Symptoms and Syndromes

16 Oedema and ascites

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1 Water and electrolyte balance

► **Water** is an indispensable factor of life. By means of carefully coordinated regulatory mechanisms, the *water equilibrium* and hence the reservoir of body water is held constant. It is important to keep water intake and output in balance to maintain *isovolaemia*. (s. fig. 16.1)

Water is present in a free (non-osmotically bound) state and as a chemically bound hydrate solid structure. • The **clearance** of free water is controlled by vasopressin; it is calculated from the volume of urine/minute minus the osmolal clearance. A normal daily fluid intake of 1,700−2,200 ml (25−30 ml/kg BW) in addition to some 300 ml oxidation water is balanced by a fluid discharge of approximately 1,500 ml as urine, about 100 ml in stools, roughly 600 ml as perspiration and some 400 ml as expired air. (s. fig. 16.1)

About 60% of the body's weight (ca. 55% in women) consists of water. The reservoir of body water is distributed between the **intracellular space** (ca. 40% of BW) and the **extracellular space** (ca. 20% of BW). The extracellular compartment consists of plasma fluids (ca. 4% of BW) and interstitial water (ca. 16% of BW), the latter also containing transcellular water (ca. 2.5% of BW). Because of its high degree of permeability, the body water is evenly shared between the intracellular and extracellular compartments. The water distribution between plasma and interstitium, regulated by **Starling's forces,** depends on the hydrostatic and colloidosmotic pressure gradients along the capillary walls. • **Disturbances in the excretion of water** are derived from (*1.*) an increase in ADH activity, (*2.*) a reduction in distal filtrates available in the nephron, and (*3.*) greater absorption of water in the distal nephron, independent of ADH. Disruptions in the body water pool cause changes in serum sodium or serum osmolality.

► **Electrolytes** are subject to dissociation into negatively charged anions and positive cations. The vital *electrolyte balance* guarantees the respective uptake and discharge and ensures the correct presence and distribution. This regulatory process is closely linked to the water equilibrium. The intracellular and extracellular spaces differ in their electrolyte content. (s. tab. 16.1)

	Plasma	Interstitial space (mval/l)	Intracellular space (mval/l)
Cations			
Sodium	142	145	10
Potassium	4	4	160
Calcium	5	5	2
Magnesium	2	2	26
	153	156	198
Anions			
Chloride	101	114	3
Bicarbonate	27	31	10
Phosphate	2	2	100
Sulphate	1	1	20
Organic acids	6	7	–
Proteins	16	1	65
	153	156	198

Tab. 16.1: Constituents of the most important electrolytes (in mval/l) in extracellular and intracellular fluid

► An **ionogram** of the fluid spaces compares the cation and anion content in milliequivalents, since it is not the weight, but the chem-

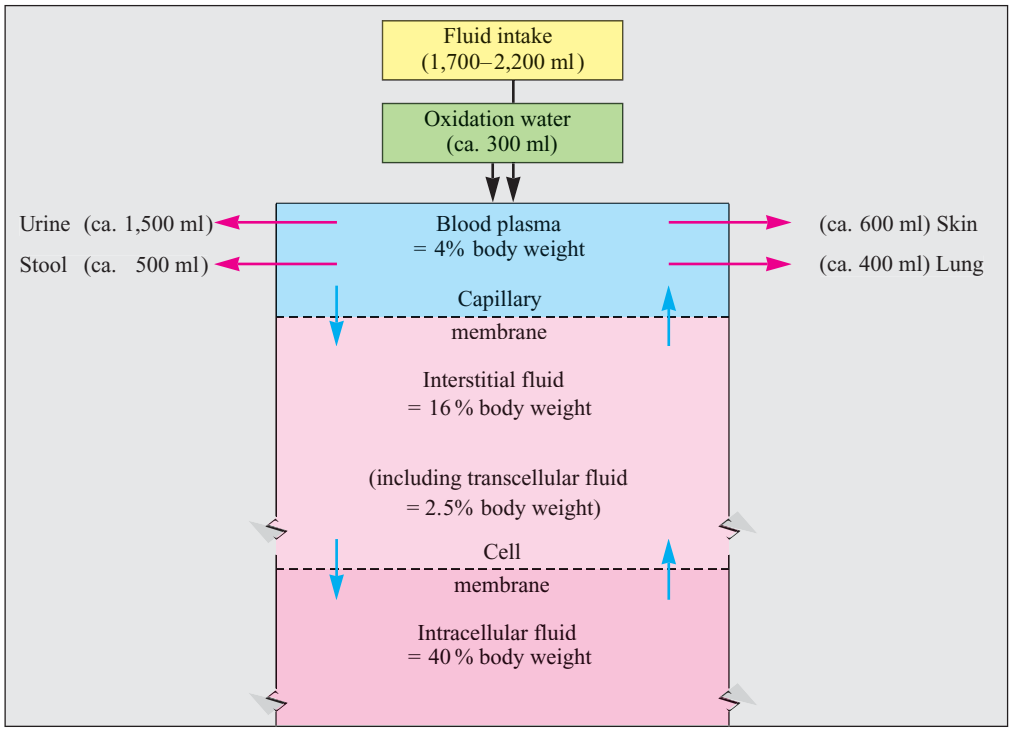

Fig. 16.1: Fluid spaces and exchange of water (blood plasma + interstitial fluid = extracellular space, intracellular fluid = intracellular space)

ical-binding potential (mval) of the ions that determines the electrochemical reactions between them. The electrolytes, which are partially integrated into the structures of the cells, do not develop any osmotic activity. For this reason, there is no osmotic gradient between the intracellular and extracellular space despite the difference in the distribution of ions (153 and 156/198 mval). • Apart from this, the ionogram also provides information on the osmotic pressure (mosmol) of the respective fluid. This value does not depend on valence, but on the number of particles dissolved in each litre of solution (= **osmolarity**; mmol/l) or per 1 kg water (= **osmolality**; mosmol/kg). All fluids with an osmolality of 285–295 mosmol/kg are isotonic with respect to plasma. (With 1-valent ions, mval, mmol and mosmol are identical; with 2-valent ions, 2 mval correspond to 1 mmol or 1 mosmol). The osmolality of urine is twofold to threefold the osmolality of serum (up to ca. 1,300 mosmol). • The normal **pH value** ranges between 7.35 and 7.45 in the extracellular fluid (blood plasma and interstitium) and between 6.8 and 7.0 in the intracellular fluid.

A number of transport systems guarantee the differing compositions of intracellular and extracellular fluid. Ion displacement gives rise to the development of concentration gradients between these two compartments. Water flows passively through the cell membranes in the direction of the hyperosmolar space. The regulatory mechanism of the so-called **Donnan equilibrium** takes effect (and generates a relative condition of ion equilibrium). To a certain extent, the compensation of osmolarity between the intracellular and extracellular spaces by way of fluid displacement in line with the **Darrow-Yanett principle** supports the homoeostasis process with the aim of maintaining iso-osmosis.

Isotonicity of the extracellular space is regulated by (*1.*) thirst mechanism, (*2.*) ADH, and (*3.*) dilution and concentration potential of the kidneys. • Maintenance of extracellular **isovolaemia** is effected by a change in renal sodium excretion. For this reason, disturbances in the sodium supply primarily result in changes in the extracellular fluid volume. • **Isohydria** is also continually regulated within the normal range.

► When fever occurs, the organism loses about *500 ml fluid* and some *25 mmol salts* per day for each one-degree rise in body temperature.

2 Definition

Depending on the extent of the extracellular volume, disorders of water and sodium balance are categorized as **dehydration** (= hypovolaemia) and **hyperhydration** (= hypervolaemia). In accordance with the behaviour of serum osmolality and serum sodium, hydration is subdivided into isotonic, hypotonic and hypertonic forms. Should it no longer be possible to achieve iso-osmosis owing to sustained or permanent disruptive mechanisms, the physiological regulatory processes gain ever-increasing pathophysiological significance – creating a vicious circle.

2.1 States of hydration

In the field of hepatology, three varying states of hydration are important:

(*1.*) **Isotonic dehydration** due to isotonic loss of fluid on account of diuretic therapy, diarrhoea, ascites taps or loss of blood (= extracellular space decreased, overall sodium status depressed, serum osmolality and serum sodium normal).

(*2.*) **Hypotonic dehydration** as a result of the loss of sodium from long-term diuretic therapy and from diarrhoea as well as due to inadequate sodium intake (= extracellular space decreased, intracellular space increased, overall sodium status depressed, surplus of free water, hypo-osmolality and hyponatraemia).

(*3.*) **Isotonic hyperhydration** due to hypernatraemia with generalized oedema in decompensated liver cirrhosis (= extracellular space enlarged, overall sodium status elevated, serum osmolality and serum sodium normal).

2.2 Oedema and anasarca

The term **oedema** (το οιδημα = the swelling) describes a rise in the extracellular fluid volume due to isotonic hyperhydration. Oedema is a *symptom* with multiple causes, yet no illness. • The term **anasarca** refers to a massive, generalized soaking of the subcutaneous tissue ("tissue dropsy"). (s. fig. 16.2)

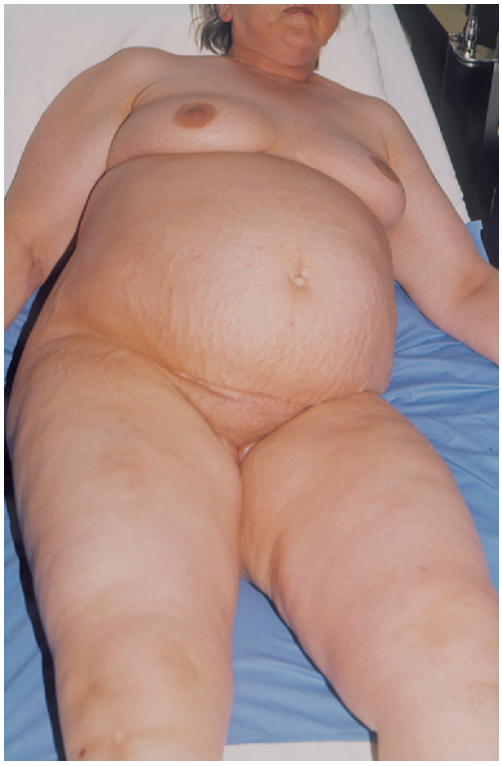

Fig. 16.2: Pronounced anasarca in portal ascites as a result of alcoholic cirrhosis

Anasarca is a circumscribed or diffuse, practically painless accumulation of serous liquid (generally poor in protein at first, but in most cases more rich in protein later on) in the skin, mucosa, parenchymal organs and nerve tissue. • The *clinical manifestation* of oedema can only be discerned during a physical examination if the enlargement of the extracellular space amounts to at

least 3−5 litres. *Latent oedema* ("pre-oedema") can be identified by an increase in body weight of >1 kg within four to five days. (s. fig. 15.2)

Oedema disease: It has not yet been clarified to what extent the so-called oedema disease, a chronic generalized condition of hydration of the interstitial tissue, may be regarded as a disease in its own right.

2.3 Ascites

► Erasistratos (ca. 300−250 BC) already recognized the connection between ascites and hepatic disease; he objected to the puncturing of ascites as being a non-causal and unnecessary measure. A. C. Celsus (30 BC−50 AD) postulated the link between ascites and renal disease or a poor general condition (carcinoma?); he coined the term "ascites". (s. pp 6, 7) • In animal experiments, it was possible to induce ascites by means of ligature of the inferior vena cava below the diaphragm (R. Lower, 1671). F. Th. Frerichs (1858) observed oliguria and renal dysfunction in cirrhosis patients. In 1863 A. Flint demonstrated that in cirrhotic patients with ascites, the morphology of the kidneys was normal − thus there must be a functional disorder in the renal area. With portal hypertension, E. H. Starling (1884) and R. Heidenheim (1891) found an increase in the lymphatic flow in the thoracic duct. • In 1943 D. Adlersberg et al. detected a reduced excretion of free water in cirrhosis patients with ascites. Proof of increased sodium retention was obtained by E. B. Farnsworth et al. in 1945. With these observations, made some 60 years ago, two essential pathophysiological findings were made in cirrhosis-induced ascites.

The term **ascites** (= hydraskos or abdominal dropsy) is defined as an accumulation of fluid in the abdominal cavity during the course of various diseases. Commensurate with the respective underlying disease, there is no homogeneity in the aetiology and pathogenesis of ascites. Hence ascites is not a disease as such, but rather a *symptom* of the advanced or severe course of an underlying disease. Generally, its prognosis is poor. The two-year rate of survival is about 50%. In liver disease or liver cirrhosis, the occurrence of ascites can give a clue to decompensation. • *Usually, ascites occurs in liver disease prior to the development of oedema.*

3 Pathogenesis

3.1 Oedematization

The **filtration pressure** (= difference between hydrostatic capillary pressure and tissue pressure) furthers the discharge of plasma fluid from the arterioles; as a result of the higher protein content of the plasma, the **colloidosmotic pressure** promotes the backflow of interstitial fluid into the venules. In the arteriole, the hydrostatic pressure is 40−45 mm Hg; it drops down to 10−15 mm Hg in the direction of the venous capillary loop. Both the colloidosmotic pressure and the tissue pressure remain unchanged at −25 to −30 mm Hg or −2 to −5 mm Hg along the arterial and venous parts of the capillaries. Consequently, an effective filtration pressure of 10−15 mm Hg is generated in the arterial capillary loop and of −10 to −15 mm Hg in the venous loop. (s. fig. 16.3)

The **pathogenesis** of oedema is derived from a change in these physical forces. The net flow from one compartment to the other is altered accordingly, as is the volume of the respective fluid space. (s. fig. 16.1) A disrupted distribution of the fluid can also be caused by damage to the capillary endothelium as a result of chemical, thermal, mechanical, toxic or immunological influences. This gives rise to a greater degree of permeability with increased protein transfer into the interstitium. • A reduction in the colloidosmotic pressure along the passage of the capillary results in less interstitial fluid being transported into the vascular lumen. (s. tab. 16.2)

1. **Deposition of interstitial liquid is augmented**
   - with increased hydrostatic capillary pressure
   - with increased permeability of the capillary endothelium
2. **Removal of interstitial fluid is restricted**
   - with depressed colloidosmotic pressure in the vascular lumen (e. g. hypalbuminaemia)
   - with augmented protein transfer into the interstitium
   - with decreased lymphatic drainage

Tab. 16.2: Causative factors of oedematization

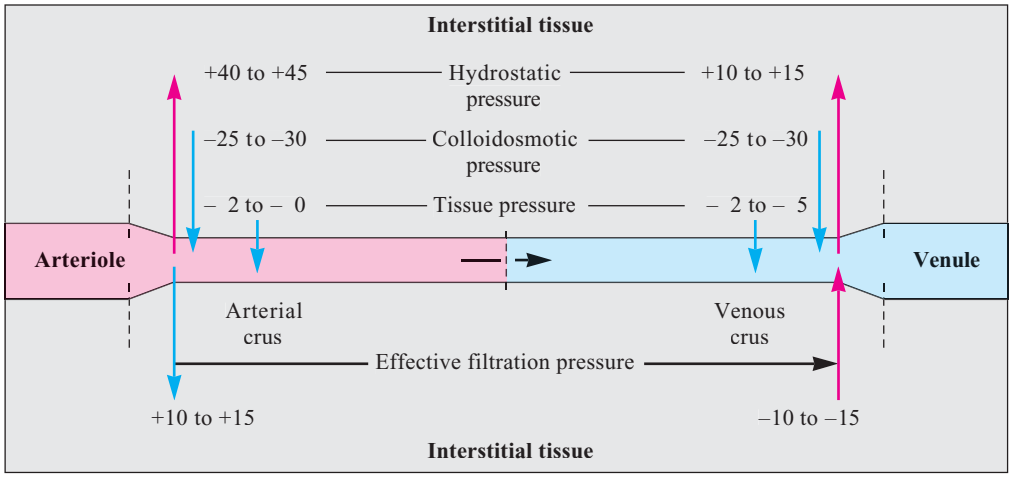

Fig. 16.3: Fluid exchange between plasma and interstitial tissue (mm Hg)

The *primary event* in oedematization is the renal retention of sodium, which provokes a greater feeling of thirst with an increase in ADH secretion. The result is renal water retention. • *A total of about 1 litre of water is retained per 140 mmol (ca. 3.3 g) sodium.*

In liver diseases involving elevated hydrostatic pressure (e.g. as a result of portal hypertension), the inflow of fluid into the interstitium is increased, whereas the return of fluid into the vascular bed is decreased due to the depressed colloidosmotic pressure (e.g. as a result of hypalbuminaemia). Likewise, a boost in capillary permeability leads to an outflow of fluid into the interstitial tissue. (2, 5, 8, 12)

3.2 Formation of ascites

3.2.1 Mechanical factors

The complex pathogenesis of ascites calls for focus on four mechanical factors. (s. tab. 16.3) The pathogenic significance of the respective factors can differ considerably in relation to the underlying diseases and at the same time vary greatly from individual to individual.

1. Increase in hydrostatic pressure
– portal hypertension
– narrowing of the inferior vena cava at the level of the diaphragm
– disruption of anatomic blocking mechanisms in the hepatic veins
2. Reduction in colloidosmotic pressure
3. Disturbance of capillary permeability
4. Insufficiency of lymphatic drainage

Tab. 16.3: Mechanical factors in the formation of ascites

1. **Increase in hydrostatic pressure:** Portal hypertension due to structural changes in the liver or its vessels, with peripheral and sinusoidal impediment to the outflow of blood, leads to blood stasis in the vessels, which are dilated by pressure. This inevitably generates an increase in hydrostatic pressure. The sinusoidal increase in pressure signals a greater retention of sodium in the kidneys. Another cause of ascites is constriction of the inferior vena cava at the level of the diaphragm resulting from regeneration nodes found in cirrhosis, especially since the inflow of blood into the liver is clearly increased at the same time. Disruptions of the anatomic blocking mechanisms in the hepatic veins may constitute further mechanical causes of elevated hydrostatic pressure.

