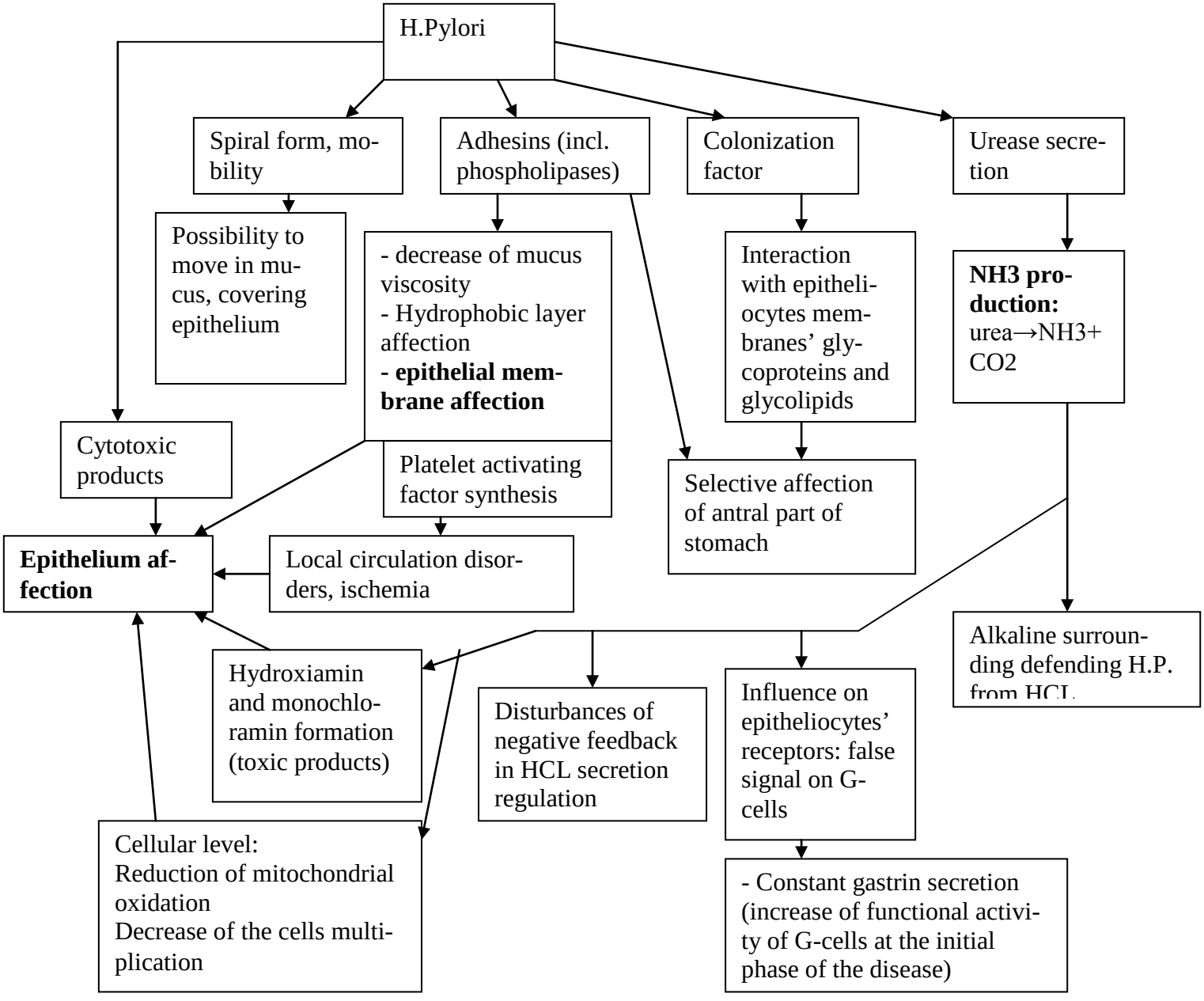


Achlorhydria leads to pronounced hypergastrinemia (> 1000 pg/mL) due to loss of acid inhibition of gastrin G cells. Hypergastrinemia may induce hyperplasia of gastric enterochromaffin-like cells that may lead to the development of small, multicentric carcinoid tumors in 5% of pa-

tients. Metastatic spread is uncommon in lesions smaller than 2 cm. The risk of adenocarcinoma is also slightly increased but has been overemphasized.

Clinical peculiarities:
- rapid progression is usual, especially in patients over 50 and in those with severe mucosa affection; progression rate is 20 times more than in population (in case of corpus of the stomach affection; in case of antral part affection more common stable course of the disease is seen)
-often associated with B12-deficiency anaemia and stomach polyps and 2.9 fold increase of stomach cancer frequency.

B-type: Bacterial
Aethiology: presence of H.Pylori: intensively stained spiral-formed gram-negative bacteria with doubled membrane and covered by glycocalix, the last being an important adhesion factor. Other adhesion factors are phospholipase A and C, these also enable epithelial membranes affection.H.P. resides beneath the gastric mucus layer adjacent to gastric epithelial cells.



H.Pylori: comments

Although H.Pylori is not invasive, it causes gastric mucosal inflammation with polymorphonuclear neutrophils and lymphocytes. The mechanisms of injury and inflammation may in part be related to the products of two genes, vacA and cagA.

Prevalence of HP infection (USA):

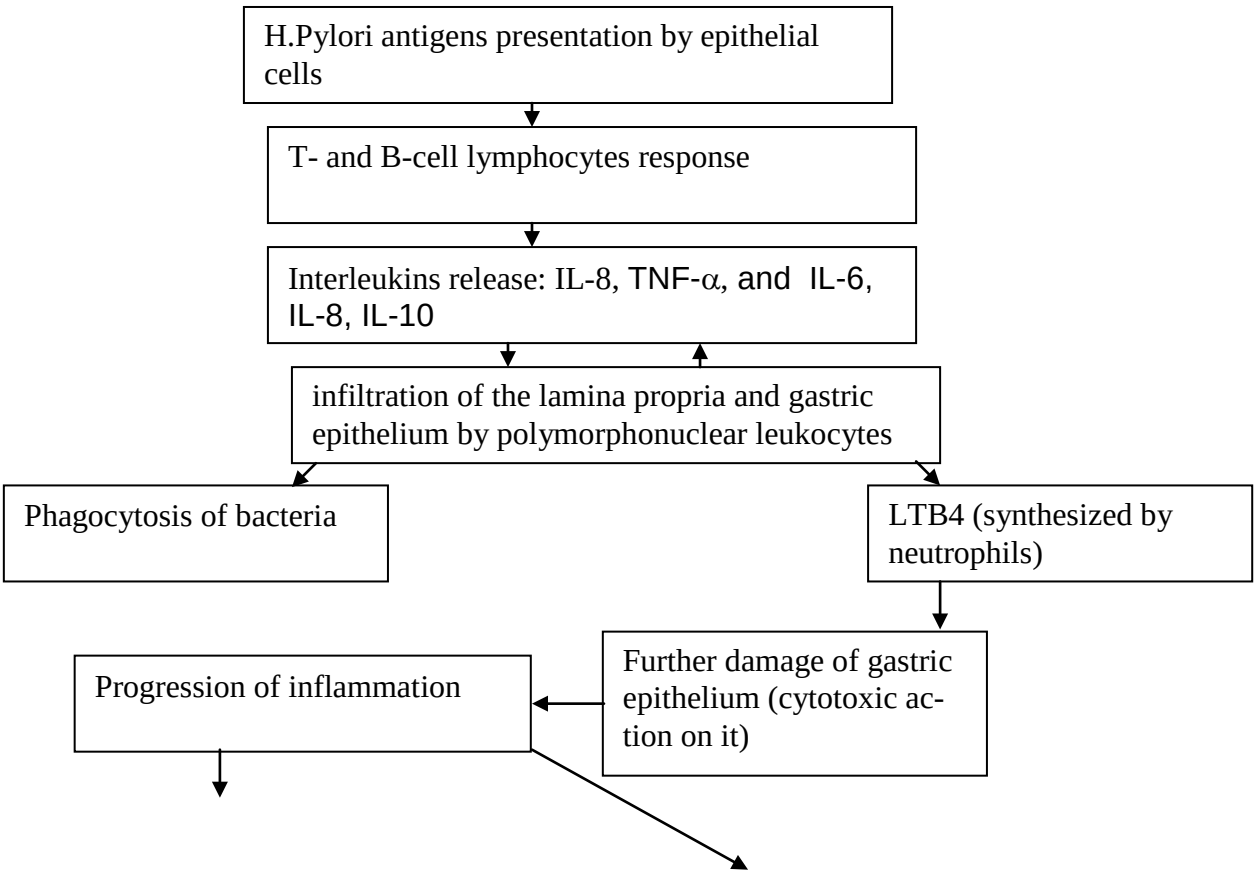
- less than 10% in Caucasians under age 30 and over 50% in those over age 60.
- higher in non-Caucasians and immigrants from developing countries and is correlated inversely with socioeconomic status.

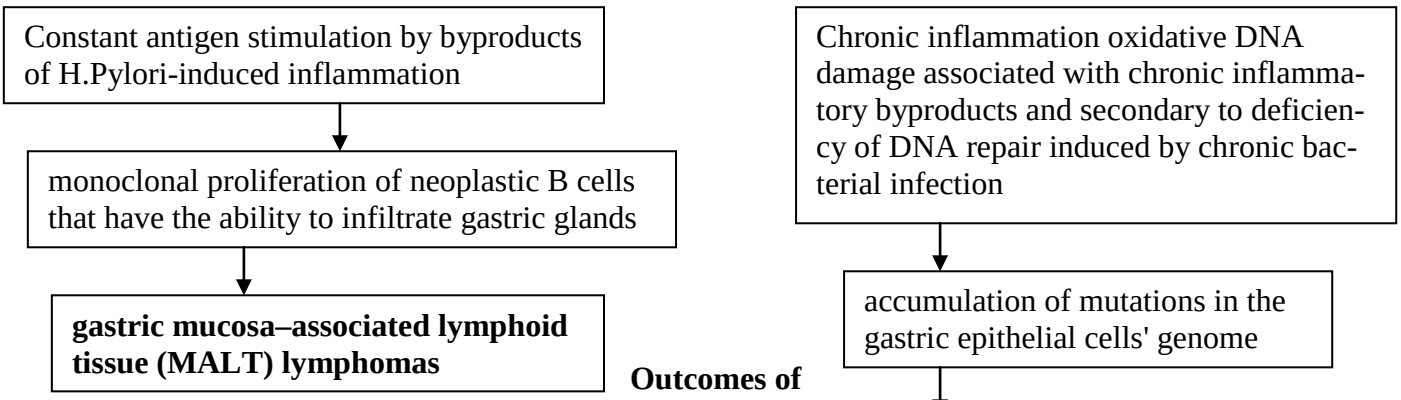
Transmission: from person to person, but the mode of spread is not known. The majority of infections are probably acquired in childhood.

