blood. Therefore, the increased level in AST can occur e.g. due to septicaemia, or other states in which hypoperfusion and anoxia lead to a transient impairment of hepatocytes. The recovery of circulation very quickly lowers the AST plasma level. Necrosis of hepatocytes brings about also the mitochondrial fraction, and the level of AST in blood is high.

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 synthetised 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 inevitably 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, vacuolization, 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 periportal 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

virus and the host organism. The common cause of liver impairment resides in the attack of lymphocytes to viable, antigen expriming hepatocytes. Typical morphological changes in hepatitis include infiltration of lobules by mononuclear cells (small Ly, plasma cells, eosinophils), degeneration and necrosis of hepatocytes, hyperplasia of the Kupffer cells and various degrees of cholestasis. In addition to the above mentioned changes, the regeneration of hepatocytes with the development of rosettes and pseudoacini currently take place.

- **Viral hepatitis A** (VHA) is a frequent type of viral hepatitis. It is spread world-wide and occurs in epidemies especially in children and young people. The source of infection resides in contaminated food and the transmission takes place by the oral pathway.

  The **virus of hepatitis A** is a RNA virus. Its replication takes place in the liver. Hepatitis A virus is also present in bile, stool and blood (at the end of the incubation period and in acute phase of VHA). Antibodies against the virus belong to the IgM class, in later period to that of IgG. Carriership does not exist.

  In addition to the liver, the disease afflicts also other organs, e.g. the heart, gastrointestinal tract, pancreas and spleen. The preicteric (prodromal) phase lasts for two weeks. Viraemia in this period causes anorexia, nausea, vomiting, diarrhoea, headache, malaise, and febrility. During this phase the AST serum level increases. Urine contains bilirubin and urobilinogen. Yet, the serum bilirubin does not increase significantly.

  The icteric period lasts for 2–3 weeks. The development of icterus usually brings about an improvement in the patient's subjective state. Urine becomes darker and stools are lighter due to the cholestasis. The serum bilirubin increases and its level manifests the stage of icterus. 1–2 weeks after the appearance of jaundice, the serum AST reaches its maximal values. The blood yields leukopenia with relative lymphocytosis. The liver is moderately enlarged. The **pathological changes in hepatocytes** vary and occur simultaneously. Necrosis may be of solitary, focal or diffuse characters. Simultaneously with the latter, the regeneration of some hepatocytes and activation of the mesenchyma take place. Number of cells with phagocytic abilities, including the Kupffer cells, increases. Histiocytes, plasmocytes and granulocytes enter the periportal spaces. Later, fibroblasts develop, causing thus the proliferation of collagenous fibers. This histologic picture is maintained practically until the recovery of the clinical state (6–8 weeks) takes place.

  During the subsequent period, the jaundice withdraws and in a majority of cases the disease retreats during 3–6 weeks. Simultaneously with the disappearance of jaundice, the physical and psychical activities return. Sometimes the patient still suffers from weakness, increased tiredness, arthralgia or dyspeptic disturbances for several months after the termination of the disease. This state is referred to as **posthepatitis syndrome**. It involves a functional disturbance and the afflicted patients are especially young neurovegetatively unstable people. The VHA prognosis is very good as the majority of patients are completely healthy. A severe course of the disease with fulminant hepatic necrosis and hepatic coma leading to death is exceptional (0.1 %). VHA never progresses into chronicity.

- **Viral hepatitis B** (VHB). It is estimated that the hepatitis B virus (HBV) is present in 300 millions of carriers, foremostly in Africa and the Far East. HBV is transmitted by blood (transfusions, contaminated needles) or by sexual intercourse, foremostly in homosexuals (the virus is present in the semen and saliva). The vertical transmission from mother to child during birth or soon after birth is the most world-wide frequent pathway of transmission.