2. **Reduction in colloidosmotic pressure:** The colloidosmotic pressure in the plasma is lower in liver cirrhosis patients. This results from (*1.*) restriction in the synthesis of albumin (which is, however, only clinically manifest after three or four weeks due to the half-life of plasma albumin), (*2.*) greater loss of protein-rich fluid in the abdominal cavity, and (*3.*) dilution of the vascular volume. A critical concentration of albumin in the plasma is deemed to be about 3 g/100 ml (ca. 435 µmol/l). Below this albumin value, there is a clear correlation between portal hypertension and the formation of ascites. • *The coexistence of portal hypertension and hypalbuminaemia (critical concentration 2.5–3.0 g/dl) is an important prerequisite for the formation of ascites.*

However, the significance of the decreased colloidosmotic (oncotic) pressure is not as great as has been hitherto assumed. Nevertheless, when the hydrostatic pressure is raised at the same time, **incongruity between these two Starling forces** is created, and fluid escapes into the abdominal cavity. This process is greatly furthered by the disparity between lymph production and lymph transport. These mechanical factors (s. tab. 16.3) may effect the formation of ascites, yet they cannot produce large quantities of ascitic fluid. Such a development, however, can be expected if capillary permeability is additionally heightened due to toxic or inflammatory causes.

3. **Disturbance of capillary permeability:** Capillary permeability is increased by endotoxins, inflammations or immunological processes. As a result, the degree of permeability for protein-rich fluid is greater. For this reason, it is no longer possible to maintain a colloidosmotic pressure gradient, which is why the hydrostatic pressure (in the absence of any counteraction from the colloidosmotic pressure) triggers an outflow of fluid into the abdominal cavity. In contrast to the sinusoids with their high potential permeability for protein-rich fluid, intestinal capillaries are only minimally pervious to protein, so that low-protein fluid passes into the abdominal cavity. Because of structural changes in the sinusoids, however, their degree of permeability to protein diminishes as the cirrhotic disease progresses.

4. **Insufficiency of lymphatic drainage:** Insufficient lymphatic drainage is of paramount pathogenic importance, which is why the theory of lymph imbalance became a subject of discussion regarding the formation of ascites. (s. p. 300) Initially, it is possible to compensate the rise in transsinusoidal lymph filtration by greater drainage via dilated lymph vessels. (s. figs. 7.7; 16.4) The normal capacity of the thoracic duct of 0.8–1.5 litres/day can thereby be raised five to ten times the standard amount and, with ascites, even to over 20 litres/day. In cases where the quantity of lymph is greater than the amount which can be removed, the lymph passes from the liver surface into the abdominal cavity (= *mechanical or mural lymph vessel insufficiency*). (s. tab. 16.4)

1. Dynamic lymph vessel insufficiency	
Lymph volume	↑
Lymphatic drainage	↗
2. Mechanical lymph vessel insufficiency	
Lymph volume	↑
Lymphatic drainage	↘
3. Mural lymph vessel insufficiency	
Lymph volume	↑
Lymphatic drainage	↓

Tab. 16.4: Stages of lymph vessel insufficiency with cirrhosis (s. fig. 16.4)

► This development of ascites may progress through to the formation of numerous **lymphocysts** around the vascularized liver capsule and to the extravasation of protein-rich lymph, above all via ruptured lymphocysts. • *This laparoscopic finding has often been termed* ***"liver weeping"***. (s. fig. 16.5)

None of these mechanical factors can be considered "ascitogenic" in their own right. Nevertheless, they may be responsible for triggering a vicious circle in the formation of ascites due to the full impact of the mechanisms involved in elevated renal sodium and water retention.

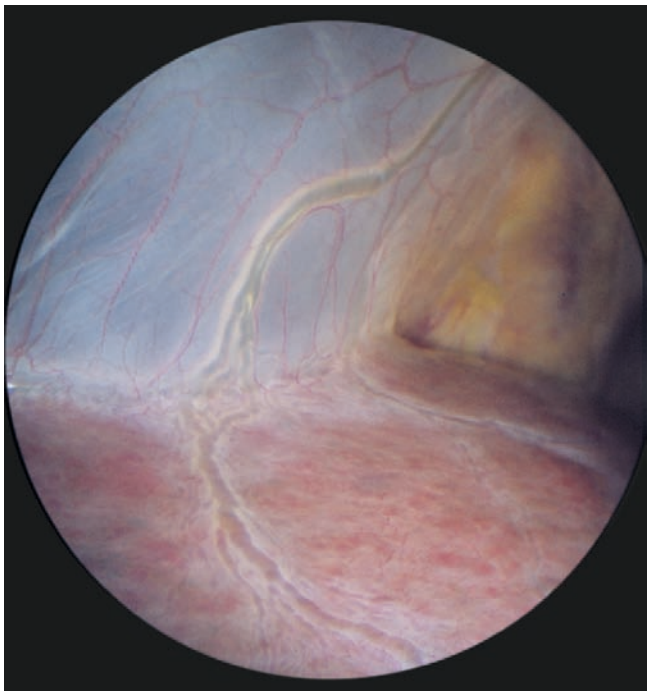

Fig. 16.4: Lymphostasis in the region of the liver capsule of the left liver lobe (lower part) and the falciform ligament

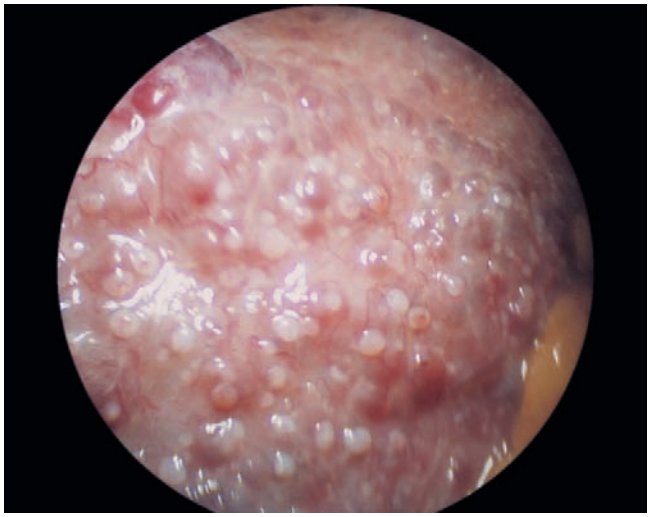

Fig. 16.5: Numerous, partially ruptured lymphocysts (light red, dot-like ruptured openings) on the liver surface with extravasation of protein-rich lymph (= *liver weeping*) in alcoholic cirrhosis

3.2.2 Biochemical factors

A great number of humoral or hormonal substances are involved in the formation of ascites, which is itself triggered by mechanical or physical factors. (s. tab. 16.5) Although the respective effects are largely known, their pathogenic significance in the formation of ascites must be rated differently in each individual case.

The **difficulty in assessment** is based on a number of *plausible reasons*, which can also explain the differing, often even controversial, examination results and the interpretations derived from them:

(*1*.) The formation of an active substance as well as its inactivation or breakdown depend on the individual functional capacity of the liver.

(*2*.) The signals necessary to activate or increase the formation of a substance or a regulatory system depend on the point in time and intensity of a specific pathophysiological situation as well as on the respective liver disease and the developmental phase of the ascites.

(*3*.) The various active substances as well as the sympathetic nervous system display a multitude of interactions, so that it is probably not so much the measuring of the individual factors that allows assessment of the respective pathophysiological situation, but rather their collective interpretation.

(*4*.) A number of individual feedback effects of the biochemical and nervous regulatory systems intervene in the various pathogenic phases, as outlined in the different ascites theories. (s. p. 300)

Renin Angiotensin II Aldosterone	↑ ↑ ↑, N
Antidiuretic hormone (ADH)	↑
Prostaglandin E_2 Prostacyclin Thromboxane	↓ ↓ ↑
Atrial natriuretic factor (ANF) Renal natriuretic factor (RNF)	↓, N ?
Prekallikrein Bradykinin	↓ ↓
Endotoxins	↑
Endothelin	↑
Oestrogens Prolactin	↑, ? ↑, ?
Catecholamine	↑

Tab. 16.5: Predominant changes in the concentration of biochemical factors in the blood and urine in portal ascites (N = normal)

1. **Renin-angiotensin-aldosterone system (RAAS):** The first description of aldosterone (S. A. Simpson et al., 1953) reflected awareness of its sustained effects on the electrolyte balance, which is why this hormone secreted by the adrenal cortex was originally given the name *electrocortin*. Aldosterone differs from the other adrenal cortex hormones by one "aldehyde oxygen", from which the name **ald-o-sterone** was derived. • The activity of the renin-angiotensin-aldosterone system is kept in balance by its own feedback mechanisms. Liver diseases have a lasting impact on this regulatory system by changing the formation and breakdown of the substances involved.

The **main stimuli** of the RAAS are hypovolaemia, hypotension, hypoxia, hyponatraemia, hyperkalaemia and an inadequate renal

circulation, as well as upright posture or physical strain; the **ancillary stimuli** include adrenocorticotropin (ACTH), thyroxine, oestrogen, ammonia and serotonin, to name but a few. Yet the extent to which these factors play a primary or a secondary role in the individual instance of ascites formation is still not clear. • Given a half-life of aldosterone of 30−35 minutes in the circulating blood, the effect sets in within 45−60 minutes mainly at the distal tubular nephron as a sensitive regulator of sodium transport by stimulating the sodium-potassium ATPase at the interstitial cell membrane.

A **rise in aldosterone** leads to hypernatraemia (with retention of water), loss of potassium (with a hypokalaemia syndrome), loss of H-ions (with a tendency towards metabolic alkalosis) and loss of magnesium and chloride. • Angiotensin II effects a contraction of the vasa efferentia and reinforces the absorption of sodium at the proximal tubular nephron with subsequent retention of water. The serum levels of renin and aldosterone are closely correlated. The increased renin values do not depend on the degree of severity of ascites. Even with a redistribution of the intrarenal blood flow from the cortex, which is normally well-supplied with 80−90% to the renal medulla (= *shift development*), a greater release of renin results with higher aldosterone values. • Nevertheless, augmented serum values of aldosterone are only detectable in some patients with severe liver disease. This finding together with the wide fluctuation range of renin and aldosterone values as well as an absence of the circadian rhythm of the RAAS show that diverging values are found with the different phases of activity of the RAAS in the pathophysiological stages of ascites.

► In severe liver disease or advanced cirrhosis, the occurrence of **secondary aldosteronism** must be anticipated and initially rated as an *epiphenomenon*. Nevertheless, at a certain point, the activated RAAS can act as a signal for a boost to the renal retention of sodium and may intervene in the pathogenesis of ascites. The aldosterone value and the renal excretion of sodium are closely and inversely correlated. Yet a higher aldosterone value is not always accompanied by reinforced retention of sodium. This is indeed the case if the feedback by means of sodium is ineffective (= *escape phenomenon*). The refilling of the plasma volume may lead to normalization of the renin and aldosterone values, yet not to normalization of sodium excretion. The reduction in increased aldosterone values is usually accompanied by reinforced natriuresis and diuresis − as has been observed after bilateral adrenalectomy. (s. p. 321) Cirrhosis patients with ascites thus usually show a reduced life expectancy if the renin-plasma value is increased, whereas the prognosis is clearly better if the renin value is normal. (for further reference, see 2, 4−6)

The findings and observations described in the literature as well as the convincing efficacy of the aldosterone antagonist *spironolactone* confirm the importance of the RAAS in the genesis of renal sodium retention and hence also in the formation of ascites.

2. **Antidiuretic hormone (ADH):** In cirrhotic and ascitic patients, the ADH level is usually elevated. (s. tab. 16.5) With a reduced effective plasma volume, ADH is released by non-osmotic stimulation in the neurohypophysis and possibly broken down in the liver at a reduced rate. The plasma activity of ADH largely correlates with that of the RAAS and the sympathetic nervous system. ADH stimulates the nervous synthesis of prostaglandins. It would appear that cirrhotic patients can be divided into excretors and non-excretors as regards the suppression of ADH secretion.

3. **Prostaglandins:** As vasodilators of the renal medullary vessels, prostaglandins influence the blood volume of the kidneys as well as glomerular filtration. They counteract vasoconstriction and thus help to maintain the glomerular filtration rate (GFR), even in cases of hypotension or hypovolaemia. Prostaglandins are natriuretic and diuretic in their action. They interact with the RAAS, the ADH and the kinins as well as with the sympathoadrenal system. Prostaglandins are formed from arachidonic acid, which may, however, be reduced in cirrhotic patients. • From the clinical point of view, it is important that acetylsalicylic acid or indometacin, for example, inhibit the synthesis of prostaglandins and hence bring about a reduction in sodium excretion, urine volume and diuretic efficacy. (s. tab. 16.5)

PGE_2 promotes the renal circulation and the excretion of sodium, while $PGF_{2\alpha}$ has an inhibitive effect in this respect. (No validated information on PGD_2 is available.) Prostacyclin increases the renal circulation, whereas thromboxane gives rise to renal vasoconstriction and reduced excretion of sodium and water. The vasodilatory prostaglandins are stimulated by noradrenaline and angiotensin II in correlation with the degree of hypovolaemia and sodium retention. An important pathogenic role may well be played not only by a reduction in prostaglandin PGE_2 and an increase in thromboxane, but also by an imbalance between the individual prostaglandin fractions.

4. **Natriuretic factors:** Animal experiments and clinical investigations point to the existence of these biochemical factors. After acute volume loading in healthy volunteers, it was possible to detect substances with a natriuretic effect in the blood and urine − *yet this was not the case in cirrhotic and ascitic patients.*

► In 1981 the natriuretic effect of an atrial myocardial extract was described for the first time (A. J. Debold et al.). Confirmation of this **atrial natriuretic factor (ANF)** as a peptide hormone was presented in 1983 (T. G. Flinn et al.). The half-life of this factor, also known by the name of *cardiodilatin*, is about three minutes. Receptors for ANF are found in the liver and the kidneys. The ANF leads to a rise in the glomerular filtration rate and in the excretion of sodium. The diuretic, natriuretic and vasodilatory effect is restricted by hypovolaemia and hypotension. The RAAS is inhibited by an i. v. injection of ANF. An increase in atrial pressure is considered to be the main stimulus for the release of ANF, whereas physical exercise, thyroxin, ADH and adrenaline prove less stimulating. In cirrhotic and ascitic patients, normal as well as significantly elevated ANF concentrations are found. This large divergence in values most probably depends on the current volume status (reduced or increased plasma volume) of the respective ascites phase. (1, 13, 193) (s. tab. 16.5)

► In 1989 a **renal natriuretic factor (RNF)** was detected for the first time and termed *urodilatin* (P. Schulz-Knappe et al.). As examinations have hitherto shown, urodilatin is formed in the medial nephron of the kidney and causes a distad inhibition in the absorption of water and sodium. Like ANF, its half-life is approximately three minutes. (3) • Today, *urodilatin is deemed to be important for the regulation of the water and electrolyte balance*, whereas ANF is most probably of limited significance for the excretion of sodium and its influence on sodium homoeostasis in liver cirrhosis (with or without ascites) remains unclarified. (s. tab. 16.5)

5. **Kallikrein-kinin system:** This system acts in a vasodilatory, diuretic and natriuretic manner. In cirrhotic and ascitic patients, there are lower prekallikrein and bradykinin levels as well as less renal kallikrein activity. The reduction in kallikrein excretion in the urine correlates with (*1.*) depressed glomerular filtration rate,

(*2.*) elevation of aldosterone values, and (*3.*) changes in the synthesis of prostaglandin. Nevertheless, as with ANF and RNF, there is still much to be resolved as regards the pathophysiology of cirrhotic patients with concomitant ascites. (s. tab. 16.5)

6. **Endotoxinaemia:** Different degrees of endotoxinaemia are often detectable in patients suffering from severe liver disease as a result of restricted hepatic endotoxin clearance. There is a correlation between endotoxinaemia and renal dysfunction, and renal blood flow is reduced. Nitrogen monoxide is also released. By reducing endotoxinaemia (after treatment with polymyxin B, for example), the diminished functional activity of the kidney improves and diuresis as well as natriuresis increase. (s. tab. 16.5)

7. **Endothelin:** Endothelin-1 is a polypeptide with a vasoconstrictive effect. It is generally elevated in portal ascites. The rise in endothelin correlates significantly with augmented ADH, ANF and endotoxins. It would seem to have an additional impact on the development of disrupted renal function. (20, 63) (s. tab. 16.5)

8. **Sympathoadrenergic factors:** Even at an early stage, the activity of the sympathoadrenal system is enhanced in cirrhotic patients due to a rise in sinusoidal pressure (probably via a glutamine-mediated *hepatorenal reflex*). As a result, the levels of **noradrenaline** and **adrenaline** rise and continue to do so as the decompensation progresses. These substances have a vasoconstrictive effect in the region of the efferent vessels and hence stimulate the retention of water and sodium. Noradrenaline values and natriuresis are closely and inversely correlated, not only because of the altered renal haemodynamics, but also through the alpha receptors situated at the proximal tubulus. Moreover, the increased activity of the sympathetic system stimulates the secretion of renin with subsequent activation of the RAAS. Due to the continuing decompensation, the greatly elevated catecholamine values might also be partly attributable to inadequate inactivation in the liver (and kidneys). (12) (s. tab. 16.5)

3.2.3 Increase in renal sodium retention

An increase in the retention of sodium occurs in the early stages of severe liver disease, particularly in liver cirrhosis, without any disruption of the water balance. This early tendency towards sodium retention can be detected using the *NaCl-tolerance test*. The retention of sodium reduces the sodium excretion rate in the urine to < 10 mval/day (normal rate: 120 to 220 mval/day). Diuresis is not primarily restricted; patients with ascites and oedema react to an excessive intake of water with an adequate excretion of diluted urine, albeit in the virtual absence of sodium excretion. The limited sodium excretion derives from increased, mainly proximal tubular reabsorption of sodium and not from diminished glomerular filtration. Overall maintenance of the liver architecture is usually accompanied by undisturbed sodium excretion, despite existing portal hypertension (such as in primary biliary cirrhosis). Marked sodium retention is, however, usually found in alcoholic-toxic cirrhosis. For this reason, such patients are not only the ones most frequently affected by ascites and oedema, but as a rule they display the most serious forms. This is probably also due to additional biochemical and hormonal factors which are present to a greater degree in patients with alcohol-related liver disease.

