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**.

7.20.0.1 Prehepatic jaundice

This group includes the impairments which develop by an excessive production of bilirubin. If the supply of bilirubin excceds the maximal conjugation capacity of the liver, it accumulates in the blood (hyperbilirubinaemia). Overproduction of bilirubin takes place due to:

- **increased haemolysis** (hereditary or acquired haemolytic anaemias, posttransfusion haemolytic reaction),
- **resorption of excessive haematomas** (injury, catheterisation, rupture of vascular aneurysm) or excessive infarction (pulmonary infarction),
- **ineffective erythropoiesis**, when the produced haemoglobin is not effective in peripheral tissues and has been broken down already in the bone marrow. This group referred to as shunt hyperbilirubinaemia, includes megaloblastic anaemia caused by the deficiency of the intrinsic factor (pernicious anaemia, resection of stomach, polyposis of the stomach) or deficiency of folic acid and vitamin B_{12} (resection of the terminal ileum, blind intestinal loop, intestinal diverticulosis, fuctional intestinal impairments). A pronounced jaundice in this group of hyperbilirubinaemia is rare.

Prehepatic jaundice is characterized by an increased level of non-conjugated bilirubin in the blood. As the liver takes up and degradates the high amount of pigment, the bile and stools are dark (pleiochromic bile, hypercholic stool). Urobilinogen produced and absorbed in the intestine in an increased amount is not taken up by overloaded hepatocytes and it appears in urine. Also in severe anaemia, when complicated by e.g. hypoxaemia, fever or vascular collapse, the liver ability to eliminate bilirubin decreases.

7.20.0.2 Intrahepatic jaundice

Due to didactic purposes it is wise to divide intrahepatic jaundice into groups according to the site of the most marked disturbance taking place during the metabolism and transport of bilirubin.

1. Disturbances of bilirubin uptake

The **Gilbert's syndrome** (icterus iuvenilis intermittens) is characterized as a functional impairment of the transport of organic anions in hepatocytes. This dominantly hereditary disease resides in the decrease of bilirubin uptake, assumedly due to a decreased binding capacity of the transport protein (ligandin). At the same time the process of conjugation is hindered due to the defect of UDP-glucuronosyltransferase (so called infantile conjugation system). This moderate hereditary disturbance is manifestant usually as late as in the second decade of life. A permanently subicteric patient develops a pronounced jaundice usually only due to stress (intercurrent infection, physical exercise, fasting, alcohol).

Transient non-conjugated hyperbilirubinaemia which develops after administration of drugs (certain tetracyclines), x-ray contrast substances, pigments (bromsulphthalein) is explained by a competitive inhibition of the ligandin. This mechanism assumedly evokes also a moderate hyperbilirubinaemia in coincidence with fasting, when the produced metabolites compete with bilirubin in binding to ligandin.

2. Impairments of bilirubin conjugation

Impairments of bilirubin conjugation develop due to absolute or relative insufficiency of UDP-glucuronosyl transferase (UDP-GT). An impairment of bilirubin conjugation most frequently occurs in newborns in whom it is already possible to find several differences:

- conjugation system during the intrauterine development of the foetus matures already in the tenth lunar months and closely after birth it is still relatively incapable of increasing its activity appropriately. Ligandin is similarly "immature".
- in this period the foetal haemoglobin is broken down implying an increased bilirubin supply
- binding capacity of serum albumin to bilirubin is lower,
- the blood-brain barrier is still not sufficiently mature which enables the entrance of bilirubin into CNS

The above mentioned facts imply that the presence of jaundice in 50 % of healthy newborns is not

considered to be a pathological state (**physiological jaundice of the newborn**). It supervenes on the second or third day after birth, and in consequence of a rapid increase in the conjugation capacity it disappears up to six days. The level of unconjugated bilirubin in the blood is on the upper limits of the physiological standard for newborn (130 μmol/l).