  The **virus of hepatitis B** is a DNA virus. The entire virus appears in the electrone microscope as so-called Dane particle which is constituted of the internal nucleus formed by the nucleus of hepatocyte and the external superficial layer (HBsAg) formed by multiplication in the cytoplasm. The internal nucleus contains DNA, DNA-polymerase, nuclear antigen (HBcAg) and antigen e (HBeAg). Replication takes place exclusively in the liver and it is possible to assume that the virus becomes a component of the nuclear protein of the host cell. In this way it

can take part in the development of hepatic tumours – hepatomas. It is possible to detect the virus in blood in form of nuclear (HBcAg and HBeAg) and mainly superficial (HBsAg) particles. The superficial particles contain further antigenic subdeterminants (a, d, y, w, r), characterising the geofraphical differencies. In relation to hepatitis B, it is necessary to mention the **virus of hepatitis D** (delta-antigen). Hepatitis D virus is a defective RNA virus which needs the virus of hepatitis B for its own transmission. It occurs in the nuclei of hepatocytes and occasionally in the cytoplasm. It can be transiently identified in coincidence with acute VHB, especially in narcotic addicts. Its main significance resides in the fact that it can cause a severe hepatitis in the carriers of the hepatitis B virus.

The clinical picture of VHB is the same as that of VHA. Furthermore, the prodromal phase can be manifested by the immune response with transient urticaria, maculopapulose exanthem or polyarthritis afflicting small joints. The disease can proceed more severely than that of VHA. Occasionally, arthritis or glomerulonephritis occur due to the formation of extrahepatic immune complexes. The course of the disease depends on a number of factors, including the virulence of the virus and both immunocompetence and the age of the patients. The disease usually terminates by a complete recovery. Approximately 1 % of cases manifest the symptoms of fulminant hepatitis. A proportion of hepatitis cases (5–10 %) progresses to chronicity and patients become permanent carriers of the virus.

- **Viral hepatitis C** (VHC), earlier referred to as non-A, non-B hepatitis, is caused by an RNA virus and is responsible for a majority of post-transfusion hepatitis in countries where the blood is not tested for VHB markers. It also occurs in drug addicts and homosexuals. Acute hepatitis has a more moderate course than those of VHA and VHB. The extrahepatic manifestation includes arthritis, agranulocytosis, aplastic anaemia, as well as diffuse neurological problems. Fulminant hepatic failure is rare, but the progression to chronicity is frequent (50 %).

- **Viral hepatitis E** (VHE) is transmitted in faecal-oral manner and occurs in epidemies in Asia, south Africa and Mexico. It is characteristic by high mortality rate in pregnant women (20 %). A majority of cases terminate with no consequences and do not bring about chronic hepatic impairment.

Hepatitis F and G have already been described too.

7.19.2 Chronic hepatitis

The hepatitis lasting for more than 6 months is defined as being chronic. The most frequent causes of chronic hepatitis include: viruses of B and C hepatitis, alcohol, xenobiotics and autoimmune processes. The clinical signs of chronic hepatitis vary. Most frequently they involve permanent tiredness, malaise associated with depression and gastrointestinal difficulties – inappetence, nausea, meteorism. Since this disease is frequently asymptomatic, the basic criterion for the assessment of the diagnosis of chronic hepatitis resides in the persistence of histological changes. On the basis of the latter, two main types of chronic hepatitis are distinguished: chronic persistent hepatitis and chronic active hepatitis.

- **Chronic persistent hepatitis** (CPH) is a benign state with a relatively good prognosis. It is frequently asymptomatic. Laboratory tests display only a moderate increase in AST. The liver biopsy reveals the chronic inflammatory infiltrate which is present in the enlarged portal tracts. The basic architecture of the liver is however intact. Only in rare cases, solitary necroses of hepatocytes (piecemeal necrosis) or moderate fibrosis are present. This state can persist for several months or years, with no tendency of progression. A majority of patients develop neither chronic active hepatitis, nor cirrhosis.

