Symptoms and Syndromes

12 Jaundice

12 Jaundice

► For doctor and patient alike, the phenomenon of **jaundice** evokes the idea of a disease of the liver or of the bile ducts. • Indeed, awareness of the condition of jaundice is undoubtedly as old as medical science itself. (s. pp 6, 7) • Thus Aretaios of Cappadocia (circa 200 AD) described icterus (jaundice) in such an exact way that his definition can be accepted even today: *"If a distribution of bile, either yellow, or like the yolk of an egg, or like safron, or of a dark-green colour, takes place from the viscus, over the whole system, the affection is called icterus".*

1 Definition

The term **jaundice** or **icterus** is used to depict the yellowish discolouring of the skin, mucous membranes and body fluids evident as a result of hyperbilirubinaemia in excess of 2.5 mg/dl, with subsequent deposition of bile pigments in tissue which is rich in elastin. In cases of severely impaired liver function or renal insufficiency, bilirubin values can rise dramatically. • The term **subicterus** is used to describe a low-grade icteric condition occurring in the region of the white sclera with a serum bilirubin value of >1.8 mg/dl; for this reason, it is also known as *scleral icterus.* (s. pp 84, 106, 224)

Jaundice is a **disorder in the metabolism of bilirubin** (s. p. 37); it is thus neither directly related to the bile acid metabolism (s. p. 39) nor to *cholestasis. (see chapter 13)* • **Jaundice is a symptom and not a disease. It can occur with and without cholestasis.**

2 Localization of bilirubin

Bilirubin is a hydrophobic organic anion. It shows a varied affinity to the individual tissues, so that differentiation can be made between bilirubinophilic and bilirubinophobic tissues (F. Rosenthal, 1930). Above all, tissue which is rich in elastin (skin, sclera, intima of the vessel wall, ligaments) absorbs bilirubin rapidly and intensively. Jaundice is thus first manifested at the sclera, where it remains detectable longest. Subsequently, the face, chest and abdomen as well as inner organs (such as the liver) and, to a lesser degree, the extremities are the most affected areas. Cartilage and nerve tissue are rarely yellow-coloured as a result of the icteric condition, and if so, only to a minor degree. The soles of the feet and palms of the hands only show slight icteric staining, if at all. • Saliva, lacrimal fluid and gastric juice are not stained icteric-yellow. Cerebrospinal fluid occasionally contains bilirubin and takes on a yellow hue, such as in hepatic coma (D.S. Amatuzio et al., 1953) or Weil's disease (W.H. Cargill Jr. et al., 1947).

In obstructive jaundice, bilirubin enters the lymphatic vessels, so that the lymphatic fluid is already icteric when it enters the thoracic duct. Exudates and transudates are always yellow-coloured in correlation to the serum bilirubin values, although they contain less bilirubin (in accordance with their lower protein content) than the serum itself. Due to their larger protein content, exudates are more icteric in colour than transudates. • Icteric colouring is hardly or not at all evident on paralyzed parts of the body. It would appear that bilirubin concentration also depends on normal nerve function. As a rule, jaundice is not detected in the region of an oedema (J. Meakins, 1927; J.H. Page, 1929).

3 Different shades of jaundice

► The respective colouring of jaundice depends on a number of different factors. The reddish shade in hepatitis patients used to be defined as **rubin jaundice;** the lemon yellow with a reddish hue observed in haemolysis was known as **flavin jaundice** (*flavus* = Latin for *yellow*) and the greenish shade observed in long-term cases of obstructive jaundice was called **verdin** or **green jaundice.** In obstructions lasting for several months, greyish-green to greenish-black tints were observed with jaundice, resulting in the term **melas jaundice** (from the Greek word *melas*, meaning *black*). (s. p. 84) • These colour differences, as interesting as they might be in the individual case, are of little help in differentiating between the various types of jaundice – ***nearly every shade is possible in every single jaundice patient!***

Differential diagnosis: Jaundice has to be clearly delimited from **carotene jaundice** or **xanthodermia**, which may appear after an abundant ingestion of carrots, blood oranges and mangoes or the use of medication and cosmetic agents containing carotene. • **Lycopenaemia** can occur after an excessive ingestion of tomatoes. • A yellowing of the skin similar to that seen with increased serum bilirubin levels sometimes appears after an intake of **quinacrin** or **busulfan**.

4 Clinical classification of jaundice

► The **classification of jaundice** introduced by J.W. McNee (1923) still holds true today. It distinguishes between (*1.*) haemolytic, (*2.*) parenchymal, and (*3.*) obstructive. (s. p. 7) • Equally important is the classification of jaundice put forward by H. Ducci (1947), which comprises various forms (*1.*) prehepatic, (*2.*) intrahepatic, and (*3.*) posthepatic.

Forms: In line with their *mechanisms of development* and *localization*, the various forms of jaundice can be subdivided into a well-established classification scheme consisting of three groups. (s. tab. 12.1).

1. Prehepatic jaundice
= overproduction jaundice
= repression jaundice

2. Intrahepatic jaundice
a. Dysfunction of bilirubin transport
- diminished bilirubin uptake in the liver cell = absorption jaundice
- dysfunction of intracellular bilirubin transport (i.e. premicrosomal)

b. Dysfunction of bilirubin conjugation
= conjugation jaundice (i.e. microsomal)
- congenital
- postpartal
- acquired

c. Dysfunction of bilirubin excretion
= excretion jaundice (i.e. postmicrosomal)

3. Posthepatic jaundice
= obstruction or regurgitation jaundice
a. Extrahepatic jaundice
b. Intrahepatic jaundice

Tab. 12.1: Localization and developmental mechanisms of the various types of jaundice

Three types of bilirubin are found in the serum: unconjugated (indirect), conjugated (direct), and covalent albumin-bound bilirubin (direct). *(see chapter 3.3)*

(*1.*) **Unconjugated** bilirubin IXα is almost insoluble in water and therefore reversibly bound to albumin in the blood (< 1% free bilirubin remaining). Bilirubin enters the hepatocytes via transporters (= bilitranslocases) and becomes dissociated from albumin. Transport inside the hepatocytes is facilitated by the two carrier proteins, Y (= ligandin) and Z (= transport reserve).

