7.5 Diseases of the stomach and duodenum

7.5.1 Gastritis

Gastritis is inflammation of the gastric mucosa. It is manifestant by histopathologic changes. Its clinical manifestation can be present as well. Gastritis can bring about an undesirable development of morphological changes resulting in metaplasia, dysplasia and carcinoma. Regarding the causes and pathogenesis, we can distinguish three groups of gastritis:

- erosive (haemorrhagic) gastritis,
- non-erosive gastritis
- unusual or specific forms of gastritis

Regarding the clinical aspect, the symptomatology varies greatly. Therefore, various dyspeptic and postprandial difficulties are due to the absence of morphological findings incorrectly diagnosed as gastritis.

7.5.1.1 Erosive (haemorrhagic) gastritis

Erosive (haemorrhagic) gastritis develops in a large number of patients who use aspirin, or other non-steroidal anti-inflammatory drugs (NSAID). Therefore, this type of gastritis is usually referred to as NSAID gastritis. At the mucosa there are petechiae, erosions and mucosal ulcerations. Superficial gastric lesions can cause chronic blood losses and the development of hypochromic anaemia.

Similar changes in the gastric mucosa may develop in patients exposed to severe stress. Therefore they are observed in patients hospitalized in intensive care units, in coincidence with acute diseases and surgical interventions, hypothermia, and trauma. Even burns can cause gastric ulcer, referred to as Curling's ulcer. Trauma, CNS disturbances, or surgical intervention can cause ulcerations which are referred to as Cushing's ulcers. Excessive alcohol abuse causes haemorrhages which are revealed by endoscopic examination and referred to as haemorrhagic gastritis.

7.5.1.2 Non–erosive (atrophic) gastritis

Non-erosive gastritis is usually divided into type A which is localised in the fundus, and type B which is localised in the antrum. Inflammatory infiltration can be minimal. Observations of cellular dysplasia and metaplasia of the gastric mucosa are frequent. The development of hyposecretion is a common consequence of atrophic changes in the mucosa. The cause of non-erosive gastritis is not precisely known. Helicobacter pylori infection is now recognized as major cause of chronic gastritis beginning by acute neutrophilic gastritis lasting 7–10 days, associated sometimes with clinical symptomatology. After penetrating the viscous mucus most microbes penetrate regions of the tight junctions between adjanced mucosal epithelial cells. Epithelium responds with cellular exfoliation and regenerative changes. If the Helicobacter pylori is not eradicated comes to disbalance between gastrin overproduction and multiplication of histamin producing cells, what can lead to pathological circulus vitiosus and at the end to atrophy. In non-erosive gastritis the mucosal atrophy, achlorhydria and vitamin B_{12} malabsorption dominate. Antiintrinsic factor antibodies are present. The intrinsic factor depletion usually accompanies such finding. After some time, pernicious anaemia can develop.

7.5.1.3 Specific forms of gastritis

In the past, gastritis occured mostly in consequence of tuberculosis and syphilis. Currently, gastritis dominates in coincidence with AIDS. This group includes also gastritis due to infectious diseases of proximate and remote organs. Oesophageal candidosis can develop on the background of gastritis.

7.5.2 Peptic ulcer

Peptic ulcer refers to **ulcerations in the upper part of the gastrointestinal tract**. This chronic disease is manifestant by characteristic signs. Ulcerations occur especially in the proximal part of the duodenum and in the stomach. The pathogenesis is based on the effect and relationship of two common factors, namely hydrochloric acid and pepsin. Ulcers developed in coincidence with Zollinger-Ellison syndrome are considered to constitute their independent form. It is caused by excessive production of gastrin by

gastrin-secreting islet cell tumours (gastrinoma) located most commonly in the head of pancreas. Gastrinomas also have been located less commonly in other sites (duodenum, antrum).

A decisive responsibility for the development of the peptic ulcer, as presented above, resides on the **gastric acid and pepsin**. They can be referred to as being aggressive factors. Against them, stands the mucus layer constituting a protective mechanism against auto-digestion.