Acute infection with H pylori may cause a transient clinical illness characterized by nausea and abdominal pain that may last for several days and is associated with acute histologic gastritis with polymorphonuclear neutrophils. After these symptoms resolve, it is believed that the majority progress to chronic infection with chronic, diffuse mucosal inflammation characterized by polymorphonuclear neutrophils and lymphocytes. Inflammation may be confined to the superficial gastric epithelium or may extend deeper into the gastric glands, resulting in varying degrees of gland atrophy (atrophic gastritis) and metaplasia of the gastric epithelium to intestinal type epithelium.

Although chronic H pylori infection with gastritis is present in 30–50% of the population, the vast majority are asymptomatic and suffer no sequelae. H pylori infection is strongly associated with peptic ulcer disease; however, only 15% of people with chronic infection develop a peptic ulcer (see section on peptic ulcer disease).

Host response to H.Pylori infection and HP infection outcomes:





Outcomes of H.Pylori infection:

- asymptomatic chronic gastritis
- chronic gastritis with clinical symptoms
- peptic ulcer
- gastric mucosa–associated lymphoid tissue (MALT)
- gastric adenocarcinomas

Clinical and morphological peculiarities of HP-associated gastritis:

- begins in young age
- begins with the superficial changes of antral mucosa
- further increase of morphological changes with lymphoplasmocytes' infiltration, lymphoid folliculi formation, erosions and gut metaplasy of the epithelium
- different functional changes, including high acidic production due to the different degree of the fundal mucosa affection as well as G-cells pathology (increase of activity at the early stages with subsequent dystrophy and death)
- dominating of proliferation processes over cells differentiation, so the epithelium is not mature

Acid secretion level depends also on the zone of stomach involved.

- inflammation affecting the gastric corpus: parietal cells are inhibited, leading to reduced acid secretion. Continued inflammation results in loss of parietal cells, and the reduction in acid secretion becomes permanent.
- antral inflammation alters the interplay between gastrin and somatostatin secretion, affecting G cells (gastrin-secreting cells) and D cells (somatostatin-secreting cells), respectively with increase of gastrin secretion (see scheme above).

***H pylori*–associated chronic gastritis progresses with the following 2 main topographic and morphological patterns that have different clinical consequences:**

- Antral predominant gastritis is characterized by inflammation and is mostly limited to the antrum. Individuals with peptic ulcers usually demonstrate this pattern of gastritis.
- Multifocal atrophic gastritis is characterized by involvement of the corpus and gastric antrum with progressive development of gastric atrophy (loss of the gastric glands) and partial replacement of gastric glands by an intestinal-type epithelium (intestinal metaplasia). Individuals who develop gastric carcinoma and gastric ulcers usually demonstrate this pattern of gastritis.

Morphological outcomes (variants):

1. gradual involvement of duodenum with pyloroduodenitis development
2. gradual involvement of proximal parts of stomach with transformation to AB gastritis

Chronic H pylori gastritis is associated with a four- to sixfold increased risk of gastric adenocarcinoma and low-grade B cell gastric lymphoma (MALToma).

C-gastritis (Chemical)

1. **Reflux-gastritis** (15% of all the gastrites): with duodenogastral reflux and toxic (membranolytic) affection of the epithelial cells by bile components: lysolecitin, bile acids-detergents, the last ones also cause lipids affection of the epitheliocytes' walls and mucus-bicarbonate barrier destroying.

The classical form of reflux gastritis is gastritis after stomach resection. Constant reflux of above mentioned products into the small stomach cavity caused toxic affection of the mucosa. In some cases H.Pylori infection may appear with "mixed" C-B forms of gastritis development

2. Iatrogenic affection: more rare - up to 5%; more often caused by NSAIDs; with primary antral part affection.

Morphology of chronic gastritis:

1. Inflammation:
- proprior layer infiltration by mononuclear cells and lymphocytes (mild changes may be revealed even in healthy)
- in gastritis neutrophils, eosinophils and basophils infiltration is also present
- infiltration degree correlates with gastritis activity
2. Atrophy with progressive reduction of stomach glands number. Reduction of main (pepsin-synthesizing) and parietal (acid-synthesizing) cells number.
3. Disregeneration and cells maturation disturbances, correlating with the duration of the disease:
- after specialized cells death (see 2) they are replaced by more primitive mucus-synthesizing cells.
- Metaplasia: replacement of the specialized cells by the different kind of epithelium: gut-like metaplasia (morphological features of gut epithelium) pyloric metaplasia (replacement of main glands of corpus and fundus by mucosa, typical for pyloric part).

Classification

Modified Sydney classification (Sydney system): worked out in 1996 in Huston

Type of gastritis	Synonims	Aethiological factors
I. **Non-atrophic**	Superficial, diffuse antral chronic, antral gastritis type B	H. Pylori, other factors
II. **Atrophic**	Type A, diffuse gastritis of corpus of stomach	Autoimmine
- Autoimmune - Multifocal	Associated with B12-anaemia	H.Pylori, nutrition peculiarities, environmental factors
Special forms		
Chemical	Reflux-gastritis, C-type	NSAIDs, bile, chemical substances
Radiation-induced		Radiation
Lymphocytic	Variolomorphic, chronic erosive, associated with gluten disease	Idiopatic, immune mechanisms, gluten, H.Pylori
Non-infectional	Isolated granulomatosis	Crone's disease, sacroidosis, Vegener's granulomatosis, idiopatic
Eosinophylic	Food allergy, other allergens	Allergy-induced

Other infectious		Bacteria (other than H.pylori), viruses, fungi, parasites
Collagenous	Systemic connective tissue inflammatory diseases	Immune mechanisms, genetic factors

Classification of 1965-66 workgroup:

I. Aethiological: endogenous and exogenous (see above)
II. Pathogenetic: A, B, AB, C
III. Morphologic:
1. Superficial gastritis
2. Atrophic gastritis of different severity grade
3. Remodelling (metaplasia) gastritis
a) gut metaplasia
b) glands pylorisation
c) atrophic-hypertrophic gastritis
4. Hypertrophic
IV. Localisation
1. Diffuse (pangastritis)
2. Focal (antral, pyloroduodenal)
3. Fundal (very rare)
V. Functional
1. With normal ore moderately increased secretion
2. With secretion insufficiency of different degrees from initial to histamine-resistant achlorhydira and achylia
VI. Clinical course
1. Phase – exacerbation, remission, recovering exacerbation
2. Stage – compensation, subcompensation, decompensation
VII. Special forms
1. Rigid antrum-gastritis
2. Hypertrophic gastritis (Menentries). Polipous gastritis
3. Erosive haemorrhagic
VIII. Concomitant gastritis

- Addison-Birmer's anaemia
- Gastric cancer
- Mediogastral ulcers

Clinical manifestations

Syndrome	Pangastritis	Antral B gastritis
Pain	Localised in high epigastrium, are early (due to gastric distension), without radiation, are related to the food, increased in amount, fatty or roasted Pain is aggravated during walking or standing Pain equivalent – sensation of heaviness and discomphort in epigastrium after eating	Spastic pain: more intensive, rhythmic, ulcer-like character, appear 2-3 hours after eating (late pain; in contrast to peptic ulcer there are no night pains)
Gastric dispepsy	Loss of appetite, sourness or metal-like flavor in mouth, early satiation, belching (air or food), nausea (more severe after excessive food), vomiting, which doesn't lead to improvement of condition	Acidic complains: acidic belching; heartburn or burning in epigastrium
General symptoms:	Very rare – weight loss, increased appetite to piquant food, adinamia, hypotonia, increased	

	salivation, polyhypovitaminosis (cheilitis, dry skin, gingivitis)	
Damping-syndrome may be present	Paroxysmal weakness, patient becoming speepy, pallor, perspiration, marked increase of peristaltic. The paroxysms finish by defecation.	
Objective	Diffuse painful palpation zone in epigastrium, tongue covered by white coating and with smoothed papilles	
Secondary gut dispepsy	Diarrhea, especially after milk and fatty food consumption, meteorism	Constipation or trend to constipation

Special forms of gastritis:

Other infection-related gastritis (other than HP-associated):

- in HIV (Cytomegalovirus), Treponema pallidum and M.tuberculosis-infected patients, as well these after bone marrow or solid organ transplantation. (due to immune system suppression). Endoscopic findings include thickened gastric folds and ulcerations.
- Fungal infection with Candida may occur in immunocompromised patients.
- Bilrot-II anastomoses with secondary achlorhydria and bacterial affection of duodenal loop

Granulomatous Gastritis

Chronic granulomatous inflammation may be caused by a variety of systemic diseases, including tuberculosis, syphilis, fungi, sarcoidosis, or Crohn's disease. These may be asymptomatic or associated with a variety of gastrointestinal complaints. Patients with idiopathic isolated granulomatous gastritis (this diagnosis is established only when known entities associated with granulomas are excluded) are usually older than 40 years at presentation and have epigastric pain, weight loss, and vomiting secondary to pyloric obstruction.

Endoscopic findings in granulomatous gastritis include mucosal nodularity with cobblestoning, multiple aphthous ulcers, linear or serpiginous ulcerations, thickened antral folds, antral narrowing, hypoperistalsis, and duodenal strictures. Extensive gastric involvement may resemble linitis plastica.

Radiation-associated gastritis

Small doses of radiation (up to 1500 R) cause reversible mucosal damage, whereas higher radiation doses cause irreversible damage with atrophy and ischemic-related ulceration. Reversible changes consist of degenerative changes in epithelial cells and nonspecific chronic inflammatory infiltrate in the lamina propria. Higher amounts of radiation cause permanent mucosal damage, with atrophy of fundic glands, mucosal erosions, and capillary hemorrhage. Associated submucosal endarteritis results in mucosal ischemia and secondary ulcer development.

Coagulation necrosis varying from focal to diffuse with secondary inflammation is also typical. Reduction of symptoms is revealed in 4 months (in non-severe cases)

Lymphocytic gastritis:

- pathologic immune answer on HPylori, the last one found in less amounts than in B gastritis.
- gluten disease – revealed in 50% of patients with classical forms of gluten disease; the last one leads to increase of stomach mucosa permeability and increase of intraepithelial lymphocytes number

- hypertrophic Menentries gastritis with diffuse or polip-like hyperplasia of superficial epithelium of corpus and fundus of stomach, the signs being not present in antrum. Lymphocytic gastritis can be the phase of Menentries disease development; its pathogenesis in this case may be related with protein loss
- stomach lymphoma: rate of lymphocytic gastritis is revealed in 32% of stomaches, received from patients after gastric lymphoma surgery

Clinical manifestations include fluctuating abdominal pain, nausea, and vomiting. There is no established effective therapy.

At endoscopy it shows enlarged folds and aphthoid erosions, with the appearance of small, heaped-up, volcanolike mounds pocked with a central crater. This endoscopic pattern has also been described as varioliform gastritis.

