Symptoms and Syndromes

20 Acute and chronic liver insufficiency

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1 Definition

The term "liver insufficiency" denotes a breakdown in the functions of the liver. The syndrome of functional liver failure covers a wide spectrum of clinical, biochemical and neurophysiological changes. In principle, liver insufficiency can occur without previous liver damage as well as with already existing liver disease. It is characterized by a deterioration in the synthesizing, regulatory and detoxifying function of the liver. This final stage of liver disease terminates in hepatic coma.

2 Systematics

2.1 Partial and global insufficiency

Serious liver disease can affect the 12 main metabolic functions of the liver, with their 60–70 even more important partial functions, to widely differing degrees. (s. tab. 3.1) The result is either *global insufficiency* or *partial insufficiency*, each with very varied clinical and biochemical symptoms. The failure of certain metabolic functions is responsible to a greater or lesser extent for the development and intensity of liver insufficiency. Impairments in the functions of detoxification and protein metabolism are particularly significant in this respect.

2.2 Compensation and decompensation

The **compensated stage** does not usually display any signs of liver insufficiency (except possibly jaundice), nor are there any typical ailments. Functional parameters that can be quantified in routine laboratory tests (such as cholinesterase, albumin, Quick's value, bile acids) may still be normal or only minimally impaired in the individual instance. In contrast, liver tolerance tests (galactose, indocyanine green, etc.) demonstrate a reduction of liver function which is already quite considerable.

The **decompensated stage**, i.e. manifest liver insufficiency, can present as *cellular decompensation* (e.g. in the case of acute liver failure due to toxic or inflammatory mass necrosis) or be expressed only in the form of *portal decompensation* (e.g. in cases of postsinusoidal intrahepatic portal hypertension). • As a rule, chronic liver insufficiency is accompanied by a *combined decompensation* with a loss in function of the liver cells and, at the same time, the sequelae of portal decompensation (collateral varicosis, encephalopathy, ascites, hepatorenal syndrome, variceal bleeding). *(see chapters 15–19 and 35)*

2.3 Acuteness and chronicity

Depending on the time period involved in the course of the disease, **acute liver failure** without pre-existing liver disease can initially be differentiated by massive liver cell disintegration due to a variety of causes. • In contrast, **chronic liver insufficiency** with pre-existing liver disease is mostly found in advanced liver cirrhosis with a progressive loss of function. • A *sudden necrotising episode* is also able to precipitate the change from chronic and still compensated liver insufficiency into acute liver failure ("acute on chronic") in the same way that acute liver failure which has been overcome can develop into chronic liver insufficiency.

2.4 Hepatic coma

Hepatic coma can be subdivided according to its aetiology as follows: (*1.*) *hepatocyte disintegration coma* (= endogenous coma as a result of the loss of parenchyma), (*2.*) *liver cell failure coma* (= exogenous coma as a result of metabolic disorders, almost always in the presence of cirrhosis), (*3.*) *electrolyte coma* (= so-called "false" coma due to dyselectrolytaemia, almost always iatrogenic), and (*4.*) *mixed forms of coma.* (s. pp 214, 276, 381) (s. tab. 15.5)

3 Acute liver insufficiency

► J.W. Morgagni (1761) was probably the first to describe acute yellow atrophy of the liver, i.e. hepatic coma. Acute liver failure can be seen as identical to the "acute yellow atrophy" described by K. Rokitansky in 1842. This acute and severe clinical picture was subsequently termed "bilious dyscrasia" (P.J. Horaczek, 1844), "icterus gravis" (C. Ozanam, 1849), "acholia" (F. Th. Frerichs, 1858), "hepatolysis" (R. Ehrmann, 1922), "hepatodystrophy" (G. Herxheimer, 1935) or "liver dystrophy" (R. Böhmig, 1949). The terms "hepatargia" (H.I. Quincke, 1899) and "hepatic coma" were used to denote the final stage, which usually sets in at the end of acute or chronic liver failure. • Acute liver failure in the course of acute viral hepatitis was termed "fulminant hepatitis" by W. Lucké et al. (1946), who also defined a subacute form with a less severe course. (35)

3.1 Definition

Acute liver failure (ALF) is defined as an acute clinical picture with *jaundice* due to a most severe disorder in the liver function and/or massive liver cell necrosis which, without any pre-existing liver disease, culminates in *hepatic coma* (= endogenous coma) within 8 weeks. Potentially, the condition is fully reversible (C. Trey et al., 1970). • In addition, *coagulopathy* must also be present (D.F. Schafer et al., 1989).

Courses of disease

Clinically, there are three different courses of disease following the onset of **jaundice:** (*1.*) fulminant or *hyperacute liver failure* (= occurrence of hepatic encephalopathy in the 1st week), (*2.*) *acute liver failure* (= occurrence of hepatic encephalopathy between the 2nd and 4th week), and (*3.*) *subacute liver failure* (= occurrence of hepatic encephalopathy between the 5th and 8th week). • Surprisingly, however, it could be shown that 30–40% of the hyperacute forms survived in spite of the development of hepatic coma and cerebral oedema. As opposed to this, the subacute forms displayed a survival rate of only 10–20%, despite a lower frequency of cerebral oedema and better liver function. (s. tab. 20.1)

	Hyperacute liver failure	Acute liver failure	Subacute liver failure
Encephalopathy	++	++	++
Duration of icterus in days	0–7	8–28	29–72
Cerebral oedema	++	++	(+)
Quick's value	↓	↓↓	↓
Bilirubin	N-↑	↑↑	↑↑
Prognosis	favourable	poor	poor
Survival rate	30–40%	5–10%	10–20%

Tab. 20.1: Characteristics and prognosis of acute liver failure and its subtypes (modified according to J.G. O'Grady et al., 1993) (N = normal)

3.2 Morphology

In the **pathological-anatomical context,** *hepatomegaly* due to hyperaemia is often found at the outset. During the further course of disease, this can develop into *liver atrophy* as a result of parenchymal loss.

► **Histologically,** acute liver failure shows a wide range of uncharacteristic changes. (*1.*) Depending on the underlying cause, the morphological picture of **acute necrotizing hepatitis** can be witnessed with extensive confluent cellular destruction. The extent of necrosis, measured by way of the morphologically evidenced hepatic volume fraction of the still functioning liver parenchyma, yields relatively reliable information on the chance of survival (J. Scotto et al., 1973). Given a normal value of 85% **hepatic volume fraction** (HVF) of intact liver cells for each volume unit of the total liver, a decrease to < 30% (threshold 28–35%) would possibly mean that the patient is unlikely to survive. (*2.*) In acute liver failure caused by toxins or hypoxia, **massive fatty degeneration** of the hepatocytes can vary substantially. In diffuse fatty degeneration featuring minute vacuoles and damage to the organelles, liver cell necrosis cannot, as a rule, be detected (e.g. acute fatty liver during pregnancy, Reye's syndrome, in association with tetracycline or valproic acid). (*3.*) Between these two "classical" morphological manifestations, there are also **compound forms,** i.e. courses of disease with a variety of histological changes of different intensities and combinations. On occasions, it is also possible to identify histological findings which point to a certain cause of the disease. (40, 57)

From a morphological point of view, acute liver failure is potentially reversible, so that even **complete regeneration** can be attained. Precursory cellular necrosis is hence less of a determinant than the capacity to regenerate.

There have been reports on the transition from virus-induced acute liver failure to **chronic hepatitis.** As the final stage of fulminant viral hepatitis (also known as acute liver dystrophy or submassive hepatitic necrosis), a **postdystrophic scarred liver** ("potato liver") can develop. (s. fig. 35.14) Cicatricial distortions with a continuing effect, regenerative processes, intrahepatic vascular disorders and hypoxia-related damage lead to the conclusion that a *posthepatitic, postdystrophic scarred liver may well be a special form of cirrhosis.*

Neither the functional state of liver insufficiency nor hepatic coma can be recognized histologically.

3.3 Pathogenesis

The common target structures for the various causes of acute liver failure are usually the cellular and subcellular biomembranes of the hepatocytes. Among other things, any damage to these biomembranes causes a massive inflow of calcium into the liver cells, which results in a severe disorder of the cell milieu and ultimately in cell death.

In cases of **oxygen deficiency,** the oxidative stress is mainly localized in the extracellular spaces. This is where the Kupffer cells and neutrophils are involved in complex self-stimulating mechanisms, which can lead to the formation of inflammatory mediators and cytotoxic substances. • An important pathogenetic aspect is the extent of the "priming effect", which generally results in the increased production of oxygen radicals. The complex process of **lipid peroxidation** likewise effects massive liver cell damage in the form of self-perpetuation. • Excessive **immunological reactions,** which occur in acute liver failure due to viral hepatitis, halothane hepatitis, etc., are of great significance. There are also isolated cases in which **biotoxometabolites** are produced and may act as neo-antigens. (s. fig. 3.11)

► Consequently, severe damage to liver cells and widespread necrosis are usually the result of a network of altered cellular and humoral reactions, which for their part are often the initial cause of acute liver failure due to their synergistic and interactive effects (H. Popper et al., 1986). Systemic reactions are responsible for the fact that other organs and functional sequences are equally affected, thus creating a wide spectrum of clinical findings and complications.