(*2.*) **Conjugated bilirubin** is now formed in both rough and smooth ER, where it is conjugated with glucuronic acid. The result is a water-soluble bilirubin monoglucuronide and subsequently the respective diglucuronide. This glucuronidation process is catalyzed by uridine diphosphate-glucuronosyltransferase, which occurs as two isoenzymes. Excretion of bilirubin into the bile (20−40% as monoglucuronide, 60−80% as diglucuronide, 0.5−2.0% as unconjugated bilirubin) is actively carried out by ATP-dependent transporters (cMRP2, cMOAT). Bilirubin is transported into the bowels in mixed cells (together with bile acids, cholesterol and phospholipids). Bacterial glucuronidases then produce apolar, water-insoluble, unconjugated bilirubin, which is converted to urobilinogen by bacterial reductases.

(*3.*) **Delta bilirubin** is a small amount of conjugated bilirubin in the serum irreversibly bound to albumin by covalent bonding. In laboratory tests for bilirubin levels, delta bilirubin is determined together with conjugated (direct) bilirubin. • In pronounced and prolonged jaundice, the delta bilirubin level rises proportionally. The half-life of conjugated (direct) albumin-bound bilirubin is about 17 days, which is the same as albumin. This accounts for the relatively slow regression of jaundice.

Unconjugated (= indirect) hyperbilirubinaemias

1. Bilirubin overproduction
- Haemolysis
- Dyserythropoiesis
- Jaundice from pulmonary infarction, from large haematoma, from repeated blood transfusions, occasionally in postoperative icterus
- Repression of bilirubin from its albumin binding by endogenous or exogenous substances

2. Diminished bilirubin uptake
- Long periods of fasting
- Flavaspidic acid, rifampicin, *etc.*
- Sepsis
- Right heart failure
- Portacaval shunt
- Gilbert-Meulengracht syndrome (on occasions)

3. Diminished bilirubin storage

4. Dysfunction of bilirubin conjugation
- Congenital disorders
  - Crigler-Najjar syndrome
  - Gilbert-Meulengracht syndrome
- Severe neonatal icterus
- Acquired disorders
  - medication-induced toxicity (e.g. ethinyloestradiol, gentamycin)
  - hyperthyroidism
  - hepatocellular diseases

Mainly conjugated (= direct), on occasions also combined, hyperbilirubinaemias

1. Diminished bilirubin excretion
- Congenital dysfunctions
  - Dubin-Johnson syndrome
  - Rotor syndrome

2. Dysfunctions of the hepatocytes
- Acquired dysfunctions
  - acute viral hepatitis
  - acute liver failure
  - liver cell necrosis in severe shock
  - chronic aggressive hepatitis
  - liver damage due to alcohol toxicity
  - pronounced storage diseases
  - severe fatty liver
  - liver cirrhosis
  - congestive liver
  - toxic liver damage

3. Biliary obstruction
- Extrahepatic obstruction
- Intrahepatic obstruction
  - mechanical
  - toxic

4. Special forms
- Recurrent intrahepatic cholestasis
- Recurrent cholestasis in pregnancy
- Postoperative jaundice (on occasions)

Tab. 12.2: Different forms of jaundice classified in relation to the metabolic disorder of bilirubin and glucuronidation of bilirubin

Bilirubin conjugation: Another way to subdivide the different forms of jaundice is based on bilirubin conjugation, which enables all forms of jaundice to be classified into **two systems:** unconjugated and conjugated forms of hyperbilirubinaemia. This particular systematization can result in overlapping terminology or produce pathogenetic combinations. (s. tab. 12.2)

4.1 Prehepatic jaundice

Haemolytic syndrome: Prehepatic jaundice is usually generated by haemolysis. Overproduction of bilirubin results in unconjugated hyperbilirubinaemia, whereby the serum bilirubin level is rarely in excess of 5 mg/dl. *Unconjugated bilirubin* cannot pass through the kidney, so that no traces of bilirubin are detectable in the urine despite the icteric state. • The bile is pleiochromatic and lithogenic. Chronic prehepatic jaundice can give rise to cholelithiasis due to the formation of pure pigment gallstones. In severe cases of haemolysis, the *conjugated bilirubin* in the serum may also increase, so that bilirubin is now detectable in the urine. As a result of haemolysis-related hyperbilirubinaemia, increased formation and renal excretion of *urobilinogen* occur. (s. tabs. 5.8; 12.1) (s. pp 38, 106) (s. fig. 5.3)

Causes: Apart from the multicausal facets involved in the haemolytic syndrome or the disorders leading to haemolysis (e. g. erythrocyte defects, toxins, noxae, antibody-mediated or mechanical factors), other causes of prehepatic jaundice are worthy of mention:

(*1.*) **Dyserythropoiesis** refers to an increasing presence of abnormal erythrocyte precursors in the bone marrow and spleen (with splenomegaly, but no hepatomegaly) due to ineffective erythropoiesis and early labelled bilirubin production *(primary shunt hyperbilirubinaemia)*. Jaundice is indicated by serum bilirubin levels of 1.5−8.0 mg/dl between the ages of 20 and 30. Levels of urobilinogen in the urine are elevated, and normoplastic erythroid hyperplasia occurs in the bone marrow. Prognosis is good. (3, 10)

(*2.*) **Pulmonary infarction jaundice** following extensive haemorrhagic pulmonary infarction with haemolysis of the erythrocytes which have passed into the alveoli.

(*3.*) **Haematoma jaundice** with retrogression of large haematomas due to the fact that 1 litre of blood produces about 5 g bilirubin, which is 20 times the normal daily bilirubin production.

(*4.*) **Postoperative jaundice:** In some cases, postoperative hyperbilirubinaemias may also be caused by haemolysis, in particular when unconjugated bilirubin is detectable. (2, 7, 15)

(*5.*) **Blood transfusions:** Haemolysis is due to the shortened lifespan of transfused erythrocytes.

(*6.*) **Displacement of bilirubin** from its albumin bond. Various endogenous substances (e. g. long-chain fatty acids and bile acids) or exogenous compounds (e. g. medication, such as ampicillin, ajmaline, quinidine, furosemide, indomethacin, probenecid, rifampicin, sulphonamide, etc., and X-ray contrast media) can compete with bilirubin, not only with respect to its specific binding site, but also for its carrier protein.