3.2.4 Theories of ascites formation

To explain the complex mechanisms of ascites formation, **four hypotheses** have been developed in the light of experimental and clinical findings: (*1.*) underfill theory, (*2.*) overflow theory, (*3.*) lymph imbalance theory, and (*4.*) vasodilation theory. (s. fig. 16.6)

1. Underfill theory: According to the underfill theory (S. Sherlock et al., 1963), the development of ascites is set off by mechanical factors and physical mechanisms ("imbalance of the Starling forces"). As a result, the effective plasma volume is reduced (= *volume deficiency concept*).

The **reduced intravasal volume** leads to a stimulation of volume receptors. In addition, the renin-angiotensin-aldosterone system and the sympathoadrenergic system are activated; the ADH level rises. This leads to a reduction in the glomerular filtration rate (GFR). The result is increased tubular sodium reabsorption, i.e. retention of sodium. Yet a reduced glomerular filtration rate is not a prerequisite for sodium retention, since this can occur even with normal GFR. • This mechanism of ascites formation through the primary reduction in the effective plasma volume is reinforced by (*1.*) growing insufficiency of the lymph vessels as a result of portal hypertension, (*2.*) decrease in peripheral resistance due to the opening of intrahepatic and systemic arteriovenous anastomoses, and (*3.*) enhanced formation or diminished breakdown of substances with a vasodilatory effect. (s. fig. 16.6)

2. Overflow theory: The overflow theory (F.L. Liebermann et al., 1970) (7) is based on the principle that retention of sodium already exists as a primary event and hence causes a *volume expansion concept*.

Continuous damage to the liver architecture or a boost to the portal pressure are accompanied by a **salt-retaining signal** (with an antinatriuretic impact) being sent to the renal tubuli. Ascites formation, already triggered by the mechanical or physical factors described, is now significantly reinforced by the sodium-retaining effect with an "overflow" from the intravasal volume. The result is a further reduction in the effective plasma volume, which increasingly stimulates the volume receptors and activates the biochemical, hormonal and neural systems. (s. fig. 16.6)

► These two hypotheses, the *"underfill theory"* and the *"overflow theory"*, do not explain the development of ascites in each individual case. Neither do the two concepts exclude one another. They would appear to describe the respective disrupting mechanisms of the water and salt balance as being dependent on the degree of severity of the existing liver disease. • Discussion centres on the early stage of ascites formation being influenced by the overflow hypothesis, which would also explain the better efficacy of diuretics in this phase. • By contrast, the late stages of portal ascites are thought to be characterized by the theory of volume deficiency, which implies that greater therapeutic success would only be achieved by refilling the intravasal volume (once diuretic therapy has failed). (8, 10, 11)

3. Lymph imbalance theory: The lymph imbalance theory (C.L. Witte et al., 1980) (16) contradicts the "classical" concepts of underfill and overflow. This theory is based

on the idea that the disruption of the equilibrium between the extravasation of fluid from the intravasal space and its reflux into the vascular system initiates the formation of ascites; in other words, the lymph production or the actual lymph quantity can no longer be drained via the lymph vessels. (s. tab. 16.4) (s. figs. 7.6; 16.4–16.6)

The **disrupted drainage of the lymph** is attributed to (*1.*) obliterated diaphragmatic lymph vessels, (*2.*) dilated visceral lymph vessels with subsequent clearly decelerated flow velocity, and (*3.*) limited lymph kinetics at the transition between the lymphatic system and the venous system. More and more disturbances in the fluid balance between plasma and interstitium increasingly activate the adrenal hormonal systems with elevated retention of sodium and water; the lymph imbalance continues to grow.

4. Vasodilation theory: The vasodilation theory (R.W. SCHRIER et al., 1988) (14) is a variant of the underfill concept. The initial pathophysiological change in cirrhotic patients is deemed to be peripheral arterial vasodilation, in particular in the splanchnic area, with a lower degree of vascular resistance. This leads to hyperdynamic circulation with an augmented cardiac output. The opening of arteriovenous anastomoses continues to reduce the degree of peripheral vascular resistance. The subsequent

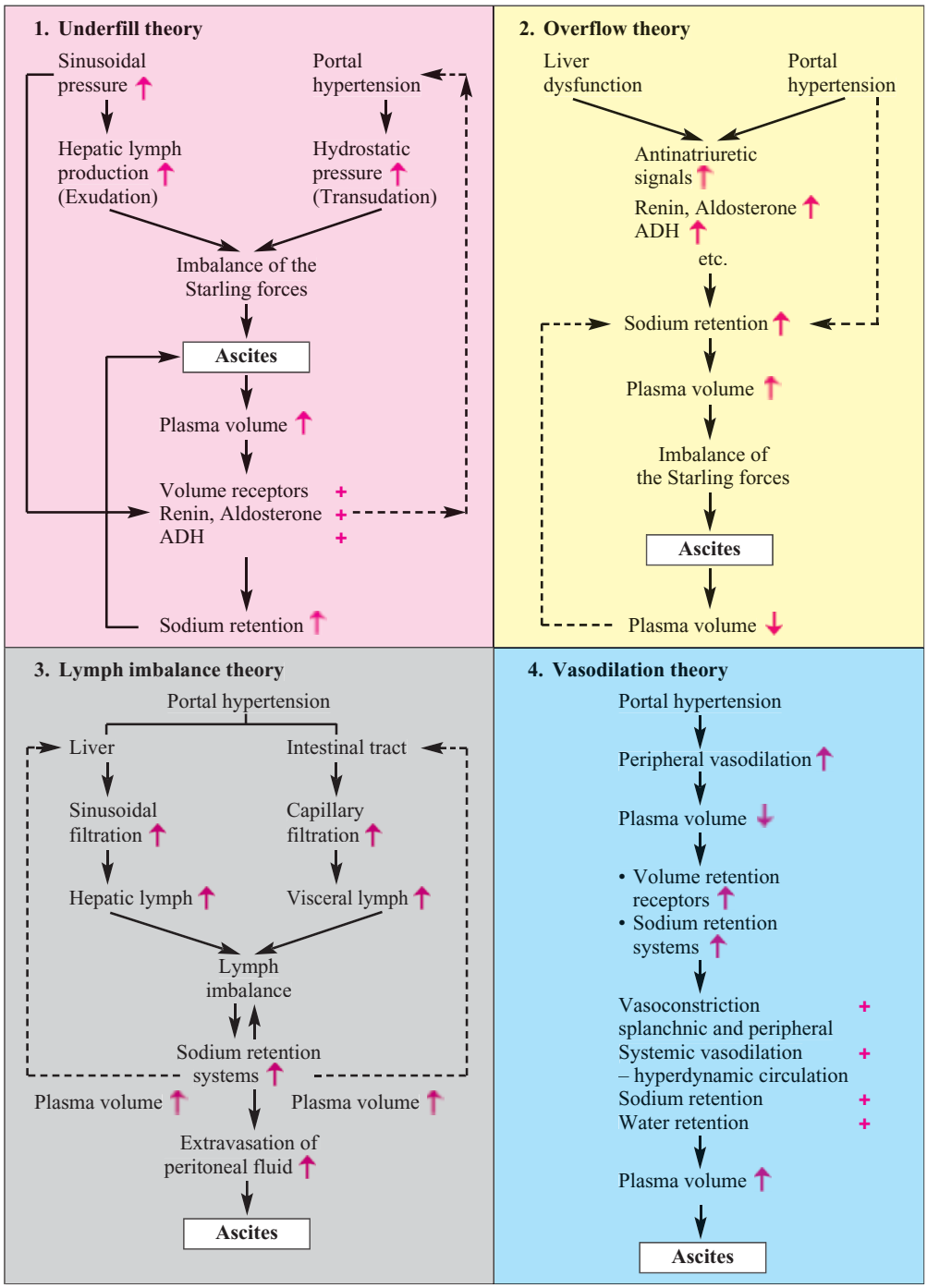

Fig. 16.6: Diagram of the main pathogenic mechanisms in the formation of ascites according to the four different theories

decrease in the effective plasma volume raises the levels of endothelin, renin, aldosterone, noradrenaline and vasopressin with subsequent renal vasoconstriction as well as the retention of sodium and water. The outcome is a further increase or a normalization of the plasma volume. • This is why, in certain stages of ascites, the serum and urine values of these biochemical factors are (surprisingly) found to be within the normal range. (s. fig. 16.6)

Continuing deterioration of the liver disease results in renewed increase in peripheral vasodilation with a further drop in plasma volume. • Under the influence of *endotoxins* and *cytokines* (tumour necrosis factor, interleukins, etc.), *nitric oxide synthases* are expressed in the liver, blood vessels and other organs, forming large quantities of **nitric oxide** (NO). As highly potent vasodilators, nitric oxides effect a dilatation of the vessels with a reduction in the peripheral resistance. • Other **mediators of vasodilation** are prostaglandins, bradykinin, glucagon, false neurotransmitters, PAF, ANF, etc. Despite maximum activation of the sodium and water retaining systems, vasodilation and volume deficiency can ultimately no longer be offset; ascites begins to develop. (8, 9, 15)

Synopsis

Ascites formation is a complex, pathophysiological process with multifactorial pathogenesis. Severe (acute or chronic) liver diseases, mainly cirrhosis, have their own principal pathogenetic factors which give the respective starting signals at the appropriate time. • In the individual case, one of the four ascites theories hitherto discussed can explain ascites formation, whereas in other cases, the pathogenic sequences of two or three concepts are mixed, each with its own particular intensity and specific timing. • There are some hints that the early phase of ascites is predominantly accompanied by "overfilling" as a result of growing sodium retention (with simultaneous imbalance in the pressure of the vascular system and the lymphatics), while the late phase is chiefly evoked through "underfilling" (due to NO activation with simultaneous vasodilation). Some of these biochemical and sympathoadrenergic mechanisms act as mutual stimulators, inhibitors or additive factors and can even have a potentiation effect, depending on their momentary effectiveness. The importance of the respective mechanisms cannot be estimated in the individual case. (s. fig. 16.6) (s. tabs. 16.3, 16.5)

► *Sinusoidal portal hypertension* with increased hydrostatic pressure and decreased colloidosmotic pressure are of considerable, probably paramount importance for the onset of ascites formation. Further influencing factors could be the growing imbalance between augmented lymph production and drainage as well as the higher degree of capillary permeability.

At the same time, the elevated sinusoidal pressure values transmit biochemical signals for a compensatory retention of sodium in the renal tubules. Likewise, "functional hyperaldosteronism" occurs at an early stage and the sympathoadrenergic system is activated with its impact on splanchnic and renal haemodynamics; both events serve to counter volume deficiency and hypotension. The physiological effects of the various biochemical factors may vary under pathological conditions, depending on the respective ascitic phase; for this reason, they can be difficult to assess. Reciprocal interactions also render it more difficult to evaluate the individual factors.

► *Ultimately, decompensation of the water and electrolyte balance is the result of* (*1*.) splanchnic and peripheral arterial vasodilation, (*2*.) subsequent marked reduction in the effective arterial blood volume, (*3*.) increase in renin, aldosterone, vasopressin and noradrenaline, (*4*.) renal vasoconstriction with retention of sodium and water, and (*5*.) inadequate compensation of the plasma volume as a result of progressive hypalbuminaemia.

4 Aetiology of ascites

4.1 Differential diagnosis

Numerous diseases can cause ascites. In terms of *aetiology*, liver diseases, malignant processes and chronic cardiac diseases rank right at the top. Yet inflammatory, renal, metabolic, vascular and endocrinological causes also have to be borne in mind when drawing up a differential diagnosis. The mechanisms at work in the formation of ascites are often still unresolved, as is the case, for example, in hypothyroidism, diseases of the ovaries or the POEMS syndrome (P.A. Bardwick et al., 1980). (92, 154) (s. tab. 16.6)

4.2 Hepatogenic ascites

It is not clearly understood why in some cases oedema without ascites and in other cases ascites without oedema as well as ascites together with oedema or even pleural effusion without ascites occur. Ascites often develops during the course of liver disease (= *hepatogenic ascites*), in particular in chronic liver diseases with portal hypertension (= *portal ascites*). (s. tab. 16.7) • Various mechanical, biochemical and neural disorders overlap in their effects and pathways, depending on the underlying liver disease. Only rarely is ascites found in diseases with presinusoidal localization of portal hypertension (e.g. portal vein thrombosis) or with minor restrictions in the synthesis of albumin (as in biliary cirrhosis). • Formation of ascites occurs in about 50% of

1. **Liver diseases** (75−80%) (s. tab. 16.7)
   (= *portal ascites*)
2. **Malignant processes** (10−15%)
   (= malignant ascites)
   − abdominal tumours
   − metastases
   − Hodgkin's disease
   − leukaemia
3. **Cardiac diseases** (3−5%)
   (= cardiac ascites)
   − congestive cardiac insufficiency
   − constrictive pericarditis
4. **Peritonitis** (2−3%)
   (= inflammatory ascites)
   − through bacteria, parasites, fungal infection
   − eosinophilic peritonitis
   − postoperative starch peritonitis
5. **Pancreatic diseases** (1−2%)
   (= pancreatic ascites)
6. **Renal diseases** (1−2%)
   (= renal ascites)
   − nephrotic syndrome
   − extracorporeal dialysis
7. **Vascular diseases**
   − thrombosis of the mesenteric vein
   − obstruction of the inferior vena cava
   − peritoneal vasculitis
8. **Malnutrition**
9. **Protein-losing gastroenteropathy**
10. **Whipple's disease**
11. **Amyloidosis**
12. **Endocrinopathies**
    − hypothyroidism
    − ovarian hyperstimulation
    − syndrome of inadequate ADH secretion
    − struma ovarii
    − Meigs' syndrome
13. **Familial paroxysmal polyserositis**
14. **Formation of fistulas (e. g. pancreatic cysts)**
15. **POEMS syndrome**

Tab. 16.6: Ascites formation and various possibilities for differential diagnosis

all cirrhotic patients within ten years of the diagnosis being established. About half of these patients die within two years of the initial occurrence of ascites. Oedema and/or ascites develop during the course of the disease in about two-thirds of all cirrhotic patients. Statistically, alcoholic cirrhosis is most frequent.

Surprisingly, alcoholic fatty infiltration of the liver and alcoholic hepatitis often display ascites as well, mostly only discernible when applying ultrasonic methods of examination. This might suggest that certain pathogenic mechanisms in the formation of ascites (such as increase in portal pressure, structural sinus changes, and stimulation of biochemical or sympathoadrenergic factors) are favoured or become more intense as a result of alcohol (and possibly also its chemical additives). • Ascites can also occur in severe acute viral hepatitis, in which case the course of disease deteriorates considerably. (28, 43, 61)

1. Liver cirrhosis
2. Alcoholic hepatitis
3. Acute liver failure,
   severe acute viral hepatitis
4. Obstruction of the hepatic veins
   − massive fatty liver
   − cardiac liver congestion
   − Budd-Chiari syndrome
5. Neoplasia of the liver
6. Cystic liver
7. Liver fibrosis
   − sarcoidosis
   − schistosomiasis
   − syphilis
8. Arteriovenous shunts,
   arterioportal fistula
9. Portal vein thrombosis
10. Obstruction of the superior vena cava with LeVeen shunt
11. Nodular regenerative hyperplasia
12. Condition after liver transplantation

Tab. 16.7: Causes of hepatogenic or portal ascites

We were able to observe pronounced oedema, anasarca and massive ascites with concomitant signs of hepatic encephalopathy in a case of so-called ***hepatitis oedematosa*** (E. Gautier et al., 1952). *The patient was successfully treated by means of aldosterone antagonists.* (43)

5 Diagnosis of ascites

5.1 Clinical findings

Ascites may onset suddenly or slowly and unnoticed over the course of several weeks. There is a diminished tendency to sweat and the patient's skin often appears sallow and dehydrated. • With regard to the quantity of the fluid, ascites may be classified into different levels of intensity: *mild*, *moderate* or *tense*.

Physical methods: A *latent oedema* can be recognized by the deposition of fluid in the tissue (increase in body weight of > 1.0 kg in 4−5 days). (s. fig. 15.3) It is neither visible nor palpable. A *manifest oedema* typically shows dimpling upon digital compression. • *Ascites* without concomitant deposition of tissue fluid is generally diagnosed by a distinct increase in body weight. Detection of ascites by means of physical examination is only possible when an amount of fluid in excess of 1.5−2.0 litres is present. (30) This is best achieved when *dullness* is ascertained by percussion of the abdomen with the patient in the knee-elbow position. Larger amounts of ascitic fluid produce a typical *change in percussion sound* when the body position is altered; there is also *dullness in the flanks* and ultimately a noticeable *fluctuation wave* (i.e. ascites thrill due to excessive free fluid under tension). Reduced *movability* and/or corresponding *ele-*

vation of the diaphragm can also be detected by percussion. (s. p. 83) • *Meteorism* is deemed to be a precursory state of ascites *("first the wind and then the rain")*.