- As well as the latter, the **chronic active hepatitis** (CAH) can similarly proceed asymptomatically, but in contrast to CPH, it is characterized by progression of the pathological process in the hepatic parenchyma which can lead to liver failure. Therefore CAH was previously referred to as chronic aggressive hepatitis. Approximately 3 % of patients with hepatitis B progress

to CAH, especially if superinfection with deltavirus is involved. In addition to hepatitis C, the further important triggering etiologic factors include also some drugs (methyldopa, isoniazid, nitrofurantoin). The main histological sign of CAH resides in minute disseminated necrosis of hepatocytes on the interface between the parenchyma and inflammatory infiltrate. The inflammatory infiltrate constituted of lymphocytes and plasma cells penetrates from the portal space into the lobule. This process brings about disruption of hepatocytic plates around the portal triads and changes the architecture of the lobules. Fibrous septa develop isolating small groups of hepatocytes.

The cellular immune mechanisms play dominant role in the pathogenesis of CAH. It is assumed that lymphocytes become sensitive to the changed or new antigens which are exprimed from the surface of hepatocytic membranes. Humoral immune mechanisms can be responsible for some extrahepatic impairments in CAH. Out of them e.g. arthritis, rash, and glomerulonephritis can take place in consequence of the deposition of the circulating immune complexes.

Since CAH is a serious progressive disease, it is important to distinguish it from CPH which does not require therapy. Untreated CAH often terminates fatally within five years, the cause of death residing in liver failure. Death in the later period usually occurs in consequence of complications associated with liver cirrhosis.

7.19.3 Acute hepatic failure

If the liver disease progresses to hepatic encephalopathy within several days or 2–3 weeks, it is referred to as fulminant hepatic failure. Fortunately, acute failure is rare and takes place due to viral hepatitis and hepatitis caused by drugs (isoniazid, antidepressives, halothane) and toxic substances (e.g. mycotoxins of Ammanita phalloides, phosphorus, carbon tetrachloride).

The development of hepatic failure significantly varies. It especially depends on the liver condition and the age of a patient. All inducing factors indeed cause identical morphological changes. Necrosis of hepatocytes is either dispersed in the entire parenchyma, or afflicts individual irregular areas. A complete destruction of the adjacent lobules with the disintegration of hepatocytes results in the collapse of the reticulin net. The portal triads remain intact.

The inflammatory reaction can be surprisingly moderate. The progressive loss of liver tissue can reduce its weight to 500 g and the liver is transformed to a small tender organ covered by a wrinkled and a too large capsule. Fulminant hepatitis is foremostly manifested by icterus, encephalopathy, coagulopathy with bleeding, renal failure with disturbances in the electrolyte balance, cardiovascular instability, ARDS, sepsis etc.. According to the severeness of the affliction and immunity abilities of the organism, the mortality rate varies between 25 and 90 per cent. If the patient survives several weeks, the regenerative abilities of the remnant hepatocytes can be applied. The regenerative process can entirely restore the former architecture of the tissue. Massive destruction of the liver, however, results in the irregular regeneration with the development of nodules (**postnecrotic cirrhosis**).

7.19.4 Chronic hepatic failure

Chronic hepatic failure develops in consequence of a wide scale of acute and chronic liver diseases. If the activity of the pathological process in these states exceeds the regenerative abilities of the liver, the hepatic functions are slowly and gradually deteriorated. Chronic hepatic failure is characterized by a slow development of symptoms, fluctuating progression, and sometimes also by a transient disappearance of symptoms.

The biochemical markers of hepatic functional impairment are accompanied especially by the neuropsychical (hepatic encephalopathy) and haematological (haemorrhage) symptoms. Bleeding is caused by a decreased synthesis of the factors of coagulation, decreased number of thrombocytes and (providing it is present) by increased pressure in the portal vascular bed. The deterioration of this state usually induced by exogenous factors can lead to hepatic coma with high mortality.