Haemolysis: Irrespective of the aetiology and pathogenesis of haemolysis, certain *symptoms* are generally observed. (s. tab. 12.3)

1. Serum bilirubin ↑
− mainly indirect bilirubin, seldom > 5 mg/dl
2. Urobilinogenuria +, bilirubinuria +
− only in severe haemolysis
3. $LDH_{1,2}$ ↑
4. Haptoglobin ↓
5. LDH/GOT quotient > 12
6. Reticulocytes > 20‰
7. Splenomegaly: frequent
8. Liver biopsy: normal
− possible detection of haemosiderin
9. Erythropoiesis in the bone marrow ↑

Tab. 12.3: General signs of haemolysis

4.2 Intrahepatic jaundice

Multiple influences may cause a disorder in the metabolism of bilirubin inside the hepatocyte. This dysfunction may be localized in the *premicrosomal, microsomal* or *postmicrosomal* region of the liver cell. (s. tab. 12.2)

(*1.*) **Diminished bilirubin uptake** in the liver cell may result jaundice. This is possibly caused by bile acids, medication or chemicals (e. g. vermicides such as flavaspidic acid). Extensive periods of fasting (N.A. Gilbert et al., 1907; E. Meyer et al., 1922) (< 300 calories/day, > 48 hours) and toxaemia with sepsis (14, 18, 23) can also give rise to unconjugated hyperbilirubinaemia.

(*2.*) **Reduced storage of bilirubin** can be caused by the bilirubin competing with exogenous substances for binding to the Y protein or with long-chain fatty acids for binding to the Z protein. Thus bilirubin may diffuse back from the liver cell into the blood.

(*3.*) **Dysfunction of the glucuronosyltransferase activity** is mainly attributed to congenital defects, resulting in functional, unconjugated hyperbilirubinaemias. In contrast, acquired impairment of glucuronidation as a result of medicaments (chloramphenicol, pregnanediol, testosterone, etc.) or due to hypothyroidism is deemed to be rare. This particular form of jaundice shows an increase in indirect bilirubin without occurrence of bilirubinuria. Medication-induced jaundice is rarely due to an inhibition of glucuronosyltransferase activity, because other enzyme systems in the biotransformation process (phase 2) show overlapping effects.

(*4.*) **Dysfunction in the secretion of bilirubin** is also a cause of jaundice. The mechanisms involved in the excretion of bilirubin into the biliary capillaries are, however, largely unresolved, and thus the starting points of the disruptive factors remain unknown. This dysfunction is a postmicrosomal regurgitation jaundice with higher levels of both unconjugated and conjugated bilirubin.

► *Congenital defects* include the Dubin-Johnson syndrome and Rotor syndrome. (s. tab. 12.4) Both of these diseases present a genetically determined disorder in the secretion of bilirubin.

► *Acquired liver diseases* (e. g. cirrhosis, liver cell necrosis in severe shock (11), pronounced toxic liver damage, cardiac congestion (11, 17), alcohol-related and medication-induced diseases of the liver) very frequently

cause jaundice as a result of disorders in the secretion of bilirubin. The uptake, storage and conjugation of bilirubin are usually not impaired. A number of medicaments merely produce elevated bilirubin levels (so-called *jaundice type*). • Intrahepatic jaundice − with and without cholestasis − is most frequently attributed to acquired defects of the respective functions of the liver cell as a result of pronounced liver damage. Conjugated (sometimes even unconjugated) hyperbilirubinaemia is evident in connection with bilirubinuria and urobilinogenuria. The greater the liver damage, the higher are the frequency and degree of severity of jaundice (possibly even with additional cholestasis).

► *Additional cholestasis:* Isolated defects in the transport mechanisms of bilirubin not only display jaundice, but also an impairment in bile secretion. The outcome is additional intrahepatic, nonobstructive cholestasis.

4.3 Posthepatic jaundice

This form of jaundice is initiated by a *mechanical obstruction* in the region of the extrahepatic or intrahepatic bile ducts, which is why the terms "mechanical jaundice" or "obstructive jaundice" are also common. The congestion of the bile flow is either *incomplete* or *complete*. Bile stasis results in dilation of the extrahepatic and intrahepatic bile ducts, allowing *hepatomegaly* to develop. (8, 9, 16, 19) (s. tab. 12.1)

Histologically, obstructive jaundice is characterized by biliary thrombi in the canaliculi as well as the storage of bile pigments in hepatocytes and Kupffer cells. These changes are most pronounced at the centres of the lobules, since there is less chance of outflow here than in the lobular periphery.

Biochemically, a change in structure relating to the mucopolysaccharides (neuraminic acid?) and monohydroxy bile acids probably accounts for the formation of biliary thrombi. Some of the "underhydroxylated" bile salts appear in crystalline form; the bile becomes increasingly viscous and its flow is impeded. This defect in the excretion of bile salts culminates in dysfunctions in the secretion of bilirubin, which is why bilirubin is regurgitated into the blood. The bile which accumulates in the bile ducts ultimately becomes mucous and white because of the reabsorption of bile pigments by the epithelia of the small bile ducts.

Extrahepatic obstructive jaundice is caused by stenosing processes. The region of Vater's papilla is particularly affected, for example by inflammations, stones, duodenal diverticula, carcinoma, parasites, cicatricial stenosis or adenomatosis. In this respect, special mention should also be made of carcinoma, cicatricial strictures and gallstones (s. figs. 8.14, 8.15; 33.15, 33.16), compression of the common bile duct due to a cystic duct stone (= *Mirizzi syndrome*), haemobilia, and various parasites − such as Ascaris lumbricoides (s. fig. 25.8!). All of these disorders can be found in the area of the extrahepatic bile ducts. (1, 9, 19)

Intrahepatic obstructive jaundice relates to the intrahepatic bile ducts, which can be blocked, above all *mechanically*, by inflammatory processes (cholangitis, primary biliary or primary sclerosing cholangitis), intrahepatic stones, granulomas, tumours, cysts, amyloid degeneration, eosinophilic gastroenteritis, and cystic fibrosis of the pancreas − to name but a few examples. • In addition, biliary obstructive jaundice can also be caused by *drug-induced toxicity*, e.g. with C_{17}-substituted steroids, erythromycin estolate, chlorpromazine, chlorpropamide, ajmaline, halothane, methylthiouracil. • Further intrahepatic forms of obstruction include recurrent intrahepatic cholestasis and recurrent cholestasis in pregnancy. (s. tab. 12.4)

Special forms: There are a multitude of factors involved in the pathogenesis of intrahepatic *benign postoperative jaundice;* hypoxia, hypotension, haemolysis, toxins, sepsis and medicaments are just a few of them. (1, 5, 6, 14, 18, 23) • Likewise, jaundice in *intensive-care patients* (1, 2, 7, 15) as well as after long-term *total parenteral nutrition* belong to this category. (1, 4)

5 Functional hyperbilirubinaemias

Hyperbilirubinaemia relates to functional disorders in the hepatocellular metabolism of bilirubin − with and without cholestasis (W. Siede, 1957). This means either dysfunctions regarding bilirubin conjugation (= *conjugation jaundice*) or bilirubin excretion (= *excretion jaundice*).

