7.21 Diseases of the gallbladder

7.21.1 Cholelithiasis

The presence of bile stones in the biliary pathways – cholelithiasis – is one of the most frequent causes of the diseases of the gastrointestinal tract. The bile stones are crystalline structures formed by concretion or accretion of normal or abnormal bile constituens. They are divided into three types: cholesterol stones, mixed stones and pigment stones. The cholesterol stones and mixed stones which most frequently occur in our population contain more than 70 % of cholesterol. The rest of stones are formed by calcium and bile salts, proteins, fatty acids, phospholipids and bilirubin. Pigment (bilirubin) stones are composed primarily of calcium-bilirubinate; they contain less than 10 % of cholesterol. Pigment stones are common in the Orient and Asia. In Europe they occur mostly in patients with chronic haemolytic states which display higher concentrations of bilirubin in bile. Deconjugation of soluble bilirubin may be mediated by bacteria.

The formation of the so-called lithogenic (stone-developing) bile is based on several mechanisms. The most important is the increased biliary secretion of cholesterol (drugs, obesity, high-caloric diet). Similarly decreased hepatic secretion of bile acids and phospholipids in rare inborn errors of metabolism or conditions affecting the enterohepatic circulation of bile acids (ileal diseases, parenteral alimentation) contribute to the formation of lithogenic bile. In this association the patients often appear to have a reduced activity of cholesterol-7-alpha-hydroxylase, the rate-limiting enzyme for primary bile acids synthesis.

Hence, the bile stones develop **due to the disbalance between the levels of cholesterol and bile acids plus phospholipids**. This disbalance may be due to hypersecretion of cholesterol, hyposecretion of bile acids, or both. Still, a certain role is played by the change in the mutual ratio of the cholic and deoxycholic acids in bile. The cause resides in an increased degradation of cholic acid in the intestine to deoxycholic acid which is reabsorbed to a greater extent. An important role is ascribed to the nucleation of cholesterolmonohydrate crystals, which is significantly accelerated in lithogenic bile. It may be due to either an excess of pronucleating factors (mucin glycoproteins, lysine phosphatidylcholine), or a deficiency of antinucleating factors (apolipoproteins, other glycoproteins). Nucleation of cholesterol-monohydrate crystals probably occurs within the mucin gel layer. The formation of bile stones is also supported by a decreased evacuation and stagnation of bile.

Bile stones can be **solitary**, growing to the size of a walnut, or **multiple**. They are localised most frequently in the gallbladder (cholecystolithiasis), or in ductus choledochus (choledocholithiasis), rarely in minute extrahepatic and intrahepatic biliary ducts. The symptomatology of the presence of bile stones varies greatly. The **dyspeptic syndrome** – the sensation of fullness in epigastrium, meteorismus, diffuse moderate abdominal pain which binds to dietary faults are very frequent in cholelithiasis. If the stone migrates from the gallbladder into the cystic duct or choledochus, it can cause obstruction with retrograde augmentation of intraluminal pressure and distension. This state is manifestant by **biliary colic** – sudden and intensive abdominal pain lasting for several minutes or hours accompanied by nausea and vomiting.

Cholelithiasis is a very frequent cause of further, more severe diseases in extrahepatic biliary pathways. Cholelithiasis may cause cholecystitis, cholangitis, cholestasis, as well as acute haemorrhagic necrosis of the pancreas.