3.4 Frequency and causes

Acute liver failure is a rare occurrence. It is estimated that approx. 5 cases are found out of 6,000 hospital admissions (in the USA a total of ca. 2000 patients per year, in Germany ca. 150). However, there can be wide variations in frequency due to the effect of regional differences on the individual aetiology of this disease. The causes of acute liver failure are numerous and multiform. Diabetes mellitus is an extremely high risk factor

in this respect. • Primary or secondary hepatitis viruses are deemed to be a frequent cause, although there are regional and individual variations (e. g. drug dependence, pregnancy) with regard to the predominant virus type. • A further common cause (ca. 20%) are medicaments (particularly paracetamol often taken with suicidal intent, and halothane), followed by mycotoxins, alcohol and carbon tetrachloride (such as can be found in cleaning agents or solvents, and also with "glue sniffers"), heat-stroke (up to 10% of cases), Ecstasy, and vascular diseases. (8, 13, 66, 77) (s. tab. 20.2)

1. **Primary hepatotropic viruses**
   HAV (0.2−0.3%) (6, 37), HBV (1−2%) (6, 39, 59, 65, 81), HCV (ca. 1%) (30, 65, 67, 80), HDV superinfection (ca. 20%), HEV (10−20%) (6, 30), HBV mutants, HCV + HAV (30−40%) (70)
2. **Secondary hepatotropic viruses**
   adenoviruses, Coxsackie (73), cytomegaloviruses, Epstein-Barr (20), herpes simplex (type 1,2) (69), herpesvirus-6 (1), parainfluenza virus, paramyxoviruses, parvovirus B19, varicella zoster virus, yellow fever, dengue fever
3. **Bacteria and parasites**
   leptospira, listeria (68), malaria, M. tuberculosis (25, 29), rickettsia
4. **Chemical substances**
   carbon tetrachloride (52), chloroform, nitropropane (26), trinitrotoluene, yellow phosphorus (s. tab. 30.3)
5. **Fungal poisons**
   Amanita phalloides (27, 48, 109, 120), lepiota (49)
6. **Toxins**
   B. cereus emetic toxin, microcystins of cyanobacteria
7. **Medicinal agents**
   allopurinol, amiodarone, antiretroviral agents, carbamazepine, cotrimoxazole (3), cyproterone, dapsone, didanosine, disulfiram, Ecstasy (110, 113), enflurane, flutamide, glitazone, gold, halothane, hydroxychloroquine, interferon, isoflurane, isoniazid, kava-kava, ketoconazole, lisinopril, methotrexate, methyldopa, mono-amine oxidase inhibitor, nilutamide, nimesulide, ofloxacin, omeprazole, paracetamol, phenhydane, phenothiazine, phenytoin, pirprofen, propylthiouracil, rifampicin, sulphasalazine, tetracycline, valproic acid. (s. tab. 29.4)
8. **Alcohol**
9. **Metabolic causes**
   acute fatty liver in pregnancy (44), α_1-antitrypsin deficiency, erythropoietic protoporphyria, hereditary fructose intolerance, galactosaemia, HELLP syndrome, Reye's syndrome, tyrosinaemia, Wilson's disease
10. **Ischaemia**
    Budd-Chiari syndrome, heatstroke, ligature of the hepatic artery, shock liver, veno-occlusive disease
11. **Malignant infiltration**
    leukaemia (4), massive formation of metastases, Hodgkin's disease (16), melanoma, non-Hodgkin's lymphoma (5, 54, 78), renal cell carcinoma (19), hepatocellular carcinoma (36)
12. **Autoimmune hepatitis** (43)
13. **Septic cholangitis**
14. **Heart failure** (75)
15. **Jejuno-ileal bypass** (12)

Tab. 20.2: Various causes of acute liver failure (with some references)

Paracetamol: The first report on acute liver failure due to paracetamol poisoning was published in 1966 (D. G. D. Davidson et al.). Due to induced CYP II E2, paracetamol is metabolized to the extremely reactive molecule N-acetyl-p-benzoquinone-imine (NAPQI). This binds covalently to cellular proteins. A small amount of NAPQI is neutralized by glutathione; however, with a larger quantity of NAPQI (following an intake of >10 g paracetamol), the hepatic glutathione supplies are used up, so that the NAPQI becomes highly toxic. (s. fig. 20.3) There is hence a direct correlation between the degree of glutathione consumption and the severity of liver cell damage. The loss of glutathione can be compensated by i.v. administration of the glutathione precursor N-acetylcysteine. (s. p. 383)

Amanita phalloides: Mycotoxins, especially α-amatoxin, are extremely hepatotoxic as a result of the inhibition of mRNA polymerase B and the blocking of RNA synthesis. The lethal dose is approx. 0.1 mg amatoxin/kg BW (1−3 fungi = 10−50 g), depending on the patient's age and state of health as well as the respective degree of intestinal absorption and diffusion in the tissue. The heat-resistant mycotoxins (amanitines) are capable of enterohepatic recirculation. (s. pp 383, 571)

3.5 Clinical findings

The overall picture of acute liver failure is first and foremost determined by the clinical findings. The symptoms are dramatic and subject to swift change. The course of disease can advance within a matter of days or, in a subacute form, take several weeks. (7, 8, 13, 56, 60, 66, 77)

General symptoms: The acute clinical picture develops swiftly with conspicuous symptoms, such as fatigability, loss of appetite, nausea, weakness, lassitude, meteorism, apathy and disruption of the circadian rhythm.

Encephalopathy: Rapidly, often within 1 or 2 days, there is evidence of dysarthria, muscle tremor, finger tremor, lack of concentration and asterixis. Restlessness, hyperkinesis and hallucinatory experiences are evident. Even screaming attacks have been observed. These symptoms, which can still be classified under stages I and II, are fully reversible. Nevertheless, lethality of 30−35% must be anticipated in stage II. In contrast, stage III is clearly less reversible. Somnolence, stupor with confusion, deviant behaviour, hyperreflexia, Babinski's reflex, clonus and spasticity as well as nystagmus are now observed. There is usually still a response to acoustic stimuli. The EEG shows a slowing down of basic activity (0.5−3.0/sec.) together with mainly biphasic and triphasic potentials. Lethality rises to over 50%. In stage IV, the patient is in a deep coma. There is evidence of areflexia, an absence of any corneal reflex and loss of tonicity; the brain waves flatten out to an isoelectric line. Irrespective of therapy, lethality is 80−90%. (s. tab. 15.5)

Cerebral oedema: As from coma stage III, cerebral pressure can increase (75−80% of cases) owing to water retention and/or vasodilation with hyperaemia, yet with a subsequent reduction in cerebral perfusion and hypoxia. Intracranial cerebral compression is >20 mm Hg. Cerebral oedema is vasogenetic and/or cytotoxic, the latter feature appearing to predominate. Clinical symptoms include disorders in the respiratory rhythm (in particular tachypnoea), hypertension and bradycardia as well as increased muscular tonus. Singultus suggests damage to and impending constriction of the brain stem. The pupils are dilated due to the pressure on the oculomotor nerve. Occasionally, chemosis develops, which is a fatal prognostic sign. (2) Intracranial blood circulation sinks rapidly. In 30−60% of cases, cerebral oedema is fatal. (10, 11, 38, 62, 64, 74, 76)

Jaundice: With the foudroyant disintegration of liver cells, a comatose condition can set in within a few hours, even before jaundice is identified. In most cases, however, jaundice is already present. The intensity and time of onset vary. Severe jaundice (>20 mg/dl) is considered to be a poor prognostic sign.

Hepatic foetor: The sweet aromatic smell of the exhaled breath (mercaptan derivatives) is accepted as a reliable sign of acute liver failure, but it is not always present. The administration of poorly absorbable antibiotics (e.g. paromomycin) usually improves the condition of hepatic foetor or even eliminates it temporarily. (s. pp 87, 267)

Fever: Fever often occurs; for the most part, it remains at 38 °C, but septic temperatures are possible. • In some cases, this may well be a question of *aetiocholanolone fever*, whereby aetiocholanolone can also be quantified in the serum. • *Bacterial infections* are likewise a cause of fever and require appropriate treatment. *Toxins* may also be responsible for the febrile condition (tissue toxins, endotoxins). (s. p. 738)

Liver size: The liver may have normal size or it can be enlarged due to hyperaemia or massive fatty infiltration. A rapid shrinking of the liver to less than 1000 ml in volume ("dystrophy", "acute atrophy") − requiring sonographic or CT monitoring at the bedside − is deemed to be a poor prognostic sign.