Eosinophilic gastritis

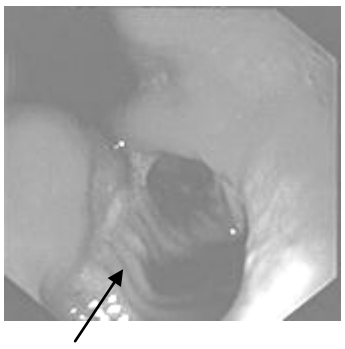
- chronic recurrent disease, revealed in all the age groups and characterized by marked eosinophils infiltration of mucosa and other layers in case – asthma, allergy (including skin allergic diseases), hypersensitifity to food proteins
- mostly antral part is affected, sometimes proximal intestine
- eosinophil abscesses can be revealed in lamina propria, epithelium
- often other organs are involved – gut and oesophagus
- blood eosinophylia is present

Clinical manifestations:

- anemia from mucosal blood loss
- abdominal pain
- early satiety
- postprandial vomiting.

Treatment: with corticosteroids is beneficial in the majority of patients.

Menentrier's (Ménétrier's**) gastritis =** Hypertrophic Gastropathy**:**



- diffuse or polip-like hyperplasia of superficial epithelium of corpus and fundus of stomach, the signs being not present in antrum; thickened mucosa giant folds looking like a section of brain or cobble-stone road; prolapse of thickened folds to duodenum is possible

The cause is unknown.

Clinical manifestations:

- signs, similar to these in antral gastritis; nausea, epigastric pain, weight loss, and diarrhea.
- oedemas, hypoalbuminemia (protein loss through gastric mucosa)
- anaemia
- bleeding may occur if erosions are placed at the apex part of folds

Treatment is directed at symptoms. Gastric resection is required in severe cases. There are case reports of resolution of symptoms and improvement in histologic appearance after H pylori eradication.

Zollinger-Ellison's syndrome

- hypertrophic gastropathy caused by increase of the main and parietal cells in deep glandular layer of corpus and fundus of stomach, increase of G-cells in antrum
- numerous peptic ulcers are seen in stomach and duodenum

- 2 types of the syndrome: type 1 (marked G-cells hyperplasy in antrum) and type 2 (gastrin-producing tumor)

Gastritis in graft versus host disease

Graft versus host disease (GVHD) follows allogeneic bone marrow transplantation or transfusions, especially in patients who are immunocompromised. Patients with isolated gastric

Ischemic gastritis

Ischemic gastritis is believed to result from atherosclerotic thrombi arising from the celiac and superior mesenteric arteries.

In some textbooks, gastritis is also divided into three categories:
- erosive and hemorrhagic gastritis
- nonerosive, nonspecific (histologic) gastritis
- specific types of gastritis, characterized by distinctive histologic and endoscopic features that may be diagnostic of a disorder.

	Erosive gastritis	Nonerosive, non-specific	Specific:
Aethiological factors	- alcoholics - critically ill patients, - NSAIDs - chronic stress, -portal hypertension. - caustic ingestion - radiation.	Usually H.Pylori	See above
Clinical manifestations	Often asymptomatic; may cause epigastric pain, nausea, and vomiting, hematemesis (“coffee grounds”), melena; usually not significant bleeding.	See B gastritis	
Endoscopic	- subepithelial hemorrhages, - petechiae, - erosions. Lesions are superficial, vary in size and number, and may be focal or diffuse. No significant inflammation on histologic examination, though gastropathy may be present.	See B gastritis	
Types	In this group also NSAID gastritis, Alcoholic gastritis and Portal hypertension gastropathy are included	- due to H pylori infection - associated with pernicious anemia, - lymphocytic gastritis	

Laboratory and instrumental diagnosis

1. **Endoscopic examination** (in suspected H.Pylori-associated gastritis –w ith biopsy and investigation aimed on HP search)

- Confirms diagnosis
- Confirms HP presence (biopsy)
- Diagnosis of erosive gastritis: 2 types of erosions: flat ones "bleeding tears" or elevated, with necrosis focus in center (variolomorphic gastritis), more often lymphocytic origin is proved by histological investigation
- Diagnosis of Menentries disease – mucosa is folded, looks like brain section

Endocopic criteria of gastritis:

- marked diffuse oedema
- marked diffuse hyperemia
- haemorrhages
- vulnerability of the mucosa
- trend to bleeding of the mucosa
- flat or elevated erosions
- changes of the vessels (may be either smoothed and hardly seen or marked)
- atrophy
- smoothed or hypertrophic folds
- presence of H.Pylori (biopsy)

Special stains to identify *H pylori*, such as Warthin-Starry, Giemsa, or Genta stain are used to identify H.Pylori.

2. **Gastric secretion**

	Basic (1^{st} hour of investigation)	Histamine –stimulated acid production (2^{nd} hour)
Healthy males	3.3+0.3 mmol/hour (0-9)	11.5+0.9 (6.25-26)
Healthy females	2.3+0.21 (0-7)	8.5+0.6 (4.5-20)
Atrophic gastritis	0.75+0.03	1.36+0.05

Antral gastritis may lead to mild increase of secretion due to G-cells activation

3. **pH-metry**
4. **Serum IgG antibodies to H pylori** are detectable by ELISA, and kits are commercially available. Highly sensitive, these tests do not necessarily denote ongoing, active infection. **At least, performed 2 times.** After successful H pylori eradication with antibiotics, antibody levels decline slowly over 6–12 months but may remain positive.
5. **Noninvasive 14C- and 13C-urea breath tests.** Because these urease breath tests indicate active infection, they may become the tests of choice for noninvasive screening for H pylori infection or for verifying eradication after antibacterial therapy.
6. immunological test (blood) for H.Pylori antibodies presence evaluation – 2 times
7. blood analysis (haemogram)
8. serum proteins and protein fractions
9. urinanalsis
10. coprogram (cytology, test for occult bleeding)
11. ultrasonic examination of the abdominal organs

12. Additional methods:

- *Screening method for gastritis with marked atrophy and for gastric cancer* in regions with high incidence of these diseases: **measuring serum levels of the pepsinogen I–to–pepsinogen II ratio**. Pepsinogen I (PGA, PGI) ; level of PGA in the serum decreases as loss of gastric chief cells during gastric atrophy occurs, resulting in a decreased PGI/PGII ratio. However, the sensitivity and specificity of the assay is relatively low, with 84.6% and 73.5% values, respectively, reported in a recent study.
- *For autoimmune gastritis***: Antiparietal and anti-intrinsic Castle's Factor (IF) - antibodies in the serum**

Diagnosis formulas

1. Chronic B gastritis, exacerbation, with moderate atrophic changes and secretion insufficiency, HP ++++
2. Erosive gastritis, exacerbation. Stomach bleeding (date) HP +++
3. Chronic A gastritis, remisiion. HP (-). Addison-Birmer's anaemia (date). Diffuse stomach corpus polyposis.

Differential diagnosis. Aims of diagnostic measurements:

1. Confirm presence of gastritis (clinical syndromes+endoscopy+secretion investigation+HP). Differential diagnosis with non-ulcer dyspepsia, cancer, peptic ulcer
2. Investigation of the other digestive system organs to reveal their affection (usually gastritis is not isolated disease).
3. To determine is gastritis the main or concomitant disease

Clinical course: fluctuating, with exacerbations and remission, the first ones being usually treated in out-patient conditions

Gastritis forms as pre-cancer conditions (risk groups)

1. Fundal A gastritis with marked decrease of secretion
2. Gut metaplasia
3. Variolomorphic gastritis
4. Addison-Birmer's anaemia-associated gastritis
5. Menentries gastritis
6. Polipous gastritis
7. Atrophic gastritis associated with mediogastral uncers in persons over 40

All risk group patients are to perform endoscopic investigation with histological examination of biopsy-obtained material every year

Indications for hospitalization (mostly with diagnostic purposes):

- resistant, prolonged exacerbations
- progressive course, especially after 40 years old, associated with weight loss, anaemia
- special forms of gastritis
- complications (bleedings etc)

Outcomes:

Successful eradication of H pylori infection may be achieved in over 85% of patients, after that gastritis may resolve.

- cancer in case of prolonged course with atrophy and displasia
- peptic ulcer
- bleedimg
- B12- and Fe-deficiency related anaemia

Treatment:

Autoimmune gastritis

1. Dietary treatment – food intake in small portions, 5-6 times a day; no food with irritant action on gastric mucosa can be used
2. During exacerbation – 2-3 weeks of anti-inflammatory treatment by phytopreparations: milfoil, mint, St-John's wort, flowers of chamomille, root of valeriana, leaves of plaintain (drew in hot water)
3. In case of severe pain – prokinetics and spasmolytics (Domperidon – Motilium-peripheric D2-dophaminereceptors antagonist 10 mg x 4 times daily – 3 times 30 min before meals and once before sleeping; dicetel etc)
4. Stomach function correction: stimulation (Limontar) or replacing (in case of marked decrease) treatment. Replacing treatment includes Acidin-pepsin or intake after meals.
5. Vitamins complexes - courses lasting 1-2 months
6. Pancreatic secretion correction (if symptoms are present) – Creon, Mesim
7. Anabolics (Retabolil) or i.v. infusion of aminoacids mixtures (Alvesin) are used in marked protein metabolism disturbances

HP-associated gastritis

1. **Eradication treatment schemes (similar to these in peptic ulcer).**

1 variant: 7-days lasting by 3 drugs		
Omeprasol (Losec, Omes etc) or Rabeprasol (Pariet) or Lansoprasol (Lansofed, Lansap) or Ranitidin bismuth citrates (Pylorid)	20 mg x 2 times daily 20 mg x 2 times daily 30 mg x 2 daily 400 mg 2 times daily	7 days
Claritromycin (Clacid) Or Amoxicillin (Flemoxin) Or Tetracyclin	250 x 2 while eating 500 mg x 4 or 1000 mg x 2 with eating 500 mg x 4 or 1000 mg x 2 with eating	7 days
Metronidasol Or Furasolidon	400-500 mg x 2 with eating 0.2 x 2 while eating	
Second variant: three drugs scheme based in bismuth preparation		
De-nol Metronidasol Amoxicillin	240 x 2 400 x 3 500 x 3	7
De-nol Furasolidon Amoxicillin	240 x 2 100 x 4 500 x 4	14
De-nol Claritromycin Amoxicillin	240 x 2 250 x 2 1000 x 2	7
De-nol Metronidasol Tetracyclin	120 x 4 400 x 4 500 x 4	7
De-nol Claritromycin Tetracyclin	120 x 4 250 x 4 250 x 4	10
De-nol Metronidasol Claritromycin	240 x 2 400 x 2 250 x 2	10
De-nol Furosolidon	240 x 2 100 x 2	7

Claritromycin	250 x 2	
De-nol Claritromycin Omeprasol	120 x 4 500 x 2 40 x 2	7
Reserved variant: 7-10 days lasting treatment by 4 drugs		
Omeprasol (Losec, Omes etc) or Rabeprasol (Pariet) or Lansoprasol (Lansofed, Lansap) or Ranitidin (Zantak) Or Famotidin (Quamatel etc)	20 mg x 2 times daily 20 mg x 2 times daily 30 mg x 2 daily 150 x 2 40 x 2	7-10 days
Potassium salt of bismuthi citrates Or De-nol	108 mg 5 times daily with meals 120 mg 4 times daily with meals	7-10 days
Tetracyclin Or Amoxicillin (Flemoxin) Or Asitromycin (Sumamed etc) Or Rovamycin	200 mg 5 times daily or 500 mg 3 times daily with meals 500 mg 4 times daily or 1.0 g 2 times daily with meals 500 mg 2 times daily with meals 3 mln units 2 times daily with meals	7-10 days
Metronidasol or Furasolidon	200 mg 5 times daily with meals 0.1 g 3 times daily wit meals	7-10 days

1. De-nol, used in most of the schemes, except its anti-HP- effect, also works as cytoprotector (accumulation of growth factor in affected zone, inhibits its destruction by pepsin, binds bile acids reducing their detergent and thus cytotoxic properties)
2. Omeprozol, Rabeprasol, Lansoprasol are proton pump inhibitors, which influence on H+ transport from epithelial cells to stomach lumen and thus reduce the acidic secretion
3. Ranitidin and Famotidin are H2-histaminergic receptors blockers, which reduce acidic secretion.