Aggressive factors (hydrochloric acid and pepsin). Parietal cells secrete hydrogen ions in concentration which is three times as high as the concentration of hydrogen ions present in the blood. Each secreted hydrogen ion combines with a chlorine ion. The final step in the secretion of hydrogen ions is performed by means of the proton pump which includes the specific K^+, H^+-ATPase occuring on the membranes of microvilli. This K^+, H^+-ATPase exchanges hydrogen for potassium across the microvillus membrane. The parietal cells produce a pure solution of HCl which mixes with the secretion of non-parietal cells.

The **HCl secretion is regulated by chemical, nervous and humoral factors**. The membrane of parietal cells harbours specific receptors (H_2 receptors) responding to histamin released from the neigbouring mast cells. Then there are receptors sensitive to muscarine effects of acetylcholine which is released by the vagus nerve's endings. Parietal cells contain receptors which respond to endogenous circulating gastrin. **Gastrin** is the strongest stimulator of gastric acid secretion. It occurs in form of secretory granules in G cells which are spread individually or in small clusters among epithelial cells in the medium and more profound parts of glands in the pyloric antrum. Gastrin is contained by tissues and body fluids in several forms. Its basic form in the glands of antral mucosa is represented by heptadecapeptide which is constituted of 17 amino acid remnants (G 17). Big gastrin is constituted of 34 amino acid remnants (G 34). The half-life of G 17 is shorter than that of G 34. Gastrin occurs also in the duodenal mucosa, especially in its proximal part. The effects of both gastrin and vagus nerve on the production of hydrochloric acid are tightly associated.

Stimulation of the vagus nerve supports the release of gastrin into circulation and simultaneously increases the response of parietal cells to the circulating gastrin. Consequently, the secretion of hydrochloric acid increases. Receptors of parietal cells stimulated by gastrin, affect the activity of other receptors and simultaneously activate the intracellular messenger, in this case the calcium ions. The latter activate the protone pump which produces hydrogen ions. The mucosal glands of the stomach contain **mast cells**. The cytoplasmic granules of mast cells contain large amount of histamine. Mast cells are localised in between every two or three parietal cells. **Histamine** is considerated as the last link in the chain of cholinergic or gastrin stimulations. The parietal cells contain histamine receptors, referred to as H_2 receptors. These receptors can be inhibited only partially by the classic antihistamines which inhibit H_1 receptors. **H_2 receptor antagonists** (cimetidine, ranitidine, famotidine and nizatidine) inhibit the basal secretion and secretion which appears in response to food intake, gastrin, histamine, hypoglycaemia, or stimulation of the vagus nerve. This implies that histamine has a significant role in the secretion of hydrochloric acid. The protone pump in parietal cells is activated by means of cAMP.

A decrease in gastric pH below 1.5 entirely blocks out the production of gastrin. Somatostatin which inhibits also the release of gastrin, is produced by D cells in the mucosal glands in the pyloric antrum. Its local effect can also be applied as D-cells are localised in the proximity of G-cells. **Pepsin** has a significant position in the pathogenesis of the ulcerative disease of the stomach and duodenum. It is produced from pepsinogen which is secreted by the chief cells in the gastric body and fundus (pepsinogen 1) and pyloric glands (pepsinogen 2). The production of pepsinogen is followed by its conversion to an active proteolytic enzyme – pepsin. The conversion is carried out under the influence of hydrochloric acid. Pepsin has its optimum of effect at pH ranging from 1.5 to 2.0. When pH increases to 4.0 the activity of pepsin is gradually brought down and at the value of 7.0 it is entirely inhibited.