Unconjugated hyperbilirubinaemias

As a result of impaired bilirubin conjugation, unconjugated lipophilic bilirubin IXα increases (80−85% of the total bilirubin gives rise to an *indirect diazo reaction*). This free bilirubin passes unhindered through biological membranes and has a toxic impact on cells. Many factors may affect the various stages of the metabolic process, which is incomplete up to this point. Cholestasis is absent. (47, 62) (s. tab. 12.4)

5.1 Neonatal and infant jaundice

5.1.1 Physiological neonatal jaundice

In about 90% of all neonates, jaundice occurs after the first two to five days of life and rarely exceeds 6 mg/dl serum bilirubin. In premature infants, bilirubin levels can rise to 10−12 mg/dl. • The **cause** is related to various factors: (*1.*) reinforced degradation of haemoglobin as a result of the short erythrocyte survival span of 70−90 days (120 days in adults), (*2.*) reduction in cellular transport proteins, above all ligandin, (*3.*) deficiency of uridyltransferase and glucuronosyltransferase, and (*4.*) increasing intestinal absorption of meconium bilirubin. After about ten days, newborn jaundice subsides with

Unconjugated hyperbilirubinaemias
= indirect positive diazo reaction

1. **Neonatal jaundice**
   Neonatal
   - Physiological neonatal jaundice
   - Jaundice in pyloric stenosis
   - Jaundice in intestinal obstruction
   - Blood group incompatibility
   - Hereditary haemolytic anaemias
   - Breast-milk jaundice

   Connatal-hereditary
   - Lucey-Driscoll syndrome
   - Zellweger's syndrome (s. p. 242)
   - Infantile Refsum's disease (s. p. 242)
   - Hereditary haemolytic anaemia
   - Dyserythropoiesis
2. **Crigler-Najjar syndrome**
   - Type I
   - Type II (= Arias syndrome)
3. **Gilbert-Meulengracht syndrome**

Conjugated (partly combined) hyperbilirubinaemias
= direct positive diazo reaction

1. **Dubin-Johnson syndrome**
2. **Rotor syndrome**

Conjugated (partly combined) hyperbilirubinaemias with elevation of biliary acids *(see chapter 13)*

1. **Recurrent intrahepatic cholestasis in pregnancy**
2. **Recurrent intrahepatic cholestasis**
   - Benign forms
     - *Summerskill-Tygstrup* type
     - *Aagenaes* type
   - Progressive form
     - Byler's syndrome *(Clayton-Juberg type)*
3. **Idiopathic connatal or neonatal hepatitis**

Tab. 12.4: Functional, partly neonatal, partly connatal-hereditary hyperbilirubinaemias

out any further consequences. Bilirubin also acts as an antioxidant and can thus provide protection from oxygen radicals, if necessary. • Peripartal complications can, however, reinforce or prolong this state. This may occur in infantile hypothyroidism or when medication is administered directly to the infant as well as via breast milk (particularly when bilirubin is displaced from its albumin binding by drugs). In more pronounced jaundice, phototherapy and an increase in the oral intake of fluids may be advisable. (45, 48, 51, 56, 61, 71)

5.1.2 Kernicterus

Kernicterus may occur as the result of immaturity of the blood-brain barrier in *severe neonatal icterus* and can occasionally be found in *premature infants* as well, with bilirubin levels usually higher than 20 mg/dl. Unconjugated bilirubin is deposited in the basal ganglia of the hippocampus and the hypothalamus nuclei as bilirubin-phosphatidylcholine precipitate, where it gives rise to neuronal necroses. *Risk factors* (e. g. asphyxia, acidosis, hypothermia, hypoglycaemia, sepsis with lower UPT activity, and medication) promote the occurrence of the dreaded kernicterus. • In clinical terms, sucking weakness, vomiting, attacks of fever, convulsions, reflex anomalies, shrill shrieking, apathy and muscular hypotension can be observed, with subsequent muscular hypertonicity, cramps, opisthotonus, strabismus, nystagmus and apnoea. The lethality rate is about 75%. Survival is accompanied by cerebral paresis, deafness and retardation. • *Therapy* focuses on exchange blood transfusions, plasmapheresis and phototherapy (430−470 nm; 8−12 hours daily). (13, 25, 28, 63, 68, 73).

5.1.3 Lucey-Driscoll syndrome

This is a familial form of neonatal hyperbilirubinaemia (J. F. Lucey et al., 1960) (55) and can probably be attributed to the inhibitive effect of a progestagen steroid in the maternal blood serum, which impedes bilirubin conjugation. Babies show sucking weakness. Bilirubin values can be in excess of 6 mg/dl. This disorder, which occurs from approximately the second day of life onwards, regresses after two to three weeks. There is no hepatomegaly or splenomegaly; bilirubin and urobilinogen cannot be detected in the urine. The prognosis is good. In severe (extremely rare) cases, exchange blood transfusions may be indicated.

5.1.4 Breast-milk jaundice

Prolonged neonatal breast-milk jaundice is found in 0.5−1.0% of all breast-fed infants as from the fourth day and within the first two weeks of life. Bilirubin levels are drastically elevated (15−25 mg/dl). Nevertheless, this clinical picture does not generally give rise to kernicterus. Even if breast-feeding is discontinued immediately, the condition can take up to 10 weeks to regress. Possible causes are long-chain fatty acids or a pregnane derivative (pregnane-3-α-20β-diol) in the breast milk; this steroid inhibits glucuronosyltransferase activity. Apart from that, intestinal bilirubin uptake is elevated. (24, 42, 74, 75)

5.1.5 Blood group incompatibility

Rh-erythroblastosis occurs in 0.2‰ and ABO erythroblastosis in 0.6% of all pregnancies. In clinical terms, the course of the latter disease is usually more moderate. Due to severe haemolysis, unconjugated bilirubin levels rise rapidly, often reaching relatively high values. • *Therapy* includes phototherapy, exchange blood transfusions and administration of immunoglobulin (500 mg/kg BW).