3.6 Laboratory parameters

At present, there is no specific laboratory investigation which facilitates the diagnosis of acute liver failure. In view of the severity of this clinical picture, there are, however, a number of laboratory parameters which show marked pathological changes and thus require full diagnostic clarification. Activin A serum levels were elevated, especially in patients with acute liver failure, due to a paracetamol overdose. This did not affect the final outcome, but was possibly a factor in the inhibition of liver regeneration. Serum follistatin was also increased in patients with fulminant liver disease. (28) Furthermore, the laboratory values allow an assessment of the complications involved and an evaluation of the prognosis. (7, 8, 13, 14, 56, 60, 66, 77)

► Various laboratory values are indicative of severe complications and thus considered to be **criteria** pointing to a poor prognosis. (s. tab. 20.3)

Decrease in cholinesterase	<500 U/l
Decrease in factor V	<20%
Fall in Quick's value	<20%
Group-specific component protein	<34 µg/ml
Hyperkalaemia	due to renal failure
Hypoalbuminaemia	<2.5 g/dl
Hypocalcaemia	due to pancreatitis
Hyponatraemia	<120 mval/l
Hyponatriuria	<10 mmol/l
Lactatacidosis	>3.5 mmol/l
Phosphataemia	>2.5 mg/dl
Rapid drop in transaminases	subnormal values
Rise in bilirubin	over 20 mg/dl

Tab. 20.3: Criteria for a poor prognosis in acute liver insufficiency

1. **GPT, GOT, GDH, LDH:** These enzymes are greatly elevated in accordance with cell destruction (GOT ⩾ GPT). A decrease in enzyme values during the further course of disease can be a sign of regressing cell necrosis, marked parenchymal loss or a disorder in enzyme synthesis. A rapid drop in the initially elevated enzyme values is considered to be an unfavourable prognostic sign.

2. **Bilirubin:** Serum bilirubin shows a pronounced and varied increase, although the conjugated bilirubin does not rise at all, or only minimally, since uptake and conjugation remain intact for a considerable period of time.

3. **Quick's value:** A drop in the coagulation factors II, V, VII, IX and X is a reliable indicator of the still remaining liver function. Factor VIII increases. With massive liver cell destruction, a dangerous decrease in factors V and VII is witnessed within 1 or 2 days (corresponding to the half-life of the factors) together with a reduction in Quick's value and Colombi's index (<60−80%). (45, 47, 71) (s. p. 105)

4. **Cholinesterase:** During the further course of disease, cholinesterase decreases in relation to its longer half-life and likewise allows a reliable assessment to be made of the remaining liver function. (s. p. 103)

5. **Electrolytes:** There is evidence of *hyponatraemia* (= dilutional hyponatraemia or reinforced natriuresis) as well as *hypokalaemia* (= inadequate supply, intensified kaliuresis, outflow of potassium into the body cells due to i.v. glucose infusions). The serum values of *magnesium, phosphate* and *zinc* are also lower as a rule.

6. **Group-specific component protein:** This substance (= α_2-globulin) is synthesized in the liver and binds actin. GCP is released upon hepatocyte decay; its pronounced reduction in the serum results from the decrease in synthesis in acute liver failure.

3.7 Complications

► The course taken by acute liver failure varies in each case as a result of the respective complications, which also decidedly worsen the prognosis. Close-meshed and targeted laboratory investigations can usually identify

complications early enough, so that successful therapy might still be possible.

Coagulation disorders: Some 35–55% of patients with acute liver failure are in danger of suffering from serious gastrointestinal bleeding. Extensive cutaneous haemorrhages also occur frequently. In addition, disseminated intravascular coagulation (DIC) sometimes develops. As a result, bleeding and coagulation disorders number among the most frequent causes of death (20–25%). Pathophysiology is based on the diminished synthesis of coagulation and fibrinolysis factors and inhibitors as well as a decrease in the breakdown of activated factors, a functional disorder of thrombocytes or thrombopenia, and latent consumptive coagulopathy. It is of great help to determine PTT and factor V. A high level of the thrombin-antithrombin III complex (TAT) points to a poor prognosis. The simultaneous development of portal hypertension in individual cases promotes a tendency towards nasopharyngeal and gastrointestinal bleeding. (47, 71)

Renal failure: In about 50% of patients with acute liver failure, renal insufficiency develops. This can be expressed in three forms: (*1*.) *prerenal kidney failure* due to hypovolaemia, (*2*.) *acute tubular necrosis*, mainly secondary as a result of circulatory hypotension with cylindruria, a higher concentration of sodium in the urine (50–70 mmol/l) and a reduced urine creatinine/serum creatinine quotient (<20) or urine urea/serum urea quotient (<3), or (*3*.) *hepatorenal syndrome.* (41) (s. tab. 17.3)

Respiratory insufficiency: In general, respiratory alkalosis (pCO_2 < 30 mm Hg, pH > 7.5) is initially present, triggered by intensified respiration and tachypnoea. Despite this hyperventilation, there is evidence of hypoxia, which is largely due to a disorder in oxygen diffusion. The causes for this are microthromboses, interstitial formation of oedema and increased peripheral vasotonia. Central biochemical mechanisms together with an inadequate cerebral blood circulation as a result of a reduction in pCO_2 reinforce the respiratory insufficiency. Approximately 80% of patients in coma stages III and IV require artificial respiration. A total collapse of the pulmonary function can be occasioned by pneumonia (ca. 50% of cases) as well as by the leakage of fluid and/or bleeding in the lung area.

Acid-base disorders: Initial metabolic alkalosis (resulting from decreased urea synthesis with reduced bicarbonate consumption) may be superimposed by respiratory alkalosis as an outcome of disorders in lung function. During the further course, metabolic acidosis (with renal insufficiency) and respiratory acidosis (with pulmonary insufficiency) can be expected. In advanced or severe stages of the disease, lactate acidosis may develop in some 50% of all comatose patients owing to restricted gluconeogenesis.

Circulatory disorders: In general, acute liver failure is initially accompanied by hyperdynamic circulation. During the further course, approx. 80% of patients develop hypotension, which above all results in a considerable reduction in hepatic, cerebral and renal perfusion. At the same time, peripheral vasodilation is usually witnessed. Bradycardia, generally resulting from cerebral oedema, worsens the cardiovascular conditions and is considered to be a poor prognostic sign. Ultimately, the patient does not respond to volume expansion and catecholamines.

Hypoglycaemia: In 25–40% of cases, hypoglycaemia develops and can all too easily be overlooked. The cause is seen to be a reduced glycogen content in the liver, diminished glycogen synthesis and gluconeogenesis as well as hyperinsulinaemia due to reduced degradation of insulin in the liver. (21) It is often difficult to eliminate such hypoglycaemia, even with i.v. glucose infusions. • Furthermore, there is a danger of **hypokalaemia** and even **hypophosphataemia,** necessitating phosphate substitution with continuous monitoring of the serum values of phosphate and calcium (reactive hypocalcaemia is dangerous).

Pancreatitis: The frequency of hyperamylasaemia is reported to be 55% of patients with acute liver failure; in 20–30% of cases, pancreatitis could be identified clinically and sonographically. The cause is multifactorial.

Infections: Because of their greater susceptibility, about 80% of patients with acute liver failure are subject to the threat of bacterial infection, which in 10% of cases is also the reason for their death. The typical signs of an infection, such as fever or leucocytosis, are often absent. However, increased levels of *procalcitonin* (>0.58 ng/ml) are deemed to be a valid marker of bacterial infection. The respiratory tract and the urinary passages are most frequently affected. Regular bacteriological examinations (sputum or urine as well as catheter after removal) should therefore be carried out. Haemocultures have to be checked for both aerobians and anaerobians. Multiple serological tests may be necessary for aetiological clarification. There is also a risk of fungal infections. (50)

3.8 Prognosis

The survival rate in acute liver failure is given as 10–40%. This rate varies widely owing to a number of reasons. There is a *better prognosis* for poisoning from paracetamol or Amanita phalloides, for example, since successful therapy procedures have already been established for these forms of intoxication. Younger patients (10 to 40 years of age) generally have a better prognosis. This also applies to HAV infection. A *poor outcome* can be expected in Wilson's disease or Budd-Chiari syndrome and in coma stages III and IV (lethality over 80%) due to the development of complications (in particular bleeding, renal or respiratory insufficiency, infection) – especially with younger (<10 years) or older patients (>40 years). Acute liver failure which is due to halothane, the application of various medicaments or viral hepatitis (delta superinfection, HEV in pregnancy) likewise has a less favourable prognosis. • *Laboratory parameters* such as serum bilirubin, coagulation factors (PTT, factor V, Quick's value), galactose test and cholinesterase have proved to be most helpful in assessing the course of disease, the liver function and hence the prognosis. (14, 18, 23, 42, 45, 57, 60, 77)

3.9 Regeneration

The regenerative ability of the liver is of utmost importance for overcoming such a severe disease. (40) After a regeneration period, an intact cell mass (hepatic volume fraction) of >45% is required for survival. (40) Various factors are indicative of good regeneration: rising values of α_1-foetoprotein (and also γGT), HGF, EGF, THFα, TNFα and interleukin-6 as well as a decline in serum phosphorous levels. (14) It was possible to improve *regeneration* by means of hepatotropic substances, such as *insulin* and *glucagon* (G. Starzl et al., 1975), so that these substances are also referred to as "goodies" for the liver (S. Sherlock, 1976). Subsequent investigations proved to be contradictory. (24, 79) An increase in the regeneration rate of the liver cells can possibly be achieved either by hepatic arterial infusion of PGE_1 (55) or by *silymarin* through

stimulation of RNA synthesis (J. Sonnenbichler et al., 1976). (s. pp 40, 867) (s. fig. 3.5)

4 Chronic liver insufficiency

4.1 Definition

Chronic liver insufficiency is due to the progression of an already existing chronic liver disease. This generally tends to be advanced cirrhosis of varied aetiology. Basically, however, any liver disease can be a potential cause of chronic liver insufficiency. Alcohol and infections as well as certain medicaments are also deemed to be common causes. A great number of substances and events can trigger liver insufficiency.