In the **premature infant**, the glucuronosyltransferase activity is less, and the neonatal jaundice may be more pronounced. It supervenes also on the second or third day, but fades away slower in accordance with the process of maturing of the conjugation system. The most difficult cases can yield an increase in bilirubin above the critical value of 340 μmol/l. Such values indicate that unconjugated bilirubin is apt to enter CNS. The deposition of bilirubin in the basal ganglia rich in lipids leads to the development of **bilirubin encephalopathy** (kernicterus). Kernicterus is the most severe complication of unconjugated hyperbilirubinaemia. It is manifestant by inappetence, apathy, hypotonia, decreased tendon reflexes, tonic spasms. If the infant survives, it usually remains permanently handicapped (rigidity, chorea, deafness for high tones, etc.). The danger of the development of bilirubin encephalopathy in newborn increases the presence of substances in the blood which compete with the unconjugated bilirubin in its bond to albumin (organic anions in acidosis, salicylates, sulphonamides, some antibiotics). In such a case the proportion of the free fraction of the unconjugated bilirubin is higher, and can lead to the entrance of pigment into CNS already at values of total bilirubin being 150–200 μmol/l.

Some substances of steroid nature can cause a transient inhibition of UDP-GT, assumedly by competition. A typical representation of this disturbance is **familial neonatal hyperbilirubinaemia** (Lucey-Priscoll syndrome). Essentially it is a transient inhibition of UDP-GT by steroid factor, present in the maternal serum. Jaundice appears already after birth.

In some breast-fed infants, jaundice has been ascribed to the presence in breast milk of pregnane–3 beta, 20 alpha-diol, an inhibitor of glucuronosyltransferase. Jaundice supervenes later, and persists for more than three weeks. When the infant is removed ved from the breast, the **"breast-milk jaundice"** subsides.

Hypothyreoidism delays the normal maturation of UDP-GT and the neonatal jaundice can be prolonged for weeks or months.

Crigler-Najjar syndrome is an especially severe congenital disease. It occurs in two forms:

- **Type I**, originally described by Crigler and Najjar is an autosomally recessive disease caused by the absence of the genetic equipment for UDP-GT. The unconjugated bilirubin exceeds 15–20-fold its normal values and if therapy is not applied immediately, the child dies due to the consequences of the bilirubin encephalopathy.

- **Type II** is an autosomally dominant form with a moderate clinical course. It involves a partial deficiency of UDP-GT. In comparison with form I it ussually does not occur in newborns, but in adolescents and adults. Therefore the neurologic complications are uncommon. The bile contains a variable amount of conjugated bilirubin with a significant increase in monoconjugates.

All types of jaundice of this group show an increased level of unconjugated bilirubin in the blood.

3. Impairments of elimination through the canalicular membrane

A. Isolated impairments in bilirubin secretion

Dubin-Johnson syndrome is a genetically determined disorder of the excretion of the conjugated bilirubin and other organic anions (e.g. bromsulphthalein) from hepatocytes into bile. The impairment resides in the transport systems on the canalicular membrane of the cell. The disease is characterized by chronic jaundice caused by an increased level of the conjugated bilirubin in the blood. In the liver the striking feature is the presence of a dark brown pigment in the hepatocytes localised centrilobullarly (so-called black liver). Patient with Dubin-Johnson syndrome may be asymptomatic with the exception of jaundice. Despite the icteric colouring, the patient does not suffer from pruritus, hence already the clinical picture gives the hint of isolated impairment of the excretion of pigment.

Rotor syndrome in many aspects resembles the Dubin-Johnson syndrome, however the brown pigment is not present in hepatocytes. This rare disease is inherited as an autosomal recessive trait and is genetically distinct from the Dubin-Johnson

syndrome. The presented functional hyperbilirubinaemias (Gilbert, Dubin-Johnson, as well as Rotor syndrome) have the attribute of being benign. Even a long-term observation of patients with these impairments (15 and more years) has not revealed any signs of hepatic damage.