2. **Cytoprotectors:** in exacerbation of the disease:

- Sucralfat (Venter): binds with proteins of affected mucosa and thus forms the protecting film in the affected zone; the drug has local acidity reducing effect without influence on intra-stomach pH, binds bile acids.

Dose is 1 g 3 times daily (1 hour before meals) and before sleeping.

3. **Antacids:** if high secretion and acidism signs are present. Non-reabsorbing antacids are preferred:

Phosphalugel – 1-2 packs 40 min before meals or 1 hour after it
Maalox – 1-2 tab 1 hour after meals and before sleeping
Gelusil-Lac and Gastal also can be used

4. **Peripheral cholinolytics:** in case of moderate increase of secretion with pain syndrome – Metacin, Platiphyllin, Belladonna, Bucospan

Peptic ulcer

Definition

Peptic ulcer disease is a clinical-anatomical term, identifying a chronic relapsing disease with a trend to progression, caused by either pathological influences of the aggressive factors on gastroduodenal mucosa (the most important of these are acidic-peptic factors and H.Pylori) or decrease of the defense mechanisms of the mucosa. These factors lead to relapsing formation of the ulcers in gastroduodenal mucosa. The disease is manifested by pain and dispeptic syndromes of different degree with possible development of life-threatening complications.

Chronic duodenal ulcer and chronic benign gastric ulcer are often grouped together as peptic ulcers. Although the two diseases have many similarities, they differ in some important aspects such as epidemiology, natural history, outcome, and management. So, they are defined as the manifestation of the peptic ulcer disease with two different localizations: gastric and duodenal. These conditions are managed clinically as separate, although related, diseases.

Prevalence:

6-10% of adult population.

Males: females ratio is 4:1 being for duodenal ulcer 1:4-1:7 and for benign gastric ulcer – 1:2 – 1:4. In average, in males onset of the disease is about 5-7 years earlier than in females. In young people males dominate; in females increase of prevalence in menopause is revealed.

Age: Maximal prevalence is revealed in 40-60 years old.

Localization: Duodenal ulcers are more common, ratio gastric: duodenal ulcer being 1:4; in young people it reaches 1:13; in aged people increase of gastric ulcers frequency is revealed; the ratio is 1.7:1.

Aethiology (the most important factors are underlined)

1. **Genetic factors - predisposition to ulcer disease**

A. Factors proved to be significant:

- high level of maximal acid stomach output
- increased level of pepsinogen I in blood serum
- increased secretion of G-gastrin by G-cells of antral zone as a response to food stimulation
- increase of parietal cells mass

B. Other genetic factors

- O (I) blood group
- Absence of ABH antigens secretion ability to the saliva and stomach fluid (non-secretors) – these patients have 1.5 fold increased rate of duodenal ulcer
- Defect of factors, defending duodenal mucosa – α1-antitripsin and β2-macroblobulin
- Absence in blood of gut component of alkaline phosphatase
- Increase of pepsinogen-1, serum and RBC0 cholinesterases in blood

- Decrease of SIgA secretion
- HLA-antigens: in general - B5 antigen, in Russian population – B14 and B15.

C. In general, hereditary factors are found in 30-40% cases of duodenal ulcer, in stomach ulcers – significantly more rare.

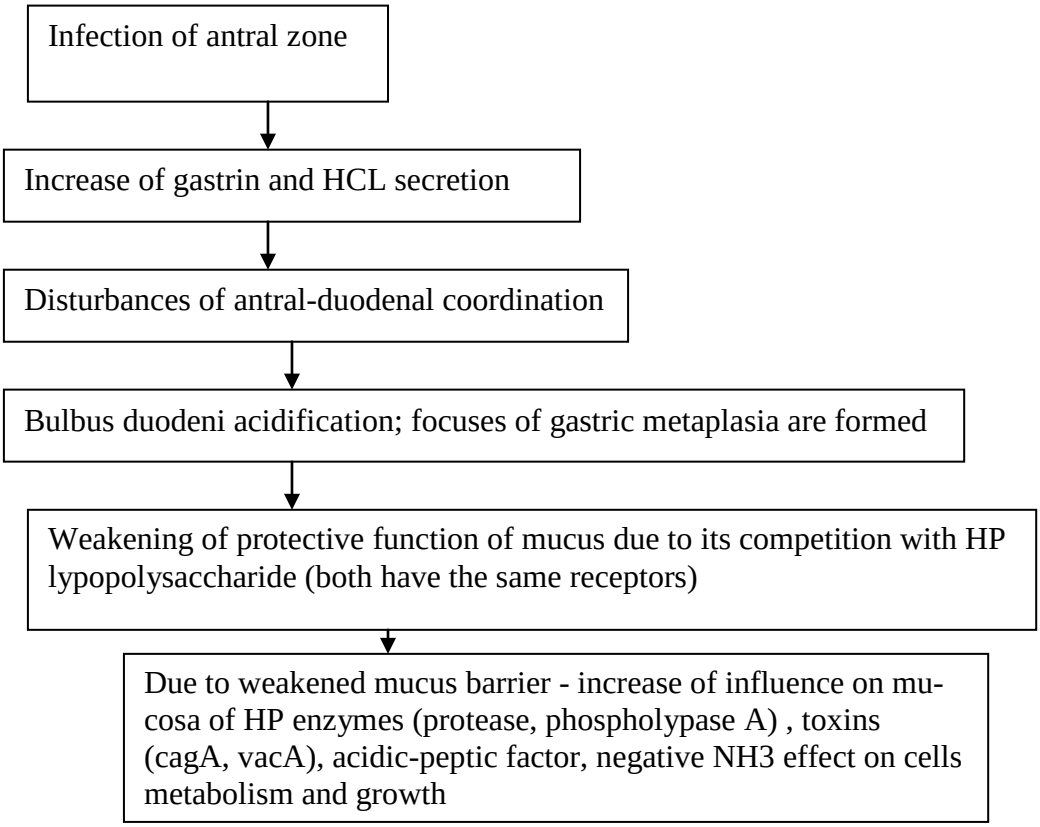
2. Stresses, especially chronic psychlolgical and emotional overstrain; their role gives possibility to some authors to consider peptic ulcer as psychosomatic disease; however their role needs to be proved from points of view of evidence-based medicine
3. Smoking: prevalence of peptic ulcer in smokers is 2.1 fold higher than in non-smokers; in smokers more aggressive course of ulcer is revealed; treatment in these cases is usually less effective
4. Alcohol is known to influence on mucus and bicarbonic barrier of gastric mucosa; high alcohol concentrations lead to acute stomach affections and decrease of gastric secretion; low concentrations stimulate acidic production
5. NSAIDs lead as well as to acute gastric erosions and to exacerbation of the present chronic ulcers
6. Irregular nutrition (usually associated with other life style factors – see 2-4)
7. **Helicobacter pylori**: is found in pyloric mucosa bioptates in 60-80% of gastric ulcer cases and in 85-100% of duodenal ulcer cases; the eradication treatment usually leads to remission of ulcer and decrease of further relapses; relapses are usually associated with reinfection. One of the main local aethiological factors.

However, peptic ulcer is a polyethiological (multifactorial) disease, where all the above mentioned factors lead to the changes of interactions between defense and aggression factors (among the last ones are microbal and acidic-peptic factor), thus the individual course of the disease is determined.

Pathogenesis: disequilibrium between defense and aggressive factors

Defense factors	Aggression factors
1. Mucus forms gel, covering epithelial cells: - barrier against H+ ions and pepsin migration into gastric and duodenal mucosa - bicarbonates are kept under the mucus gel, constant slow diffusion of bicarbonates through gastric lumen also protects from acidic-peptic aggressive factor 2. Second component of defense: epithelial cells in stomach, enterocytes and goblet cells of duodenum, producing mucus and bicarbonates 3. Normal blood supply: - insufficient development of capillary network was proved to predispose to local ischemia - truncus coelicus stenosis is found to predispose to peptic ulcer 4. Mechanisms, inhibiting acidic secretion (antral-duodenal acidic brake): in healthy these mechanisms are activated in pH 2.5-2.0; in peptic ulcer patients – in lower pH; these changes are due to antral B gastritis, which plays central role in duodenal and mediogastric ulcer pathogenesis 4. Localization of ulcer is related to the focus of the desadapted mucosa with lowest regeneration potential	Acidic and peptic factor: HCL: its concentration is 1 mln times higher than in blood Microbal factor - H.Pylori: Colonisation and persistence factors: low immunogenity, suppression of lymphocytes by HP polypeptides, antigen mimicry to Lewis blood group antigens and other (see gastritis) factors "Ulcerogenic" types of HP were revealed and proved to have peculiarities, improving their adhesion and influencing ability to destroy gastric cells. For example, vacuolizing cytotoxin leads to vacuolization of cytoplasm and thus to cells destruction HP was proved to cause reduction of cells growth, DNA synthesis, apoptosis activation.

The scheme below shows the role of HP in duodenal ulcer



In duodenal ulcer, HP can be revealed only in zones of gastric metaplasia: in the marginal zones of ulcer or at the are of 1-2 sm near ulcer or in the near-scar zone. Increase of acidic production in stomach and long-time acidification of duodenum lead to focal gastric metaplasia of duodenum and thus to HP invasion. Microbal factor lead to changes of mucus qualities and to epithelium affection as a result of cytotoxic HP effect.

Morphology
All the non-traumatic defects of mucosa are subdivided to erosions and ulcers.