The clinical picture of chronic liver insufficiency comprises both a **compensated** and **decompensated** form. These two stages of manifest chronic liver insufficiency affect the hepatocellular area or the portal system either exclusively or predominantly (= **cellular** or **portal** compensation or decompensation); mostly they occur as a *combined form* of disease. The resulting spectrum of clinical and laboratory findings will reflect either a **global** or **partial** insufficiency of the liver. (s. p. 376)

4.2 Clinical findings

General manifestations of the disease: The clinical picture of chronic liver insufficiency is characterized by general symptoms such as fatigue, apathy, lack of appetite, lack of concentration, infirmity, sensation of repletion and meteorism.

Clinical findings: Organ-related so-called "minor signs" of liver insufficiency can be observed over a certain period of time. (s. tab. 20.4)

1. **Gastrointestinal tract**
   - meteorism
2. **Dermis and mucosa**
   - itching
   - skin stigmata of liver disease
   - tendency to "bruise"
   - nasal haemorrhage and ulorrhagia
   - tongue changes
3. **Stools**
   - intermittent acholic stool
4. **Urine**
   - intermittent dark urine
5. **Changes in the blood count**
   - anaemia
   - leucopenia
   - thrombopenia
   - macrocytosis
6. **Fever**
7. **Splenomegaly**
8. **Endocrine disorders**

Tab. 20.4: So-called "minor signs" of chronic liver insufficiency

► Increasing and constant *meteorism* ("first the wind and then the rain") and intermittent characteristic changes in the colour of *stools* and *urine* are distinct signs of impending insufficiency. The "blossoming" of *spider naevi* or an intensification of *palmar erythema* as well as *tongue changes* (e. g. the transition of the moist "scarlet tongue" into a dry "raspberry tongue") are often observed. Obvious features of the blood count are: *anaemia* (due to bleeding of the skin or mucosa, folic acid deficiency, reduced erythrocyte survival time) and *thrombopenia* (due to consumptive coagulopathy, dilutional thrombopenia with plasma dilution, immunothrombopenia, sequestration in splenomegaly and toxic inhibition of the bone marrow).

4.3 Decompensation

Decompensation in chronic liver insufficiency is characterized by the development of severe, life-threatening **complications:**

1. **Ascites and oedema**
2. **Coagulopathy and bleeding**
3. **Hepatic encephalopathy**
4. **Hepatorenal syndrome**
5. **Hepatopulmonary syndrome**
6. **Reduction in liver functions**

4.3.1 Reduction in liver functions

Of particular significance is the serious impairment of essential tasks performed by the liver such as the **detoxification function** (ammonia detoxification, biotransformation, radical scavenger function, clearance abilities of the RES, etc.), the **synthesis** of vital proteins and the **regulation** of biochemical systems and substances – these are considered to be precursors of complicative developments. Any insufficiency of bilirubin metabolism is reflected in increasing **jaundice**, likewise deemed to be an unfavourable sign with respect to prognosis.

4.3.2 Hepatic encephalopathy

The term **hepatic encephalopathy** (HE) describes the entire field of neuropsychiatric symptoms which can be found in patients suffering from acute or chronic liver disease. The term **portosystemic encephalopathy** (PSE) stresses the presence of portosystemic shunts, which are as a rule associated with liver cirrhosis. • **Hepatic coma** (in stages III and IV) is the ultimate and total loss of consciousness (coma = deep, sound sleep). In clinical terms, 4 (or 5) stages can be defined, but the latent or subclinical stage as well as stages I and II may progress so rapidly that only the comatose final stage is actually witnessed. Generally, chronic liver insufficiency is seen as a liver failure coma, i. e. exogenous coma. Recurrent hepatic encephalopathy points to the existence of a chronic liver disease, particularly liver cirrhosis. Serum levels of TNF correlates positively with the severity of HE. *(see chapter 15)*

4.3.3 Ascites and oedema

Ascites and *oedema* are also found in severe hepatic diseases, pointing to serious disorders in the water and electrolyte metabolism. These complications are signs of decompensation in liver cirrhosis or chronic liver insufficiency. At the same time, *pleural effusion* may also be evident. Cirrhosis-related pleural effusion without concomitant ascites has been described as a rarity. *(see chapter 16)*

4.3.4 Hepatorenal syndrome

All liver diseases resulting in liver insufficiency can also give rise to the hepatorenal syndrome. This syndrome is most frequently found in decompensated liver cirrhosis ("renal insufficiency in the terminal stage of cirrhosis"). It involves massive vasoconstriction of the renal cortical vessels with a critical drop in the glomerular filtration rate (urine production < 500 ml/day, possibly developing into anuresis). At the same time, systemic vasodilation and hyperdynamic cardiac function are generally witnessed. The survival time is very short. Lethality is approx. 95%. *(see chapter 17)*

4.3.5 Coagulopathy and haemorrhage

In 15–30% of patients with liver cirrhosis, coagulopathy leads to clinically relevant haemorrhagic diathesis. Dangerous and considerable *bleeding* may occur (nasal, gingival), and there may well be pronounced cutaneous haemorrhages; the latter occasionally occur as sugillations, ecchymoses and petechial haemorrhages (s. fig. 20.1) or as disseminated petechiae, especially around postoperative scars. (s. fig. 20.2) Gastrointestinal bleeding can be assigned to the upper gastrointestinal area in 80–85% and to the lower intestinal area in 15–20% of cases. *(see chapter 19)*

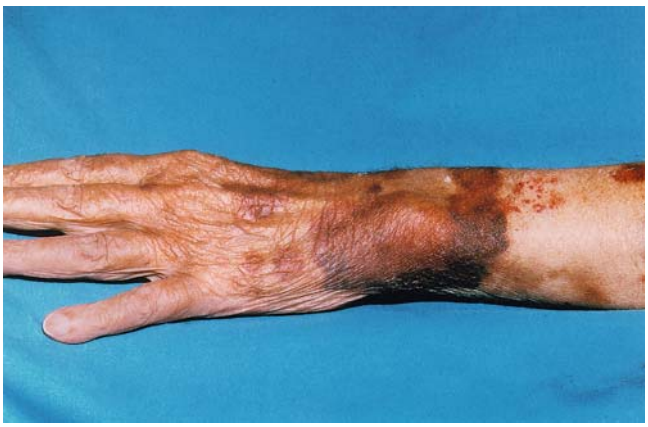

Fig. 20.1: Sugillations, ecchymoses and petechial haemorrhages in liver cirrhosis (with "paper money skin" and white nails)

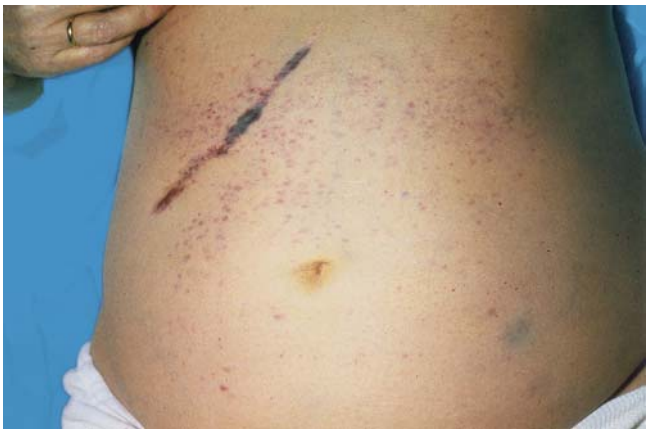

Fig. 20.2: Extensive purpura in the abdominal area with bleeding into the cholecystectomy scar

4.4 Acute-on-chronic liver insufficiency

This condition describes acute liver failure in cases of hitherto well-compensated liver disease. The result is a sudden deterioration in clinical status accompanied by jaundice as well as hepatic encephalopathy and/or the hepatorenal syndrome.