7.5.2.1 Mechanisms protecting the mucosa from autodigestion

The protection within the stomach is carried out by mucus. Mucus is produced continuously by gastric mucous cells of the gastric mucosal epithelium and gastric glands. The production of mucus is increased in response to mechanical stimuli, chemical irritation and cholinergic stimulation. Mucus consti-

tutes an insoluble layer lining the surface of mucosa in width of 0.6 mm. In addition to the mucus layer, a soluble phase of mucus is present also in gastric juice. Mucus is basically constituted of glycoprotein. It is a heterogenous substance containing glycosylated polymers joined by disulphidic bridges. Gastric mucus contains also fatty acids. This condition contributes to its viscosity and ability to slow the diffusion of hydrogen ions. Mucus maintains the pH gradient between the epithelial surface and gastric lumen. Preservation of the intact quality of mucus requires the mucus to maintain its neutral values of pH. In addition to its proteolytic activity, mucus procures a one-way flow of hydrogen ions and inhibits the backward diffusion of pepsin. Mucus yields bacteriostatic properties. It is indeed interesting that the gastric mucus also contains antigenic determinants.

Under normal circumstances, the **mucus layer ideally adheres to the mucosal surface**. It constitutes a one-way barrier against the backward diffusion of hydrogen ions into the cells through the mucus. This fact can represent a very important factor which principally protects the mucosa from impairment inducible by pepsin. The mucous barrier can be easily disturbed by e.g. bile acids, ethanol, and weak organic acids. The mucous barrier can be disturbed by a number of drugs, especially nonsteroidal antiinflammatory drugs and salicylates (aspirin). An **impairment of mucus** does not have to be comprehended in the morphological sense. It is manifestant in the fact that mucus, albeit morphologically present, ceases to represent a barrier for the penetration of hydrogen ions. The impairment can involve a break down of the disulphide bonds. Bile acids can alter the currently existing electric charge of the mucus. The impairment of the mucous barrier in the above mentioned sense can represent the cause of cellular impairment by acids and pepsin. Consequently, histamine can be continuously released from mast cells thus leading to permanent secretion of hydrochloric acid. This impairment can be succeeded by impairment of small vessels with mucosal haemorrhages and erosions. The principal condition, under which the protective properties of mucus come into effect, is represented by normal blood flow via the gastric mucosa. Each reduction in the blood flow is associated with a backward diffusion of hydrogen ions. Then the stage of impairment depends on the accordance between the participating factors.

In the protection of gastric mucosa, a significant role is played by endogenous **prostaglandins** which are present herein in a large amount. Foremostly the E series of prostaglandins can inhibit the mucosal impairment in several modes. They especially stimulate the secretion of mucus and bicarbonate in gastric and duodenal mucosae. Prostaglandins participate in optimalisation of gastric mucosal blood flow. They also maintain the integrity of gastric mucosal barrier and enhance regeneration of impaired mucosa.

7.5.2.2 Duodenal ulcer

Duodenal ulcer is a **chronic and recurrent disease**. The duodenal ulcer is strictly demarcated, most frequently oval lesion. Its diameter does not exceed 1 cm, rarely reduces below 3 mm. In cases of such a reduction it is not radiologically detectable. It can be confirmed but by endoscopic examination or post mortem. Duodenal ulcers extend into submucosa and muscularis propria. The defects are usually surrounded by granulation tissue and to a certain extent by fibrosis. The base of the ulcer contains blood or exudate with erythrocytes and cellular inflammatory infiltration. More than 95 % of cases develop an ulcer localised approximately 3 cm from the junction of the pyloric and duodenal mucosae. The prevalence of duodenal ulcers is not precisely known. It occurs in 6–15 % of the population. The past years yield a moderate decrease in the occurrence of duodenal ulcers especially in men. Approximately 10 % of the population have or have overcome duodenal ulcers. Duodenal ulcers occur 3 times more often than gastric ulcers.