7.19.5 Hepatic cirrhosis

Cirrhosis is an irreversible change in the structure of the liver, representing the ultimate stage of the large group of liver diseases of various etiology. The most frequent cause of cirrhosis is represented by

chronical ethylism (historically referred to as Laennec's cirrhosis), progressive chronical hepatitis (especially B,C,D), endogenous metabolic impairments, long-term cholestasis (biliary cirrhosis) and venostasis due to heart failure (cardiac cirrhosis).

The diffuse alterations of the parenchyma are characterized by chronic inflammation with extensive fibrotisation and impairment of the normal structure of the liver. Hepatocytes succumb to degenerative changes, even necrosis. Proliferation of hepatocytes results in a solitary development of so called hyperplastic (regenerative) nodules. This substitution, however, is not fully functionally valuable, therefore this obsolete designation of regenerative nodules is currently abandoned. The histologic picture distinguishes:

- **micronodular cirrhosis** in which hyperplastic nodules are smaller than 3 mm. They are surrounded by fibrous septa. Cirrhosis diffusively afflicts all lobules and is most frequently caused by alcoholic impairment,
- **macronodular cirrhosis**, in which the size of nodules varies from 3 mm to several centimeters. Among the nodules it is possible to find normal lobules. This type is the most frequent consequence of hepatitis B.

Since the main problem of cirrhosis resides in the **progressive fibrosis**, it is necessary to solve the question: which factor initiates and preserves this process? In normal liver, the interstitial collagens I and III are concentrated especially in portal triads. The collagenous net among hepatocytes is constituted of fine fibers of type IV localised in space of Disse. In cirrhosis, collagens I and III accumulate in all parts of the lobule and bring about a serious restriction of blood flow and disables the diffusion of solutes between the hepatocytes and plasma. The accumulation of collagen within the space of Disse is associated with a loss of fenestration of sinusoid endothelial cells. This process then deteriorates the movement of proteins. The main source of this **excessive collagen** appears to reside in so-called Ito cells. During the development of cirrhosis these cells are activated and transformed into cells similar to fibroblasts with contractile properties, participating thus in the deterioration of the blood flow in the cirrhotic liver. The stimuli for the deposition of fibrous tissue are not yet known, but a significant role is played by mediators of inflammation (TNF-alpha, TNF-beta, IL-1). However, since fibrosis can develop without apparent inflammation, it is also necessary to admit a direct stimulation of the production and deposition of collagen by toxic substances.

The pronounced changes in the hepatic structure create the foundation for severe functional impairments. The reduction and destruction of the vascular bed brings about hypoxia of the parenchyma which is of permanent and progressive charater. This process results in a decrease in the overall metabolic capacity of the liver. The reduction of the sinusoid surface, compression of the vessels by islets or regenerating tissue and fibrotic narrowment of portal vessels represent a presupposition for the development of portal hypertension. The altered structure of the biliary tract causes impairments in bile drainage.

The symptoms of cirrhosis do not correlate precisely with the stage of impairment and the disease is often latent for a long period. Merely, unconspicuous dyspeptic difficulties arise, accompanied by physical and psychical fatigue. The fatigue and adynamia graduate in subsequent stages. Exacerbation of the disease takes place together with icterus varying in intensity. The typical changes in the skin – spider naevi are manifestant in the area of the superior vena cava (neck, chest, arms). Assumedly the cause resides in inappropriate vasodilatation or high activity of oestrogens (spider naevi are normal findings in pregnant women and they occur also in women using contraceptives). Palmar and plantar erythemas document an overall impairment of the vasomotor tonus. Leukonychia (white and fragile finger nails) documents low level of serum albumin and is not specific for the diseases of the liver. Feminisation in men characterized by gynecomastia, testicular atrophy and reduction in axillar, chest and pubic hair is common especially in alcoholic cirrhosis and haemochromatosis. It is caused not only by high level of oestrogens, but also by complex gonadal and hypothalamic dysfunction. Women with cirrhosis develop amenorrhea. Deteriorated blood coagulation is manifestant by skin haemorrhages ranging from petechiae to suffusions and gingival bleeding. **Biochemical changes do not have to be necessarily pronounced**. However, they are distinctly positive foremostly during the activation of the process. The activity of transaminases increases (especially AST). The activity of alkaline phospatases is suppressed