5.1.6 Hereditary haemolytic anaemia

Thalassaemia, spherocytosis, sickle-cell anaemia and glucose-6-phosphate dehydrogenase deficiency are rare causes.

5.1.7 HELLP syndrome

Pre-eclampsia is characterized by hypertension, proteinuria and oedema. It develops in 3−5% of primiparas

(0.5 % in multiparas) from the second trimester of pregnancy. The liver is involved in 10−20% of cases (elevated transaminases). • **Eclampsia** is associated with additional features, such as seizures and/or coma (0.1−0.2% of pregnancies). The liver is involved in 70−90% of cases. There are elevated liver enzymes as well as portal/periportal infiltrates and cell necroses. • **HELLP syndrome** is a complication of (pre-)eclampsia. It comprises **h**aemolysis (s. tab. 12.3), **e**levated **l**iver enzymes and **l**ow **p**latelets. Usually, the HELLP syndrome develops in the third trimester, but, in about 30% of cases, it is postpartal. All patients show damage to the vascular epithelium and activation of the coagulation cascade (D-dimer is elevated in 40−50% of cases), resulting in deposition of fibrin along the sinusoids and development of microthrombi. Additionally, there are ischemic necroses of hepatocytes (partially confluent); haemorrhages and, occasionally, haematomas are observed beneath the liver capsule, with the danger of spontaneous rupture. • *Treatment* is aimed at controlling hypertension (e.g. nifedipine, because this drug also has a therapeutic effect on the liver). Prednisolone may be indicated. Delivery must be made immediately after fetal lung maturity has been determined.

5.1.8 Crigler-Najjar syndrome

► In 1952 the clinical picture of this congenital, familial, nonhaemolytic type of jaundice was described by the American paediatricians J.F. Crigler and V.A. Najjar (31).

The **cause** is a hereditary recessive (or dominant in type II) autosomal deficiency in UDP-glucuronosyltransferase. Consanguinity is common within the families affected. The gene is located on chromosome 2.

Type I: This (rare) Crigler-Najjar syndrome can be attributed to the *almost total lack* of the two isoenzymes in bilirubin UDP-glucuronosyltransferase activity as a result of (homozygous) mutations in UGT-1A1 locus. Consequently, hepatic bilirubin clearance is reduced to 1−2% of the standard rate. Bilirubin is excreted as unconjugated bilirubin IXα or in the form of polar diazo-negative metabolites. Because of the absence of conjugation, severe unconjugated hyperbilirubinaemia with bilirubin values of 18−50 mg/dl occurs during the first days of life. Within a few days, kernicterus develops with pronounced neurological disorders. (50) Stools and urine are of normal colour, the bile is colourless. The liver and spleen are not enlarged. All hepatic laboratory parameters are normal. Except for the presence of biliary thrombi, the histology of the liver is quite regular. As a result of the biliary thrombi in the dental canaliculi, the teeth can take on a yellow colouring, and enamel hypoplasia appears. • The *course of disease* is progressive and generally lethal. The mean life expectancy ranges between 6 and 18 months. Only a few of the 150−200 patients whose case histories have so far been published reached puberty. Recently, however, a successful pregnancy was observed. (36) • *Therapy* consists of exchange blood transfusions and plasma separations as well as intensive phototherapy (8−12 hours daily), possibly in combination with cholestyramine, agar, zinc and calcium carbonate or calcium phosphate. Indol-3-carbinol is also recommended as an inductor of CYP 450-1A1/-1A2. Liver transplantation may be indicated. (72)

Type II: In this Crigler-Najjar syndrome (I.M. Arias, 1962) *(Arias syndrome)* (26), glucuronosyltransferase activity is *merely reduced*, since only one isoenzyme has a (heterozygous) defect. Bilirubin conjugation is only minimally restricted. Bilirubin is largely excreted as monoglucuronide. The uptake of bilirubin into the liver cell might also be impaired. Jaundice generally occurs within the first year of life, but also during the following 20−30 years. (28) Bilirubin values fluctuate between 6 and 20 mg/dl. A more pronounced rise in bilirubin levels can be caused by various stress factors (e.g. fasting, infections, acidosis, metabolic dysfunctions). In such cases, kernicterus occasionally occurs. Like type I, type II does not display any particular stigmata: the colour of the stools and urine, the size of the liver and spleen as well as the laboratory parameters are normal. Now and again, histology displays biliary thrombi while, as with type I, hypertrophy of the smooth endoplasmic reticulum and of the Golgi apparatus is also in evidence. • The *course of disease* is more moderate, so that prognosis is usually good. Nevertheless, repeated attacks of kernicterus can culminate in permanent neurological damage (intention tremor, changes in the EEG, impaired intelligence). • As *therapy*, phenobarbital (3 × 60 mg) in combination with calcium phosphate has proved useful. Phototherapy, also in combination with albumin infusions, is likewise indicated. (13, 28, 36) Alternatively, phenytoin or phenazone can be applied. The effect is derived from the induction of the glucuronidation enzyme and the enhancement of the synthesis of the Y protein. Careful guidance of the patient is important, particularly in order to avert attacks of kernicterus. (40, 41, 45, 46, 48, 65, 71, 77)

5.2 Jaundice in adults

5.2.1 Gilbert-Meulengracht syndrome

► In 1901 A. Gilbert and P. Lereboullet described a clinical picture using the term *cholémie simple familiale.* (38, 39) The *icterus intermittens juvenilis* (59) described by E. Meulengracht in 1939 (subsequently termed familial, nonhaemolytic jaundice or constitutional hyperbilirubinaemia) proved to be identical.

The **frequency** of this harmless disorder in the metabolism of bilirubin is quite high: it affects 5−12% of the population. The syndrome is 4 times more common in men than in women. Frequency in the affected families lies between 5% and 55%. • *Genetic transmission* is dominant autosomal with differing degrees of penetrance, which accounts for the heterogeneous clinical picture. Sporadic occurrences of this syndrome have also been observed. The gene is located on chromosome 2.

The **pathogenesis** is characterized by several mechanisms: (*1*.) elevated production of hepatic haem bilirubin; (*2*.) in some 60% of the patients, minor haemolysis is evident due to a lower survival span of erythrocytes; (*3*.) the activity of the glucuronosyltransferase is diminished (by about one third of the norm) due to mutations in UGT-1A1 locus, and there is above all a deficiency in monoglucuronosyltransferase activity, because bilirubin monoglucuronide excretion in the bile is considerably higher than is the case in healthy persons; (*4*.) disorders in membrane fluidity are responsible for reduced bilirubin uptake in the hepatocytes. Ligandin and Z protein levels in the hepatocytes are reduced. • However, none of these mechanisms in itself provides an explanation for the symptoms of the Gilbert-Meulengracht syndrome.

