Acute abdominal pain always represents an urgent situation. It is an intricate and serious problem. It may represent a significant symptom of a condition which if not treated immediately ends up by death of the afflicted patient. Acute abdominal pain requires rapid and precise diagnosis and in many cases it is inevitable to operate. Therefore, despite the fact that it would be possible to object that the discourse on acute abdominal pain belongs to the domain of clinical medicine, we are going to present several important matters on this symptom.

Acute abdominal pain most frequently occurs in the diseases of the digestive tract as follow: acute appendicitis, cholecystitis, pancreatitis, intestinal obstruction, perforation of hollow organs, intestinal infarction, intestinal strangulation, acute diverticulitis.

Acute abdominal pain can arise also due to disturbances of other than digestive organs. It may be due to: rupture of aortic aneurysms, rupture in extrauterine pregnancy, pneumonia, renal stones, haemolytic crisis, acute hepatitis and acute porphyria.

The judgement of abdominal pain requires to take into consideration the onset of pain, its course and accompanying symptoms, such as fever, nausea, vomiting, constipation and diarrhea. The latter represents a supremely valuable symptom which aids to assess the correct and qualified diagnosis.

7.18 The Liver

The liver is the largest parenchymatous organ in the human body. Its task in organism is irreplaceable. Liver failure, or experimental hepatectomy incurs death in several hours. Hepatic functions can be divided into four groups:

1. synthesis of a large amount of special proteins, carbohydrates and lipids
2. regulation of the balance between GIT and systemic circulation which maintains a stable level of amino acids and glucose
3. production of bile salts and bicarbonate necessary for the correct digestion in GIT
4. excretion of larger and more hydrophobic metabolites, foreign substances and a number of drugs

Optimal procurement of these mutually distinct functions is in accord with hepatic structure, including the blood and bile pathways. The overall blood perfusion via the liver represents one fourth of the cardiac output at rest. The blood inflow is procured by the hepatic artery (25%) which brings in blood rich in oxygen, and the portal vein (75%) which supplies the liver with blood rich in nutrients from the splanchnic area. Both vessels enter the liver and terminally reach the sinusoids. The sinusoids already contain mixed blood which directly bathes the hepatocytes. The blood delivers important metabolic products. After taking up some nutrients and eliminated waste products (some waste products are taken up, whereas others are excreted by hepatocytes) the blood is drained through the central veins (venae centrales) which represent the beginning of the efferent blood pathways subsequently merging into the inferior vena cava. The hepatic parenchyma microscopically appears as a system of hexagonal lobuli, the centres of which contain a central vein.

However, regarding the functional aspect, the hepatic parenchyma is divided into acini. The acinus is localised among several central veins and its centre is constituted by so-called portobiliary space (terminal triad), which contains the terminal branch of the portal vein, terminal branch of the hepatic artery and the bile duct. The functional efficiency, resistance, as well as the enzymatic equipment of hepatocytes is determined by its localisation – its distance from the portobiliary space. The periportal zone (zone 1) resides in the close vicinity of terminal triad and it is perfused by blood being still rich in oxygen and nutrients. The function of the intermediary zone (zone 2) changes according to the overall supply of the liver by blood. The central zone (zone 3) is localised in the vicinity of central vein, i.e. at the periphery of acini. The blood flowing to the cells of the latter zone is poor in oxygen and nutrients which have been taken up in the previous two zones. Therefore the cells of this zone are predominantly liable to impairment in coincidence with e.g. shock and other disorders of circulation. According to the enzymatic equipment, the cells of the periportal zone primarily synthesize proteins, the cells of the central zone carry out glycolysis, lipogenesis and processes of biotransformation.
The following text is going to deal with the microanatomic localisation of the terminal blood pathways and the onset of bile ducts in relation to hepatocytes, as well as with the structure of hepatocytes regarding their function.

It is within the acinus that arteriole empties into the portal venule and the mixed blood percolates through the sinusoid toward the central vein. The sinusoid is lined by endothelial and phagocytic Kupffer cells. Unusually large fenestrae in the endothelial cells facilitate an easy transgression of large molecules from the blood to the hepatocyte plasma membrane. The capillary space, which occurs between the endothelial lining cells and hepatocytes (space of Disse), represents the onset of the lymphatic pathways. The sinusoidal membrane, that portion of hepatocyte plasma membrane bordering the space of Disse – constitutes rich microvilli which enlarge the surface of resorption of substances brought in by the blood. The lateral portion of sinusoidal membrane, bordering the intercellular space, is relatively flat. The canalicular membrane, which consists of many irregularly spaced microvilli, carries out intensive processes of elimination. The canalicular membranes of two adjacent hepatocytes joined by junctional complexes circumscribe the canalicular space – canalculus. The different plasma membrane domains differ in their associated transport systems and in their physical properties. Canalicular membrane, as compared with the sinusoidal membrane, has a higher content of the sialic acid, higher molar cholesterol/phospholipids ratio and lower fluidity. These special properties presumably facilitate the secretion of bile acids and lipids and protect the membrane from the detergent effect of canalicular bile.