There are a number of *causes* including (*1.*) well-known hepatotoxic factors (e. g. superimposed viral infection, alcohol consumption, hepatotoxic drugs, intoxication) and (*2.*) endogenous factors (e. g. sepsis, variceal bleeding, gastrointestinal haemorrhage, diarrhoea, hypoxia). Acute liver failure is frequently the result of a chain of damaging events, like a vicious circle.

The clinical and laboratory *findings* of this sudden deterioration largely correspond to those of acute liver failure (see above). This also applies to potential *complications* such as coagulopathy, HE, ascites and/or HRS.

5 Therapy

Except for the treatment of, for example, paracetamol intoxication and Amanita phalloides poisoning, there is no causal therapy for liver insufficiency. All conservative treatment measures are based on **four principles:**

1. Prevention and treatment of complications
2. Substitution of substances which cannot be adequately produced in the liver as a result of hepatic synthesis disorders
3. Bridging the period of time until toxins have been eliminated, liver functions and regenerative processes have improved or liver transplantation can be carried out
4. Promotion of liver regeneration

► **Intensive care:** Patients with ALF or with decompensated chronic liver insufficiency (such as coma stages II–IV, refractory ascites, hepatorenal syndrome, disseminated intravascular coagulation, gastrointestinal bleeding) require monitoring and treatment in an intensive care unit, preferably in a transplantation centre. (7, 13, 60, 66, 77)

5.1 General therapeutic measures

Intensive care involves monitoring the *cardiovascular system* (blood pressure, pulse, ECG) and *respiratory frequency.* The patient's *temperature* and *urine excretion* have to be recorded every hour. The *body weight* is documented every day using a weighing bed. The water equilibrium should be carefully monitored. Consistent *preventive measures against infection* must be guaranteed for those patients who are particularly at risk. Regular physical measures for the *prevention of pneumonia* are a necessity. A moderate *head-up position* (30–40°) is recommended. • A *central venous catheter* (monitoring central venous pressure, parenteral feeding), a *nasogastral tube* and a *suprapubic bladder catheter* are positioned for supply and monitoring purposes. *Nasal oxy-*

gen supply is advisable. The insertion of an epidural *intracranial pressure probe* is essential for early identification of cerebral oedema.

Provided the patient does not have a paralytic ileus, **enteral feeding** via a nasogastral tube is advisable to prevent villous atrophy and thus reduce the risk of bacterial translocation. • **Parenteral feeding** (1,600−2,000 kcal/day) consists of a continuous intravenous supply of glucose and fat emulsions (MCT). Hypertriglyceridaemia may, in the case of lipid infusions for example, point to a lipid metabolism disorder, but it can also be due to increased glucose intake, which results in fatty degeneration of the hepatocytes and a corresponding reduction in liver function. Fructose, sorbitol and xylitol must be avoided! The supply of either liver-adapted amino acids or branched-chain amino acids (BCAA) is generally recommended for chronic liver insufficiency − but not advisable in cases of acute liver insufficiency, because almost all amino acids are elevated in the serum in endogenous hepatic coma. A high daily dosage of water-soluble vitamins (possibly divided into two doses) is important. Administration of zinc is recommended.

Electrolytes (Na, K, Ca, Mg) and **blood sugar** must be carefully monitored, and any deviation from the norm should be corrected immediately. The risk of **hypophosphataemia** must be eliminated by early parenteral substitution. During refractory episodes, such as those involving the acid-base equilibrium and **hyperhydration,** haemodialysis is usually indicated. In **hypoalbuminaemia,** substitution with salt-free albumin is necessary. • With about 75% of patients, **artificial respiration** is called for, the aim being controlled hyperventilation.

N-acetylcysteine is believed to promote the supply of oxygen to the tissues. (72) As a result, this substance, which is free from side effects, was also recommended for cases of CCl_4 intoxication (52) and is even considered helpful in acute liver failure with a different aetiology.

As a **prophylaxis** against bleeding in the upper gastrointestinal area, *H_2 antagonists* and omeprazole are recommended. • The timely and repeated administration of *fresh plasma* (FFB) as well as of antithrombin III has proved to be the most effective measure for balancing plasmatic coagulation disorders.

Bacterial infections are extremely common as a result of serious impairment of the cellular and humoral resistance (ca. 80%). Close-meshed bacteriological investigations are required in the frequent absence of clinical signs of infection. This leads to early antibiotic therapy based on an antibiotic sensitivity test. Although an antibiotic prophylaxis is not actually recommended, it should nevertheless be considered in the individual case, since the spreading of an infection has a decidedly negative impact on prognosis. Administration of **selenite** (i.v.) may be advisable. Around 30% of patients develop a fungus infection, with a mortality rate of 50%. The administration of amphotericin B or fluconazol is an effective prophylactic measure. • Bacterial or fungal infection can also be effectively suppressed by *intestinal restimulating of the bacterial flora* or **intestinal sterilisation** by means of neomycin (or paromomycin), a combination of nystatin and gentamicin, or lactulose. (50, 53) (s. pp 277, 280, 304)

EPL: In a pilot study, it was possible to achieve recompensation and lasting stabilization in 9 out of 10 patients suffering from severe liver insufficiency by i.v. administration of a new galenic form of polyenylphosphatidylcholine. (32) • This clinical result might be supported by the finding that a considerable deterioration in liver function was associated with a deficit of essential phospholipids (= EPL). (15) (s. p. 865)

5.2 Specific therapeutic measures

Paracetamol intoxication: Liver damage due to paracetamol (>10 g) becomes manifest within ca. 48 hours after intake. (s. p. 378) For this reason, it is essential first of all to remove the non-absorbed fractions by *gastric lavage* and *intestinal cleansing*. As medicinal treatment, i.v. administration of the glutathione precursor *N-acetylcysteine* is the therapy of choice (L. F. Prescott et al., 1977). Dosage is 150 mg/kg BW with glucose as a rapid i.v. infusion (15−20 minutes), followed by 50 mg/kg BW over 4 hours and finally 100 mg/kg BW during the next 16 hours (= about 300 mg/kg BW within 20 hours). This therapy has to be commenced as soon as possible (no later than 12−15 hours after intoxication), even though a hepatoprotective effect can still be achieved up to 36 hours later. A serum concentration of <200 µg/ml within 4 hours or <60 µg/ml within 12 hours after intake can be considered prognostically favourable. (s. fig. 20.3)

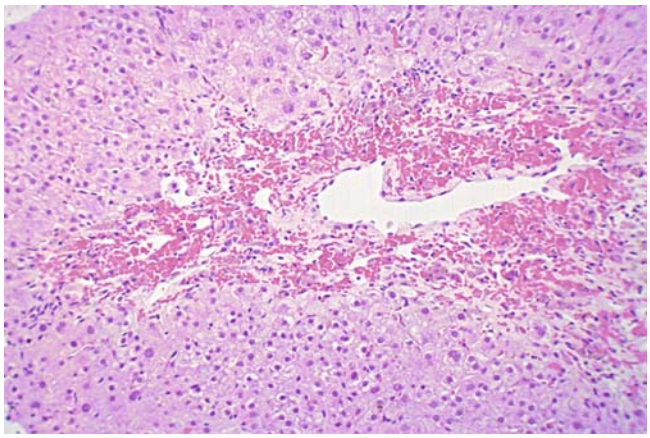

Fig. 20.3: Centrilobular, two-week-old liver cell necrosis resulting from paracetamol intoxication (HE)

Amanita phalloides poisoning: After a symptom-free latent period of about 12 hours, the gastroenteric phase sets in. (s. pp 378, 571) In this type of intoxication, it is imperative to carry out *gastric lavage* and *intestinal cleansing* as soon as possible with the help of saline agents using a nasogastral tube. The intestinal administration of medicinal charcoal is recommended. *Diuresis* must be enhanced by the administration of frusemide, if necessary with simultaneous volume substitution (CVP of about 10 cm H_2O). After another low-symptom period of about 1 day, the hepatorenal phase sets in. The uptake of Amanita phalloides poison into the liver is inhibited by *penicillin* (1 mega unit/kg BW/day as i.v. solution over 3 days). The therapeutic efficacy of silymarin and *silibinin*

was first detected in animal experiments in 1975 (G. Vogel et al.) and subsequently confirmed by a number of clinical studies. The recommended dose of silibinin is 30 (−50) mg/kg BW/day, administered in 4 separate doses in i.v. glucose infusions, each lasting 2 hours, over a period of 3 to 4 days. Penicillin and silibinin can (and should) be applied in combination. There is no specific antidote for Amanita toxins. Given timely and appropriate therapy, morbidity and mortality are surprisingly low. • In cases of therapy failure or a critical course of disease, liver transplantation may be indicated.