Puddle sign: In 1959 a very reliable physical sign was described which is present with as little as 120 ml of peritoneal fluid. This phenomenon also makes it possible to differentiate shifting dullness due to fluid-filled loops of bowel from that due to collections of free intra-abdominal fluid. The puddle sign is generally not influenced by obesity. (44)

Inspection: Pronounced cases of ascites are characterized by marked *protrusion* of the abdomen. The *umbilicus* becomes everted or bulging. The distance between the navel and the symphysis appears diminished as a result of caudal displacement of the former. With large quantities of ascitic fluid, the *abdominal skin* is taut and shiny. In long-standing cases of ascites, striae distensae, together with expanded collateral veins radiating from the navel, may be visible. Increased ascitic pressure sometimes causes a *hernia* (inguinal, femoral, umbilical or cicatricial). (s. fig. 16.7) (39, 46, 54)

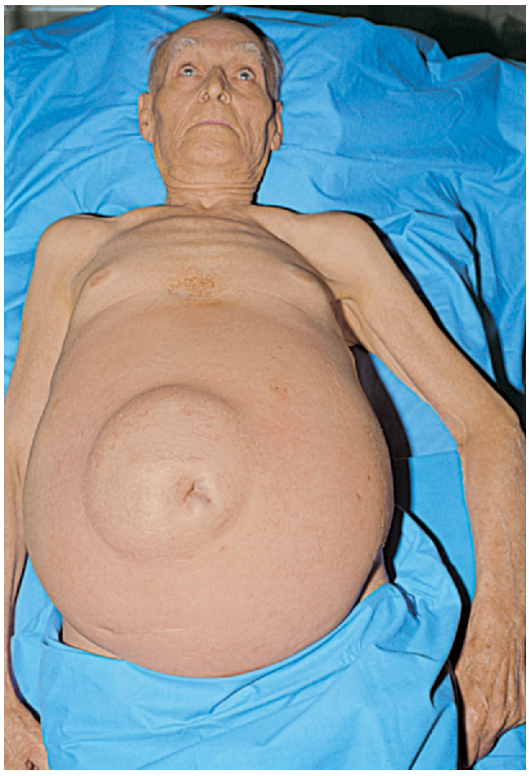

Fig. 16.7: Massive refractory ascites with large umbilical hernia. Muscular atrophy and loss of subcutaneous fatty tissue

Occasionally, *scrotal oedema* and *anasarca* are detectable. Ascites does not correlate with the incidence and extent of peripheral oedema. (s. figs. 16.2, 16.13)

5.2 Imaging procedures

Sonography: Sonography facilitates the early diagnosis of ascites (< 200 ml). If the fluid accumulates at certain preferred sites, it is possible to detect amounts of < 50 ml. In minimal and localized accumulation of fluid, sonographically guided tapping and collection of ascitic fluid as well as special examinations provide a swift and confirmed diagnosis. With massive ascites, floating intestinal loops are occasionally found, forming the so-called *sea anemone phenomenon*. (25) (s. p. 141)

Radiology: Ascites has a diffuse appearance similar to ground glass. In the individual case, various ascites-related clinical findings are observed (elevation of the diaphragm, plate-like atelectasis, cardiac rotation, hiatus hernia, distended intestinal loops, etc.). Extensive ascites may cause organ displacement (e. g. dislocation of the stomach or kidneys) or vascular compression (e. g. functional blocking of the inferior vena cava). (23, 27) The quantity of fluid can be 30 litres or more (as much as 70 litres has been recorded!). (s. figs. 16.7, 16.13)

Hepatic hydrothorax (C. S. Morrow et al., 1958) is evident during the course of liver cirrhosis with ascites in 0.4–12.0% of cases. The mean frequency is about 6%, although in two-thirds of the cases, a right-sided effusion (with the author's own patients, a bilateral effusion) was ascertained. (62) (s. fig. 16.8) • Hepatic hydrothorax is a transudate: cell count < 1,000/mm^3, protein concentration < 2.5 g/dl, total protein effusion to serum ratio < 0.5, LDH effusion to serum ratio < 2.3, serum to pleural fluid albumin gradient > 1.1 g/dl. (s. also fig. 16.9) (17, 36, 45, 50, 51, 62)

► Over a period of ten years (1952–1963), I examined in-patient records at the University Medical Hospital in Giessen retrospectively. On evaluation of **25,682 documented cases,** 2,534 patients were found with pleural effusion (= 9.8%) validated by radiology or autopsy. • The **frequency** of hepatogenic pleural effusion was 110 cases (= 4.3%). I found four cases of a right-sided hydrothorax and two cases of bilateral hydrothorax in 6 patients with severe *viral hepatitis*. Hydrothorax was identified in 104 patients with *cirrhosis*. • The **localization** was, however, bilateral in 69%, left-sided in 18.7% and right-sided in 12.3%. • This **controversial finding,** which contrasts with the literature, is explained by the fact that an X-ray of the thorax was taken in each case of cirrhosis and that angle effusions or minimal infrapulmonal effusions were detected by autopsy in deceased patients. *(see footnote *)*

Causes of hepatic hydrothorax, which can occasionally appear sanguinolently as a result of the cirrhosis-related bleeding tendency, are (*1.*) congenital or acquired defects of the diaphragm (65), (*2.*) diaphragmatic lymph paths, and (*3.*) increased pressure in the azygous vein/hemiazygous vein system. With rising intra-abdominal pressure (caused by large-volume ascites, coughing, pressing, etc.), congenital or acquired gaps may form between the muscle fibres of the diaphragm. These small

*) *Kuntz, E.:* Pleural effusions. Differential diagnosis, clinical aspects, and therapy. Urban and Schwarzenberg, München, 1968, 207 pages, 74 figures.

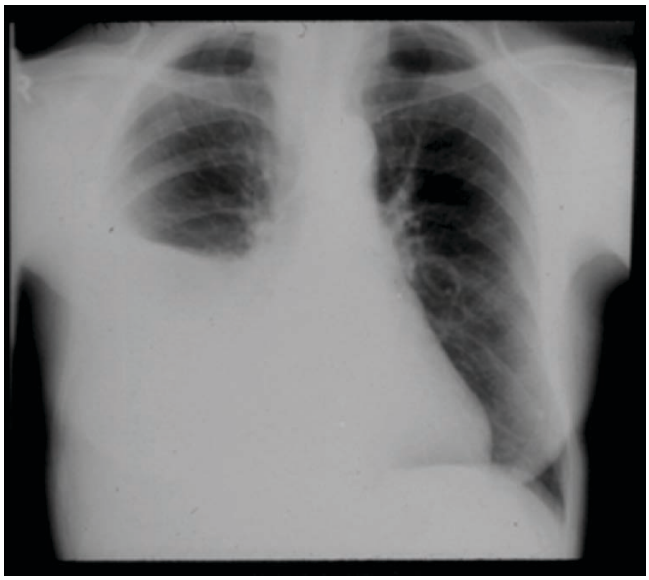

Fig. 16.8: Right-sided hepatic hydrothorax in liver cirrhosis

herniations (so-called pleuroperitoneal blebs) may rupture and allow fluid to move from the abdominal cavity into the pleural space. Occasionally, such diaphragmatic defects can be demonstrated by magnetic resonance imaging (65) or thoracoscopy. • It is clinically significant that considerable pleural effusion can even be present in liver cirrhosis *without concomitant ascites*. In cases of pulmonary complaints (e. g. dyspnoea), this possibility should be considered and investigated. (42, 53) • *Therapy* corresponds to that of ascites (s. pp 310, 312) and involves the administration of albumin. (s. p. 314) Thoracocentesis, if necessary repeated, in addition to i.v. infusion of octreotide and paracentesis (s. p. 315) is recommended. In the case of treatment failure, TIPS and eventually liver transplantation may be indicated.

Spontaneous bacterial empyema is found in 1−2% of patients with cirrhosis and ascites. The diagnosis is based on a positive bacterial test in the pleural fluid and a WBC count in excess of 250/mm^3 (or a negative bacterial culture with a cell count exceeding 500/mm^3) − which is analogous to spontaneous bacterial peritonitis. (95) (s. p. 308)

Computer tomography: A CT scan is only indicated in individual cases where there are problems with the differential diagnosis (e. g. in acute pancreatitis or suspected tumours). The sensitivity of fluid detection is, however, extremely high, since it is possible to demonstrate as little as 25 ml. (40)

In patients with cirrhosis, CT sometimes demonstrates a mesenteric oedema (*"misty mesentery"*). (49) Such a mesenteric, omental and/or retroperitoneal oedema can vary from a moderate infiltrative type to a pronounced oedema compressing the mesenteric vessels. (32)

Laparoscopy: Laparoscopy should be carried out in all cases which could not be clarified or precisely defined by means of clinical and biochemical laboratory examinations of the blood and ascitic fluid or using imaging procedures. (s. p. 164) If a large amount of ascitic fluid is removed by laparoscopic paracentesis, it is essential to substitute volume and protein. (s. p. 315)

Oesophagogastroscopy: An ascites-related gastro-oesophageal reflux can result in reflux oesophagitis. However, this does not provoke the onset of bleeding from oesophageal varices.

Disorders of *cerebral functions* on the one hand and of the *water and electrolyte balance* on the other hand are the earliest and most reliable hints of the onset of decompensation in severe liver disease, especially cirrhosis. • In clinical terms, they can be easily diagnosed as latent hepatic encephalopathy (by carrying out psychometric tests) and/or latent oedema (by recording the increase in body weight). • For this reason, these examination methods are also considered to be of fundamental importance in the follow-up of chronic liver disease. (s. fig. 15.3)

5.3 Laboratory diagnosis

A **diagnostic puncture** is required to withdraw ascitic fluid. In extensive ascites, this can be performed without ultrasound guidance, whereas with smaller and localized accumulations of fluid, it is always necessary to carry out ultrasound-guided puncture. The ideal entry site is deemed to be the left lower abdominal quadrant (exactly opposite McBurney's point). Prior to puncturing, the skin should be shifted tangentially over the puncture mark, leaving a Z-shaped puncture channel on removal of the needle. This guarantees more reliable protection against any postpuncture leakage of ascitic fluid. Complications are very rare. (143) The tapping of ascitic fluid is considered a safe procedure. Using a thin needle (0.4 mm in diameter) or a special puncture needle, some 50 ml fluid are withdrawn, which suffices for a wide range of laboratory investigations. However, for bacteriological or cytological examinations (possibly following centrifugation), 200−250 ml are required. Biochemical parameters are always of great importance. (24, 26, 38, 60, 66, 74) (s. fig. 16.10)

1. Colour: The impressive range of colours found in individual cases is indeed interesting, yet of no great help in the differential diagnosis. A rough definition of the various forms can be given as follows, analogous to pleural effusion *(see footnote p. 304)*:

• *serous ascites* (e. g. hepatogenic, pancreatogenic, malignant or inflammatory) can be clear or turbid, green, straw-coloured or bile-stained; (s. fig. 37.25)

• *haemorrhagic ascites* (e. g. in malignant disease). In liver cirrhosis, ascites is only rarely blood-tinged;

• *turbid ascites* (e. g. bacterially or parasitically infected, malignant or pancreatogenic, in the Budd-Chiari syndrome);

• *chylous ascites* (e. g. in cirrhosis due to impaired lymphatic drainage) has various causes: malignant disease, whipple disease, radiation, tuberculosis, intestinal lymphangiectasia. Lymphostasis can be assumed to exist if the total lipids of the ascitic fluid are twice as high as the plasma value and/or the triglyceride concentration is greater than 400 mg/dl. Therapy with orlistat has proved successful. (29, 31) (s. fig. 16.9)

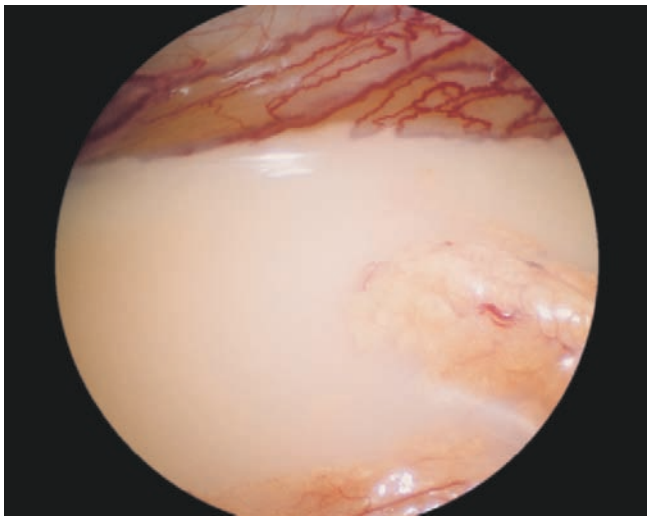

Fig. 16.9: Chylous ascites with pronounced portal hypertension as a result of posthepatitic (HBV) coarse nodular cirrhosis

2. Protein content: Depending on the protein content of the ascitic fluid or its specific gravity, differentiation is made between a transudate and an exudate. • A **transudate** is deemed to be a serous, fibrinogen-free fluid, low in cells and protein, of non-inflammatory genesis. The protein content is <2.5 g/dl (specific gravity <1,015). • An **exudate,** generally inflammatory or malignant, is rich in cells; the protein value exceeds 3.0 g/dl (specific gravity >1,016), and the bilirubin quotient (ascites : serum) amounts to more than 0.6. (35) • The **albumin gradient** (albumin value in the serum minus albumin value in ascites) is usually >1.1 g/dl in portal hypertension and <1.1 g/dl in malignant or inflammatory ascites, with a sensitivity of about 80%. (56) This gradient correlates well with the portal vein pressure. The reliability of differentiation seemed to improve with a discrimination limit of 1.5. (60) (s. fig. 16.10)

In of long-standing ascites, **protein content** can drop due to reduced permeability of the sinusoids to protein or as a result of presinusoidal obstruction. However, because of its aetiology or as a result of diuretic therapy, protein content may increase. In 15–20% of cirrhotic patients with ascites, protein values of up to 4.3 g/dl are found. • ***Even with a threshold ranging between 2.5 and 3.0 gldl, the transudate vs exudate concept does not work as well with ascites as it does with pleural effusion!*** • The inconclusive information obtained from the ascites protein value sometimes becomes more reliable if the cell count is also determined. (52, 60, 74)

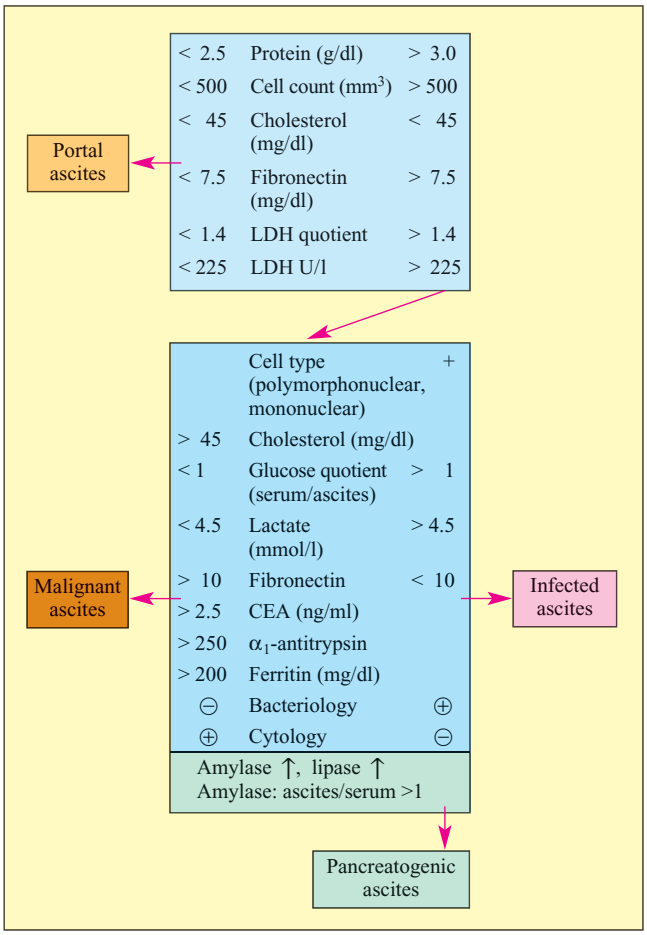

Fig. 16.10: Diagnostic steps used to differentiate between portal, infected, malignant and pancreatogenic ascites (modified from J. Schölmerich, 1990)

3. Cell count: To determine the cell count and cell type, it is advisable to use an EDTA tube (monovette) for the ascitic fluid. The cell count for a transudate is generally below 250/mm³ and for an exudate above 1,000/mm³. Specificity is ca. 90%, and sensitivity is ca. 60%. The absolute count is more reliable in connection with a normal or raised protein value (transudate or exudate). However, in up to 30% of cases, there were cell counts in portal ascites of >500 and in 5–20% of cases even >1,000 leukocytes/mm³. In patients with malignant ascites, the cell count was in excess of 1,000/mm³ in more than 50% of cases. In individual instances of hepatogenic or malignant ascites, a higher number of polymorphonuclear cells were also detected. These results make identification of spontaneous bacterial peritonitis very difficult. Evidence of **polymorphonuclear neutrophils** (>250/mm³) suggests the presence of infected ascites. More than 80% of patients with spontaneous bacterial peritonitis show a higher value. The predominance of **lymphocytic cells** in ascites (>20% of the total leukocyte count) – with an additional ascites-blood-glucose quotient of <0.7 – suggests tuberculous peritonitis. (24, 60) In suspected tuberculosis, the Ziehl-Neelsen staining method, and possibly also PCR, is necessary.