Hepatocytes contain multiple mitochondria. This fact suggests that the hepatocytes have functions that are energetically demanding. The smooth part of the endoplasmic reticulum is the site where the detoxication and conjugation processes are carried out together with the synthesis of enzymes. The granulated part of the endoplasmic reticulum procures the synthesis of proteins (albumin, coagulation factors). Lysosomes contain hydrolytic enzymes and acid phosphatases, as well as accumulated pigments (lipofuscin, ferritin, bilirubin, copper). The Golgi complex participates in the transport of certain solutes from blood to bile (bile acids, bilirubin). This fact is proved by its dense occurrence in the pericanalicular cytoplasm under the condition of increased bile secretion. In the proximity of the canalicular membrane, microfilaments are concentrated. The microfilaments are contractile structures constituted of polymerized actin. They form a pericanalicular network. A coordinated contraction of this network (possibly involving changes in cytosolic calcium concentration) bring about a peristaltic wave which shifts the bile into larger collecting structures. The canaliculi gradually gain their own wall, thus changing into ductules (cholangioles) which coalesce and form larger biliary ducts. Both right and left hepatic ducts emmerge from the hepatic port and constitute the common hepatic duct (ductus hepaticus communis) which is joined by the cystic duct from the gallbladder, thus constituting the common bile duct merging into the duodenum. In this site common bile duct contains a muscular sphincter of Oddi which inhibits an uncontrollable leakage of bile into the duodenum.

7.18.1 Metabolism in liver

7.18.1.1 Metabolism of proteins

The liver is the main site of the synthesis of the majority of plasma proteins as well as the main site of their degradation. Among the number of proteins synthesized within the liver, the greatest significance in relation to hepatic diseases resides in albumin and prothrombin. Albumin’s main function is to maintain the intravascular oncotic pressure and the transfer of substances soluble in water, such as fatty acids, bilirubin, hormones and drugs. Since albumin has a relatively long halftime of breakdown (cca 21 days), its level almost does not change in coincidence with acute hepatic diseases. Long-term reduction of the albumin synthesis in chronic liver diseases, however, evokes hypalbuminaemia with all consequences including the development of ascites. Serum albumin is therefore the sensitive marker of the synthetic function of the liver and a significant indicator of the severity of chronic hepatic diseases.

An insufficient synthesis of prothrombin is externally manifest in dependence on the function of other coagulation factors, a majority of which are synthesized in the liver. A common symptom of impaired synthesis is a prolonged blood coagulation time. The liver receives amino acids from GIT and muscles, and regulates their plasma levels by pro-
cesses of glyconeogenesis and transamination. The liver is responsible for the modification of plasma amino acids composition. Aromatic amino acids – phenylalanine, tyrosine, methionine – are preferentially transformed to urea, whereas amino acids with branched chains – valine, leucine, isoleucine – are selectively shifted to the periphery, where they are preferentially metabolized in muscles. This selectivity disappears in severe diseases of the liver. It is possible that the resultant change in the ratio of plasma concentrations of these two groups of amino acids can incur damage to the metabolism of brain neurotransmitters and contribute to the development of portosystemic encephalopathy.

Amino acids are degraded in the liver by transamination and oxidative deamination, giving way to the formation of ammonia, which in turn is further converted to urea and eliminated by the kidneys. Severe hepatic impairments coincide with the failure of this chief pathway of elimination of the nitrogenous waste from organism.

7.18.1.2 Metabolism of saccharides

The maintenance of the stable level of glucose in the blood represents the further function of the liver. It acts as the entrance gate for glucose accepted by organism with food. An excess of glucose which is lead in from GIT during digestion is converted to glycogen. However during fasting, the latter represents the source of glucose. The main metabolic pathway is glycogenolysis. After the depletion of glycogen reserves, it is foremostly the lactate, pyruvate, glucogenic amino acids and glycerol originating from fat reserves by lipolysis. As long-term fasting depletes the above mentioned sources, the organism utilises ketone substances and fatty acids as alternative sources of energy, and tissues adapt to the lower consumption of glucose. The main tool of the metabolic control of glycaemia maintenance are hormones as insulin, glucagon, catecholamines and glucocorticoids. The supply of glucose by gluconeogenesis under conditions of hepatic diseases is well preserved. Hypoglycaemia represents a threat solely in severe liver failures.