Erosions	Ulcers

	Acute	Chronic
- Superficial (only epithelium being affected) - Don't affect the muscular layer of the mucosa - size is more often 2-3 mm or less - usually numerous, situated in antral part of stomach and in duodenum	Reach muscular layer or penetrate it, may penetrate serosa (penetrating forms) Round or oval-shaped, the size varies from very small up to several centimeters Oedema of the marginal zone, fibrin and debris covering may be present on the bottom; the last one also can be clear May be single or numerous (3-5)	Reach muscular layer or penetrate it, may penetrate serosa (penetrating forms) Round, triangle, crater, pyramid-shaped or irregular shape Size may vary and be up to 6-8 cm (giant ulcers). Bottom and marginal zone are dense due to fibrous tissue. Callous ulcer – with dense corn-like connective tissue in bottom and marginal zone May be single or numerous (3-5)

Recovery leads to epithelium growth on the connective tissue, which has poor developed vasculature, so this zone has increased vulnerability and predisposed to defect formation at the same zone.
Recovery from acute ulcer is accompanied by total epithelization and delicate pink scar formation. Chronic ulcer causes irregular-shaped, sometimes star-shaped rough scar causing later organ deformation.
Initially pink (red) scar, rather friable in structure later becomes white and more dense.
Complications morphology:
- In case when chronic ulcer reaches serosa, the last one becomes more dense and forms wrinkles, so perigastritis and periduodenitis as well as the commisures with the nearby organs develop.
- Destruction of vessels may lead to bleeding.
- Penetration to nearby organ may be present

Classification
International classification of the diseases, traumas and death causes (10^{th}) :

- gastric ulcer
- duodenal ulcer
- peptic ulcer of undetermined localization
- gastrojejunal ulcer

Severity degrees:

	Mild	Moderate	Severe
Exacerbations rate	Once per 2-3 years or more rare	Every year	2-3 times per year and more frequent

Workgroups classification (usually used in practice):

I. Obligatory characteristics

1. Localisation: gastric, duodenal; other sites of digestive system (oesophagal, jejunal etc); combined
2. Form:

- acute

- chronic: a) recurrent b) persistent
    3. Phases: exacerbation, reducing exacerbation (subremission); remission
    4. Complications: bleeding; perforation; penetration; gastroduodenal stenosis; malignisation

II. Non-obligatory characteristics

1. Disease course: mild, moderate, severe
2. Localization:

- gastric: cardial, subcardial, fundal (mediogastric), prepyloric (antral), canalis pyloricus
- duodenal: located in bulbus; located in postbulbar zone
- combined ulcers with both duodenum, and stomach affection

3. Gastric secretion: normal, reduced, increased.

Clinical manifestations

The most typical features are underlined.

1. Pain

	Characteristics
Localization	Epigastrium: Gastric ulcer – mostly in center and to the left from l.mediana Duodenal ulcer – in pyloroduodenal zone
Intensity	From very mild up to rather severe, when patient presses the abdomen by the fist and immediately needs to take in the pain-relieving drug
Relation to food intake	Early: 1st hour after meals Late: 1.5-3 hours after meals **Fasting:** are relieved by food intake **Night** (nocturnal): awake the patient at night (usually at the same time); usually the patient has near his bed a glass of warm milk which can relieve pain sometimes even directly after beginning of drinking
Duration	Different
Radiation	Usually not present
Relieved	By food, by antacids intake; by belladonna preparations; by heat application; by causing vomiting due to antiperistaltics, the last one abruptly stops the pain
Cause	The exact cause of ulcer pain is not clear: it is not always directly related to intraduodenal acidity, but is rapidly relieved by antacids. Possible mechanisms: Duodenal – spastic by origin; mediogastric – spastic+distension mechanism, related to hypotonus of stomach due to chronic gastritis. The role of spastic and motoric mechanisms is confirmed by spasolytics effect (pain relief): atropine, plathyphyllin, metacin

2. Gastric dyspepsy

Symptom	Characteristic
Nausea	Very rare
Vomiting	Classical sign: vomiting at the highest point of the pain; the vomiting leads to pain relief. However, nowadays vomiting in ulcer is rather rare. Sign of pyloric-duodenal obstruction (inflammatory-spastic or scar origin) : vomiting by excessive acidic substance Even episodic vomiting relieve the pain, thus it can be caused by patient
Belching	First of all, by air or by acid. Usually in mediogastral ulcers and due to chronic gastritis.
Heartburn	May precede ulcer, sometimes for several years. Daily periodic rhythm is present, especially in case of combination “pain-heartburn”. Sometimes may be pain equivalent. Sometimes may be the sign of secondary weakness of cardial sphincter and gastroesophagal reflux.

Also increased appetite may be present in combination with fear of eating due to the pain presence,

4. Gut dyspepsy

Usually present in exacerbation: spastic gut diskinesy with constipation. Dense, dry fragmented stools "stools of sheep".

5. **Objective examination:** usually non-specific

- Locally painful palpation
- Mendel's symptom (painful percussion – viscerosensory reflex) – in 20-30%
- Local muscular tension (visceromotoric reflex) – usually in duodenal ulcers

Indeed, severe ulceration to the point of perforation or haemorrhage can be virtually symptomless. Thus approximately 50 per cent of patients who die from a peptic ulcer are unaware of their ulcer at the time of their final, fatal admission.

Atypic course: dominating dyspepsy syndrome, constipation, loss of body weight or astenic-neurotic syndrome.

Clinical manifestation and localization of ulcers

Cardial and subcardial (5-6 cm distal to the oesophagal-stomach junction)	Males over 40-45 Early pain (10-30 miin after meals) near processus scyphoideus, sometimes radiating to precordial or substernal region, left subcostal zone; pain is not intensive More often belching, nausea, sometimes vomiting dominate, More often associated with diaphragmal hernia. More often complication - bleeding
Curvatura minor	Very severe pan, sometimes fasting and night pain; often dyspeptic syndrome
Curvatura major	Non-typical, smoothed manifestations; differential diagnosis with gastric cancer. Repeated endoscopies with biopsies are indicated.
Medial and lower 1/3 of the stomach body	Pain 30-60 min after meals
Antral (prepyloric)	Manifestations are similar to these with duodenal ulcer; late, fasting and nocturnal pain. Repeated endoscopies with biopsies are indicated for differential diagnosis with cancer, especially in persons over 40.
Canalis pyloricus	Very intensive pain with difficulties of stomach emptying. Spastic and inflammatory character of pyloric obstruction. Acute food retention syndrome with numerous vomiting by acidic substances, fluid loss and electrolytes' disorders. Complications are frequent (penetration, perforation, haemorrhages due to rich vascularisation of the zone)
Postbulbar zone	5-7% of all ulcers of stomach and duodenum; in most of cases in men; intensive pain; severe bleedings (75-80%) , the last sometimes being the only symptom.
Combined ulcers	In 5-10% of cases. Primary localization is, mostly, duodenum, after that gastric ulcers appear, mostly in angle zone or may be in antrum. Changing of the localization site may be present (recovery from duodenal ulcer with appearance of gastric one). Descending process is extremely rare (more early development of stomach ulcers). In 50% the symptoms don't change and gastric ulcer is revealed by endoscopy. In other 50% the course becomes more severe, with more intensive and prolonged pain, food retention syndrome, severe heartburn, even vomiting by acidic substances.

Giant ulcers (more than 2 cm in diameter: in 5% of cases; mostly due to the trophic changes in aged patients with atherosclerosis of the arteries supplying gastroduodenal zone and caused by it chronic ischemia.
Due to slow recovery and scar formation, as well as trend to repeated bleedings gives possibility to recommend surgical treatment, even in cases of histologically proved benign character of ulcers, especially because there is an opinion about higher malignization rate.

Laboratory and instrumental diagnosis

1. Endoscopic investigation

Erosions	Ulcers		
	As a whole	Acute	Chronic
Superficial epithelium defects, round-shaped, 1-2 mm diameter, bottom with bloody or dark brown covering. Surrounded by hyperemia border. The bleeding may take place at the border.	Size is usually 1-2 cm, shape round or oval, bottom may be with bloody covering. Borders are well defined, may be mildly elevated over the surrounding mucosa.	More often numerous, associated with erosions. May be flat or crater-formed and are surrounded by bright inflammation rim. The underlying condition is usually superficial gastritis or duodenitis. Localized on curvature minor and posterior wall; in duodenum – at all the walls except inferior.	Exacerbation: round or oval-shaped with sharp outline and highly elevated borders with periulcerous oedema and infiltration. Bottom is dark with bloody or dark brown covering. Reduction of inflammation leads to decrease of depth of ulcer, it becomes more flat. Recovery causes lineal or star-like scars, at the first time they are friable and red-colored ("red scar"), then with increase of density it becomes white – mature "white scar"

Ulcers or scars are usually located in curvature minor, pyloric and prepyloric part of stomach, less frequent are posterior wall, subcardial and cardial region. May be single, doubled ("kissing" ulcers in bulbus duodeni) or numerous.

Basing only on ulcer appearance, even for experienced specialist is difficult to define exactly between benign and malign ulcer. Thus, numerous biopsies are indicated in case of suspected (clinically or endoscopically) malignancy.

2. Gastric secretion evaluation

	Normal, mmol/hour	Increase of acidic production, mmol/l	
		Relative ("risk zone")	Absolute
Basic	Males 0-5 (mean – 2.5) Females – 30% less (less number of pyloric cells)	5.5-10.0	More than 10.0
Maximal (maximal dose of histamine use or pentagastrin use)	Males 16-26.0 (mean 22.0)	28.0-35.0	More than 36.0

Typical for duodenal ulcer is basic secretion being more than 8-10 mmol/hour

3. X-ray. Reveals about 60-70% of ulcers.

- "Recess" syndrome (focal protuberance on stomach or duodenum outline with barium retention. If ulcer is flat or situated at the place where movement of barium is accelerated, or filled by remaining food masses or blood clots, the symptom may be not revealed.
- Folds convergention towards the scar, stomach or duodenum deformation in case of perigastritis and periduodenitis
- Increase of gastric secretion (fluid revealed in stomach, the investigation is performed before breakfast)
- Regional spasm
- Increase of certain focus motility
- Changes of process of stomach emptying, its tone and peristaltics
- De Kerven's symptom="finger symptom" – drawn in circulatory muscles at the controversial side.

Modern X-ray technic (electron-optic adapters, video etc) gives possibility to reveal about 90% of ulcers.

4. H.Pylori test: urease breath test, antibodies in blood, biopsy histology.
5. Blood search in stools (Gregersen's test)

Diagnostic formula

1. Peptic ulcer disease, recurrent course with frequent relapses, exacerbation. Ulcer and moderate scar deformation of bulbus duodeni.
2. Peptic ulcer disease, recurrent course with rare relapses, exacerbation. Curvatura minor ulcer with bleeding at 2.09.01, mild severity degree.