The production of hydrochloric acid in the stomach is an inevitable condition for the development of duodenal ulcers. A part of patients yield an increased secretion of hydrochloric acid, but a part of them have normal secretion. Patients with duodenal ulcers have 1.9 billion parietal cells with the maximal capacity of 42 mmol of HCl per hour. Persons without duodenal ulcers have approximately 1 billion parietal cells with the maximal secretion of 22 mmol of HCl per hour. Some patients have an increased secretion of pepsin and an increased level of pepsinogen I in the serum. **Ulcers develop where there is an unfavourable balance between the acid-pepsin secretion and the protective properties of mucus**. After

an intake of fully valuable food the patients with duodenal ulcers yield normal concentrations of gastrin in the serum. However, after an intake of food high in protein, the serum levels in comparison with healthy people increase. After adminstration of gastrin the patients with gastric ulcers yield a higher secretion of hydrochloric acid when compared with healthy people. Furthermore, intragastric acid does not inhibit sufficiently the release of gastrin. Evacuation of the stomach is enhanced, resulting in an increased supply of acid into the duodenum.

Duodenal ulcers occur more frequently in patients with a positive family history concerning this disease. Duodenal ulcers occur prevalently in persons with the blood group 0. An increased incidence is observed in the presence of HLA–B_5 antigen. An increased level of pepsinogen I in the serum is present in 50 % of patients.

Cigarette smoking relatively closely correlates with the occurrence of duodenal ulcers. Smoking does not increase the gastric secretion, but deteriorates microcirculation. It inhibits, however, the pancreatic bicarbonate secretion and accelerates emptying of stomach content into the duodenum. The occurrence of duodenal ulcers in smokers is higher than that in patients with chronic renal failure, alcoholic cirrhosis, hyperparathyreosis and a chronic obstructive disease of the lungs.

80 to 100 % of patients with duodenal ulcers yield the presence of Helicobacter pylori. It is not known as to whether it plays the etiologic role. However, it has a negative impact on the velocity of healing processes.

Anxiety and psychological stress can cause an exacerbation of ulcer activity. However, it is not clear as to whether these factors play the primary part in the pathogenesis of ulcers.

Epigastric pain is the main symptom of duodenal ulcer. It usually appears in 90 minutes to 3 hours after a meal. The pain wakes the patients at night. It withdraws after a meal and antacids. The ulcers have a tendency to penetrate. If an ulcer penetrates the pancreas, it causes pancreatitis. It can perforate the gastric wall and penetrate the peritoneal cavity. A massive gastrointestinal haemorrhage can develop. Some duodenal ulcers are not manifestant clinically. They are detected accidentally in coincidence with endoscopic examinations. Ulcers localised in the pyloric canal are not considered as being gastric. They are classified as duodenal ulcers as their clinical symptomatology is equal to those localised in the duodenum.

7.5.2.3 Gastric ulcer

Gastric ulcers most frequently occur in the sixth decade of life. They are more frequent in males. Ulcus ventriculi is a **variously profound defect capable of penetration**. Histologically it resembles the duodenal ulcer. The difference resides in the fact that the surrounding tissue is more markedly afflicted by local gastritis, often with intestinal metaplasia. A prevalent proportion of ulcers is localised in sites with more intensive acid production, most frequently in the site of the interface between the gastric body and so-called physiological antrum. Benign ulcers are rarely localised in the subcardial area.

The **production of acid in patients with gastric ulcers is either normal, or decreased**, the latter being more frequent. Some patients yield achlorhydria. 10–20 % of patients with gastric ulcers also have duodenal ulcers. It is mostly probable that the development of gastric ulcers is prevalently based on the principle of mucous barrier impairment. In comparison with duodenal ulcers, the patients with gastric ulcers yield a significantly increased serum gastrin levels. This is valid in patients with gastric acid hyposecretion. In these patients, the evacuation of the stomach is delayed. It is assumed that regurgitation of the duodenal contents together with bile takes place. This event can impair the mucous barrier with resultant back-diffusion of secreted hydrogen ions.

Epigastric pain is the most common symptom, although not so typical as in coincidence with duodenal ulcers. Gastric ulcers tend to heal, however, they often reoccur in the same location. A number of gastric ulcers is asymptomatic. Haemorrhage is a frequent complication. Obstruction and perforation are less frequent. Obstruction occurs when the ulcer is localised in the pyloric canal.