7.21.2 Cholecystitis

Acute inflammation of the gallbladder develops most frequently in consequence of cholelithiasis (calculous cholecystitis). The bile stone can stick in the draining part of the gallbladder or in the cystic duct which disables the free draining of bile and causes chemical irritation and inflammation. Chemical inflammation is caused by the release of lysolecithin (due to the action of phospholipase on lecithin in bile) which is toxic for the mucosa. The normal glycoprotein layer is impaired and the epithelium is directly exposed to the detergent effect of bile salts. The inflammatory process in the mucosa and wall of

the gallbladder is enhanced also by prostaglandins which are released from the distended wall. The distension and increased intraluminal pressure simultaneously result in ischaemia of the gallbladder mucosa and wall. These chemical and mechanical influences cause inflammation even prior to the bacterial contamination which usually takes place later. The gallbladder at the culmen of inflammation is thickened, oedematous and hyperaemic, filled with turbid bile containing a large amount of fibrin and pus. The state of the gallbladder containing only pus is referred to as gallbladder **empyema**. The gallbladder in severe cases changes into a greenish black necrotic sack with larger or smaller perforations – **gangrenous cholecystitis**.

Approximately 5–10 % of cases of acute cholecystitis develop without the presence of bile stones (**acalculous cholecystitis**). The causes of the inflammation include serious trauma and burns, difficult parturitions, simultaneous failure of several organs, sepsis, etc. The gallbladder is usually large and tense, with evident weakness and slowness of evacuation. The main cause is considered to be the ischaemic impairment of the gallbladder as the cystic artery is the terminal artery without collateral circulation.

Acute cholecystitis usually begins as an attack of biliary colic which does not withdraw and is accompanied by fever and further signs of inflammation (leukocytosis, high rate of erythrocyte sedimentation). Anorexia associated with vomiting can lead even to extracellular volume depletion. The appearance of jaundice signifies either obstruction of the biliary pathways by a stone, or a state when the oedematous inflammation involves the bile ducts and surrounding lymph nodes. Acute cholecystitis can be the cause of severe complications. The bile stasis is inclined to become complicated by e.g. bacterial superinfection which spreads via lymphogenic and ascendent pathways and causes an inflammation of intrahepatic biliary ducts (cholangitis), perforation with the development of abscess, rupture with generalized peritonitis, fistula with bile or stone drainage into the adjacent organs etc.

Chronic cholecystitis develops in 90 % of cases in consequence of repeated acute cholecystitis or due to permanent mechanical irritation of the wall of the gallbladder. The gallbladder is shrunk, its wall is thickened, fibrotically changed and physiologically unfunctional. The disease often has a latent course with dyspeptic difficulties after dietary faults, with infrequent acute exacerbations. A prolonged total obstruction of the cystic duct causes that the lumen of the obstructed gallbladder fills and progresively distends with mucus (**mucocele**) or clear transudate (**hydrops**) produced by mucosal epithelial cells.

7.22 Gastrointestinal hormones

The contacts of the human organism with the surrounding environment are intermediated by complicated neurohumoral pathways. The neurohumoral connection with the gastrointestinal tract represents an extensive labyrinth, the junctions of which are only partially known.

The major contact of the gastrointestinal tract with the external environment represents the food intake. Almost all gastrointestinal hormones are secreted as a response to the accepted food.

Gastrin is produced by G cells of the antral glands of the duodenum and small intestine. Coffein and wine (not destilates) stimulate its release similarly as proteins and amino acids (especially fenylalanine and tryptophane). GRP (gastrin-releasing peptide) and its equivalent in apmhibians – bombesin, have a stimulating effect whereas somatostatin (SMS) supresses its release. Gastrin belongs to the strongest secretogogues of the gastric juice. It affects the motility and trophics of the gastric and intestinal mucosae. The antagonist of gastrin – proglumid – inhibits the growth of the cellular line of colorectal carcinoma in tissue cultures.

Cholecystokinin (CCK) is produced by I cells of the duodenum and upper jejunum. As most important function is considered to be the stimulation of the secretion of pancreatic juice, induction of the contractions of the gallbladder and relaxation of Oddi's sphincter, as well as the lower oesophageal sphincter. CCK stimulates the peristalsis of gastric antrum, small and large intestines, causes hypertrophy and hyperplasia of the pancreatic cells, improves the lymphatic flow and moderately stimulates the gastric secretion. It belongs to the so-called hor-