Cerebral oedema: *Mannitol* (0.5 g/kg BW or 100 ml, each as 20% solution) is used to treat the dreaded cerebral oedema. If renal function is sufficient, this course of therapy can be repeated every 1 to 4 hours, as required. Serum osmolality should not exceed 320 mosm/l, and intracranial pressure should not go above 20 mmHg. When renal function is restricted, dehydration should only be effected by means of haemofiltration. *Artificial respiration* is required (often as PEEP ventilation). Continuous monitoring of the intracranial pressure by means of an epidural *intracerebral pressure probe* is extremely helpful. Frequently, there is increased susceptibility to cerebral convulsibility; therefore, phenytoin should be administered at an early stage. Therapeutic application of *thiopental* (A. Forbes et al., 1989) as i.v. solution (up to 150 mg/hour) calls for intracranial pressure probe monitoring. (22) Other means of lowering the intracerebral pressure include the use of aminophylline, ranitidine, luxus oxygenation and semirecumbent positioning. (9, 17, 22, 34, 63) A prophylactic reduction in pCO_2 down to 25−35 mm Hg through **hyperventilation** can be advantageous in the initial stage of a brain oedema. (17, 63) Moderate **hypothermia** (core temperature down to 32−33 °C, for 10−12 hours) may be useful in reducing the intracerebral pressure and cerebral blood flow as well as the cerebral uptake of ammonia. (31)

Ornithine aspartate (40 g/8 hours as intravenous infusion) (51) and **flumazenil** are advisable for the treatment of hepatic precoma and coma.

Dopamine (2 to 4 µg/kg BW/hr) should be administered at an early stage to stabilize the circulation and the renal blood flow. • **N-acetylcysteine** can be applied during oxygenation due to its positive effect on stabilizing the blood circulation and improving the serum coagulation factors. • **Indomethacine** reduces cerebral ammonia uptake.

Prostaglandin: The positive results achieved by the application of PGE_1 were reported in 1987 (M. Abacassis et al.). According to a subsequent prospective study, 71% of patients with fulminant and subfulminant hepatitis survived. (55, 61) The effect is attributed to improved arterial flow and regeneration of the liver (0.1 to 0.6 µg/kg BW/hr by means of perfusor for up to 18 hours, with the dosage gradually being phased out). • *Beware of hypotension!*

Glucocorticoids were first administered with some success in acute liver failure by H. Ducci et al. in 1952. Good results were also achieved in the treatment of severe alcoholic hepatitis with liver insufficiency (R. A. Helman et al., 1971). The application of glucocorticoids in autoimmune hepatitis with acute liver failure did not prove successful. (43) • The first report containing good results after treating fulminant viral hepatitis B with **anti-HBs plasma** was published in 1971 (D. J. Gocke). • The treatment of fulminant hepatitis B with **interferon alpha** did not progress beyond initial attempts (S. Levin et al., 1989).

Lamivudine (100 mg/day) proved to be effective: it was possible to achieve a lasting improvement in liver function and to avoid liver transplantation. No side effects were observed.

In view of the loss of complex biochemical liver functions, drug intervention in the metabolic processes of the liver should be as varied as possible − even the use of therapeutic agents which are not clinically controlled may be biochemically or pharmacologically justified.

► For a detailed description of **treatment measures** see: *hepatic encephalopathy* (chapter 15.9), *ascites* (chapter 16.9), *hepatorenal syndrome* (chapter 17.5), *coagulopathy and bleeding* (chapters 19.1.7 and 19.2.6).

5.3 Liver support systems

The most important survival factor in acute liver failure is the **patient's age**. In the 15 to 25-year age group, 30−50% of patients survive, whereas those older than 30 years have hardly any chance of survival. It would appear that the good regenerative ability of the liver in young people is the best guarantee for survival. • An attempt must be made at **bridging the decompensatory phase** by means of optimum intensive care and monitoring of the cerebral pressure as well as by applying clinically proven or indeed new therapeutic procedures or medication until the liver has adequately regenerated or until liver transplantation can be carried out. • Basically, there are **three techniques** available for bridging the compensatory phase: (*1*.) extracorporeal systems (*2*.) biosynthetic artificial livers or hybrid organs, and (*3*.) transplantation of hepatocytes. (85, 95, 96, 106)

5.3.1 Extracorporeal systems

1. **Exchange transfusion** (C. Lee et al., 1958): This method was used to fractionate and repeatedly exchange the entire circulatory blood of a patient. However, based on the results of subsequent studies (G. Baltzer et al., 1971; A. G. Redeker et al., 1973), this procedure can no longer be recommended.

2. **Haemoperfusion:** The removal of both water-soluble and protein-bound substances from the plasma was first attempted by means of a haemoperfusion circuit, using a column filled with activated charcoal (D. C. Schechter et al., 1958; H. Yatzidis et al., 1964). Both the unwanted binding of corpuscular components and the danger of embolization from charcoal particles could largely be eliminated by coating the activated charcoal with a biocompatible membrane, i.e. microencapsulation (T. M. S. Chang et al., 1964). Because of the greater aggregation of thrombocytes, however, thrombopenia often ensues. This event can generally be prevented by the administration of prostacyclin (C. A. E. Gimson et al., 1980). Unfortunately, however, this procedure causes a loss of insulin and other hormones. (88)

3. **Cross-circulation:** *Homologous* cross-circulation with healthy volunteers was first attempted by J. M. Burnell et al. in 1965. • Due to multiple problems, S. C. W. Bosman et al. introduced *heterologous* cross-circulation using a baboon in 1968; baboons are the only animal species which can tolerate human blood for 5 to 7 days.

4. **Plasmapheresis:** This procedure is a further development of blood exchange (M. J. Lepore et al., 1967). The patient's plasma is separated by centrifugation or other appropriate techniques and discarded, so that the protein-bound and fat-soluble toxins circulating in the plasma are removed. This plasma volume is replaced by fresh plasma. At the same time, the separated corpuscular components of the patient's blood are reinfused. Serious complications may arise from the transmission of viral hepatitis and the occurrence of transfusion-related lung disorders (ARDS). Nevertheless, the method involved is simple and has been carried out successfully in individual cases (87, 91) even as plasma exchange with the administration of a high plasma volume (1.3 l/hr over 8 hours). • It has proved to be much more successful when the serum (ca. 3 l

fresh frozen plasma/day) is infused into the femoral artery rather than into the vein (G. Brunner et al., 1991).

5. **Plasma perfusion:** In 1974 patient plasma separated by plasmapheresis was for the first time passed through activated charcoal and artificial resin in order to absorb toxins. In this way, the patient's own purified plasma is reinfused together with the solid components of the blood. This procedure produces fewer side effects and is easy to carry out.

6. **Total body wash-out:** This technique is a modification of exchange transfusion. The circulatory system is washed out with electrolyte solutions and then refilled with donor blood whilst the patient is in a state of hypothermia (G. Klebanoff et al., 1972).

7. **Haemodialysis:** In 1968 temporary improvement could be achieved for the first time by means of haemodialysis in a patient presenting with fulminant hepatic failure (W.M. Keynes); this was repeated later in 1977 (R. Oules et al.). The procedure, however, is not generally recommended. It may be indicated in renal failure, acid-base disorders or with hyperhydration. Following haemodialysis, substitution of reduced amino acids is necessary.

8. **Haemofiltration:** This procedure turned out to be of more value than haemodialysis. No dialysate fluid is required. Instead, a solution containing buffered bicarbonate is used to replace the ultrafiltrate. In fulminant hepatic failure, continuous venovenous haemofiltration is recommended because of its advantages for the circulation and metabolism. Heparin or prostacyclin can be used as anticoagulants (C.A.E. Gimson et al., 1980).

9. **Haemodiabsorption:** The BiologicDT system is a combination of haemodialysis and haemoadsorption (S.R. Ash et al. 1992). (82) Plasma separation was subsequently added to this system (S.R. Ash et al., 1998). (83) This newly developed BiologicDTPF facilitates direct plasma contact with the haemodiadsorber. The system, which makes use of both a charcoal and a cation exchanger, dialyzes blood across a parallel plate dialyzer with a cellulose membrane. So far, results have been disappointing – only lactate, creatinine and bilirubin were reduced.

10. **Albumin dialysis:** The aim of albumin dialysis is to remove both soluble metabolites and albumin-bound substances (ABS) from the blood of patients with acute liver failure. (s. tab. 20.5)

benzodiazepines	fatty acids
bile acids	phenylalanin
bilirubin	several peptides
carbon hybrids	tryptophan
copper	*etc.*

Tab. 20.5: Albumin-bound substances (ABS) relevant in acute liver failure

SPAD: Single-**p**ass **a**lbumin **d**ialysis was the first method to be developed. The blood of the patient is extracorporeally dialyzed through an albumin-impermeable membrane against albumin in the secondary circuit. The loaded albumin is discarded.