4. Bacteriology: Ascites should be checked for aerobes and anaerobes by using haemoculture bottles. With infected ascitic fluid, the bacteriological examination yields a specificity of 100%, but a much lower sensitivity. It is possible to detect gram-negative bacteria in about 70% of cases, gram-positive microorganisms in some 25% of cases and anaerobes in about 5% of cases. In total, a bacterial infection of the ascitic fluid is present in 8–10% of cirrhotic patients. It is often hardly possible to distinguish between spontaneous and secondary bacterial peritonitis. (60, 66)

5. Cytology: Cytology has a specificity of 97–100% for the detection of malignant ascites. By contrast, the sensitivity is far lower, especially since the endothelial cells of the peritoneum are very similar cytologically to the malignant cells.

6. Cholesterol: In malignant ascites, the cholesterol level is clearly raised (R.A. Rovelstad et al., 1958). In differentiating the condition from portal ascites, the sensitivity is 90%, and the specificity is 95%. A threshold range of 45–48 mg/dl is deemed appropriate. Cholesterol determination is thus a valuable parameter for ascites. (41, 58) (s. fig. 16.10)

7. Fibronectin: The values of fibronectin in malignant ascites are significantly higher than in cases of portal ascites. Given a threshold value of 7.5 mg/dl, it is possible to differentiate between the two forms of ascites with a sensitivity of 100% and a specificity of more than 95%. The combined determination of cholesterol and fibronectin allows malignant ascites to be identified reliably. (33)

8. pH levels: The pH value in infected ascitic fluid is usually reduced to <7.31 by acid residues (such as lactate, oxalate, succinate and fumarate), which occur mainly in anaerobic glycolysis. With hepatogenic transudate ascites, pH levels are higher than 7.45 and the pH gradient (serum value minus ascites value) amounts to <0.10. In malignant ascites, the values are hardly any different. In isolation, the pH value and pH gradient have little meaning, whereas in connection with the protein value or cell count and cell type, they can be seen as helpful supplementary findings. (21, 55)

9. Lactate: The same assessment is true for the determination of lactate in ascitic fluid. The increase in this acid residue in infected ascitic fluid (>4.5 mmol/l) is proportional to the decrease in the pH value. Malignant ascites generally yields values of <4.5 mmol/l. (55, 60) (s. fig. 16.10)

10. LDH quotient: The LDH quotient (ascites value : serum value) is usually <1.4 in portal ascites, whereas in infected or malignant ascites, values of >1.4 are usual. The absolute discrimination value is given as being higher than 400 U/l.

11. Ferritin: The values in malignant and inflammatory ascites were regularly higher than those found in portal ascites. (60)

12. α_1-antitrypsin: The identification of α_1-antitrypsin yielded a respective specificity and sensitivity of >95% in distinguishing between portal and malignant ascites. In cases with a malignant genesis, the values were nearly always elevated to >120 mg/dl. (64)

13. Other examinations focused on the biochemical differentiation of ascites, such as determining cholinesterase, coagulant activity (22) and interleukin-6 (18) as sensitive parameters for bacterial infection as well as evaluating the receptors (p55 and p75) for the tumour necrosis factor. (19) An ascites/serum quotient for a_1-foetoprotein of >1 suggests hepatocellular carcinoma; an amylase quotient of >1 is found in pancreatitis.

► As early as 1964 and in later publications, it was possible to demonstrate the significance of **glycoproteins** (hexosamine, fucose, sialic acid [34], etc.) and *cholinesterase* for the detection of non-inflammatory, inflammatory or malignant disease and their follow-up as well as for the distinction between transudate and exudate in a so-called **phlogogram** (E. Kuntz, 1964). *(see footnote on page 304)* Because of the significance and pathophysiological features of the mucopolysaccharides, appropriate biochemical parameters are likely to be of further interest. • In addition, elevated values of **hyaluronic acid** have been found in the ascitic fluid of cirrhotic patients.

Due to clinical, laboratory and therapeutic differences, it is possible to distinguish between simple and problematic ascites. The latter includes: (*1.*) recurrent ascites, (*2.*) refractory ascites, (*3.*) diuretic resistant ascites, and (*4.*) diuretic intractable ascites. (s. tab. 16.8)

	Simple ascites	Problematic ascites
Quantity	mild, moderate	tense
Manifest HE	∅	+
Natriuresis **Sodium in serum** **Albumin** **Creatinine** **Potassium in serum**	>20 mmol/day >130 mmol/l >3.5 g/dl <1.5 mg/dl 3.6–4.9 mmol/l	<10 mmol/day <130 mmol/l <3.5 g/dl >1.5 mg/dl <3.5 mmol/l >5.0 mmol/l
Diuretic therapy	mostly sufficient	insufficient

Tab. 16.8: Differentation of ascites according to its severity

The combination of several biochemical parameters in a diagnostic **stepwise approach** generally facilitates an adequately reliable differentiation between portal, infected, malignant and pancreatogenic forms of ascites. (s. fig. 16.10)

6 Complications of ascites

Ascites formation is generally accompanied by multiple complications. These mean considerable distress for the patient and constitute a genuine threat to life. Complications call for extra therapeutic measures, which are often quite complex. For this reason, emphasis should always be placed on any dangerous developments. As a rule, these are mechanical, bacterial, or metabolic in nature. (s. tab. 16.9)

Mechanical complications

1. Increased physical immobility
2. Respiratory impairment
   (= dyspnoea as a result of restrictive ventilation)
   - due to hepatic hydrothorax
   - due to an elevated diaphragm or plate-like atelectases
3. Elevated portal venous pressure
4. Compression of vessels
   - inferior vena cava syndrome
   - renal vein
5. Formation of hernias
6. Ruptured umbilical hernia
7. Dislocation of organs
   - intra-abdominal
   - cardiac rotation, diminished cardiac function
8. Promotion of a gastro-oesophageal reflux

Bacterial complications

1. Spontaneous bacterial peritonitis

Metabolic complications

1. Disturbances of electrolyte metabolism
2. Disturbances of protein metabolism, catabolism
3. Changes in pharmacokinetics
4. Hepatic encephalopathy
5. Hepatorenal syndrome

Tab. 16.9: Complications arising from ascites

Even though the mortality rate of spontaneous bacterial peritonitis can clearly be reduced by antibiotics, it still remains a very real danger for the patient. The hepatorenal syndrome has a very poor prognosis with a mortality rate of about 95%. *(see chapter 17)*

7 Spontaneous bacterial peritonitis

In severe liver diseases, particularly in cirrhosis, but also in acute viral hepatitis, bacterial infections are frequent. (70) In approx. 25% of cases, these infections are the cause of death. If there are additional complications (e.g. gastrointestinal bleeding, protein deficiency, invasive interventions, endotoxinaemia, liver metastases, continuous abuse of alcohol) culminating in a further weakening of the body's defences, the cause of death is attributable to bacterial infection in > 50% of cases.

7.1 Definition

Spontaneous bacterial peritonitis (SBP) (H.O. Conn, 1964, 1971) is the term used to describe bacterially infected ascitic fluid in liver cirrhosis where the exact source or path of infection is not known. It displays a high number of polymorphonuclear neutrophils (> 250/mm^3), a protein content which is usually < 1.0 g/dl and a positive bacterial culture (> 90%).

7.2 Forms and frequency

In terms of the number of neutrophils and the microorganisms identified, SBP can occur in ascites in **three forms** (71, 81, 82, 85, 86):

1. **Classical (complete) SBP:** > 250/mm^3 polymorphonuclear neutrophils together with positive ascites culture; this constellation is the most frequent form.

2. **Culture-negative neutrocytic ascites:** < 250/mm^3 neutrophils together with negative ascites culture; it appears in 4–5% of patients suffering from cirrhosis with ascites and in up to 35% of cases with suspected SBP. This form does not differ from classical SBP as regards symptomatology, clinical and laboratory findings or efficacy of the antibiotic therapy required.

3. **Culture-positive neutrophil-low ascites:** < 250/mm^3 neutrophils and mostly monoculture-positive ascites; gram-positive infectious agents predominate. As a rule, this form shows an asymptomatic course and a more favourable prognosis. It is interpreted as a bland bacterial infection with good defence potential (i.e. transient colonization). Antibiotic therapy is not required, but ascites follow-up examinations are indispensable in order to initiate any necessary antibiotic treatment in good time.

Each of these three forms of SBP has to be delimited from **secondary bacterial peritonitis.** In bacterial ascites, several types of microorganisms, including fungi, can usually be identified after subculturing. The cell count exceeds 10,000/mm^3, the LDH value is elevated (> 225 U/l), and the glucose concentration is < 50 mg/dl.

The **frequency** of SBP is 10–25%. (69–71, 81, 96) With coexistent HE, it was found to be 36%, whereas in the absence of HE, SBP was detectable in only 10% of cases. Culture-negative ascitic fluid can be identified with SBP in up to 50% of cases and bacterascites in up to 30% of cases. (70, 87) **Relapses** occur at a rate of 43–69% per

year. An ascitic protein concentration of <0.75 g/dl is considered a significant predictive factor for a relapse.

7.3 Pathogenesis and predisposing factors

► **Acquired immune defect syndrome in cirrhosis:** Even if pathogenesis has still not been fully resolved, it is generally attributed to various regulatory defects in the immune system (*1.*) reduction in the opsonic and bactericidal activity of the ascitic fluid, (*2.*) impaired function of the RES phagocytosis system, and (*3.*) leukocytic functional deficiency. A decrease in C_3 concentration in the ascitic fluid (<20 mg/dl) reduced the bacterial content and, according to the literature, led to the occurrence of SBP in 47% of cases within a short space of time.

► **Bacterial infection:** This multifactorial weakness in defence allows bacterial penetration of the ascitic fluid to be effected by (*1.*) transmural migration in portal hypertension with greater permeability of the intestinal wall, (*2.*) systemic bacteraemia in terms of haematogenic dispersion (particularly in urinary tract and bronchopulmonary infections), above all in the presence of intrahepatic and extrahepatic shunts *(portal vein bacteraemia)*, (*3.*) invasion of bacteria via the Fallopian tubes, and (*4.*) lymphatic flow into the ascitic fluid (e.g. via leaks in the lymph vessels or lymph nodes).

Predisposing factors often interact to produce a greater effect in the individual case (68, 70, 80, 81, 88):

(*1.*) reduction in the bactericidal and **opsonic activity** (C3 < 20 mg/dl) and in the **ascitic protein value** (<1.0 g/dl) as well as a dysfunction of the polymorphonuclear neutrophils;

(*2.*) **dysfunction of the liver** (e.g. bilirubin >3.5 mg/dl, thrombocytes <98,000/mm^3) as a result of an accompanying decrease in antibodies or RES functions;

(*3.*) **poor nutritional status**;

(*4.*) upper gastrointestinal **bleeding** and application of balloon tamponade or varicosclerosation;

(*5.*) **invasive measures** such as endoscopic or angiographic techniques or peritoneovenous shunting (some 20% of cases) with a mortality rate of about 25%;

(*6.*) **infusion of vasopressin**, which leads to a deterioration in the circulation of the intestinal mucosa and hence to easier penetration by microorganisms;

(*7.*) **bacterial foci** with systemic bacteraemia through arteriovenous anastomoses.

7.4 Clinical aspects

1. Pathogen detection: The decisive diagnostic criterion of SBP is the detection of the pathogen. This cannot be adequately achieved using conventional techniques. **Bedside inoculation** of 10 ml ascitic fluid per haemoculture bottle is recommended with a cultivation period of five to seven days at 37 °C, with subcultivation on days 1, 2 and 7. The yield of positive cultures is thus doubled. • Demonstration of *one* type of pathogen is considered typical for SBP (>90%), whereas determination of *several* types of pathogens or anaerobes generally suggests secondary peritonitis. • In 60−80% of cases, gram-negative aerobes are found, half of which (40−50%) are E. coli. A small fraction is comprised of Klebsiella, Citrobacter, Proteus, Enterobacter and Streptococcus (94) etc. Gram-positive microorganisms were detected in 25−30% and anaerobes in 4−6% of cases. Isolated reports have been published on the identification of Clostridia (72), Salmonella (75), Chlamydia trachomatis (78, 89) and Listeria monocytogenes (79, 84).

2. Cell count: The second important criterion of SBP is deemed to be a higher cell count (>250 polymorphonuclear neutrophils/mm^3). As a result, early diagnosis is possible with a sensitivity of 92% and a specificity of 95%. A higher leukocyte count in ascitic fluid does not correlate with peripheral leukocytosis (or vice versa). Mechanical assessment of the cell count, however, also identifies lymphocytes, serosal surface cells and peritoneal macrophages. For this reason, it is imperative to distinguish the polymorphonuclear neutrophils (and possibly the number of mononuclear forms) in the ascitic fluid smear. (66, 70, 74, 96)

3. Chemical parameters: The additional determination of chemical parameters (*decreased:* fibronectin, pH value, glucose, cholinesterase, etc.; *increased:* lactate, LDH, etc.) can improve the certainty of the SBP diagnosis in individual cases and also provide a clearer picture of its severity. (74, 76, 83, 93, 96)

4. Clinical findings: In 10−50% of cases, SBP follows an *asymptomatic* course. Each sudden or inexplicable deterioration in the course of disease, manifestation or aggravation of HE, non-response to appropriate diuretic therapy, continued increase in ascites or signs of the onset of renal insufficiency all point clearly to SBP. • *Clinical symptomatology* can also develop slowly in cases of long-standing ascites. By contrast, SBP may pursue a more rapid course, with pronounced findings in the presence of existing as well as simultaneously developing ascites. (69, 70, 74, 78, 80, 86) (s. tab. 16.10)

• Fever	• Decreased bowel sounds
• Abdominal pain	• Nausea
• Abdominal guarding	• Tendency to diarrhoea
• Onset of HE	• Reduced diuresis
• Meteorism	• Arterial hypotension

Tab. 16.10: Symptoms of spontaneous bacterial peritonitis

7.5 Prophylaxis and therapy

In decompensated cirrhosis or gastrointestinal bleeding, the use of antibiotics is recommended for the prevention of SBP as well as to avert a relapse. This is especially true if predisposing factors for SBP are present. In cirrhosis with ascites, SBP occurs in about 80% of hospitalized patients within the first week. For this reason, SBP is deemed to be a *nosocomial infection* (H.O. Conn, 1987) although other investigators regard the patient's domestic surroundings as the most common site of

infection. Such complications of ascites, which still have a poor prognosis despite cost-intensive therapy, should be prevented by suitable prophylactic measures.

Prevention is achieved through simply reducing the ascitic volume by means of efficient diuretic therapy, so that the total protein and complement factors in ascites rise significantly. *Paracentesis* can also be helpful if the protein deficiency is compensated at the same time. • Long-term application of *lactulose*, possibly in short-term combination with *neomycin* or paromomycin, is recommended. This is especially true when there are signs of an onset of hepatic encephalopathy.

Recommended *antibiotic prophylaxis* includes *neomycin* (1 g), *colistin* (1.5 million units) or *nystatin* (1 million units) four times a day. Antibiotics which have been tried and tested are *norfloxacin* (400 mg/day), *cefotaxime* and *ceftriaxone*. They result in selective intestinal decontamination as well as bactericidal action in the serum, ascitic fluid and urine. Because of the possible impact of norfloxacin on the central nervous system, special caution should be exercised during the initial stages of HE. Primary prevention with norfloxacin in high-risk patients yielded a reduction in SBP frequency from 17% to 2% and from 32% to 0%, respectively. (67, 77, 80, 82, 86, 90)

Whenever $>250/mm^3$ polymorphonuclear neutrophils are detected, immediate **antibiotic treatment** is called for using (*1*.) amoxicillin-clavulanic acid, (*2*.) cefotaxime (and other third generation cephalosporins), (*3*.) gyrase inhibitors such as norfloxacin, and (*4*.) aztreonam. The latter, however, does not act against gram-positive microorganisms, so that there is a danger of gram-positive proliferation. *Therapy* lasting four to five days (longer application is of no further advantage) with cefotaxime (perhaps combined with metronidazole in the possible presence of anaerobes) or amoxicillin-clavulanic acid can provide a success rate of >80%. Consequently, an *exploratory puncture* and follow-up examination of the ascitic fluid after a 48-hour antibiotic therapy is imperative. • In accordance with the **antibiogram,** it may prove necessary to change the initial antibiotics. Success is, however, usually achieved within a few days, using the substances of first choice (cefotaxime, cefoxitine, amoxicillin-clavulanic acid). Therapy results can be markedly improved through simultaneous administration of albumin (1.5 g/kg BW). (91) In order to avert a relapse, norfloxacin is recommended; this reduces the relapse rate from 68% to 20%. (71) The previously high mortality rate (some 90%) could be lowered to 40−78%, and in a recent study even to 37%. (67, 69, 73, 86, 88, 96)

Selenite: With the additional administration of selenite (e. g. 500 µg as short-term infusion), it is apparently possible to improve the survival rate even further.

8 Conservative therapy of ascites

"When the liver is full of water that flows off into the abdomen and the body is distended, then death is near." (Hippocrates)

Oedema and ascites call for extensive therapeutic measures. The daily life of the liver patient is additionally impaired by this condition, which may even be life-threatening. Awareness of the pathogenic factors makes it possible to apply prophylactic measures to prevent a disruption of water-electrolyte homoeostasis and to ensure appropriate therapy. (37, 47, 48, 57, 58)

In pathophysiological and prognostic terms, even ascites that can "only" be identified by ultrasonic methods is a **sign of decompensation** − either decompensation which is still latent, yet unstable, or decompensation which is slowly increasing by itself! • This latter condition ultimately calls for more severe measures (also involving more side effects) than merely moderate and cautious efforts to restore the patient to a stable state of recompensation, which should be as lasting as possible.