7.18.1.3 Metabolism of lipids

The liver has a special position in the metabolism of lipids. Hepatocytes are abundantly equipped by enzymes responsible for the synthesis and oxidation of fatty acids, the synthesis of cholesterol, phospholipids and the apoprotein part of plasma lipoproteins. They are also the singular site of beta-oxidation of fatty acids with the production of ketone substances. They take up free fatty acids from circulation. The free fatty acids serve as the substrate for the synthesis of phospholipids and triacylglycerols.

The liver has a major part in the metabolism of transport lipoproteins. Lipoproteins with high density (HDL) are synthetized in the liver and intestines. Their major share is represented by protein and a their minor share by triacylglycerols. They represent the most important system of transport of phospholipids. In addition to the kidneys, the liver is the main site of HDL catabolism.

Lipoproteins with low density (LDL) are produced in the plasma during catabolic processes of lipoproteins with very low density (VLDL). They are the chief transporters of cholesterol. A majority of them are degraded in the liver after their binding with high-affinity receptors. VLDL which contain as much as 60% of triacylglycerols, are synthetised foremostly in the liver and represent the endogenous synthesis of triacylglycerols.

Chylomicrons have the lowest density. Together with VLDL, they are considered as being the main carriers of triacylglycerols. They are produced in the cells of intestinal mucosa and represent the chief form of transport of fat from food. They appear in the plasma during the postprandial period and disappear in several hours. They are catabolised by the lipoprotein lipase in peripheral tissues and by the hepatic lipase in the liver. The next significant role of the liver resides in the metabolism of cholesterol. The liver takes up a major part of the exogenous cholesterol and at the same time it is the main site of the synthesis of the endogenous cholesterol. Cholesterol is eliminated from the liver by both blood and bile. The main product of cholesterol catabolism are the bile acids.

7.18.1.4 Metabolism of bile acids

Bile acids (BA) are synthetized in hepatocytes from cholesterol. The limiting factor of the velocity of its synthesis is the cholesterol-7alpha-hydroxylase. Primary bile acids – cholic and chenodeoxycholic acids conjugate with glycine and taurine in the endoplasmic reticulum. The conjugation increases their
solubility, thus enabling their elimination into bile and currently makes the molecule more resistant to precipitation by divalent cations (e.g. Ca$^{2+}$). The conjugation significantly decreases the possibility of passive absorption from the biliary tract and small intestine. Conjugated BA are too large to penetrate paracellular junctions and their charge hinders their movement through the lipid parts of apical membranes of the biliary and intestinal epithelia. This enables them to pass through the intestine in high concentration and to reach the terminal ileum. In the intestine, the bile acids act as detergents – their main function is to solubilize lipids. Approximately 90% of bile acids are reabsorbed in the terminal ileum. A small part of bile acids which has passed through the ileocecal valve, enters the anaerobic environment of the cecum. Herein, under the influence of bacterial enzymes, secondary bile acids – deoxycholic and lithocholic acids are produced. A small part of bile acids deconjugates, partly under the influence of bacterial enzymes. Primary and secondary bile acids return back to the liver. They are taken up by hepatocytes. According to the actual needs, they are recycled and again secreted into bile (enterohepatic circulation). The remnant 5–10% are excreted daily in stool, and therefore their overall pool must be repleted by de novo synthesis.

The enterohepatic circulation of bile acids represents a continuous flow of transporting molecules which transfer lipids and substances soluble in fat from the intestinal lumen into intestinal mucosa and cholesterol from the liver to intestine, thus enabling thus its elimination by stool. This movement is enhanced during digestion and hindered during fasting, but never ceases.

The enterohepatic circulation of bile acids includes chemical pumps (transport systems of hepatocytes and enterocytes), mechanical pumps (biliary tract, small intestine, blood circulation), valves (sphincter of Oddi, ileocecal valve) and storing spaces (gallbladder, small intestine). The enterohepatic circulation is thereafter enabled by the impermeability of the cellular membranes for conjugated BA. The relative impermeability or the epithelial lining of the biliary pathways and proximal part of the small intestine maintain the concentration gradient of BA, which is a thousand-fold higher in the bile and small intestine than in the surrounding cells. An efficient extraction of bile acids by hepatocytes from the portal blood inhibits their entrance into the systemic circulation. Solely a small, relatively stable fraction of BA escapes. This fraction is taken up during the repeated perfusions via the liver (thereby the concentration of BA in the systemic circulation is directly proportional to the load of bile acids that are lead into the liver from intestine in each moment – their level in blood increases during digestion and decreases between meals, however does not exceed 8 µM). The half-time of BA in the systemic circulation is only several minutes. Binding of BA to plasma albumin (70–99%) inhibits their entrance into the extracellular space and glomerular filtrate. A small fraction of bile acids which escapes into the glomerular filtrate is efficiently reabsorbed in the renal tubules, and that is why they are not present in urine of healthy people.