MARS: The SPAD method was further developed into a combination of dialysis, filtration and adsorption (= **m**olecular **a**dsorbent **r**ecycling **s**ystem). (103). The patient's blood is fed through a hollow-fibre filter and dialyzed against an albumin dialysate. The ABS (s. tab. 20.5) pass through the pores in the filter and become bonded. Plasma proteins, hormones and vitamins are not lost. The albumin dialysate is recirculated in a closed circuit where it is fed through a second dialyzer and two adsorber columns which bind the ABS. The albumin dialysate is returned to the hollow-fibre filter. It is dialyzed against a bicarbonate solution in order to remove the excess water and water-soluble substances (ammonia, creatinine, urea, iron, copper) as well as to stabilize the electrolyte and glucose levels and the pH value. The results obtained to date are promising. (93, 101, 104) (s. fig. 20.4)

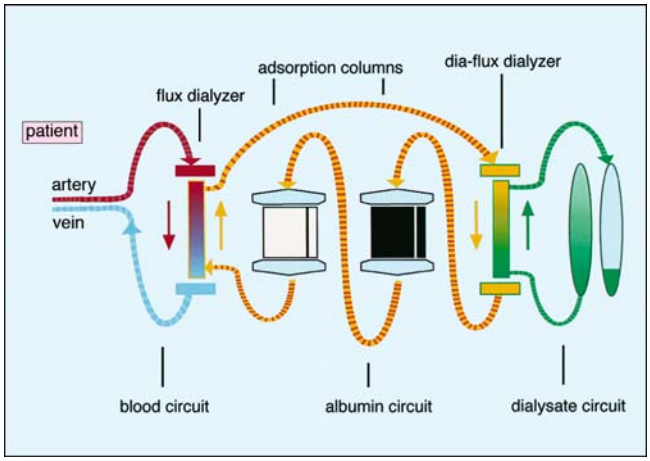

Fig. 20.4: Diagram showing the molecular adsorbent recirculating system (MARS)

FPSA: Fractioned **p**lasma **s**eparation and **a**dsorption is a very efficient and multifactorial method, employing membranes and adsorbants. (86) It is additionally characterized by the use of microparticles (2.0–3.5 µm), which are recirculated in suspension using high-speed flow (2–4 l/min) to optimize the in-line filtration process. In a further development, a special sulfone filter is applied.

Prometheus: In the meantime, the Prometheus method has been introduced. (97) Here, the plasma is separated out by an albumin-permeable filter and cleaned in a secondary circuit via an adsorber together with conventional high-flux haemodialysis. Direct contact between the albumin plasma and the adsorber helps to increase the efficiency of this method.

► These liver support methods serve to detoxify the organism for a limited period of time. They are regarded as **supportive measures** in intensive care. Survival time has often been prolonged, yet only in isolated cases has the overall life-span of the patient been extended. These methods of treatment, which are costly and involve considerable resources, can only be carried out in medical units that are equipped with all the facilities of intensive care and thus in a position to effect epidural brain pressure measurement, blood purifying processes and liver perfusion methods. • Only young patients between the ages of 15 and 25 have a real chance of survival (40 to 50%), provided they receive optimum intensive care. With patients over 30, supportive techniques should only be applied to bridge the time period until a liver transplantation can be carried out.

However, **conservative treatment** may be attempted for 4 or 5 days under the following conditions irrespective of *age*: (*1.*) there may be a chance of regeneration during this period that can be made use of; (*2.*) this period of time does not preclude the patient's chances of liver transplantation (which generally calls for 2 to 4 days' preparation time); (*3.*) should there be no signs of recovery or regeneration, not even in younger patients (< 30 years), transplantation is nevertheless indicated. • After 4 or 5 days, however, severe *complications* develop, also

in younger patients, which render transplantation difficult or even impossible. Especially, older patients (> 30 years) should always undergo liver transplantation without delay.

5.3.2 Bioartificial systems

Temporary substitution of the liver function using hepatocytes (e. g. in haemofiltration systems or bioreactors) is conceivable in acute liver failure, possibly in conjunction with activated charcoal filtration or with plasma separation. The importance lies in bridging the phase of acute liver failure until compensation of the liver function or liver regeneration is achieved.

The bioreactor is filled with capillaries in which the patient's blood circulates; some of this blood has already been oxygenated extracorporeally. The efficacy of the system depends on an efficient exchange of the corresponding substances in both directions as well as stable hepatocyte functions. It is possible to use human (allogeneic) or animal (xenogeneic) hepatocytes as well as cell cultures (immortalized cells or tumour cell lines). If human cells are taken, 10^{10} hepatocytes per patient are required – as would be needed for a conventional liver transplant. With regard to the use of animal hepatocytes, there is a possible risk in that no solution has yet been found to the question of zoonosis transmission and there may be an immune reaction to foreign antigens. Bile flow also remains a problem. (90, 98, 99, 107, 108)

1. The so-called "artificial liver" system was first developed by K. N. Matsumura et al. (1978). This procedure comprised haemodialysis across a **suspension of vital hepatocytes.** • Such semi-artificial liver was first used clinically in 1987 on a patient with bile-duct carcinoma and acute liver failure (K. N. Matsumura et al.).

2. The binding of microsomal **liver enzymes to synthetic carriers** is a promising method of temporarily compensating important liver functions (G. Brunner, 1981).

3. **Bioartificial liver (BAL):** Freshly isolated hepatocytes of pigs, immobilized on collagen-coated microcarriers, remained vital in-vivo and in-vitro over a longer period of time in a perfusion system; they were able to conjugate bilirubin and synthesize proteins. These results provided the basis for developing an extracorporeal bioartificial liver (A. A. Demetriou et al., 1986). In more advanced systems, plasma was perfused through an activated charcoal column and a fibre system with cultured pig liver cells. (90, 95, 98, 108) • With the help of a BAL, the plasma is separated by centrifugation and directed into a reservoir in order to increase both the plasma and metabolite flow. By integrating an activated charcoal column, it is possible to effect a greater elimination of toxins. The separated plasma reaches the hollow-fibre bioreactor, where it is perfused through the previously inserted hepatocytes (7 ± 1 hours). • Such a system yielded increased production of coagulation factors in a patient with alcohol cirrhosis (D. F. Neuzil et al., 1993). (s. fig. 20.5)

4. **Extracorporeal liver assistance device (ELAD):** Attention has recently focused on temporarily replacing the liver function with hepatocytes which have been cultured in the extracapillary space of a cellulose-acetate hollow-fibre unit. Each unit contains ca. 200 g C3A cells, an amount which is necessary for successful perfusion. ELAD has proved efficacious in clinical use. (106)

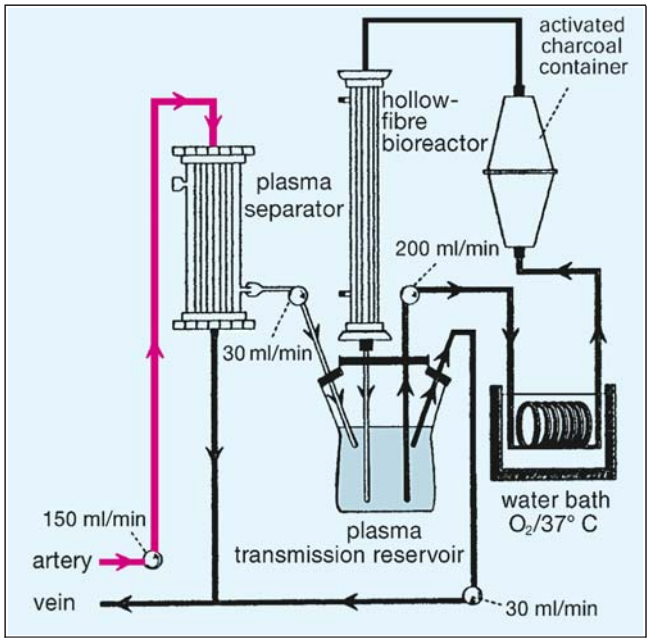

Fig. 20.5: Diagram showing a bioartifical liver (BAL) (98)

5. **BLSS:** The **b**ioartificial **l**iver **s**upport **s**ystem is made up of a blood pump, a heat exchanger to control the blood temperature, as well as an oxygenator and a bioreactor. The hollow-fibre bioreactor generally contains 70–100 g of porcine liver cells. Initial experience with BLSS is encouraging. (92)

6. **BELS:** The **B**erlin **e**xtracorporeal **l**iver **s**upport system consists of a three-dimensional accumulation of approx. 500 g pig liver cells. These cells are linked by means of capillaries and provided with oxygen independently of the patient's blood, so that they function and stay vital for several weeks. (89)

MELS: The **m**odular **e**xtracorporeal **l**iver **s**upport system was developed from BELS. In contrast to BELS, however, it consists of three modules: (*1.*) a cell module with human hepatocytes, (*2.*) single-pass albumin dialysis and (*3.*) a dialysis module for constant venovenous haemofiltration. (100)

The clinical significance of bioartificial systems will largely be dependent upon whether it is possible (*1.*) to keep functional hepatocytes alive in extracorporeal systems for an adequate period of time and (*2.*) to make such systems available at short notice for use in emergencies.