8.1 Prophylaxis

The principal prophylactic measures for ascites consist of a detailed consultation with the physician (preferably together with a family member) and strict *guidance* of the patient with efficient *follow-up* checks in the practitioner's surgery. (s. fig. 15.2) A major prerequisite for successful prophylactic measures is an appropriate *lifestyle* on the part of the patient regarding the disease.

► As far as **costs** are concerned, a one-year course of prophylactic treatment including the necessary follow-up checks and possible *early treatment of commencing water retention* is less expensive than three or four days' hospitalization. • This solely economic viewpoint is likewise true for *prophylactic measures used in hepatic encephalopathy* as well as for its early diagnosis and successful therapy at the practitioner's surgery.

The **restriction of sodium** to 7−8 g daily (or even less) is an important step. Each excessive gram of sodium which is taken up and cannot be excreted leads to a water retention of 200−300 ml. (s. tab. 16.11)

All routine activities which can be carried out in a **supine position** should indeed be performed in this way (see below). As a result, renal perfusion is improved, the sympathicotonus lessened and the tubular absorption of sodium decreased. The breakdown of aldosterone is increased by >30%, and its half-life returns more or less to normal. The central blood volume is enhanced. Removal of ascitic fluid via the subdiaphragmatic and mediastinal lymph vessels is facilitated.

Intestinal detoxification by means of lactulose, which, among other things, delays the production and/or portal uptake of endotoxins, is another important therapy step.

Should these measures prove inadequate, either because of insufficient compliance on the part of the patient or because of the advanced stage of the disease, **spironolactone** (50 mg every second day) is recommended. This dose is considered effective and sufficient (due to its longer half-life). As a rule, there are no side effects.

The patient is instructed to record his morning *body weight* (always under the same conditions) every day on a **documentation sheet** (E. KUNTZ, 1989) as well as the *frequency of stools* (e. g. under lactulose therapy) and to enter a *handwriting specimen* (usual way of writing the first and last name) every one or two days. (s. fig. 15.3) • This documentation sheet is deemed to be a useful and efficient instrument (which can be kept as a medical record) in the control and follow-up of a chronic course of disease. An ancillary benefit is that the extent to which the patient is cooperating can also be deduced from the accuracy of the entries made. (s. p. 283)

Patients should immediately consult the doctor if their body weight rises steadily by >1 kg in three to four days. This is *suggestive of a clinically not yet identifiable accumulation of water in the tissue* (= **latent oedema**). • Patients should also consult the doctor in the case of minor irregularities in their handwriting. Psychometric tests can be used to confirm or discount suspected cases of **latent HE**. (s. pp 211, 280) (s. fig. 15.3)

Self-monitoring on the part of the patient makes it possible to identify the beginning of water accumulation in the organism (>1 litre), a reduced lactulose effect (which is inadequate for intestinal detoxification) and/or a latent phase of hepatic encephalopathy. • In such cases, immediate **outpatient treatment** is generally reliable and swift in its therapeutic success.

Diuretics are not indicated as a prophylactic measure! (because of the possible activation of RAAS)

8.2 Basic therapy (stage I)

► The development of **latent oedema** can be recognized by means of daily weight checks when an increase in weight of >1 kg occurs within four days.

► **Latent ascites** (<250 ml) can be determined by sonography. Detection of fluid in the abdominal cavity signals decompensation of cirrhosis and the corresponding inefficacy of prophylactic measures. Medication is recommended as part of a stepwise therapy. To start with, the prophylactic measures for ascites should be applied more intensively and consistently. Both ascites itself and its treatment harbour risks for the patient. The earlier ascites is identified, the more successful the therapy will be, because less "aggressive" methods with minimal or no risks can be used; and, of course, the costs will also be lower. (s. tab. 16.11)

Absolute **supineness** (probably even with the head and upper body slightly lowered) promotes the excretion of water and sodium. This physical treatment significantly improves both the natriuretic and diuretic effect of a loop diuretic agent. (99, 112, 125) (s. tab. 16.11)

The aim is to break through the positive sodium balance by **restricting sodium** to ≤5 g/day (= 88 mmol). Natriuresis should amount to >80 mmol/day. Given an extrarenal loss of sodium of approx. 10 mmol/day, determination of the sodium content in 24-hour urine provides a clue to the degree of compliance with the intended sodium restriction level of ≤5 g/day − i. e. with an excretion of <78 mmol/day, the desired negative sodium and fluid balance is achieved. The efficacy of a low-sodium diet in the treatment of ascites is evident. *Dietary sodium restriction* is maintained by applying the following *rules:* (*1.*) preparation of food without salt, (*2.*) no extra salt to be added at the table, (*3.*) no use of baking powder, tinned food, highly salted food, mineral water or chocolate, (*4.*) no more than 0.25 l milk/day, and (*5.*) no use of medication or i. v. solutions containing sodium. • *Liquorice is prohibited!* • Certain herbal mixtures help patients to accept sodium restriction in the diet. Even food that does not taste salty may contain significant amounts of sodium (e. g. sodium nitrate, sodium phosphate). A marked restriction of sodium is accompanied by a parallel reduction in the general protein consumption; this must be averted by an adequate intake of lactovegetable proteins. • Patients should always be given **dietary advice!** (s. tab. 16.11)

Basic therapy (stage I)	
1. Sodium restriction (intake < 5 g/day) 2. Water restriction (intake < 1,500 ml/day) 3. Supine position 4. Intestinal detoxification (with lactulose) 5. Spironolactone (50−100 mg/day) 6. Balancing of electrolytes 7. Substitution in zinc deficiency 8. Balancing of proteins	
Success rate	**20−30%**

Tab. 16.11: Basic therapy of ascites (stage I)

Normally, the daily **fluid intake** is 1,700−2,200 ml; this includes water in a bound form (e. g. fruit, yoghurt, tomatoes). If this amount is clearly reduced or exceeded, the cirrhotic patient may suffer considerable pathophysiological disturbances. From the clinical point of view, however, it is recommended to limit the fluid intake to 1,400−1,600 ml/day during this phase of therapy (in cases of hyponatraemia even to 800 ml). An increase in

the dosage of **spironolactone** to 50−100 mg/day has proved effective. With this measure, a loss in weight of >1.2 kg in four days can be achieved in 15−20% of cases (= excretion of retained fluid). (s. tab. 16.11)

Follow-up checks regarding sodium, potassium, magnesium, the acid-base equilibrium and possibly zinc are required; if necessary, the status has to be duly balanced. • **Hyponatraemia** must not be "treated" by the intake of sodium, but by a further *restriction of fluid* (while monitoring sodium levels). (s. p. 314)

8.3 Diuretic therapy (stage II)

Ascites is a defined compartment of the extracellular fluid volume, which is difficult to mobilize. If the reduction in weight is inadequate after appropriate basic therapy (<1.2 kg after 4 days), stage II should be initiated with the cautious administration of diuretics. The steps already detailed for stage I are to be continued, whereby the intake of dietary sodium is restricted even further (≤3 g/day). (s. tab. 16.12)

The peritoneum has a surface area of about 2 m^2. It has the effect of a semipermeable membrane and can transport a total of 720−840 ml/day between the plasma and the peritoneal cavity. Spontaneous diuresis allows *300 ml/day* to be excreted, whereas with the use of diuretics some *500 ml/day* are possible. The presence of peripheral oedema, however, permits a loss of fluid of about *900 ml/day* (L. Shear et al., 1970).

The **therapeutic target** is a weight reduction of about 1.5 kg in 3 days (maximum 500 ml/day) without oedema and of 3.0 kg in 3 days (maximum 0.7−1.0 l/day) with concomitant peripheral oedema. (118)

► If diuretic therapy is to be low in complications, the following **prerequisites** are important: (*1.*) no electrolyte imbalance, (*2.*) no abnormality of the acid-base equilibrium, (*3.*) normal renal function, and (*4.*) no simultaneous application of non-steroidal antiphlogistics (since these inhibit the synthesis of prostaglandin and hence may cause renal dysfunction). • In line with the half-life of the diuretics, a *twice-daily administration* (morning, early evening) is more successful. The early evening diuretic dose is lower (e. g. xipamide 20 mg and *10 mg*). This serves to prevent renewed retention of fluid during the night which occurs as a result of the continuously decreasing diuretic effect of just one morning dose. It may also be necessary to administer a third low diuretic dose at midday (e. g. xipamide or torasemide 20/*10*/*10 mg*).

8.3.1 Pharmacology of diuretics

Of the many diuretic agents with their differing points of impact on the nephron and their respective action profiles, some preparations, even in combined application, have proved extremely successful in the treatment of portal ascites. It must be borne in mind here that liver diseases can change the pharmacokinetics of diuretics. (59, 102, 105) (s. tab. 16.12)

Never provoke abrupt diuresis. • Never stop the use of diuretics suddenly!

Diuretic therapy (stage II)	
1. **Aldosterone antagonist**	
• potassium canrenoate	(100−800 mg i.v./day)
• spironolactone	(50−400 mg/day)
2. **Saluretics**	
• etacrynic acid	(50−400 mg/day)
• etozolin	(200−800 mg/day)
• furosemide	(20−500 mg/day)
• torasemide	(10−40 mg/day)
• xipamide	(10−40 mg/day)
3. **Sequential nephron blockade**	
torasemide or xipamide	(20−40 mg/day)
combined with	
• butizide, *or*	(5 mg/day)
• hydrochlorothiazide, *or*	(25 mg/day)
• metolazone	(2.5−5 mg/day)
Success rate	**ca. 80%**

Tab. 16.12: Diuretic therapy of ascites (stage II)

1. Spironolactone (J. A. Cella et al., 1957) is the preparation of choice. Its clinical efficacy has been substantiated in numerous studies. • The onset of effect is after 8 to 24 hours. The natriuretic/diuretic action is maintained for one or two days. A faster onset of effect is given by *potassium canrenoate*, available as an i.v. application, particularly when absorption is assumed to be impaired or if oral administration is not possible. • *Spironolactone is not primarily considered to be a diuretic agent, but more a substance with neurohumoral action.* (97, 101, 103, 106, 107, 117, 121, 123, 126; quot. 4, 5)

► As a specific **aldosterone antagonist,** spironolactone acts at the basolateral side of the upper-distal tubule as well as in the collecting tubule and prevents aldosterone from contacting its receptor. As a result, aldosterone-related stimulation of the sodium-potassium ATPase is inhibited at the cell membrane. For this reason, aldosterone is unable to reach the cell nucleus with its receptor complex. Synthesis of the aldosterone-induced protein, which opens the sodium canals, is prevented. The absorption of sodium is decreased and natriuresis reinforced, whereas the excretion of potassium remains normal or is diminished. In the presence of hyperaldosteronism, spironolactone is likely to be fully effective. Although aldosterone only controls some 2 (−4)% of the glomerular filtrated sodium at the tubule, a natriuretic/diuretic effect is gradually achieved. The positive effect of spironolactone on portal ascitic fluid can be attributed to an inhibition of the aldosterone-mediated absorption of sodium in the intestine, a reduction in the portal vein pressure and an increase in the synthesis of prostacyclin in the kidney. Spironolactone has no glucocorticoid impact and no influence on the metabolism of carbohydrates. • *Due to an escape effect, it does not usually cause hyperuricaemia, hyponatraemia or hyperkalaemia*. Protein binding is 98% with a bioavailability of 60−90% and a half-life of 20 hours. In cirrhosis, the pharmacokinetics of spironolactone remains unchanged. • The transtubular potassium gradient is a guide for the diuretic management of patients with cirrhosis and ascites. (47)

Action profile of spironolactone	
Natriuria ↑ **Kaliuresis** none-(↓) **Magnesiuresis** none-(↓) **Ammonia** ↓	**Zincuria** ↓ **Hydrogen ions (in urine)** ↓ **Chloride (in urine)** ↑ **Bicarbonate (in urine)** ↑ **pH value (in urine)** ↑

▶ As a result of a tubular hypersensitivity to aldosterone, cirrhotic patients usually display *functional aldosteronism* in the early stages of increased sodium retention. This would explain the diuretic and natriuretic efficacy of spironolactone even in cirrhotic patients with normal aldosterone levels.

In no way do normal potassium values rule out hyperaldosteronism!

The *dosage* of spironolactone is 100 to 400 mg/day in two to three single doses. That of potassium canrenoate amounts to 100 to 800 mg/day. When therapy begins with potassium canrenoate, spironolactone should be administered orally one to two days prior to termination of the i.v. application to ensure a smooth transition, since the onset of its effect is delayed. In 25−30% of male patients, long-term application leads to (generally reversible) potency disorders and gynaecomastia.

2. Xipamide is classed as a low-ceiling diuretic with its effective dynamics and intensity ranking between furosemide and the thiazides. For this reason, there are no extreme peaks of diuresis during prolonged therapy. Calciuria is typical for loop diuretics. With portal ascites, xipamide has proved to be almost diuretically equivalent to spironolactone.

The **efficacy** of xipamide is reflected at various sites of the tubule and Henle's loop. It reaches its point of impact at the early-distal tubule − from the peritubular side. With a threshold dose of 5 mg, a dose dependency ranging between 14 and 60 mg is thus produced for the excretion of water and urine; when in excess of 80 mg, there are no further effects. The bioavailability is 73% and protein binding 98%.

A *dosage* of 20 to 40 mg xipamide per day is recommended in 1−2 (−3) single doses. For long-term therapy, it is advisable to prescribe 10 mg. Diuresis sets in after about one hour with a peak after two to eight hours. There is no rebound effect. The excretion of sodium and chloride is increased to an almost identical degree; calciuria, magnesiuresis and kaliuresis occur. For this reason, xipamide should be combined with spironolactone. Biotransformation of xipamide is clearly limited in cirrhotic patients, the half-life (7 hours) is not influenced. Xipamide passes into the ascitic fluid and reaches concentrations of 10−20% of the respective plasma level. It can even be used with restricted renal function, since it has no influence on renal haemodynamics.

3. Torasemide has proved successful in the treatment of portal ascites. The onset of effect takes between 15 and 30 minutes, and it reaches its peak after 6 to 9 hours. Torasemide has a high natriuretic and diuretic effectiveness, even with restricted renal function. Up to now, a *dosage* of 20 mg per day has been used (possibly in two single doses of 10 mg). A combination with spironolactone is very efficient. Torasemide is also available as an intravenous application. (98, 100, 113)

In terms of **efficacy,** torasemide is a high-ceiling, long-acting diuretic, which shows a linear and rapid rise in the dose-effect curve in a higher dose range. Bioavailability is 80−90%, with a protein binding of 98%. The half-life is three to four hours. The site of action is deemed to be the ascending branch of the loop of Henle. There are marked increases in the amounts of potassium, magnesium and sodium in the urine, but excretion of bicarbonate and phosphate remains constant. In cirrhosis, the half-life is lengthened to four to five hours and biotransformation is impaired. (100) Torasemide has a favourable sodium-potassium excretion quotient. It does not accumulate in renal or liver insufficiency.

4. Etacrynic acid, especially in *combination* with spironolactone and xipamide, markedly enhances natriuresis and diuresis. The *dosage* is increased as required (e. g. 1 × 25 mg or 50 mg to 2 × 50 mg per day). With a low-dose application in the form of a combined diuretic therapy, there is usually no risk of hepatic encephalopathy developing. The effect of etacrynic acid sets in at the ascending branch of the loop of Henle (active chloride transport). Renovascular resistance is lowered due to enzymatic activity, presumably as a result of a rise in the release of prostaglandin.

5. Furosemide is a high-ceiling diuretic. The onset of effect is rapid with a strong (unwanted) rebound. With a half-life of 1.5 hours, the length of impact is short (3−6 hours). The bioavailability is 65%, protein binding 70−80%. In cirrhosis, the half-life is lengthened and natriuresis is diminished. Reinforcement of potassium in the urine, alkalosis and hepatic encephalopathy are observed. Furosemide can promote enhanced formation of thromboxane in the kidneys with subsequent renal vasoconstriction. This could be the cause of renal failure in cirrhotic patients following high doses of furosemide. It only acts with intact PGE_2 synthesis, which is, however, often impaired in cirrhosis. (100, 102, 106, 117, 123, 126)

Follow-up checks: It is important to be aware of the pharmacological characteristics of diuretics and to carry out check-ups during diuretic therapy at short intervals, so that countermeasures can be initiated early enough in the event of therapeutic derailment. Intervals between check-ups as well as the diuretic dosage depend on the success of the treatment and the course of disease:

- Body weight and specimen of handwriting (daily) (s. pp 211, 311, 319) (s. figs. 10.1; 15.3)
- Urine volume (at the outset: each day)
- Electrolytes (at the outset: possibly each day)
- Serum creatinine (at the outset: possibly every 2−3 days)
- Acid-base status (at the outset: possibly every 3−4 days)

Success rate: With correctly applied diuretic therapy, the rate of success is about 80% (even in prolonged or recurring ascites).

Failure rate: If the diuretic therapy proves unsuccessful, investigation must initially focus on whether the therapeutic steps taken have been correctly implemented or whether exsiccosis with a contraction of the plasma volume has occurred as a result of excessively forced diuresis. Hypovolaemia leads to stimulation of the biochemical and sympathoadrenal regulatory systems with an occasionally deleterious effect on the course of disease.

8.3.2 Side effects

Diuretic treatment of ascites can, however, involve considerable hazards for the patient. Generally, one has to reckon with the following side effects: **encephalopathy** in 22−26% (as a result of 5−10% inhibition of carbonic anhydrase in the mitochondria of the liver cells), **hyponatraemia** in 40−50%, **azotaemia** in 20−40%, and **hypokalaemia** in up to 85% of cases. A rare event are **diuretic-associated oedemas**. (115)

Therefore, dose diuretics "as softly as possible"!