The **subjective complaints** of the patients are reflected in irritability, moodiness, fatigue, vegetative dysfunctions, epigastric discomfort and abdominal bloating. Such complaints, however, show no correlation with the intensity of hyperbilirubinaemia. It is still not clear whether these ailments can be regarded as concomitant symptoms (= epiphenomena) or as a sequela (= hypochondriac reaction) of jaundice.

The **clinical picture** is characterized by intermittent jaundice with bilirubin levels of 1.5 to 2.5 mg/dl; there are also phases when normal values are registered. Increased bilirubin values are not only discernible after fasting and physical exercise, but also as a result of infections, alcohol consumption, menstruation, medication and severe stress. Bilirubin levels fluctuate considerably, even during the course of several days. This syndrome usually becomes manifest between the ages of 15 and 30. It is rarely found in neonates or infants. There are no further findings: liver and spleen are normal in size; urine and stools show no noticeable changes in colour; transaminases are regular, and cholestasis is not detectable. Generally, there are no signs of haemolysis, except to a slight extent in patients with higher bilirubin values. Only in 20−40% of cases is it possible to find a defect in the uptake of organic anions (e. g. indocyanine green). (57) However, reduced glucuronidation of certain medicaments was observed (e. g. acetaminophin, clofibrate, rifampicin, tolbutamide). (32) Gilbert's syndrome is only seen as a clinically significant complication when it occurs together with thalassaemia or simultaneous ingestion of ifinotecan.

The **diagnosis** is founded on: (*1*.) normal transaminase values, (*2*.) regular ultrasound findings, and (*3*.) an elevated level of unconjugated serum bilirubin. • The diagnosis can be confirmed by various laboratory parameters, findings or tests:

(*1*.) Serum values of bile acids, haptoglobin and reticulocytes are normal.

(*2*.) The monoglucuronide/diglucuronide quotient is elevated.

(*3*.) Fasting (<400 calories per day for 2 days) raises bilirubin levels to 2 (−3) times the initial value.

(*4*.) Maintaining a diet normal in calories yet strictly lipid-free for 2 or 3 days can cause bilirubin levels more or less to double.

(*5*.) Rigorous physical exercise (sports) for 1 or 2 days results in noticeably increased bilirubin values.

(*6*.) The nicotine acid test (50 mg nicotine acid i.v.) produces a rise in bilirubin of more than 0.9 mg/dl in excess of the initial value, measured at 4 hours after the injection. The specificity and sensitivity of this test are almost 100%. (36, 44, 66)

(*7*.) Administration of phenobarbital (3 × 60 mg/day) leads to a decrease (possibly normalization) in bilirubin values.

The **histology** of the liver is normal. An accumulation of intralobular bile ducts (H. Thaler, 1982) is noticeable. There may be centroacinar deposits of higher amounts of lipofuscin. An increase of five to ten times the norm is observed in the rough endoplasmic reticulum.

No **therapy** of this "cosmetic defect" is necessary. In severe cases of jaundice, administration of phenobarbital (60−180 mg/day) or rifampicin (34) may be considered. • The *harmless nature* of this congenital, purely cosmetic ailment must be pointed out to the patient. Diets or even medication are quite out of place, as are "alternative" courses of treatment. • In isolated cases, a biopsy of the liver may be required (although this is in itself not indicated) in order to provide evidence of the harmless nature of this syndrome to the patients, who are by this time often mildly neurotic and utterly convinced that their condition is chronic and can no longer be treated. (27, 32, 48, 49, 52, 54, 55, 57, 58, 60)

Conjugated (partly combined) hyperbilirubinaemias

Conjugated hyperbilirubinaemia derives from a congenital disorder which causes decreased bilirubin excretion in the canaliculi. This is why serum bilirubin is drastically elevated during an icteric episode. More than 40% (−85%) of the total bilirubin in the serum produces a *direct diazo reaction*. Unconjugated bilirubin is also found in the blood. Bilirubin is covalently bound to albumin. Bilirubinuria and urobilinogenuria are in evidence. (47, 62) (s. tab. 12.4)

5.2.2 Dubin-Johnson syndrome

► The clinical picture which was first described by I. N. Dubin and F. B. Johnson (1954) (33) was observed at the same time by H. Sprinz and R. S. Nelson (1954). (74)

The **frequency** of this syndrome, which shows a recessive autosomal inheritance pattern, is characterized by ethnic differences. Over 200 confirmed reports have been published. The real number is considerably higher, since not all cases are actually diagnosed or communicated. The mutations are located on chromosome 10q 23−24. Genetic evidence of this syndrome can also be obtained from skin biopsies (= detection of MRP2 in fibroblasts).

► *We observed two patients who were suffering from a Dubin-Johnson syndrome, one of them in connection with acute viral hepatitis A. (s. figs. 12.1, 12.2)*

Manifestation may occur at any age, but it is usually diagnosed between the ages of 10 and 30. The disease can develop gradually or acutely, often triggered by infections, acute viral hepatitis (78), alcohol, excessive physical or mental strain, contraceptives, pregnancy, etc. • The *cause* is considered to be a dysfunction of the bilirubin transport system in the canalicular membrane

of the hepatocytes. The result is a dysfunction of (conjugated) bilirubin excretion into the bile. A deficiency of MRP 2 (MOAT) is deemed to be a causative factor.

The **subjective ailments** of patients, especially in the case of icteric episodes, include fatigue, languor, inappetence, nausea, and pain on pressure in the right epigastrium − sometimes even of a colic-like nature.

The **clinical picture** is characterized by chronic or intermittent jaundice with values between 2 and 6 mg/dl, and in rare cases between 6 and 12 mg/dl. With acute icteric episodes, values can be in excess of 20 mg/dl. The proportion of conjugated bilirubin in the serum is about 60%, almost exclusively in the form of diglucuronidated bilirubin. The liver or spleen are only occasionally enlarged (50−60% or 10−15% of cases, respectively). Both the laboratory values and the bile acids in the serum are normal; cholestasis is absent. Coagulation factor VII is frequently reduced (approx. 60% of cases). In more pronounced jaundice, bilirubinuria and urobilinogenuria are in evidence. Excretion of coproporphyrin I in the urine is elevated, but that of coproporphyrin III is reduced. (35) • The oral cholecystogram is "negative", whereas the gall bladder appears normal after i.v. administration of contrast medium.