5.3.3 Extracorporeal liver perfusion

The idea of extracorporeal liver perfusion (ECLP) for removing toxins by way of perfusion using an animal liver goes back to Andrews (1953), who used this technique for liver substitution in dogs. In 1958 J. J. Otto et al. applied this method and demonstrated a clear reduction in pathologically elevated serum ammonia values in the dog. • In 1965 B. Eiseman et al. first treated hepatic coma in humans by perfusion using a pig liver. • The use of baboon livers yielded further progress (S. Saunders et al., 1968; T. S. Lie et al., 1976). Treatment was reported to be successful in isolated cases. This procedure has been successfully taken up again, using human livers which, for medical or organizational reasons, could not be transplanted. • Vital pig livers are now also used. The fresh liver is kept in a sterile chamber where it receives the patient's blood via the portal vein and, if necessary, via the hepatic artery. There have been no reports of xenogenous infection or rejection. Although

the procedure is relatively safe, the results obtained with perfused livers from humans or baboons would appear to be better than is the case with livers taken from pigs.

5.4 Liver transplantation methods

Liver transplantation is the method of choice in all patients with acute liver failure whose spontaneous survival rate without a transplant is <20%, taking into account all the parameters. Criteria proposed by King's College or Clichy provide a useful basis for assessment. The crucial factor, however, remains the choice of the appropriate time for carrying out the transplantation: (*1.*) the possibility of eliminating decompensation by means of regeneration should be exploited; (*2.*) delayed indications should not result in complications which would prevent a transplantation from being carried out (e.g. brain-stem herniation, sepsis).

5.4.1 Orthotopic transplantation

► The **survival rate** following orthotopic transplantation in acute liver failure is 50 to 80% after 1 year and about 60% after 5 years. When the **indication** for transplantation is given, it is impossible to foresee to what extent the patient's life might be lengthened. The decision as to whether and when a transplantation is indicated continues to be arbitrary. The question of which patients will benefit most from transplantation is still unresolved − particularly since liver diseases are in general potentially reversible. However, acute liver failure due to Wilson's disease or the Budd-Chiari syndrome is an indication for liver transplantation, because these conditions are always lethal otherwise. Of all liver transplantations in Europe, a constant 10−12% are carried out due to ALF. In patients under the age of 45, this figure is 20%. Meanwhile, OLT has already been carried out on four adolescents for Ecstasy-induced liver failure. • With an isoelectric line in the electroencephalograph and with irreversible cerebral oedema, transplantation is no longer possible. The prognosis is likewise poor for decompensated liver insufficiency as a result of "acute-on-chronic failure" (e.g. acute virus infection or intoxication in cirrhosis), even after conservative and invasive intensive care therapy or indeed after liver transplantation. (20, 44, 109−111, 119, 120, 123, 124) *(see chapter 40.7)*

The following *criteria* are indicators for an **ultima ratio transplantation** in cases where the probability of survival without transplantation would be <20% (T.E. Starzl et al., 1989):

1. Foudroyant deterioration of the general state of health
2. Severe coagulation disorders
3. Coma stages III to IV
4. Metabolic acidosis
5. Liver atrophy
6. Circulatory insufficiency requiring catecholamines
7. Manifestation of septic multiple organ failure

SLT: Split **l**iver **t**ransplantation was developed as an alternative to OLT (118). The transplanted split should be around 1% of the body weight of the recipient. SLT has a higher complication rate than OLT.

LDLT: With regard to **l**iving **d**onor **l**iver **t**ransplantation, SLT has become particularly important in cases where no cadaver organ is readily available. Living donor liver transplantation was first carried out on children. The left lateral segment, usually segments II and III, of the donor's liver is used. Around 5% of OLT candidates are also suitable for LDLT. More than 2,500 living donor liver transplantations have been carried out worldwide. The donor mortality rate is 0.2−0.3%. (115, 116, 122)

5.4.2 Auxiliary partial orthotopic liver transplantation

In 1991 auxiliary partial orthotopic liver transplantation (APOLT) was successfully carried out for the first time in acute liver failure, with the subsequent possibility of dispensing with the transplant after regeneration of the patient's own liver. (112) The corresponding part of a donor liver is transplanted orthotopically as left lateral segments II and III into the acutely diseased liver. The requisite partial resection of the liver is considered difficult. (121) A European multicentre study (12 centres) achieved equally good results in 30 patients compared to orthotopic liver transplantation with the removal of the native liver (M.-P. Chenard-Neu et al., 1996). APOLT is intended as a temporary measure in acute liver failure with the aim of discontinuing immunosuppressive therapy after the patient's own liver has regenerated. So far, results imply that more complications are experienced in APOLT than in OLT.

5.4.3 Heterotopic transplantation

The concept of heterotopic transplantation of a complete or even partial ("spliced") donor liver should also be pursued further. Heterotopic transplantation involves placing an auxilliary (additional) organ in the right upper abdomen (O.T. Terpstra et al., 1988). In surgical terms, this technique is considered to be demanding due to the application of the piggy-back method (= anastomosis of the donor liver with the appropriately prepared ostium of the hepatic veins to the infrahepatic caval vein, generally cranial to the opening of the renal vein). • These two methods (APOLT and auxiliary heterotopic liver transplantation) are particularly suitable for juveniles with acute liver failure because they bridge the critical time span preceding the regeneration of the diseased liver. Immunosuppression is thus only required for a restricted period of time. The transplant shrinks or is surgically removed. Acute liver failure induced by Ecstasy was successfully overcome using this technique. (113) It allows the liver function to be compensated and gives the diseased liver time to regenerate. (117)

5.4.4 Xenotransplantation

Pigs with human immune system genes are expected to facilitate the production of transgenic donor organs (D. White, 1992). This is the basis of all endeavours to use transgenic pig liver for the purpose of xenotransplantation (J. Platt, 1993). In the future, genetic engineering should make it possible to eliminate the immunobiological risk of complement-activated, hyperacute rejection. However, the problem regarding the transmission of zoonoses has not yet been resolved. To date, a survival period of 70 days has been achieved with three xenotransplants in ALF and chronic liver insufficiency (J. Fung et al., 1997).

5.5 Transplantation of hepatocytes

Liver cells were successfully transplanted for the first time in experiments on rats (A.J. Matas et al., 1976; C.G. Groth et al., 1977). The requirements for transplantation include absolute care in the

production of an adequate quantity of **vital liver cells** of utmost purity as well as the possibility of cryopreservation and in-vitro culturing. The cells are injected locally into the implantation area or infused selectively into the organ through a vascular catheter. Special adhesive-supporting substances can be used in this process (agarose gel, micro-encapsulation into thin membranes, etc.). (125−130)

Among the experimentally tested **transplantation sites** are the spleen, kidneys, lungs, pancreas, peritoneum, greater omentum and fatty tissue. Up to now, the spleen has proved to be the most suitable. The transplantation of foetal liver cells into the spleen may even culminate in a liver lobule-like formation with bile ducts and veins − however, the functional results have (so far) been no better than with normal hepatocytes.

The question of the required **number of hepatocytes** has still not been resolved: the collapse of a certain liver function (e. g. normalization of factor VIII values in serum) can be compensated by a far lower number of hepatocytes than is the case with total liver failure (e. g. acute liver failure). Calculations made up to now have claimed that there are at least 10^7-10^8 liver cells in partially resected liver parenchyma.

Indications for the transplantation of hepatocytes predominantly involve those liver diseases in which functional failures occur in the liver cells (not in the bile ducts). • Permanent transplantation would be indicated, for example, in order to eliminate *congenital metabolic disorders* of the liver cells. In this case, hepatocytes from the patient could be used, with subsequent elimination of the defect by gene technology, as well as hepatocytes from healthy donors. A few years ago, a therapeutic effect lasting for over one year was achieved for the first time in a girl suffering from the Crigler-Najjar syndrome (I. J. Fox et al., 1998). • Human hepatocytes are most definitely more suitable than animal liver cells. The latter may well meet the requirements for a provisional substitute, but not for permanent transplantation.

Future prospects

► Looking to the future, it can be expected that the next few years will witness advances in gene technology (e. g. transgenic animal liver) and molecular biology (e. g. targeted blockade of the immune system against the liver transplant) or even produce new concepts of liver and hepatocyte transplantation.

► It is no longer too bold to pin legitimate hopes on the development of an artificial liver. The preliminary objective hereby must be to replace the most important liver functions for a longer period of time, thus affording the diseased liver of the patient a greater chance to regenerate.

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Liver support systems

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