### 7.18.1.5 Metabolism of bilirubin

Bilirubin is the terminal product of degradation of haemoproteins, especially that of haemoglobin. Heme is converted to biliverdin and further to bilirubin by mononuclear phagocytic cells which include also the Kupffer cells of the hepatic sinusoids. The produced lipophilic, insoluble bilirubin (nonconjugated) circulates in plasma bound tightly to albumin. The contact with hepatocytes brings about the dissociation of the bilirubin-albumin complex. After the transgression through the membrane it is transported by means of cytoplasmic transport proteins (Y protein, ligandin) to the endoplasmic reticulum where it conjugates in presence of uridine diphospho-glucurono-y-ltransferase (UDP-GT) to bilirubin monoglucuronide and bilirubin diglucuronide. Conjugated bilirubin is soluble in water which enables its active secretion into bile. The intestinal flora in terminal ileum brings about its hydrolysis and an immediate reduction to colour-less tetrapyrols, commonly referred to as urobilinogens. Approximately 20% of the formed urobilinogen is absorbed, returned by portal circulation into the liver where it is partially degraded and secreted into bile. Only a minimal amount of urobilinogen escapes from liver and is eliminated into urine.

### 7.18.1.6 Production of bile

The production of bile resides in the movement of water, electrolytes and other bile constituents from the sinusoid blood (or from hepatocytes) into the
canaliculus. Their movement from the sinusoid into the canalicular space can be carried out in two ways: transcellular movement – through the sinusoidal (or lateral) and canalicular membranes, or paracellular movement – from the intercellular space through the tight junctions between the adjacent hepatocytes. Since these tight junctions are relatively permeable for anorganic ions, this pathway leads the majority of Na⁺, Cl⁻, and K⁺ ions.

The main driving force of the canalicular production of bile resides in bile acids. They are actively transported through the canalicular membrane into the canaliculi where they undergo condensation. In consequence of this process their density becomes approximately 1000-fold higher than that in plasma. This condition produces an enormous osmotic gradient for water diffusion. Water under basal conditions foremostly moves by transcellular pathways. The conjugated bilirubin is transferred through the canalicular membrane by its own transport system. Its elimination, however, depends to a certain extent on the elimination of bile acids. The secretion of phospholipid-cholesterol vesicles into bile depends as well on the secretion of bile acids. The smaller component of bile production, independent from bile acids, takes place on the level of canaliculi and ductuli. The membrane ATP-ase in canaliculi pumps ions into bile. By this process the ions gradually seize a certain amount of water. The bile is supplemented by fluid rich in bicarbonates which is eliminated into bile through the walls of ductuli. This process takes place under the impact of secretin. Bile acids are strong detergents which solubilize bile lipids by enclosing them into micelles (mixed micelles are conglomerates of cholesterol, fatty acids and lecithin surrounded by polar molecules of bile acids). The formation of micelles is also important for the elimination of cholesterol and phospholipids into bile and for the transport of bilirubin. The bond of bilirubin with micelles decreases its concentration in the non-micellar phase of bile and decreases thus the possibility of its backward diffusion through the membranes of biliary pathways.

7.18.1.7 Detoxification functions of the liver

Both endogenous and exogenous chemical substances undergo transformation processes in the liver. Owing to these processes their toxicity, or biological acitivities are decreased. These processes are referred to as metabolic detoxification or biological transformation. Since the liver catabolizes a large amount of hormones (steroids, insulin, glucagon, thyroxin), the chronic impairment of hepatic functions is usually accompanied by the signs of hormonal disbalance. A severe consequence of a decrease in the amount or activity of microsomal enzymes, is the delay in inactivation and elimination of xenobiotics. However, a simultaneous administration of two drugs, metabolized by the same microsomal system can also lead to modification, augmentation or decrease in the pharmacological effect of one of the drugs or both.