in coincidence with cholestasis. The concentration of albumins decreases and that of plasma gammaglobulins increases. The prothrombin time is prolonged and the concentrations of coagulatory factors (V, VII, IX and X) decrease. The blood examination displays moderate anaemia. More significant and severe biochemical findings appear in the late stage in coincidence with hepatic insufficiency.

Patients with advanced cirrhosis, regardless to the inducing cause, gradually develop syndromes which represent serious complications. Firstly, the syndrome of intrahepatic portal hypertension is involved. The further development of the disease is accompanied with symptoms of fluid retention with edema and ascites. Further deterioration of metabolic fucntions of the liver brings about hepatic (portosystemic) encephalopathy.

The intermediate cause of a majority of deaths resides in:

1. progressive liver failure
2. some of the complications in coincidence with portal hypertension
3. hepatocellular carcinoma

7.19.6 Portal hypertension

Portal hypertension is defined as a permanent increase in the pressure within the portal vein above the normal values. Normal values of the portal pressure range from 5 to 10 mmHg (0.6–1.2 kPa). Portal hypertension is considered to take place when the pressure increases above 22 mmHg (2.75 kPa, 30 cm of water column).

Portal venous system begins in the intestinal capillaries and terminates in the hepatic sinusoids and includes all veins which drain the blood from the abdominal part of the digestive tract, spleen, pancreas and gallbladder. Since the resistance of the sinusoid wall is minimal and the portal venous system has no valves, these facts imply that any increase in resistance between the splanchnic vascular bed and the right heart, retrogradely elevates the pressure in all vessels on the intestinal side from the site of obstruction. The position of the pathological resistance in relation to the sinusoids is referred to as being presinusoid, sinusoid or postsinusoid. **Obstruction in the presinusoid area** can occur before the liver (portal vein thrombosis), or in the liver before the sinusoids (e.g. in schistosomiasis). Similarly, the **postsinusoid obstruction** can be localised in the hepatic parenchyma (venoocclusive disease with affliction of the central veins), or as far as behind the liver (on the level of hepatic veins, or inferior vena cava). If the resistance in the portal system is due to hepatic cirrhosis, it is localised **on the level of sinusoids**. The compression of vessels by the islets of regenerating tissue, the reduction of sinusoid surface and fibrotic narrowment of portal vessels in this case increase the resistance and have a decisive impact on the size of portal hypertension. The portal hypertension coincides to a certain extent with an increased portal inflow. **Hyperdynamic splanchnic circulation** is currently considered to be a component of the overall hyperdynamic state with the increased stroke volume of the heart and low vascular resistance which can be observed in patients with portal hypertension. It is assumed that the development of hyperdynamic circulation is induced by several chemical mediators, e.g. vasodilatatory prostaglandins, gastrointestinal peptides, especially though by glucagon, serum bile acids and adenosine. Glucagon and bile acids enter the systemic circulation to a greater extent in coincidence with the development of the collateral circulation and has a direct vasodilatatory effect on the splanchnic arterioles. In addition to the portal hypertension, a decreased responsiveness to endogenous vasoconstricting substances (noradrenalin, angiotensin II, vasopressin) was detected. This condition is caused by postreceptor defect.