Dif.diagnosis

Chronic gastritis	In ulcer: acute pain, fasting and nocturnal pain; because of smoothed clinical manifestation in some ulcer cases final diagnose is endoscopic.
Gastroesophagal reflux	Dominating dyspepsy: recurrent heartburn ascending up to pharynx, acidic belching and nausea. Heartburn increases in lying position and in bendings. Epigastruc pain, which may be present, is not associated with food intake and are aggravated after physical exertion, bending, overeating, especially in the evening. Usually revealed in middle-aged, more often in women with increased body mass, very rare in astenics and in young.
Cancer (primary-ulcer form)	Signs, giving possibility to suspect malignancy: - age over 50 (last years– "cancer becomes younger") - early grey-haired - early old-looking appearance - low or capicious appetite - smoothed pain syndrome - marked body weight loss - decrease of vital tone - decrease of working ability - rapid tiredness appearance during the day - short ulcer anamnesis - prepyloric ulcer localization. Absence of cancer cells in biopsy is not a final confir-mation of benign ulcer; in suspected cases numerous biopsies should be performed. Signs, looking like recovery symptoms, may occur even in malign ulcers due to the cancer infiltration spreading.

Cholecystitis	If ulcer is located on the posterior wall of bulbus, pain in right zone below ribs arch may occur after meals

Especially should be mentioned differential diagnosis with functional or "Nonulcer" dyspepsia:

Up to two-thirds of dyspeptic patients have no obvious organic or biochemical cause for their symptoms that can be determined by upper endoscopy or abdominal ultrasonography. Symptoms may arise from a complex interaction of increased visceral afferent sensitivity, delayed gastric emptying or impaired accommodation to food, or psychosocial stressors.

Clinical Findings in patients with nonulcer dyspepsia:

The symptom profile is unable to differentiate reliably between nonulcer dyspepsia, peptic ulcer disease, and gastroesophageal reflux disease. Three main variants are divided: ulcer-like (fasting or night epigastric pain, rather intensive, relieved by food or antacids, usually without irradiation), diskinetic (early satiation, sensation of heaviness in epigastrium after sonsumption of small amount of food, nausea and flatulence after meals, rarely vomiting) and non-specific variant.

Diagnostic criteria:

- constant or relapsing dyspepsia (pain or discomfort), lasting no less than 12 weeks during the last 12 months
- absence of signs of organic disease revealed by case taking, endoscopic and uultrasonic examination
- absence of relief by defecation and absence of any relation with changes of frequency and character of stools

If diagnosis of nonulcer dyspepsia seems to be possible, presence of following alert signs should be evaluated:

- fever
- signs of blood in stools
- rapid weight loss
- anemia
- ESR increase

These signs indicate, that organic disease, first of all, oncology, should be suspected, and nonulcer dyspepsia is less probable.

Laboratory and instrumental examinations: similar to these in patients with gastritis and peptic ulcer. Because of high prevalence of asymptomatic and atypic stomach cancer the endoscopic examination is obligatory in patients with dyspepsia that seems to be functional.

Special types of peptic ulcers:

Zollinger-Ellison syndrome

- high relapses frequency of duodenal ulcers
- severe gastric hypersecretion
- insular adenoma of pancreas (gastrinoma)

Prevalence – 1:500 000 in population

- Intensive epigastrium pain
- Diarrhea due to enzymes inactivation by excessive HCL in gut
- High acidic production: basic is more than 15 mmol/hour
- Severe increase of gastrin level (up to 1000 pg/ml and higher; normal range being up to 100 pg/ml; in ulcer patients gastrin increase is mild)

Treatment: high doseas of Omeprazole (60-100 mg daily) with subsequent search of gastrinoma localization and surgery.

Natural course of peptic ulcer disease:

- Exacerbations are usually in spring and autumn time; in winter they are more rare and never – in summer.
- Exacerbations occur without any preceding signs, abruptly, last for 1-2 months, then the silent period returns.
- In remission, even break of dietary regimen may not cause symptoms appearance

Juvenile ulcers: onset in 15-20 y.old, in patients with hereditary predisposition; usually duodenal ulcer with high acidic production; pain is often atypical, with marked dispepsy, especially relapsing heartburn and vomiting.

Women: dependence of pain from food intake may be not so marked, often pain is located in right subcostal region, so differential diagnosis with cholecystitis is necessary.

Complicaitons of peptic ulcer

Bleeding	Due to vessels erosion. Occult bleeding is asymptomatic, revealed only by Gregersen's reaction. Severe bleeding is revealed in 10%, both in duodenal and gastric ulcers. Symptoms: - vomiting (by coffee groundings – haematin complex with Cl ions) - maelena – fluid dark stools (FeS) – in case of bleeding >180 ml - general symptoms: • blood loss 350-400 ml – mild nausea, dry mouth, weakness • blood loss is more severe – cold perspiration, tachycardia, hypotonia, soft small, sometimes filiform pulse. • 1 and more liters – haemorrhagic shoke - disappearing of pain – Bergman's sign - decrease of RBC in blood – end of 1 day – 2nd day (haemodilution) Treatment: - Rest, cold on the epigastrum, Vicasol and Decinon infusion and Ranitidin, Famotidin or Omeprosol (the last one – 40-80 mg) i.v. bolus injection; per os – 5% acidum ε-aminocapronicum 5%, Maalox etc. Polyglucin (volume-replacing treatment). - Hospitalization to surgical department - Urgent endoscopy with diathermy or laser coagulation of the vessel, Sucralfat may be placed on the ulcer zone
Perforation	Usually in 19-45 years old patients. Perforation may be to the abdominal cavity, atypic and concealed (the last one in case of the small perforation opening, small amount of food in stomach and stomach placed close to liver, omentum or gut loop; revealed in 2-15%, causes diagnostic difficulties; treatment – only operation). Perforation into abdominal cavity: - severe "knife-like" pain coinciding with the moment of perforation and gastric or duodenal masses appearance in abdominal cavity; during the 1st hours the pain is in upper abdomen, than becomes diffuse - body position with legs close to the abdomen - muscular tension (up to board-like abdomen due to peritoneum irritation) - Jober sign – tympanic percussion sound at the place of the liver dullness zone due to the gas in abdominal cavity; gas presence is confirmed by X-ray. - Additional signs are stools and gases retention and vomiting (the last revealed in 20% of patients) Periods: - pain shock

	- visible well-being - peritonitis Urgent surgery is indicated
Penetration	Appear usually in patients with prolonged anamnesis and frequent relapses. Posterior and lateral walls of duodenal bulb penetrate first of all to the head of the pancreas, more rare in large ducts of biliary tract, liver, ligaments (gastrohepatic or duodenal). Mediogastral ulcers – to corpus of pancreas and omentum minor. Usually penetration to body of pancreas dominate: - pain becomes constant, more intensive and looses daily rhythm - radiation to right, less frequent left side of back - girdling pain may be present Penetration to omentum minor - pain radiation upwards and to the right; in upper ulcers – in precordial and substernal region. X-ray sign: deep ulcer with decreased mobility, sometimes very narrow ulcers Endoscopy: round or polygonal, deep ulcers. In case of confirmed penetration, operative treatment is indicated; if not confirmed – active drug treatment may be used.
Pyloroduodenal stenosis	May be due to scar of inflammation and spasm. The last one: - numerous vomiting, at first by remaining food masses, then by excessive acidic fluid - every attempt of eating or drinking leads to vomiting at the same moment - fluid loss symptoms Stenosis due to scar formation Symptoms develop during some years. Stages of compensation: - compensated: severe heartburns dominate, so frequent use of antacids is necessary X-ray: segmented peristaltics; food evacuation is unchanged subcompensation: - Severe vomiting, sensation of heaviness in epigastrium with improvement after vomiting, so the last one is often provoked by patient. - Progressive loss of body weight - Objective: splash sound in epigastrium during palpation X-ray: hypersecretion in the morning before eating; peristaltic is present, but becomes less active with time; barium retention time in stomach is up to 4-6 hours and more Decompensation (1-2 years after compensation): - severe stenosis with food retention for several days - improvement after probe use to remove the food masses - electrolyte disorders - decompensated alkalosis - dry skin - cramps – gastric tetany Subcompensated and decompensated stenosis are indication to surgical treatment preceded by the electrolytes and proteins metabolism correction. In inflammatory stenosis atropine 0.1%-1-2 ml injection or that of Metacin 0.1% - 4 -6 ml daily may be used, more effective is modern H2-blockers (Famotidin, Ranitidin) and Omeprasol administration. Additionally prokinetics – Mothilium may be administrated.
Malignisation	About 2-3%, more often antrum ulcers

Prognosis: depends on the course of the disease.

Treatment:

Aims	
reduction of acidic production	H2-blockers: Ranitidin 300 mg in the evening, Famotidin 40 mg 2 times daily; Omeprasol 20 mg x daily, Pantoprasol 40 mg x daily, lansoprasol 30 mg x 2 daily. For patients with HP-associated ulcer these drugs are included in schemes.
Improvement of duodenal and antral motorics	Additional drugs: Prokinetics (Motilium), spasmolytics etc
H.Pylori eradication (in patients with HP-associated ulcer)	See gastritis; Rulid (Roxitromycin) can be used instead of one of given antibiotics
Increase of resistance abilities of mucosae	- Synthesic prostoglandins E and I (Misoprostol, Arbaprostil, Saitoteck) – low efficacy due to short time of action - Sucralfat 1.0 x 2 daily 30 min before meals (due to high affinity to nectrotized proteins forms a film covering ulcer) - Bismithi preparations forming colloid film over ulcer, also has anti_HP activity; for patients with HP-associated ulcer it is included in schemes.
Reduction of the irritation by food	Meals 3-4 times daily, food mostly boiled, overeating and eating in the late evening, as well as piquant food are not recommended; smoking cessation.

Indications to surgical treatment

1. Recurrent bleeding, continuing in spite of active treatment (Omeprosol, H2-blockers, coagulation)
2. Perforation
3. Pyloric stenosis
4. Exacerbation with relapse after the recent complication (including perforation and bleeding), in spite of uninterrupted course of Ranitidin or Famotidin and repeated anti-HP treatment courses.

Stomach tumours

Prevalence

4th place among all the neoplasms with equal males and females affected; mostly in patients over 60.

There is a high incidence in Japan, parts of Chile, and the mountainous regions of Costa Rica but a low incidence in the United States. In the United Kingdom, approximately 15/100000 males per year are affected. Gastric cancer is the sixth most common fatal malignancy in the United Kingdom and accounts for about 10 per cent of all deaths from malignant disease. There is a continued fall in incidence of gastric cancer worldwide. However, there appears to be an increase in the number of cases of carcinoma of the cardia.

Aethiology

- H.Pylori (I degree cancerogen - WHO) due to increase of epithelial mitogenesis with translocation of immature cells on the epithelial surfaces; HP leads to N-nitrosocomponents synthesis, which are known to be cancerogenes.

HP also decreases antioxidants content in stomach – alpha-tocopherol, beta- carotin, ascorbic acid
- Excessive nitrates in water and food due to N-nitrosoamines formation in stomach; also other substances – aflatoxins etc
- Genetic factors (higher incidence in blood group A)
- Smoking and alcohol were revealed as risk factors in USA population
- Some food peculiarities (dried fish, soya sauce, marinades, low content of vegetables and fruits in food etc) were revealed to be risk factors in Japan

Morphology
- Polypous with marked endogastric growth, plate-formed ulceration with marked outline and elevated borders
- Ulcerative-infiltrative – looking like chronic ulcer
- Diffuse (skirr) – with fibrosis-like thickening of gastric wall in general or only in antrum.