Under certain circumstances, the final products of detoxification can have a further toxic impact. E.g., owing to a high intake of alcohol, the produced acetaldehyde damages mitochondria of hepatocytes and the produced hydrogen ions cause an accumulation of fat in hepatocytes (steatosis).

7.18.1.8 Liver enzymes

Liver diseases usually bring about changes in the amount of enzymes which belong to the hepatic enzymatic equipment, or the synthesis of which takes place in the liver. This fact is being used in both routine and special enzymatic diagnostics. Since the investigated enzymes are from various cellular parts (cytosol, mitochondria, membranes, lysosomes), the changes in concentrations of individual enzymes in the blood and their mutual combinations can render certain information on the character and stage of liver impairment.

Cytosolic and mitochondrial enzymes

ALT (alanine aminotransferase) is a specific enzyme of the hepatic tissue. It exclusively occurs in cytosol. This enzyme leaves the cell already in coincidence with a moderate impairment merely increasing the permeability of the cellular membrane.

AST (aspartate aminotransferase) is constituted of cytosolic and mitochondrial fractions. In addition to the liver, it also occurs in a greater amount in the cardiac and skeletal muscles. Increased plasma levels of AST therefore occur in coincidence with an impairment of hepatocytes, cardiomyocytes and myocytes. A moderate impairment of hepatocytes associated only with an increased permeability of membranes singly allows the cytosol fraction to enter the
Membrane enzymes

They occur especially on the canalicular membrane of hepatocytes. Therefore they foremostly react to the changes concerning the composition and excretion of bile. To a greater extent, they can be synthesised due to the effect of insufficiently hydroxylated BA. The detergent effect of BA releases them to a greater extent from the membraneous surface.

ALP (alkaline phosphatase) occurs not only in the liver, but also in other tissues (bone, intestines, placenta). The hepatic isoenzyme is localised especially in the canalicular part of the hepatocytic membranes. Its increased serum level is a sensitive indicator of both segmental and complete biliary obstructions as the isoenzyme enters the blood by the reflux due to its increased production above the site of obstruction. If, together with the ALP increase, the abnormalities in gammaGT occur, it is assumed that ALP is of the hepatic origin.

GammaGT (gamma glutamyltransferase) is specific only to a small extent, but it is an outstandingly sensitive enzyme. Its serum activity already increases due to minimal cholestasis. Furthermore, its activity is increased by xenobiotics and alcohol. In case of ALP being normal, the increase in gammaGT is a reliable marker of alcohol abuse. A moderate increase in gammaGT is common even after the intake of a small amount of alcohol and therefore it does not necessarily have to indicate an impairment of the liver, providing all other tests are normal.

BGL (betaglucuronidase) is a lysosomal enzyme. Its increased activity in the blood already occurs in coincidence with the initial phase or moderate form of intrahepatic cholestasis. It is explained by metabolic activation of lysosomes per se without the membraneous permeability having to be necessarily impaired.

7.19 Pathophysiology of the liver

7.19.1 Acute hepatitis

Acute impairment of the hepatic parenchyma can be caused by many factors. Histologic changes in the parenchyma, however, essentially resemble in coincidence with various etiologic causes. Hepatocytes that yield degenerative changes (oedema, vacuolisation, cytoplasmic granulation) succumb to necrosis and are quickly replaced. The distribution of these changes in the parenchyma depends to a certain extent on the etiologic cause, but necrosis foremostly occurs in the zone 3. The extent of hepatocellular impairment can significantly vary in dependence on the etiologic cause and interindividually. The same factor can in one patient cause e.g. necrosis of only a small group of hepatocytes and in another it can entail an extensive necrosis of the parenchyma leading to a fulminant liver failure. Acute diseases of the liver usually yield the presence of centrilobular cholestasis. The extent of the inflammatory infiltrate varies, but portal and perportal tracts are infiltrated especially by lymphocytes.

The most frequent type of acute hepatic impairment is an inflammatory disease – acute hepatitis. Its cause can reside in: viruses (viral hepatitis, mononucleosis, cytomegaly), bacteria (leptospirosis, tuberculosis, brucellosis), toxic substances (alcohol, organic solvents, herbal poisons, drugs). In addition to the above mentioned factors, sepsis, inflammation in the abdominal cavity and inflammation in the vascular bed of the portal vein or in draining biliary pathways can evoke the so-called secondary hepatitis. In our environment the most frequent types of acute hepatitis are of viral etiology.

7.19.1.1 Viral hepatitis

Acute viral hepatitis is a systemic infection which afflicts foremostly the liver. Under common conditions none of the hepatotropic viruses damages the hepatocytes directly. The liver injury develops in consequence of the immunologic reaction between the