An increased pressure in the portal vein brings about the development of **collateral circulation** in the effort to deviate the blood from the high pressure portal vascular bed into the surrounding low pressure veins which merge into the inferior vena cava. The developed, so-called porto-caval anastomoses function as an advantageous shunt. The collateral vascular bed is developed in sites where the portal vascular system is in close neighbourhood with the venous system which drains the blood from the inferior or superior venae cavae. In these areas, the venous junctions which under normal conditions have no significant function, acquire the clinical impact in portal hypertension. The involved veins include the veins in submucosa of the oesophagus and stomach, veins in the submucosa of the rectum, veins of the anterior abdominal wall and the left renal vein.

The porto-caval anastomoses which develop in submucosa of the oesophagus cause the development of oesophageal varices, whereas those in the submucosa of the stomach can entail the development of gastric varices. Anastomoses in the submucosa of the rectum can rarely result in the development of haemorrhoids. Anastomoses can develop also in the anterior abdominal wall, where under normal conditions the functionless umbilical vein can act as a junction. In coincidence with portal hypertension the umbilical vein connects the portal vein with epigastric veins. The junctions between these two systems form characteristical vessels radially branching from the umbilicus – caput Medusae.

The main clinical symptoms of portal hypertension include haemorrhage from the gastrooesophageal varices, ascites, splenomegaly and hepatic encephalopathy. Their range depends to a certain extent on the development of portal-systemic collateral circulation.

7.19.7 Ascites

Ascites signifies the presence of excessive amount of fluid in the peritoneal cavity. Most frequently it develops in cirrhosis, but it can occur also in coincidence with other diseases.

Despite the fact that the prior impulse triggering the development of ascites is still not precisely known, it is proved that the accumulation of fluid is enhanced by several factors. An increased hydrostatic pressure in portal hypertension and decreased plasma oncotic pressure caused by hypoalbuminaemia in the liver diseases facilitate the transgression of fluid into the peritoneal cavity. A significant role in these processes is played by the **change in the velocity of the output and drainage of the hepatic lymph**. The thin endothelial lining of sinusoids in a healthy liver enables the leakage of plasmatic proteins already due to a small increase in sinusoid pressure. In contrast to other capillaries the oncotic pressure in sinusoids only slightly differs from the extravasal pressure and therefore a majority of fluid remains in interstitium. Under normal conditions, this fluid returns into the vessels by means of the lymphatic system of the liver. If, however, the velocity of the output exceeds the velocity of resorption by lymphatic vessels, the fluid leaks into the peritoneal cavity.

The maintainance of ascites is predominantly performed by **renal factors**. The retention of sodium and water by the kidneys is assumedly determined by systemic haemodynamic changes in cirrhosis. It foremostly involves a low peripheral vascular resistance caused by circulating vasodilatory substances. Vasodilation leads to a not complete filling of the arterial vascular space causing the barroreceptor stimulation of the renin-angiotensin-aldosteron system, sympathetic activation and the release of ADH in the effort to increase the plasma volume. The portal hypertension is then responsible for the redistribution of the maintained fluid into the peritoneal cavity. Therefore, the recovery of the circulating volume does not supervene and the stimulus of activation of the renin-angiotensin-aldosteron system persists. The velocity of ascites development varies from several days to several weeks. Ascites is predominantly accompanied by a moderate abdominal pain and overall discomfort. A pronounced ascites can cause a shortening of breath by compressing the diaphragm. However, the most severe complication leading to a higher mortality is the infection of ascitic fluid (assumedly via blood or lymph) causing the bacterial peritonitis.