Morphological types of cancer:
1. Adenocarcinoma: papillar, tubular, mucus-producing, ring-formed cells cancer
- high degree of differentiation (gut type of cancer): slow growth with late metastases
- moderate degree of differentiation
- low degree of differentiation, where the glandular structures are hardly revealed
- absence of any signs of differentiation or glandular structures – the highest growth velocity; highest degree of malignancy and the marked trend to metastases formation.

Type of cancer growth: solid (endophyte type of growth) , medullar (exo- or endophyte type of growth, trend to ulcerations), skirr (marked endophyte type of growth, infiltrative growth, the worst after-operation prognosis)

Early cancer is defined as a special form:
Small (up to 3 cm) tumor within mucosa and submucosa without growth to muscular layer and without metastases

Cytologic examination reveals 5 types of cells:
1 type – normal cells
2 type – intermediate type of cells
3 type – atypic cells (2 and 3 revealed in chronic gastritis)
4 type – suspected malignancy
5 type – malignant
The main malignization signs are: increase of size, anisocytosis, cytoplasm vacuolization, increase of nucleus and changes of its shape, numerous nucleoli, nucleus vacuolization

Pre-cancer (2001):
1. Pre-cancer conditions:
- Chronic gastritis
- Menentrier's disease
- Chronic gastric ulcer
- Gastric polyposis
- Conditions after resections etc

2. Pre-cancer changes:
- morphological changes, in which cancer may appear with higher probability, than in normal conditions (it doesn't mean, that in concrete patient cancer will develop, these changes are only promouters of cancerogenesis). First of all, gastric mucosa displasia. Marked displasia revealed in patient, needs repeated biopsies because it may mean, that cancer is already present.

Some authors also consider peptic ulcer, intestinal metaplasia, adenomatous polyps and postgastrectomy condition with intestinal metaplasia and chronic active gastritis found in the

resected stomach as the pre-cancer conditions. In the last case prolonged contact of bile with the stomach remnant leading to gastritis is one suggested mechanism, but again H.pylori may be involved.

Classifications

I. S.Choldin – clinical classification:

1. With dominating gastric symptoms (see peptic ulcer and dif. diagnosis)
2. With dominating systemic symptoms (anaemia, kacheksia, weakness, tiredness, loss of working ability)
3. Masked cancer with symptoms of other diseases
4. Latent cancer with prolonged asymptomatic course

II. Localization

1. Antrum – 60-70%
2. Curvatura minor – 10-15%
3. Cardial part – 8-10%
4. Fundus – 1%

III. Stages

1. I stage - early cancer – size up to 2 cm, within mucosa only, without metastases
2. II stage – tumor 4-5 cm, penetrating submucosa and muscular layer. Metastases to nearest lymphatic nodes or growing through the nearest organs. Usually without complications
3. III stage – tumor is penetrating subserosa or serosa, nearby organs and tissues may be involved, increase of tumor size with trend to its destruction, metastases to III and IV collectors of the lymphatic system of stomach. Numerous complications.
4. IV stage – end-stage. Total stomach affection, metastases to neck lymphatic nodes, bones, liver, lungs. The size of tumor may be different.

IV. TNMP

1. T – tumor

T1 – mucosa/mucosa and submucosa
T2 – deep invasion but no more than half of one anatomic part of stomach affection
T3 - deep invasion with affection of more than 1 anatomic part of stomach or affection of nearby organs

2. N - nodes

Nx – no metastases
Nxa – only gastric nodes
Nxb – nodes along the left gastric, transversal, common hepatic, lineal and iliac arteries and ligamentum duodenohepaticum
Nxc – nodes along the abdominal aorta, mesenteric and iliac arteries (which can't be removed at operation)

3. M – metastases

M – no signs of distal metastases
M 1 – presence of these

4. P – depth of stomach wall penetration

P1 – only mucosa
P2 – submucosal layer
P3 – muscular layer but not serosa
P4 – whole wall affection, including serosa, and is spreading to nearby organs

Clinical manifestations

1. Epigastric pain (vary in intensity, but may be constant, severe; may be relieved by food and antacides)
2. Weight loss about 10-15 kg which can't be explained by known causes
3. Loss of appetite

4. Vomiting (rare at the beginning of the disease)
5. Bleeding ("coffee grounds" or red blood or maelaena); more often – occult bleeding
6. Anaemia
7. Fever – more often irregular febrile – 1/3 of cases
8. Back pain as a sign of pancreas penetration
9. Palpable masses in epigastrium

Other signs, depending on localization:

- Cardia, sometimes with oesophagus affection – disphagia
- Antral – severe pyloric stenosis with repeated exhausting vomitings and electrolyte disorders

Early diagnosis

1. In all cases "minor signs", described in item "peptic ulcer – diff.diagnosis" are present, which are the earliest signs of cancer.

2. In all patients over 40 with gastric dyspepsia lasting more than 1-2 month endoscopic investigation is obligatory.

Metastases:

- More often – regional lymphatic nodes, liver
- Peritoneal dissemination with ascitis is possible
- Distant ones: ovarii (Crucenberg's); supraclavicular lymphagic nodes (Virchow's); fatty tissues of small pelvis (Shnizler's)
- More rare – lungs, bones

Paraneoplastic syndromes:

- dermatomyositis and acanthosis nigricans.

Laboratory and instrumental diagnosis

1. Investigations plan

- Endoscopy with biopsy
- Hamogram (anaemia and ESR (more than 30-50 mm/h) increase are rather late signs)
- Ultrasonic investigation of abdominal organs (Mts)
- Chest X-ray (Mts)
- Abdomen CT
- In case of unclear diagnosis – laparoscopy and laparotomy
- X-ray of stomach (with barium) – main method in skirr diagnosis

X-ray signs of cancer:

1. Local thickening or rupture of folds with emphasized relief of mucosa at its border
2. Primary ulcerative – ulcer-like round or oval defect; or plus-tissue with ulcer-like defect
3. Gallbladder deformation or additional tissues on its contour increase of interval between the left contour of spine and gastric wall, delay of barium in lower part of oesophagus
4. Changes of gastric shape (cascade-shaped etc)
5. Loss of peristaltic contractions
6. Tumor-like stenosis of pylorus

Factors, influencing clinical course:

1. Growth character and its spreading
2. Degree of functional disturbances caused by tumor
3. Complications (haemorrhages, penetration, perforation)

The most rapid growth is revealed in endophyte-ulcerative forms; more benign are skirr forms, In young patients course is more rapid with numerous metastases.

Prognosis:

5-year survival is about 10%, after radical operations – 20-25%, in non-operated patients no more than 4-6 months.

Treatment

1. Radical treatment – surgical, must be performed early. Chemotherapy and radiological treatment – only in special cases. In case of remaining part gastritis on after-operation period is found, 1-2 weeks of eradication treatment should be performed.

Operation is indicated in following cases (about 30% of all cancer patients):

- age up to 70-75
- absence of distant metastases
- absence of severe concomitant diseases

Operation lethal outcomes rate: about 30%
Complication of operation: damping-syndrome
Palliative operations: in case of stenosis or bleeding
Symptomatic treatment: antacids, nacrotics

Other malignant tumours of the stomach
Primary lymphoma
Prevalence:
approximately 5 per cent of all gastric malignancies and 50 to 60 per cent of all gastrointestinal lymphomas occur in the stomach in patients from the developed world.
Morphology:
usually a non-Hodgkin's lymphoma of the B-cell type arising from mucosaassociated lymphoid tissue (MALT). MALT tumours are associated with H. pylori gastritis. The tumours vary in degree of blastic transformation; the more blastic, high-grade tumours are categorized as centroblastic or, rarely, immunoblastic.
Clinical features:
indistinguishable from those of other benign or malignant lesions of the stomach; usually the patient presents with advanced disease similar to carcinoma of the stomach.
Treatment
surgical combined with radiotherapy; chemotherapy is used for widespread disease although some MALT tumours respond to H. pylori eradication.
Prognosis: varies from 75 to 95 per cent 5-year survival, depending on whether a low- or high-grade B-cell lymphoma is present.

Benign tumours and polyps
The most common benign tumour of the stomach at autopsy: leiomyoma
Morpholoby: arises from the smooth-muscle tissue but projects into the lumen.
Clinical features:

- most are asymptomatic
- occasionally - superficial ulceration with gastrointestinal haemorrhage.

Treatment: local surgical removal is done for any symptomatic lesion and is curative.
Other rare benign gastric tumours:

- lymphomas
- angiomas
- gastric carcinoids.

Gastric polyps: are relatively uncommon lesions and are found by chance in a patient being investigated for unrelated dyspepsia (2.5% of endoscopies performed due to the dyspepsia complaints).
Morphology:

- Hyperplastic (mostly inflammation-caused)
- Adenomatous (site of benign prolioferation) – 3-6% of all polyps; these ones have a trend to malignisation, especially if size is more than 2 cm.
Polyps more than 2 cm are suspected to be polypoid cancer; malignancy is also probable in case if any sign of covering mucosa changes, proliferation or ulceration is found at endoscopy.
Polyps, suspected for malignancy are to be removed by surgery.

Appendix:
Gut peptides: peculiarities and biological action
1. Localization:
- endocrine cells of the gastrointestinal tract are not grouped into anatomically distinct glands, like most endocrine cells, but are scattered through the length of the gastrointestinal tract
- Most of the gut peptides, such as cholecystokinin and substance P, have been identified within the central and peripheral nervous systems; neurocrine peptides are synthesized in nerve cells rather than endocrine cells in the gut
2. Function:
A. Principal role of gut peptides is in the integration of gastrointestinal function, and they regulate the actions of the epithelium, muscles, and nerves throughout the gastrointestinal tract
- local effects of gut peptides:
* autocrine, regulating the function of the cell secreting them
* paracrine, influencing the behaviour of neighbouring cells of different type
* local action as peptide neurotransmitters or neuromodulators
- systemic effects: neuromodulatory role in many organs; neurotransmitters or neuromodulators

Example: Somatostatin, originally identified as a hypothalamic inhibitor of growth hormone release, has been shown to have inhibitory effects in many different organ systems. It is locally released and its main mechanism of action is a direct one on neighbouring cells, for example to inhibit gastric acid and insulin secretion.

B. Many peptides, such as gastrin, secretin and enteroglucagon, probably play an important paracrine role in controlling the growth and development of the gastrointestinal tract.
C. In contrast, for most gut peptides there is little evidence that they act as true hormones in an endocrine fashion.