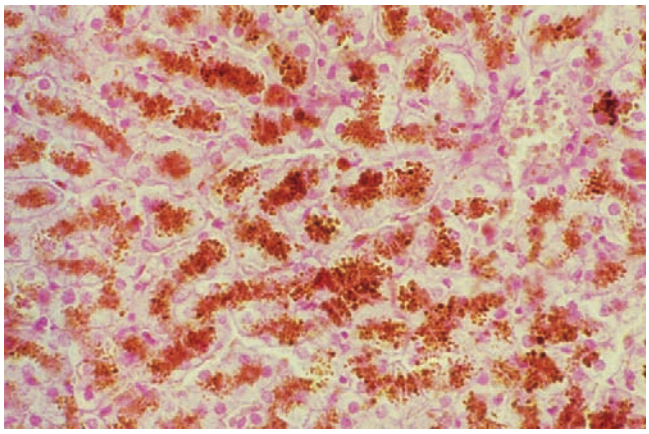

Fig. 12.1: Dubin-Johnson syndrome. (Clinically: persistent jaundice following acute viral hepatitis A.) Massive intracellular storage of lysosomal brownish pigment (Berlin blue)

Histologically, the clinical picture is characterized by the deposition of brown, coarsely grained, iron-free, melanin-like *pigments* (= ***black liver jaundice***). (s. fig. 12.2) The lipomelanin (?) is stored in the lysosomes between the cell nucleus and canaliculus, so that *pericanalicular pigment pathways* are formed. The pigment is possibly a polymerization product of catecholamines. It is detected in differing degrees of intensity and seems to fluctuate during the course of disease as well as upon regeneration of the liver cell, e. g. following acute viral hepatitis. (s. fig. 12.1) (s. p. 430)

Laparoscopically, the liver is bluish-green to bluish-black in colour (= ***black liver***). The surface is smooth and shiny, with intricate vascular multiplication; the lymphatic vessels of the capsule of the liver can appear more pronounced. (s. fig. 12.2)

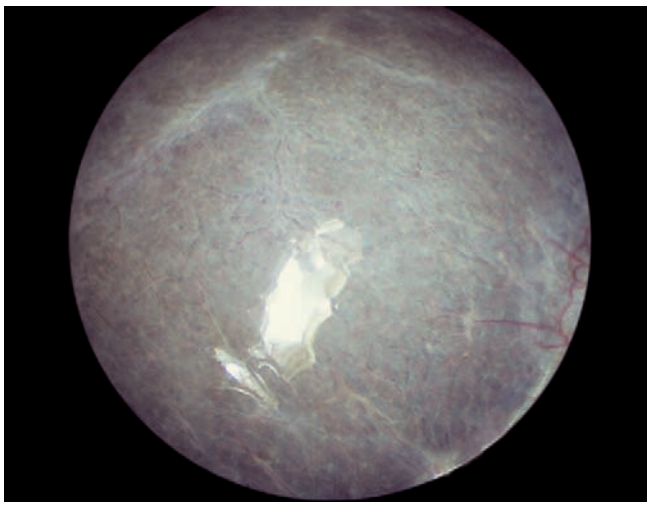

Fig. 12.2: Dubin-Johnson syndrome (so-called black liver)

Therapy is not required for this benign disease, nor is it effective. During icteric episodes, it is advisable to administer phenobarbital. The *harmless nature* of the syndrome must be explicitly pointed out to the patient, even in the case of "chronic jaundice". Stress factors, such as contraceptives, may trigger an icteric episode and should be avoided. However, there are no medical objections to pregnancy, where increased bilirubin values are often encountered. (30, 35, 43, 48, 50, 64, 69, 76, 78, 80)

5.2.3 Rotor syndrome

► The Rotor syndrome was first described by A. B. Rotor et al. in 1948 (67), after G. Canali had already reported on this form of jaundice (albeit not histologically investigated) in 1945.

This clinical picture shows a recessive autosomal inheritance pattern. In approx. 40 cases published to date (mainly concerning Filipino patients), there are no obvious signs of a gender-related preference. Conjugated hyperbilirubinaemia of this syndrome derives from a disorder of the uptake, intracellular bonding (storage) and excretion of bilirubin. Other organic anions (bromosulphophthalein, indocyanine green) are also subject to delayed excretion.

This form of jaundice is found in childhood and adolescence as conjugated hyperbilirubinaemia. Bilirubin values range between 2 and 5 mg/dl with intercurrent icteric episodes, which (as in the Dubin-Johnson syndrome) are mostly triggered by various stress factors. Bilirubinuria and urobilinogenuria may likewise appear, depending on the bilirubin values. All hepatic laboratory parameters are normal. Excretion of total coproporphyrins in the urine is elevated. (70) Oral administration of a contrast medium allows the gall bladder to be visualized. Histology of the liver shows no pathological

findings; in particular, there is no pigment deposition. • *Therapeutic measures* are not necessary, and in fact none are known. Prognosis is good. Any factors that might set off an icteric episode should be avoided. (29, 48, 79, 80)

Conjugated (partly combined) hyperbilirubinaemias with impaired drainage of bile acids

The principal symptoms of this form of disease are (*1.*) largely conjugated (partly combined) hyperbilirubinaemia with **jaundice** and (*2.*) **cholestasis** with pruritus and scratch marks. • This group includes (*1.*) recurrent intrahepatic cholestasis in pregnancy, (*2.*) benign recurrent intrahepatic cholestasis (BRIC) as well as the Aagenaes form, and (*3.*) progressive familial cholestasis (PFIC) and the Byler form. *(see chapter 13)*

6 Differential diagnosis of jaundice

► Each case of jaundice calls for differential diagnostic clarification. The clinical spectrum ranges from the so-called cosmetic, perfectly harmless defect through to malignant obstructions. (2, 5, 8, 9, 12, 16, 20–22, 62) • *It is of the utmost importance to differentiate between non-obstructive and obstructive jaundice.*