7.19.8 Hepatic encephalopathy

Hepatic (portalsystemic) encephalopathy (PSE) is a dreaded complication of acute and chronic hepatic failure. It is considered to be a **complex neuropsychiatric syndrome** caused by metabolic impairment of the central nervous system and neuromuscular system. In a majority of cases, only minimal morphological changes (edema, reaction of astrocytes) are identifiable in the brain. Especially two main impairments are responsible for the development of PSE:

1. severe impairment of hepatocellular functions
2. intrahepatic, or extrahepatic shunts of portal venous blood into the systemic circulation

These two abnormalities result in the fact that nitrogen substances are absorbed in the intestine and are not sufficiently detoxicated by the liver, causing thus changes in the brain metabolism. The **entrance of toxic substances into the brain** is assumedly facilitated also by an increased permeability of the blood-brain barrier. The most aggressive toxic substance is considered to be ammonia developing in

the process of the break down of proteins by intestinal bacteria. Further factors co-acting in the development of encephalopathy are mercaptanes, free fatty acids, intestinal endotoxins, activation of the inhibitory neurotransmitter system GABA and assumedly also the accumulation of false neurotransmitters (octopamine).

Acute onset of PSE, e.g. in cirrhosis in a stable state, has a predominantly apparent inducing cause. Most frequently it involves bleeding into GIT which is a massive source of nitrogen substances absorbed in the intestine. A similar situation is developed due to a diet rich in proteins. The disturbances of electrolyte balance can significantly contribute to the development of PSE. Foremostly the hypokalemic metabolic alkalosis, but also the metabolic alkalosis alone increases the $NH_3 : NH_4$ ratio. Hypokalemia, often caused by intensive diuretic therapy, stimulates the renal production of ammonia. Further inducing factors include the drugs which affect the CNS functions, hypoxia and acute infections, assumedly by means of the protein-catabolic effect.

PSE is manifestant by a wide range of disturbances of conciousness from inconspicuous changes in behaviour through marked confusion to heavy coma. These disturbances can be accompanied by neurological symptomatology, e.g. by non-specific changes in EEG, rigidity, hyperreflexia. A very characteristical symptom is the coarse tremor of fingers, which later develops into flapping tremor (tremor of hands from the wrist). The cause of the flapping tremor is considered to reside in a sudden intermitent inhibition of the motor tonus. Alterations in personality, mood disturbancies, loss of social barriers, confusion, inability to concentrate, apraxia and daytime somnolence are further symptoms of the amount of clinical symptoms of the hepatic encephalopathy.

7.19.9 Hepatorenal syndrome

Hepatorenal syndrome signifies **renal insufficiency in the patients with a severe impairment of the liver**, whereas the kidneys do not display any morphological cause of this state. This definition involves neither simultaneous impairments of both organs, nor the cases of cirrhosis during which the circulatory collapse has brought about acute tubular necrosis with subsequent renal failure.

The renal functions promptly improve after the recovery of liver functions. The development of the syndrome is typically heralded by **oliguria**, associated with the **increase of urea and creatinine** concentration in the blood. Pathophysiology of the renal failure remains unclear. The decrease in glomerular filtration and in elimination of sodium are evident. There are hints that the pathogenetic cause can reside in the disbalance of metabolites of the arachidonic acid.

In acute hepatic failure or advanced chronic liver disease the renal insufficiency can quickly progress to death.

7.20 Jaundice

Jaundice (icterus) signifies a yellow colouring of sclerae, skin and mucosae determined by accumulation of the bile pigment – bilirubin. Jaundice develops in pathological states of various etiology. They are commonly characteristic by the **disbalance between the production and excretion of bilirubin**. Physiological level of the total bilirubin in the plasma of adults is 3–21 μmol/l. When the concentration in the plasma increases c. three-fold, bilirubin infiltrates the tissues. It accumulates predominantly in the tissues with high contents of elastine, to which it has a significant affinity, but penetrates also into the somatic fluid with high contents of proteins (e.g. exudate). The accumulation of bilirubin in organism takes place due to:

1. increased production of bilirubin – **prehepatic jaundice**,

2. hepatic impairment, providing the hepatocytes are not normally able to take up, conjugate, or secrete bilirubin, or bile, or if bile stagnates within the liver on the level of minute bile ducts – **intrahepatic jaundice**,

3. reduction or stopping of the drainage of bile due to mechanical obstruction in extrahepatic bile pathways – **posthepatic jaundice**.