Hormones and paracrine peptides

Name	**Chemistry**	**Secretion/ localization**	**Stimulation**	**Effects**
GASTRIN-CHOLECYSTOKININ FAMILY				
Gastrin	variety of molecu-lar forms; all the boil-ogical activity resi-des in 4 carboxyte-rminal amino acids. The major molecu-lar	**G cells**: -gastric antrum (G17 predominant form) - also found in the up-per small intestine, mainly as G34. These two are the pre-	- protein in-gestion - gastric dis-tension.	- stimulation of gastric acid secretion - trophic effect on the gastric mucosa - infusion of gastrin stim-ulates gastric motor activ-ity and contraction of the

	forms contain 17 (G17; 2098 Da), 14 (G14; pentagastrin), and 34(G34;big gastrin) amino acids.	dominant circulating forms.		lower oesophageal sphincter, but the physiological significance of this action is unclear.
Cholecystokinin (CCK)	an identical, five amino-acid, carboxy-terminal sequence to gastrin, but its specificity is conferred by the adjacent 3 amino acids, and this octapeptide confers its biological activity. In gut found in 33,39, or 58 amino-acid molecular forms predominantly.	- I cells of the duodenal and jejunal mucosa. - the octapeptide CCK is a neurotransmitter in the central nervous system and a small amount is found in specific enteric neurones of the upper gastrointestinal tract.	by long-chain fatty acids and certain amino acids.	2 types of CCK-receptors and CCK action: CCK-A receptor: - stimulation of **gallbladder contraction** **- trophic effects on the duodenum and pancreas**. - CCK-A receptor antagonists potently inhibit meal-stimulated gallbladder contraction (therapeutic value in biliary colic).
THE SECRETIN FAMILY				
The secretin family comprises a number of peptides with significant sequence homology. These include, in addition to secretin, glucose-dependent insulinotropic peptide, glucagon, enteroglucagon (see below), vasoactive intestinal peptide, peptide histidine methionine, and growth hormone-releasing factor (GRF). GRF is released from the hypothalamus, mainly as a 44 amino-acid peptide, to stimulate release of growth hormone, but is also found in significant concentrations, mainly in a 40 amino-acid form, in the small intestinal mucosa, where its function is unknown.				
Secretin	27 amino-acid peptide (3056 Da), which appears to occur in only one molecular form, the whole molecule needed for full biological activity.	- S cells sparsely scattered throughout the duodenal and jejunal mucosa - stored in characteristic secretory granules Circulating concentrations lower than those of most other gut hormones.	- Main: **duodenal pH less than 4.5** - rarely - late after a meal; timing and quantities of this secretion are uncertain.	- Main: stimulating production of watery, alkaline pancreatic juices in response to acid in the duodenum. - may play an impor-tant part in the develop-ping gastrointestinal tract (particularly high concentrations in the early postnatal period)
Glucose-dependent insulinotropic peptide (GIP)	42 amino-acid peptide (5105 Da) with considerable sequence homology at the N-terminal to secretin, glucagon and vasoactive intestinal peptide.	- produced by K cells - predominantly in the upper small intestinal mucosa - also in the gastric antrum and ileum - is stored in large granules.	mixed meal, particularly carbohydrates and long-chain fatty acids	**-inhibits gastric secretions (**was originally named gastric inhibitory peptide) - component of the enteroinsular axis -stimulates insulin release
Vasoactive intestinal peptide	28amino-acid peptide neurotransmitter (3326 Da)	- widely distributed through the central and peripheral nervous systems.		- potent stimulator of small intestinal and colonic enterocyte secretion of water and electrolytes,

		- highest concentrate-ons in **submucosa of the intestinal tract (postganglionic in-trinsic nerves)**		acting via an elevation in cAMP - smooth-muscle rela-xation, both in the ali-mentary tract and in the systemic vasculature - stimulation of insulin release, counteracted by a direct glucagon-like ef-fect of VIP in stimulating hepatic gluconeogenesis and glycogenolysis, - stimulation of pancre-atic bicarbonate secretion - relaxation of the gall-bladder, pyloric sphin-cter, and circular mus-cle of the small intes-tine with contraction of the longitudinal muscle. - inhibits release of gas-tric acid but not at physio-logical concentrations in man.
Peptide histidine methionine	27 amino-acid neuropeptide with considerable se-quence homology to VIP and derived from the adjacent exon of the preproVIP gene.			mimics the actions of VIP, probably acting via the same receptor, but is less potent
Pituitary adenylate cyclase-activating peptide	recently identified peptide occurring in 27 and 38 ami-no-acid forms and with considerable sequence homolo-gy to VIP.	similar tissue distribu-tion to VIP and shares the same receptor out-side the central nerv-ous system and pituitary gland.		similar actions to VIP on intestinal secretion and motility.
PEPTIDE PRODUCTS OF PREPROGLUCAGON				
In the pancreas the major product of the preproglucagon molecule is pancreatic glucagon, but in the intestinal L cells preproglucagon is cleaved into enteroglucagon, a 69 amino-acid peptide containing the entire sequence of pancreatic glucagon, and the two glucagon-like peptides (GLPs)				
Enteroglucagon (also termed glicentin**)**		high concentrations in the mucosa of the ile-um, colon, and rec-tum.	mixed meal, particularly of carbohydrate and long-chain fatty acids	- trophic effect on the small intestinal mucosa - may be important in gut adaptation. - Enteroglucagon is fur-ther cleaved by the L cells to produce oxyntomodulin, a 37 amino-acid peptide re-

				leased into the circulation, which is a potent inhibitor of pentagastrin-stimulated gastric acid secretion.
Glucagon-like peptide 1	36 amino-acid peptide, which is secreted in a cleaved form containing the 30 carboxy-terminal amino acids			-more potent stimulus to insulin secretion than GIP - appears to be the most important incretin - inhibits secretion of glucagon - potentiates release of somatostatin. - Its infusion greatly reduces insulin requirements following a meal in type 1 and type 2 diabetics, and this effect may have therapeutic potential.
PANCREATIC POLYPEPTIDE, NEUROPEPTIDE Y, AND PEPTIDE TYROSINE TYROSINE				
Pancreatic polypeptide, neuropeptide Y, and peptide tyrosine tyrosine are peptides with structurally similar genes and propeptide molecules probably derived from a common ancestral gene				
Pancreatic polypeptide	36 amino-acid peptide (4226 Da) first isolated as a contaminant during the purification of insulin.	specific cells found at the periphery of the pancreatic islets, particularly those in the head of the pancreas, and scattered through the exocrine pancreas.	dramatically rise after meal, particularly if high in protein (at least in part due to activation of vagus).	inhibits pancreatic exocrine and biliary secretion
Neuropeptide Y	36 amino-acid peptide neurotransmitter	-often colocalized with noradrenaline -extrinsic adrenergic nerves to the myenteric plexus - intrinsic nerves in the myenteric and submucosal plexi, -highest concentrateons in the upper intestine and distal colon.		- potent vasoconstrictor, -inhibits intestinal secretion - depresses colonic motility.
Peptide tyro-sine tyrosine (PYY)	36 amino-acid peptide	-endocrine cells of the ileum, colon, and rectum - similar distribution to enteroglucagon, with which it is often colocalized	meal, particularly one containing carbohydrates or long-chain fatty acids	- to slow intestinal transit, allowing more time for absorption. -delaying gastric emptying - decreasing intestinal motility - inhibiting gastric acid secretion.
BOMBESIN AND THE GASTRIN-RELEASING PEPTIDES				

Bombesin (gastrin-releasing peptide – GRP**)**	14 amino-acid peptide (1620 Da) initially isolated from amphibian skin In man - 27 amino-acid peptide	- in the gut in the intrinsic neurones of the myenteric and submucosal plexi, - particularly in the stomach and pancreas.		- potent stimulator of gastrin, and hence of gastric acid secretion - stimulates release of motilin and cholecystokinin - stimulates pancreatic enzyme secretion. - autocrine growth factor for small-cell lung carcinomas - probably trophic effects on the developing gut.
OPIOIDS				
The opioid peptides leu-and met-enkephalin and dynorphin are widespread through the nerves of the myenteric and submucosal plexi of the gastrointestinal tract.				- inhibition of gastrointestinal secretion - increased smooth muscle contractility.
TACHYKININS : **Substance P** and number of homol-ogous peptides have now been characterized, and are collectively known as **tachykinins**, because of their rapid action				
Encoded by preprotachykinin A gene: **Substance P (**11 amino-acid peptide -1345 Da); **neurokinin-α** **Encoded by** preprotachykinin B gene - **neurokinin-β**				
Tachykinines		- neurones in the myenteric and submucosal plexi throughout the gastrointestinal tract - high concentrations in the duodenum and jejunum.		- smooth muscle contraction, - vasodilatation - inhibition of intestinal absorption.
OTHER GUT PEPTIDES				
Motilin	22 amino-acid peptide (2700 Da) biological activity resides in the 9 amino-terminal amino acids	small intestinal M cells, whose density decreases from duodenum to ileum	meal or drinking water **Macrolide antibiotics,** (erythromycin etc) are motilin-receptor agonists, hence their side-effects of diarrhoea and abdominal cramps.	- peaks in secretion coincide with initiation of the duodenal myoelectric complex, and so motilin appears to **control the reflex motor activity of the small intestine**, which occurs at approximate-ly 2-hourly intervals in the fasted state, keeping the small intestine free of debris. - role in accelerating gastric emptying and colonic transit.
Neurotensin	13 amino-acid peptide (1673 Da)	-throughout the central nervous system - enteric neurones - N cells of the ileal mucosa.	meal, particularly with high fat content, rise of level is pro-	- inhibits gastric acid secretion - inhibits gastric emptying - stimulates pancreatic exocrine and intestinal

			portional to the size of the meal	secretion.
Somatostatin	14 amino-acid peptide (1640 Da) In gastrointestinal tract occurs in 14 and 28 amino-acid forms	- widely distributed throughout the central and peripheral nervous system - found in a variety of endocrine tissues. - specific endocrine cells in the gastric and intestinal mucosa - D cells on the inner rim of the pancreatic islets - found in the enteric neural system. Five human somatostatin receptors have now been identified and cloned, the type 1 receptor predominating in the gastrointestinal tract.	small amounts of somatostatin are released into the plasma in response to physiological stimuli, including food ingestion	- inhibits the release of growth hormone -inhibits hormones release -blocks the response of the effector tissue - inhibits a wide range of gastrointestinal functions. - acts principally as a paracrine factor or neurotransmitter - may have an endocrine role.
Other peptide neurotransmitters				
Calcitonin gene-related peptide	37 amino-acid peptide produced by alternative splicing of the calcitonin gene transcript	- widespread neurotransmitter, - in gut occurs in both extrinsic sensory nerves and intrinsic neurones.		- inhibits gastric acid and pancreatic secretion, - causes relaxation of vascular smooth muscle.
Galanin	29 amino-acid peptide neurotransmitter	- gut plexi - nerves supplying the liver and pancreatic islets.		- inhibition of intestinal smooth-muscle contraction - inhibition of postprandial insulin release.
Endothelin		plexi of the gastrointestinal tract and in mucosal epithelial cells		- Role in regulation of gastrointestinal function is unknown.