7.5.2.4 Zollinger–Ellison syndrome (gastrinoma)

This disease is characterized by ulcerations in the upper part of GIT and gastrin-producing pancreatic tumor. Pancreatic tumors can vary in size from 2 to 20 cm. More than 1 tumour can occur. They are localised in the pancreatic head, which however, is not

a rule. It can be also localised in the duodenal wall and in other sites. These tumors usually grow slowly. Patients yield an increase in plasma concentration of G_{34}. Circulating gastrin has a trophic effect on the parietal cells and therefore their fast reproduction is observed. 90 % of patients with gastrinoma develop an ulcer in GIT. The clinical symptomatology resembles that of duodenal ulcer, but instead of constipation, diarrhoea is present.

7.5.3 Stress ulcers and erosions

This condition involves an impairment of GIT which is distinct from chronic peptic ulcers. Acute ulcerative lesions develop in patients with intensive stress, with shock, massive burns, sepsis and severe trauma (erosions and superficial ulcus occur in about 90 % of patients with massive burns). Impairments are multiple, ulcers are localised in the duodenum and gastric antral area. The clinical picture is dominated by gastrointestinal bleeding; erosions usually appear within 24 hours after trauma.

It is assumed that the **cause of stress ulcers or erosions resides in mucosal ischaemia with subsequent impairment induced by gastric acid**. The mechanism of stress reaction (e.g. due to an unapt situation) is partially clarified. Peptide hormones and neuropeptides secreted by gastrointestinal cells enter the circulation and subsequently enter the brain via the brain-blood barrier. Similarly, from the brain they pass into the cells of the so-called gastointestinal brain (APUD system). This pathway leads the transmission of impulses by means of complex neurohumoral mechanisms. These processes can result in motor-secretion impairments. Increased secretion of gastric juice induced by stress, or an impairment of perfusion of the gastric mucosa can lead to the development of ulcerations. Pain and hypersecretion of hydrochloric acid lead to a backward suppression of secretion. In very simple terms, the humoral reaction triggered by stress, in addition to other substances, releases endorphins which moderate the pain. Inversely, at rest, a greater amount of cholecystokinin (CCK) which represents a "hormone of easefulness" is secreted with all secretion-motoric consequences.

7.5.4 Helicobacter pylori and diseases of GIT

Great attention is currently world-widely viewed to the problem of participation of this microorganism in some diseases of the gastrointestinal tract.

Helicobacter pylori (HP) is a small, microaerophilic gram-negative bacillus. **Epidemiologic studies** have indicated that 60 % of the population above 50 years of age in modern countries, are HP seropositive. Less advanced countries yield a seropositivity already in childhood in more than 50 % of the population. In adults, the prevalence of seropositivity is 100 %. The source is not known. The importance of interpersonal transmission is suggested by evidence of its occurrence in families and custodial institutions. High seropositivity among gastroenterologists and the occurrence of microepidemies (assumedly due to the use of contaminated nasogastric tubes) suggest that the iatrogenic process of infection is possible. Helicobacter pylori is responsible for some forms of acute and chronic gastritis and its role in the development of peptic ulcer is being investigated.

This microorganism has an exclusive affinity to the cells of gastric mucosa. It especially harbours areas of the pyloric antrum. Colonisation of HP in the duodenum is restricted to areas of gastric metaplasia. It can occur in the distal part of oesophagus in patients with abnormal cylindric glandular epithelium in this area (Barret's oesophagus). HP was also found in individual cases of heterotopic gastric mucosa in the Meckel's diverticulum and in the rectum. It always resides the mucous layer above the apical surface of epithelial cells, but it occurs also in areas with close connection between the adjacent epithelial cells. It does not penetrate into the mucosa.

Helicobacter pylori releases several factors which induce inflammation, impair the epithelial cells and retard reparation of impairment localised in the tissue weakened by gastric acid and pepsin. Helicobacter pylori releases adhesins, proteases, phospholipases, chemotaxins and cytotoxins. Adhesins enable the HP to adhere to the surface of gastric epithelium. Factors that are chemotactic for neutrophils and monocytes, as well as for PAF, mediate the inflammatory response. Activated macrophages release cytokines which participate in inflammation by means of TNF-α, IL-1 and oxygen radicals. Proteases and phospholipases degrade the glycoprotein-

lipid complex of the superficial gel. The thickness and viscosity of gel is hereby reduced despite its increased production. **HP is a strong, possibly exclusive source of gastric urease**. The latter catalyses the hydrolysis of urea, thus producing alkaline microenvironment which protects the mucosa from the effect of gastric acid.