These complications occur singly or in a combined form in 30−50% of all diuretically treated patients. The more aggressive the diuretic treatment is, the more frequently these types of complications can be expected. • *Hypokalaemia*, which does not respond to potassium substitution, is possibly accompanied by (unidentified, diuretically induced) *hypomagnesaemia*, particularly in elderly patients. (122) For this reason, it may be necessary to substitute magnesium. • Thought should be given to the possibility of a *pseudo-Bartter syndrome* as a result of diuretic abuse and especially of excessive liquorice intake. • The very first signs of diuresis-related hazards call for immediate countermeasures − or even discontinuation of the diuretic therapy. *Nonsteroidal antiphlogistics are contraindicated for cirrhotic patients with ascites.*

8.3.3 Hyponatraemia

Elimination of hyponatraemia (< 125 mmol/l) is difficult. In this case, the status of body sodium is increased, and hence the body fluid as well, whereas the sodium level in the serum is lowered (= *dilutional hyponatraemia*). Treatment is effected by strictly limiting the intake of fluid (< 700−900 ml/day) and restricting salt. Albumin infusion has proved to be an effective therapy. (114, 124) • Should these measures fail to raise sodium levels in the serum and increase diuresis, i. v. administration of a hypertonic sodium chloride solution (3%) can be attempted (increasing serum sodium by no more than 1.0−1.5 mmol/l per hour and, if possible, never in excess of 130 mmol/l). This, however, automatically harbours the danger of tense ascites. For this reason, an i.v. application of furosemide should be given at the same time to promote the clearance of free water. The sodium lost in the urine (measurable in six hourly intervals after administration of a saluretic) is replaced quantitatively by the supply of NaCl. This trick produces pronounced diuresis without a "genuine" input of sodium (R. W. Schrier et al., 1973). • With intact renal function, an attempt can be made at treatment with a 5% sorbitol solution or a 10% mannitol solution. (116) Haemofiltration or i.v. application of sodium-free albumin (111) is likewise recommended. (114) • The augmented release of ADH is depressed (and sodium concentration is increased) by tolvaptan, a vasopressin-2-receptor antagonist. (127)

8.3.4 Resistance to diuretics

Resistance to diuretics occurs if the reduction in body weight ceases despite confirmed diuretic intake or if a rise in creatinine and urea restricts further diuretic application. The phenomenon of *haemodynamic resistance to diuretics* may prove problematic, i. e. the actual volume of circulating blood is reduced. (119) There is a **triad** status: (*1*.) rise in retention values, (*2*.) lower urine volume, and (*3*.) low excretion of sodium in the urine. At the same time, arterial hypotension due to pronounced peripheral vasodilation is present together with the opening of arteriovenous anastomoses. Palmar erythema or spider naevi are often seen to "blossom". (s. p. 84) The greater the peripheral vasodilation, the more pronounced is the renal vasoconstriction. As a result, it is hardly (if at all) possible for the diuretics to reach their site of action in the nephron. • Another cause of diuretic resistance is the fact that the substrate concentration required for the loop diuretics to have an effect is absent in the ascending part of Henle's loop because of the increased proximal tubular absorption of sodium − the diuretic is therefore ineffective. This renal deficiency of diuretics is wrongly equated with "resistance". *Therapy* is based on a **sequential nephron blockade**, which is achieved by combining a loop diuretic with a thiazide, e. g. torasemide (20−40 mg) (113) with butizide (5 mg), hydrochlorothiazide or metolazone as well as low-dosed ACE inhibitors. (s. tab. 16.12)

An **ornipressin infusion** and **adrenaline infusion** plus **water immersion** (up to the neck for a period of 5 hours) act on the lowered peripheral vascular resistance. • Low-dosage dopamine and prostaglandin or ANF infusions may have an effect on the increased renovascular resistance. (120) • A selective vasopressing-2-receptor antagonist induced a dose-related aquaretic response. (110)

8.4 Osmotic diuresis (stage III)

In inadequate response to diuretic therapy (stage II), osmotic diuresis is advisable in order to improve *hypoalbuminaemia* and *hypovolaemia*. (s. fig. 16.16)

Human albumin: Using i. v. application of human albumin or fresh plasma, it is possible to bring about a tem-

porary rise in the osmotic pressure and improve the glomerular plasma flow. (91, 108) • Enlarging the plasma volume causes an increase in renal perfusion and urine excretion. • *The passage of infused human albumin into the ascitic fluid is prevented or reduced by prior administration of a plasma expander (100−200 ml) to ensure a preliminary boost to the oncotic pressure.*

Mannitol: Stimulation of osmotic diuresis is possible using mannitol (10−20% solution). (116) Mannitol is neither metabolized in the body nor reabsorbed by the tubules and is excreted almost totally through the kidney. Renal circulation and renal filtration are raised, and by reducing tubular absorption (= osmotic diuresis), water excretion is increased ("diuresis starter"). The saluretic effect is, however, relatively small. In the case of restricted renal function, application of mannitol is contraindicated. If necessary, the **mannitol test** (i. v. injection of 75 ml of a 20% solution) can be carried out beforehand. With enhanced diuresis of >40 ml/hr, the kidneys still function adequately, so that it is possible to stimulate osmotic diuresis by means of a mannitol infusion.

In the individual case, these short-term measures (possibly also reinfusion of ascitic fluid) lead to a temporary improvement of hypoalbuminaemia and hypovolaemia, so that a diuretic therapy, which has been hitherto insufficient, can nevertheless be continued and successfully completed. • *If stages I−III fail to be efficacious in eliminating ascites, paracentesis is indicated.*

8.5 Paracentesis (stage IV)

► Even in antiquity, attempts were made to remove ascitic fluid by abdominocentesis (Erasistratos 300−250 BC, Celsus 30 BC−50 AD). Paulus of Aegina (625−690 AD) gave an exact description of ascitic fluid being tapped. • In the 16th century, Paré removed ascitic fluid with an inserted seton (i.e. rope made of hair) after cauterizing the abdominal wall. • In the 17th century, Santorini used a special instrument inserted through the navel to tap the abdominal cavity. • Figure 16.11 illustrates the **tapping of ascitic fluid** at that time (1672).

Fig. 16.11: Tapping ascitic fluid (1672) (German National Museum, Nürnberg)

Before resorting to invasive or even surgical procedures to eliminate ascites, paracentesis (stage IV) is indicated. Repeated (if necessary, daily) paracentesis can remove 1,000−4,000 ml ascitic fluid in one to two hours. The loss of complement factors possibly heightens the threat of spontaneous bacterial peritonitis − yet in view of the reduced protein content in the ascitic fluid, this danger is more likely to be diminished. Relief is provided to the portal and renal vessels. When correctly performed, complications are rare. (150) It is possible to repeat paracentesis without incurring any actual risks and to remove substantial quantities of ascitic fluid (4−6 [−23] litres) by means of a pump (132, 135, 137, 138, 140, 150) or even to evacuate a large amount of ascitic fluid almost totally. (128, 139, 141, 145, 149) Therapy is successful in about 95% of cases. Paracentesis of 6 litres of ascitic fluid removes 6 × 130 mmol/l sodium. Occasional circulatory dysfunction (as demonstrated by excessive activation of the RAAS) following paracentesis only rarely − or never − occurs when spironolactone and albumin substitution are applied. (s. fig. 16.17)

The following criteria are important **indications** for performing paracentesis (103, 128, 133, 141, 146, 148):

1. Lack of success or inadequate feasibility of stepwise therapy (stages I−III)
2. Extensive ascites, possibly with complications
3. Sodium excretion <10 mmol/day
4. Fractional excretion of sodium (FE_{Na}) ≤ 0.2%
5. Serum-ascites albumin gradient <1.1 g/dl (= serum albumin concentration minus ascites albumin concentration)

With regard to paracentesis, the following **measures** are to be considered (128, 133, 134, 136, 141, 145, 147):

1. Discontinuation of diuretic therapy some three to five days prior to paracentesis, maintenance of spironolactone (e. g. 2 to 3 × 50 mg/day).
2. Balancing of electrolytes, acid-base equilibrium and, if necessary, zinc substitution.
3. Replacement of sodium-free albumin (40 g or 6−8 g/litre ascitic fluid), half the amount prior to starting paracentesis; *or*: administration of 100−150 ml of a sodium-free plasma expander prior to paracentesis and prior to the replacement of albumin.
   ► *Prior administration of a plasma expander* raises the lowered oncotic pressure. As a result, the subsequent albumin intake is retained better in the blood stream (otherwise there is a possible danger of albumin loss from the "off-flow" into the ascitic fluid).
   ► Synthetic sodium-free plasma expanders are considerably (about 20 times) cheaper than albumin and equally efficient.

Results: The results of paracentesis have been good up to now: the number of successfully treated patients was higher, inpatient hospitalization was shorter, and complications were less frequent or less severe. The response to diuretic therapy improved considerably; discontinued diuretic therapy could be taken up again. (144, 145) Plasma values of renin, aldosterone and norepinephrine dropped. There was an improvement in lung volume (129, 131) and in cardiac function. (139,142) The pressure in the oesophageal varices fell. (137) • *Paracentesis of 6 litres of ascitic fluid removes 6 × 130 mmol sodium.*

Dangers: Thought must be given to averting the following dangers deriving from repeated and/or large-scale paracentesis: (*1*.) protein loss, (*2*.) loss of electrolytes, (*3*.) hypovolaemia, (*4*.) occurrence of ascitic leakage, (*5*.) occurrence of (secondary) bacterial peritonitis, (*6*.) restricted renal function, and (*7*.) acute haemoperitoneum. (130)

An **ascites fistula** following paracentesis can be widely avoided by displacing the skin tangentially to the site of puncture, so that a *Z-shaped puncture channel* is created once the needle has been removed.

Danger points 1, 2 and 3 (see above) can be related to a quotation from Paulus of Aegina (625–690 AD): *"At all events, avoid any rapid evacuation of the fluid, since there are some ignorant operators who have removed the life and soul of the patient with the fluid, thereby bringing the life of the patient to an end."*

9 Refractory ascites

Before denoting ascites as refractory to conservative therapy in cases of liver cirrhosis, it is essential to rule out *what would appear to be pathogenetically or causally derived resistance to therapy.* The multiple causes of resistance to therapy must be considered in each individual case and excluded as far as possible. This can often be extremely difficult and is sometimes even impossible. (s. tab. 16.13) • Assessment of the renal cortical blood flow is facilitated by colour-encoded Doppler sonography: successful diuretic therapy of ascites requires good circulation in the renal cortex. A continuous decrease in the cortical blood flow correlates with growing therapy resistance of the ascites.

With reliable cooperation on the part of the patient, precise adherence to stepwise therapy (possibly including repeated paracentesis) and almost total exclusion of the causes of therapy resistance, it becomes clear that true **refractory ascites** or "sequestered ascites" is present in merely 5–10% of patients with portal ascites.

The prognosis of "true" refractory ascites is infaust – unless invasive measures can be applied. These would include reinfusion of ascitic fluid, peritoneovenous shunting or TIPS. Liver transplantation is the only definitive therapy. (37, 57, 120, 151–157, 170)

1. Unresolved cause of ascites
2. Excessive sodium levels in the body
   - inadequate sodium restriction
   - extremely high proximal reabsorption of sodium
3. Hypovolaemia
4. Absence of peripheral oedema
5. Excessive volume of ascitic fluid in the abdomen
   - disturbed cardiac function
   - compression of portal or renal vessels
6. Deterioration of renal function
7. Unfavourable diuretic effects
   - inadequate diuretic absorption
   - unsuitable diuretic agent
   - incorrect dosage
   - medication-related interactions (e.g. nonsteroidal antiphlogistics, aminoglycosides)
8. Spontaneous bacterial peritonitis
9. Deterioration of liver function
   - toxic or infection-related disorders
   - gastrointestinal bleeding
10. Haemodynamic resistance to diuretics
    - peripheral vasodilation
    - opening of arteriovenous anastomoses
    - relative hypotension
    - reactive renal vasoconstriction
11. Portal vein thrombosis
12. POEMS syndrome

Tab. 16.13: Pathogenetic or causal factors which may explain apparent resistance to ascites therapy

10 Invasive therapeutic procedures

10.1 Ascites reinfusion

► In 1911 intravenous ascitic reinfusion was described as an invasive procedure to treat refractory ascites (J. Galud). This procedure was taken up again by M. Girard et al. in 1949 and by R. Emmrich et al. in 1951. In 1958 E. Adlercreutz filtered the ascitic fluid prior to intraperitoneal reinfusion and thus increased its protein concentration. (158)

Methods: In the following years, various methods were developed, all of which proved their worth and led to clinical success. Central venous pressure and sodium-potassium quotient in the urine were swiftly normalized, and diuresis increased. Pathological sodium and potassium values in the serum were adjusted. Natriuresis and the concentration of ADH were not influenced. There were no electrolyte disturbances. (132, 138, 160–167, 170)

1. **Unmodified ascites:** Careful examination of the unmodified ascitic fluid prior to direct retransfusion is imperative. (s. fig. 16.10) It is likewise essential to determine the plasminogen level in the ascitic fluid.

► By means of an automatic infusor or a roll pump, 300–400 ml/hour are reinfused through a filter system with a pore diameter of

22 µm via a central vein catheter. Reinfusion time should be limited to 8–12 hours/day, so that a daily reinfusion quantity of 3–4 (–5) litres is achieved. Reinfusion on every second day has also proved successful. This procedure can be carried out prior to the implantation of a peritoneovenous shunt. The transport volume is varied in such a way that a good response is not accompanied by cardiopulmonary complications due to hypervolaemia. Intensive monitoring of the patient is required.

2. **Modified ascites:** Reinfusion of modified ascitic fluid calls for prior "desalination" or "concentration" with the later aim of "reproteinization". (159) The concentration of the reinfused protein was four to six times higher than the protein content of the ascitic fluid. Combined with diuretic therapy, up to 13 litres were removed in 24 hours. A comparative study showed no difference in efficacy or complications between the reinfusion of unmodified and ultrafiltered ascitic fluid.

Since 1960 discussion has focused on procedures for **extracorporeal dialysis** and since 1981 they have been used successfully (J. Feldman et al.). The **ultrafiltration** of ascitic fluid by means of haemodialysis and its subsequent reinfusion was described by E.R. Hwang et al. in 1982. Additional administration of foreign protein is not necessary. (132, 138, 163) A further development of ultrafiltration could be seen in the so-called *cascade filtration* or **double ultrafiltration.** (168) This procedure is described as safe, reliable and low in complications.

Indications: Indications and contraindications largely correspond to those of peritoneovenous shunts. For the short-term or repeated application of ascitic fluid reinfusion, the following indications can arise:

1. Refractory ascites
2. Inoperability of the patient
3. Pronounced hypovolaemia, hypotension and/or hypoalbuminaemia
4. Dilutional hyponatraemia
5. Preoperative elimination of ascites
6. Emergency situation
7. Bridging renal insufficiency that is in principle reversible

Success rate: Short-term success can be achieved in about 80% of cases, many of which also have the chance of long-term therapy success. Stage II treatment is continued parallel to the reinfusion of ascitic fluid.

Complications include clotting disorders (22, 169) and the bacterial infection of ascites.