B. Impairment of bile secretion (intrahepatic functional cholestasis)

This disease includes an extensive group of pathological states which are characterized by a decreased, or blocked transport of all components of bile through the canalicular membrane. The canalicular membrane is energetically very demanding and therefore also the most vulnerable site of the hepatocyte. The functional impairment of bile elimination comes into consideration in all states leading to hepatocyte injury. The conjugation processes do not have to be damaged for a length of time and the impairment supervenes in the later phases of cellular damage. The components of bile stagnate before the canalicular membrane and regurgitate into the blood. This type of cholestasis occurs in:

- all types of **hepatitis** (viral, alcoholic, drug-induced, toxic, non-specific)
- **cirrhosis** (postinfectious, congestive)
- **focal lesions of the liver** (toxoplasmosis, malaria, etc.)

The listed impairments of the liver are not characterized only by jaundice, but (and furthermore) by a wide scale of manifestations of functional hepatic impairment from moderate dyspepsia to hepatic coma. The decrease or even absence of bile acids in the intestine results in an disturbance in the resorption of fat and vitamins. The deficiency in vitamin K is manifestant by a coagulopathy which is enhanced also by the inability of the damaged hepatocytes to synthesize prothrombin sufficiently. Since the excretory step is the one which is rate-limiting and most readily affected by injury, significant amounts of conjugated bilirubin and bile acids reenter the systemic circulation. Later also the conjugation process becomes retarded. The cause can reside in the profound impairment of cells and/or feedback suppression of the activity of UDP-GT by the accumulated conjugated bilirubin in hepatocytes. The laboratory examinations reveal an increase in both forms of bilirubin in the blood, and that of conjugated bilirubin in urine. Stool is hypocholic or completely acholic. Urobilinogen in urine is present only if the stasis of bile is not total. In case of total stasis, the reappearance of urobilinogen in urine is a good sign of the recovery of bile flow.

4. Intrahepatic mechanic cholestasis

The cause of this type of intrahepatic cholestasis is an impairment at the level of the minute bile ducts – canaliculi and ductuli. Under the influence of pathological reactions their lumen becomes narrow by hypersensitive reaction in their walls and periductal oedema or cellular reaction in their surrounding. This mechanic obstacle of bile flow consequently brings about bile stagnation and condensation leading to the formation of bile plug.

Intrahepatic cholestasis of pregnancy (reccurrent jaundice of pregnancy) appears in a small percentage of pregnant women usually in the last trimester but may develope any time after the seventh week of gestation. It is assumed that in these women an abnormal metabolism of oestrogens produces a cholestatically effective metabolites. Jaundice often reappears not only in subsequent pregnancies, but also after contraceptives. This fact suggests an equal, or similar mechanism of cholestasis development. The clinical features consist primarily of pruritus and jaundice. Pruritus is explained by retention of bile salts while the decisive factor resides in the local increase in concentration of bile salts in the skin. These symptoms of cholestasis quickly fade out after parturition.

Drug-induced cholestasis may occur in some patients following the use of oral contraceptives (oestrogens), anabolic steroids and drugs, e.g. chlorpromazine. In contrast to cholestasis after oestrogens, the cholestasis after administration of anabolic steroids can transgress to chronicity. Chlorpromazine is a typical example for the development of idiosyncratic reaction. In about 1 % of patients receiving chlorpromazine, intrahepatic cholestasis with jaundice develops after 5 weeks of treatment. It is assumed that the metabolisation of the drug results in free radicals which on the sensitive terrain change the structure of minute biliary ducts. The walls become antigenic, which is the cause of the development of local immune reaction. The development of the idiosyncratic reaction was anticipated on the grounds of the presence of eosinophilia.