Helicobacter pylori is an extremely world-wide spread infection. However, it brings about gastritis or ulcerative disease only in a small group of infected persons. On the basis of its limited incidence it is possible to state that the disease develops when supported by the presence of certain decisive factors. Unconfirmed, but still appealing are the hypotheses explaining the liability to succumb the disease on the basis of more aggressive HP strains, higher bacterial density, or exaggerated response of organism. A certain critical density of HP is assumedly inevitable to enable the neutralisation of its surrounding by urease and generation of sufficiently strong chemotactic signals supporting the active inflammation. The impacts of acid, pepsin and other impairment-inducing factors are of secondary importance.

Helicobacter pylori is alleged to be responsible for a majority of chronic active gastritis. Histologically it is moderate superficial gastritis. The superficial area of lamina propria comprises neutrophils and mononuclear leukocytes. Children develop lymphoid hyperplasia. The most common sign resides in a moderate reduction of mucus.

There is a link between the peptic ulcer and HP. The presence of HP in the antrum was found in 90 % of patients with duodenal, and 70 % of patients with gastric ulcer. HP is considered to be an important factor in the pathogenesis of peptic ulcer. However, it still remains to be clarified as to whether HP represents the causal factor of the development of peptic ulcer, or a merely auxilliary and modificating factor.

7.6 Exocrine pancreas

The pancreas is localised retroperitoneally behind the stomach. The pain coinciding with pancreatitis therefore spreads from the epigastric area into the back. The pancreatic head is in the duodenal flexure and its tail touches the spleen. Pressure on the spleenic vein (vena lienalis) can cause varicous dilatation of gastric veins. An impaired drainage of the lymph from the stomach can be caused by e.g. reactive inflammation of the pancreas. The pancreas has an outstanding position among glands in organism as it comprises both endocrine and exocrine glands.

The exocrine pancreas consists of acini which produce enzymes and alkaline fluid. Acinal cells are arranged spherically around small outlets. Pancreatic juice is drained via the major pancreatic duct which enters the duodenum together with the common bile duct (ampulla Vateri). **Anatomical conditions** in this area vary. In some individuals the pancreatic juice is drained by the Santorini's duct which is independent from the major pancreatic duct, and enters the duodenum via the minor duodenal papilla. The secretory pressure in the efferent ducts reaches approximately 200 mm H_2O. The lumen of ducts is lined with one-layer epithelium which is permeable neither for bile and trypsin, nor for E. coli suspension. At rest, the pancreas secretes approximately 2 ml of juice, after stimulation its amount reaches 5 ml. The insular apparatus is localised predominantly in the pancreatic tail. It is separated from the exocrine parenchyma by connective tissue. Endocrine pancreatic agents get into circulation via portal veins.

The arterial blood is brought into pancreas via branches of the truncus coeliacus and from the arteria mesenterica superior. The venous blood is drained from the pancreatic head into the portal veins and from the pancreatic tail into the spleenic vein.

Postganglionic fibers stimulate the enzymatic and hormonal secretions. The sympathetic postganglionic fibers from the coeliac ganglion and superior mesenteric plexus innervate the blood vessels and stimulate vasoconstriction. In general, the sympathetic nervous system inhibits the pancreatic secretion and the parasympathetic nervous system stimulates it.

Pancreatic juice is isoosmotic. It contains potassium, sodium, the most important anions include bicarbonates and chlorides which participate in a reverse ratio (an increase in bicarbonates causes a decrease in chlorides and vice versa). The potassium and zinc levels in the pancreatic juice is twice as high as those in the serum, the contents of proteins cor-