Based on a targeted and exact *anamnesis*, subjective *complaints* by the patient and careful **physical examination** (s. tab. 12.5), it is possible in most cases to make a clear distinction between four different categories of jaundice: (*1.*) haematological, (*2.*) hepatocellular, (*3.*) biliary obstructive, and (*4.*) hereditary. (s. tabs. 12.1, 12.2, 12.4)

If there is no interference in terms of **colour reactions in the urine** due to pronounced yellowing, a preliminary categorization of the jaundice form is possible. A persistently negative urobilinogen sample, concurrent with evidence of bilirubinuria, points to a complete obstruction or serious restriction of hepatic function. A persistently positive urobilinogen reaction in the absence of bilirubinuria suggests prehepatic (haemolytic) jaundice. (s. tab. 12.6)

At the outset of clinical investigations, priority is given to determining the direct and indirect *bilirubin* reaction in the serum with the help of the diazo reaction. Other **laboratory parameters** as well as the enzyme quotients (s. tabs. 5.6, 5.7) often allow the differential diagnosis of jaundice to be made at this stage. (s. tabs. 12.6, 12.7)

► **Noninvasive** procedures used consecutively are ultrasound and, if necessary, computer tomography. For the diagnosis of extrahepatic jaundice, both test procedures have about the same sensitivity and specificity, yet their degree of accuracy is no greater than that obtained through clinical and laboratory examinations. Laboratory diagnosis facilitates a precise differentiation between the types of hyperbilirubinaemia and their possible combination with cholestasis.

1. Precise anamnesis
– Start of jaundice? – Fluctuations in intensity? – Relapses? – Correlation with surgery, infusions, injections? – Correlation with pregnancy? – Journeys abroad? – Occurrence of jaundice within the family? – Alcohol abuse? – Medication? – Contact with chemicals? – Pre- or coexistent hepatobiliary diseases?
2. Subjective complaints
– Pain in the right epigastrium? – Colic? – Lack of appetite? Loss of weight? – Nausea? – Itching? – Arthralgia? – Colour changes in stools or urine? – Fatigue? – Decrease in vitality?
3. Clinical results
– Hepatomegaly? – Tenderness on pressure? – Splenomegaly? – Scratch marks? – Type and intensity of jaundice? – Skin stigmata of liver diseases? – Hyaline cast in urine sediment? – Stool and urine examination results?

Tab. 12.5: Important anamnestic and clinical findings for setting up a differential diagnosis of jaundice

1. *Ultrasound examination* is always indicated for the clarification of jaundice. The results determine the subsequent diagnostic steps. It is important to clarify whether the bile ducts are dilated, which is a hint for obstructive jaundice. (s. tabs. 6.11, 6.12) (s. p. 140)

2. *Computer tomography* can be indicated in isolated cases, particularly in order to establish the cause of obstruction or when focal lesions are present.

The diagnostic strategy for clarification of **cholestasis** and **jaundice** is outlined later in a **flow diagram.** (s. fig. 13.7) (s. p. 247)

► If a particular jaundice cannot be categorized, **invasive methods** are indicated:

1. *Liver biopsy* has often proved indispensable for the differentiation and validation of unresolved prehepatic or intrahepatic jaundice. (s. tab. 7.3)

Type of jaundice	Bile	Colour of stool	Colour of urine	Urobilinogen	Bilirubin
Prehepatic jaundice	dark	dark	normal	+	∅
Intrahepatic jaundice	light	light	dark	+	+
Posthepatic jaundice	light or ∅	acholic	dark	(+) or ∅	+

Tab. 12.6: Main colouration of duodenal bile, stools and urine as well as the results of bile pigment tests in the urine of jaundice patients (∅ = negative)

- Determination of total bilirubin with differentiation between direct (conjugated) and indirect (unconjugated) bilirubin
- Determination of cholestasis-indicating enzymes (AP, LAP, γ-GT); bile acids and bile pigments in the urine (s. tab. 12.6)
- Test for signs of haemolysis (s. tab. 12.3)
- Determination of transaminases and (possibly) enzyme quotients (s. tabs. 5.6, 5.7)
- Antimitochondrial antibodies (s. tabs. 5.20, 5.21)
- Hepatitis serology (s. tab. 5.17)
- Determination of total coproporphyrin and coproporphyrin I and III in the urine

Tab. 12.7: Important laboratory parameters for the differential diagnosis of jaundice

2. *Laparoscopy* should always be considered if the previously applied procedures have not provided any differential diagnosis.

3. *ERC* facilitates precise visualization of the bile ducts − this is also possible by means of *PTC* in cases of sonographically determined dilation of the bile ducts with suspected biliary obstruction. PTC is likewise indicated if ultrasound examination fails to produce evidence of enlarged bile ducts and/or ERC has proved inconclusive even though clinical and laboratory examinations suggest biliary obstruction. (s. pp 191, 193)

7 Therapy

Jaundice is a symptom. For this reason, there can be no standardized therapeutic concept for its treatment. Therapy is solely directed at the underlying primary cause, provided that symptom-related and curative therapeutic options are at hand.

Causal therapy: Only those forms of *obstructive jaundice* related to benign causes are open to causal treatment in the form of endoscopy (e. g. sphincterotomy) or surgery. *Operative procedures* and *interventional endoscopy* have significantly broadened the scope of therapy for mechanical jaundice, such as (*1.*) application of a stent, (*2.*) transhepatic biliary drainage, (*3.*) recanalization of strictures or stenoses, (*4.*) extraction of concrement left behind intraoperatively, and (*5.*) radiotherapy of tumour obstruction. (9, 19) • Jaundice resulting from *bacterial infection* of the bile ducts calls for the systemic and/or topical application of suitable *antibiotics*. (14, 18) • *Cholagogue agents*, which are plant extracts, have become popular as supplementary therapy for stimulating bile flow, even in long-term treatment. *(see chapter 32)*

Functional hyperbilirubinaemias: These forms of jaundice do not require therapy. It is of primary importance to provide the patient with detailed information regarding the harmless nature of such disorders. • Should short-term therapy be indicated in specific cases, this can be successfully effected with phenobarbital. Both cholestyramine and cholestipol or naltrexone can be used in the treatment of pruritus. (s. p. 249) • In Crigler-Najjar type II, it may prove effective to administer phenobarbital (together with calcium phosphate), phenazone or phenytoin. With the cholestatic forms, ursodeoxycholic acid and S-adenosyl-L-methionine can be applied. • In severe cases, exchange blood transfusions or plasmapheresis as well as phototherapy (13) and possibly even liver transplantation are indicated.

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Jaundice

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