Cholestasis in the culminating phase of the viral hepatitis can be explained by the fact that the

functional impairment of the canalicular membrane which is present in hepatitis, leads to the increase in its permeability with the penetration of macromulecules and condensation of bile. The dense bile stagnates and irritates the adjacent structures thus causing inflammation and fibrosis. This condition results in the narrowment of the ducts. Despite the final functional recovery of hepatocytes this mechanical factor disables the free drainage of bile for a certain period.

Patients with intrahepatic mechanic cholestasis usually present with signs and symptoms of cholestasis, but without pronounced signs of hepatic damage (with the exception of viral hepatitis).

7.20.0.3 Posthepatic jaundice (extrahepatic biliary obstruction)

Posthepatic jaundice develops due to partial or total obstruction of extrahepatic bile ducts. It most frequently involves an obstructions of large bile ducts (common bile duct and ductus hepaticus communis). The functional reserve of the liver is large, and therefore partial enclosures result in jaundice only in cases of obstructions taking place in a larger number of biliary ducts (75 % of draining ducts under experimental conditions). Mechanical obstacle can be caused by an intraductal enclosure (stones, parasites, structures) or compression of the biliary ducts from the outside (tumours, scars). A severe and long-lasting obstacle of bile drainage damages the walls of biliary ducts by a retrograde increase in the pressure of the stagnating bile. This condition results in regurgitation of bile. After the transgression of the pressure in biliary ducts above 25 mmHg (3.1 kPa), the supervening condition then ranges from disturbances to a complete failure of hepatocytes to secrete bile. Later, the accumulation of bilirubin in hepatocytes and high pressure negatively influence also the process of conjugation.

A total enclosure of biliary pathways is characterized by a pronounced icterus, generalized pruritus and increased bleeding due to the deficiency of vitamin K. Stools are acholic and contain fat (steatorrhea). Biochemical examinations reveal an increased level of conjugated bilirubin, bile acids, cholesterol and alkaline phosphatase in the blood and bilirubin in urine. After a certain period, in accordance with the suppression of the process of conjugation, also the level of unconjugated bilirubin increases in the blood. Total enclosures do not bring about urobilinogen in urine.

7.20.0.4 Postoperative jaundice

Owing to the performance of gradually more demanding surgical interventions, the problem of postoperative jaundice appears in the centre of attention. After so-called major surgical procedures, 17 % of patients develop a moderate and 4 % exhibit a strongly pronounced jaundice. Pathogenic mechanisms participating in the development of jaundice have their foundations in the overproduction of bilirubin, hepatocellular damage and/or extrahepatic obstruction.

Overproduction of bilirubin is caused most frequently by transfusion of stored blood. After the transfusion, within 24 hours, approximately 10 % of the administered erythrocytes break down. That means that 500 ml of blood provides c. 430 μmol of bilirubin which a healthy liver eliminates without any problems. Transfusions repeated closely one after another transgress however the capacity of the liver to eliminate bilirubin. The further source of bilirubin resides in the resorption of the blood from extravascular spaces. Rarely, e.g. in patients with the glucoso-6-phosphate-dehydrogenase defect, haemolytic anaemia occurs after anaesthesia, drugs, or after surgical intervention per se.

Hepatocellular impairment varying in its degree develops due to a number of causes. It can develop as a reaction to the administered drugs or anaesthetics, e.g. halotane. Repeated anaesthesia, in rare cases, incur hepatitis which is put into association with the hypersensitivity to halotane. Moderate reactions are however more frequent, especially in obese patients as fat-soluble halotan accumulates in the fat tissue and slowly floats away. Hepatocellular necrosis may follow profound shock. With lesser degrees of hypotension or hypoxaemia, significant impairment of hepatic function may occur. Renal impairment due to hypotension and hypoxaemia may enhance the degree of jaundice because the renal excretion of conjugated bilirubin is decreased. Sepsis as well can produce the impairment of hepatocytes and bring about jaundice, often of a cholestatic type.

Extrahepatic obstruction may occur in consequence of a surgical intervention in the abdominal cavity.