10.2 Peritoneovenous shunt

The short-term but nevertheless relatively good clinical results achieved with the reinfusion of unmodified ascitic fluid encouraged the development of another therapeutic procedure based on a similar principle, yet with long-term efficacy. (s. fig. 16.17)

► Initial attempts were based on a peritoneovenous fistula with the great saphenous vein (M. Ruotte, 1907). Later, it was the flow-controlled Spitz-Holter technique based on the principle of discharging CSF fluid from the hydrocephalus via a Holter valve (introduced by A.N. Smith in 1962) which yielded convincing success. Consequently, a variety of pressure gradient-guided **shunt valves** were described over the following years: (*1.*) pump system of G.L. Hyde et al. (1966), (*2.*) Denver valve developed from the treatment of the hydrocephalus (W.R. Waddell, 1971), (*3.*) LeVeen shunt (H.H. LeVeen et al., 1974), (*4.*) Agishi valve (T. Agishi, 1977), and (*5.*) Hakim-Cordis system (J.F. Patino et al., 1979), based on the neurosurgical method developed by S. Hakim et al. (1957). (171, 194)

Method: A silicone tube with roentgenopaque thread is positioned in the abdominal cavity with the intraperitoneal crus acting as an ascitic fluid collector. By means of a pressure-controlled valve, it is connected with the subcutaneously implanted section, the tip of which is introduced via the jugular vein or the subclavian vein into the superior vena cava. The ascitic fluid is forced through the valve as a result of the difference between the intraperitoneal and intrathoracic/central venous pressure. The valve only opens once this pressure gradient rises above ca. 3 cm H_2O. • Further development led to the production of pressure valves which could be operated manually by the patients themselves due to skilful surgical positioning. Each time the valve is pressed open, 4–6 ml ascitic fluid are transported. As a rule, the patient should use the pump five times per hour. In order to assess the effectiveness of a pump valve, certain **functional parameters** are applied: (*1.*) operative placement, (*2.*) opening pressure, (*3.*) pumping performance, and (*4.*) flow rate. In the light of these parameters, the Denver shunt (opening pressure 1–3 cm H_2O) is recommended as being most suitable despite its high flow rate (30–40 ml/min) because of its minimal obstruction rate and the possibility of non-operative recanalization. The decision as to which valve system is to be used must be taken in accordance with the four functional parameters described above and is ultimately made by the surgeon based on previous experience. (176, 183, 187, 201) (s. fig. 16.12)

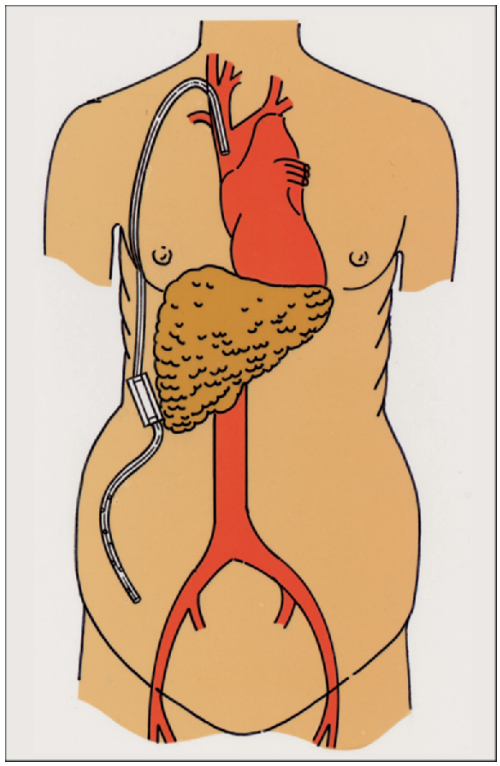

Fig. 16.12: Diagram of the positioning of a peritoneovenous shunt (with Denver valve)

Indications: The indication for a peritoneovenous shunt (PVS) must be viewed critically. (s. tab. 16.14) Before any decision is taken on the shunt implantation, the indication for TIPS or a possible *liver transplantation* must be considered and discussed with the patient. Liver transplantation provides a real opportunity to eliminate ascites permanently − generally also with a longer survival time. (181, 185, 189, 191, 202, 203)

1. **Ascites in liver cirrhosis**
   - refractory progression
   - conservatively treatable, albeit recurrent, condition
   - recurrent pleural effusions with ascites
   - hernia with ascites and respective complications
   - hepatorenal syndrome
2. **Budd-Chiari syndrome**
3. **Chylous ascites**
4. **Pancreatogenic ascites**
5. **Refractory malignant ascites**
   - with considerable strain on the patient

Tab. 16.14: Indications for a peritoneovenous shunt

Contraindications: Experience since 1974 with over 12,000 implanted peritoneovenous shunts has established a wide-scale consensus with respect to contraindications. Such contraindications, which are categorized as relative, have to be considered in each individual case. Successful treatment can, however, change contraindications into a correct indication, i.e. implantable condition. (s. tab. 16.15)

Absolute contraindications

1. Bacterially infected ascites, peritonitis
2. Severe general bacterial infection
3. Liver insufficiency
   - clotting disorders
   - hepatic encephalopathy (stages II−IV)
   - bilirubin > 10 mg/dl
4. Cardiac insufficiency
5. Respiratory insufficiency
6. Blood-tinged, highly viscous ascites

Relative contraindications

1. Increased fibrinolytic activity of the ascites
2. Previous bleeding of oesophageal varices
3. Oliguric renal insufficiency
4. Malignant ascites

Tab. 16.15: Absolute and relative contraindications for peritoneovenous shunt implantation

Complications: The frequency of postoperative complications is extremely high at 43−83% (mean complication rate 65−70%). In connection with the high postoperative mortality rate (20−22%), the question is raised as to why such simple surgery involves many complications. The **cause** can be sought in the generally poor initial condition of the patient, whose prognosis is deemed infaust anyway. Nevertheless, the opinion is also held that a considerable percentage of complications can be attributed to *avoidable mistakes.*

• Differentiation is made between **early complications** (intra- and postoperative) and (as from the first or second week) **late complications,** although no exact time spans are given. Some complications can develop at an early stage as well as at a later point in time. (173, 177, 180, 182, 186, 188, 189, 198, 201) (s. tab. 16.16)

Early complications

1. Methodological/surgical errors (10−20%) (198, 201, 206)
   - misplacement of venous crus
   - top of venous crus set at too great an angle to the vascular wall
   - flexion of the venous crus
   - venous crus too long/too short
   - ligature too narrow
   - lack of compressibility in the chamber
   - nuchal haematoma
   - injury to the recurrent nerve
   - pneumothorax
   - perforation of the coronary sinus
   - cardiac tamponade (due to perforation of the ventricle)
2. Fever (20−30%)
3. Clotting disorders (15−30%) (22, 184, 195)
   - hyperfibrinolysis
   - disseminated intravascular coagulation
4. Bleeding as a result of a clotting disorder
5. Fluid overload of the organism
   - lung oedema (178)
   - cardiac insufficiency
   - acute respiratory distress syndrome
6. Tachycardia due to misplacement of the venous crus in the right ventricle
7. Cholesterol/fat embolism in the lung
8. Bleeding of oesophageal varices (197)
9. Bacterial infection (198, 199)
   - wound infection
   - bacterial peritonitis (209)
   - sepsis
   - infection of the shunt valve
   - endocarditis
10. Leakage

Late complications

1. Shunt obstruction (10−20%)
   - fibrin-related obstruction
   - chyle-related obstruction (208)
   - thrombosis of the superior vena cava (179)
   - thrombosis of the jugular vein/subclavian vein
   - ascitic pseudocyst of the superior vena cava (205)
   - superior vena cava syndrome (197, 207)
2. Intestinal occlusion
3. Air embolism with intestinal perforation (190, 192)
4. Phlegmonous gastroenterocolitis (174)
5. Abdominal abscess
6. Renal failure
7. Liver insufficiency
8. Shunt wandering (177)

Tab. 16.16: Early and late complications following peritoneovenous shunt implantation (with some references)

Mortality: Since the surgical technique is well standardized and relatively simple, there is practically no *operative mortality* (0%−1.0%). In contrast, *postopera-*

tive mortality is put at 10−52% (mean mortality rate 20−22%), depending on the initial condition of the patient. The causes of death are: (*1.*) infections (27%), (*2.*) liver insufficiency (16%), (*3.*) cardiac and/or respiratory insufficiency (14%), (*4.*) consumptive coagulopathy/hyperfibrinolysis (15%), (*5.*) gastrointestinal bleeding (13%), (*6.*) renal failure (5%), and others (10%). (200, 201)

Risk reduction: The high frequency of mortality and complications can, however, be reduced markedly. It is possible to limit risks in the positioning of a PVS and in postoperative care by ensuring adherence to fundamental principles. Numerous examinations are called for prior to positioning a PVS as well as for the reinfusion of ascitic fluid. (s. tab. 16.17)

1. **Differential diagnosis of ascites** (s. fig. 16.10)
2. **Correct indication** (s. tab. 16.14)
3. **Consideration of contraindications** (s. tab. 16.15)

4. **Detailed preliminary examinations**
   - chemical laboratory values, blood coagulation values
   - plasminogen (and α_2-antiplasmin) in ascitic fluid
   - daily urine flow
   - daily body check
   - psychometric tests (s. p. 211)
   - Doppler ultrasonography of the jugular vein
   - central venous pressure
5. **Appropriate pre- and postoperative treatment**
   - basic and diuretic therapy (stages I and II)
   - optimal balancing of electrolytes
   - prophylactic use of antibiotics (s. pp 288, 310)
   - intestinal detoxification (s. p. 285)
   - intraperitoneal injection of dexamethasone on suspicion of increased fibrinolytic activity
   - ornithine aspartate (s. p. 287)
6. **Good cooperation on the part of the patient** (s. tab. 16.18)

Tab. 16.17: Risk reduction criteria for PVS

The determination of **plasminogen** in the ascitic fluid (with a normal value of >0.7 CTA U/ml), possibly also of *α_2-antiplasmin* (with a normal value of >0.1 IU/ml), is a priority. These values can help to estimate the risk of hyperfibrinolysis after the placing of a shunt. With a reduction in plasminogen (E. Köttgen et al., 1982) to <0.7 CTA U/ml or in *α_2-antiplasmin* to <0.1 IU/ml, there is frequently a higher fibrinolytic activity of ascites (in some 40% of patients). Plasminogen activators are formed by peritoneal macrophages, the synthesis and release of which are stimulated by intestinal endotoxins. In some 50% of patients, endotoxins can be detected in ascites, yet not necessarily at the same time in the serum as well. In these cases of greater fibrinolytic activity, the injection of **dexamethasone** (16 mg) into the ascitic fluid is indicated. As a result, the synthesis of plasminogen activators in the macrophages is inhibited. Generally, the values of plasminogen and α_2-antiplasmin rise to within the normal range after 24 hours, so that the dangers are considerably diminished following the placement of a PVS and the subsequent infusion of ascitic fluid into the blood stream (J. Schölmerich, 1987). With inadequate response of plasminogen (>0.7 U/ml) or of α_2-antiplasmin (>0.1 IU/ml), the intraperitoneal administration of dexamethasone (16 mg) should be repeated. Once values have normalized, the shunt can be placed. A repetition of the intraperitoneal administration of dexamethasone may also prove necessary during the postoperative period. • **Intestinal detoxification,** which is principally desired and which can be achieved by means of *neomycin* and/or *lactulose*, serves to diminish the complication of hyperfibrinolysis by reducing the endotoxins. Where the fibrinolytic activity of ascites is increased and the efficacy of (repeatedly administered) dexamethasone proves inadequate, it is advisable to remove the ascitic fluid intraoperatively to carry out an **abdominal lavage** with a physiological NaCl solution and to instil a saline-albumin solution prior to the operative closure of the wound. • Should **clotting disorders,** in particular hyperfibrinolysis, still occur, treatment with *protease inhibitors* (e. g. aprotinin 500,000 units as bolus, then 100,000 U/hour by perfusion over 3−4 days) is required.

Antibiotics: Administration of antibiotics (e. g. cefotaxime) is advisable, starting two days prior to and continuing for about three days after shunt placement.

Compliance: Cooperation on the part of the patient is imperative for the long-term success of a peritoneovenous shunt. Some of the complications are possibly due to negligence or inadequate adherence to the principal measures required. (s. tab. 16.18)

Success of PVS: In general, a two-year survival time in ca. 50% of cirrhotic patients with ascites is considered to be a clinical success. The mortality rate for refractory ascites is almost 100% after a short period of time. • The **efficacy parameters** of PVS can be described as (*1.*) reduction in abdominal girth and body weight with improved respiratory function, physical mobility and subjective feeling of well-being, (*2.*) greater diuresis and natriuresis, (*3.*) enlargement of the intravasal fluid volume, (*4.*) increase in the renal plasma flow and glomerular filtration rate with improved creatinine clearance (172, 187), (*5.*) reduction in ADH, NAF and renin-aldosterone values (172, 175, 193, 204), and (*6.*) diminished pressure in the portal vein system.

1. Respiratory training exercises
2. Wearing of an abdominal binder
3. If a manual pump system is placed, it should be used 5−6 times per hour
4. Appropriate life-style

5. Daily weight check and handwriting test (s. pp 211, 311) (s. fig. 15.3)
6. Correct treatment in line with stages I and II
7. Polypragmatic, albeit mosaic-like, concomitant therapy for underlying ascitic disease
8. Laboratory check-ups at acceptable intervals (e. g. potassium, sodium, creatinine, haematocrit, thrombocytes, Quick's value, haemoglobin, AT III, cholinesterase, electrophoresis)
9. Physical check-ups
10. Ultrasonographic check-ups

Tab. 16.18: Necessary measures for the patient and medical check-ups after placement of PVS

► **Our own experience** (since 1982 at Wetzlar Hospital for Internal Medicine, including the monitoring of outpatients) is founded on the use of the LeVeen shunt (8 cases) and Denver shunt (6 cases). The patients (all suffering from alcoholic cirrhosis) were selected in line with the above criteria, examined and treated (with determination of plasminogen and application of dexamethasone, if required). The survival rate in these 14 cases amounted to 10 patients after 2 years (ca. 72%), 8 patients after 3 years (ca. 57%) and 4 patients after 4 years (ca. 29%). (s. figs. 16.13, 16.14)

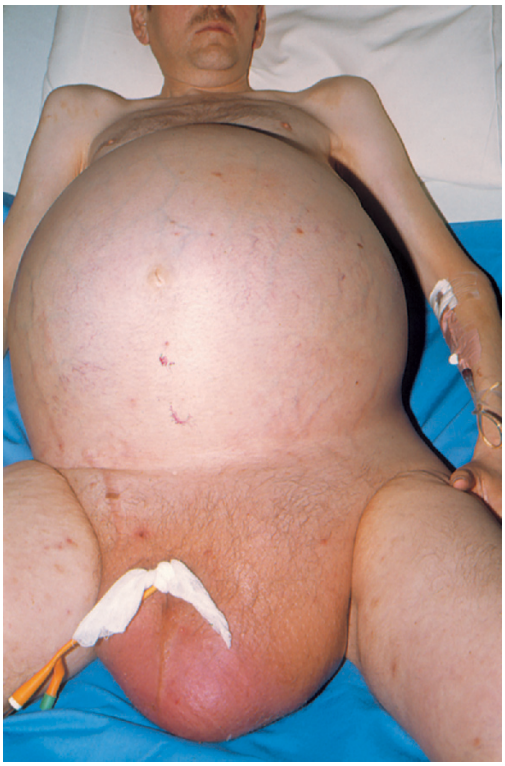

Fig. 16.13: Enormous refractory ascites in alcoholic cirrhosis. Bilateral inguinal hernia with scrotal oedema. Muscular atrophy. Hepatic encephalopathy (II−III) (same patient as in fig. 16.14)

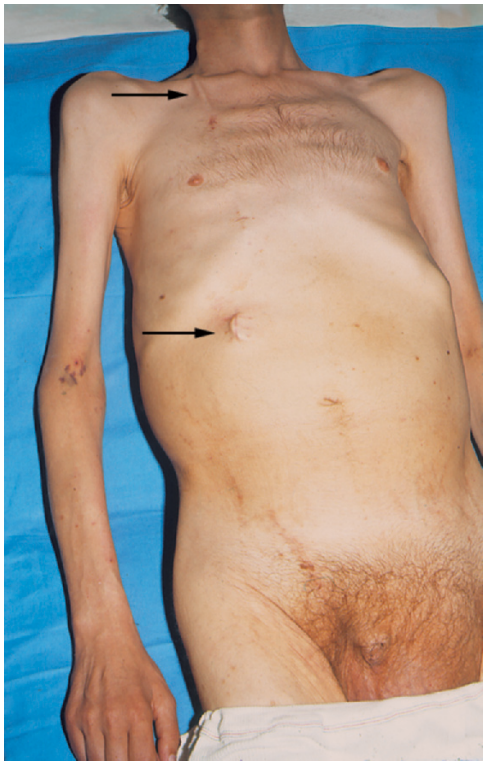

Fig. 16.14: Retrogression of ascites and oedema, increasing stabilization of biochemical and physical findings 16 weeks after placement of a LeVeen shunt (→) (survival time 45 months with two shunt recanalizations). (same patient as in fig. 16.13)

After the positioning of a PVS, there was a **survival rate** of 40−67% after one year and 20−43% after two years, with considerably improved quality of life. It is realistic to expect that a three-year survival rate can be achieved in 30−40% of these patients nowadays. Yet this calls for close adherence to and fulfilment of the criteria on risk reduction. (s. tab. 16.17) All instructions given to the patient must be duly observed (s. tab. 16.18, points 1−5), and the medical measures taken must be appropriate to the respective situation. (s. tab. 16.18, points 6−10) • *For patients with refractory ascites, the peritoneovenous shunt or TIPS can provide real help in a situation that is otherwise hopeless!*

10.3 TIPS

On the basis of animal experiments carried out by J. Rösch et al. (1969, 1971), a transjugular intrahepatic portosystemic stent shunt (TIPS) was positioned for the first time in human surgery by R. F. Colapinto et al. in 1983. The relatively minor invasive intervention achieves a clear drop in pressure in the portal circulation with haemodynamic effects similar to side-to-side anastomosis. This technique, originally introduced for the treatment of oesophageal varicose bleeding, has since been used for refractory ascites. The success rate (i. e. complete remission of ascites) is 70−75%. The TIPS leads to a reduction in plasma renin, aldosterone and the serum-ascites albumin gradient as well as an up to fourfold increase in natriuresis (such as can be observed with PVS). With both PVS and TIPS, subsequent liver transplantation is not compromised, so that these procedures can be used both for recompensation and for bridging the time prior to a transplantation. (210) (s. pp 267, 336, 368, 899) (s. figs. 16.15, 16.16)

Method: The internal jugular vein is punctured. A catheter is introduced into the right hepatic vein. A 55 cm-long needle is pushed through the catheter. With sonographic and radiological guidance, an intrahepatic branch of the portal vein is punctured (a). The portal vein system is then viewed radiologically. The tissue tract is dilated using a balloon catheter (b), and the dilated tissue tract is laid in a metal stent splint. (s. fig. 16.15)

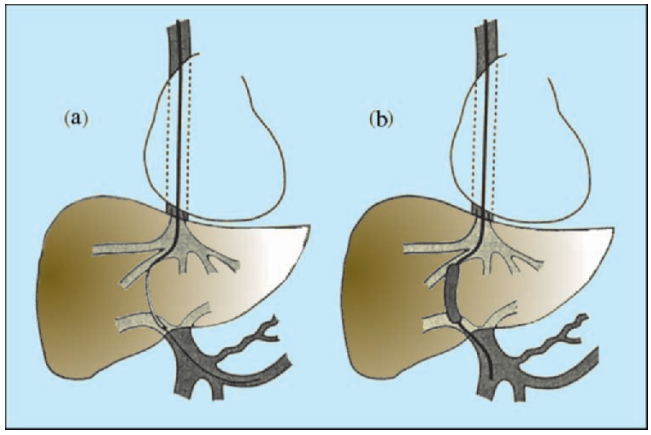

Fig. 16.15: Placement of a TIPS (according to M. Rössle et al., 1989)

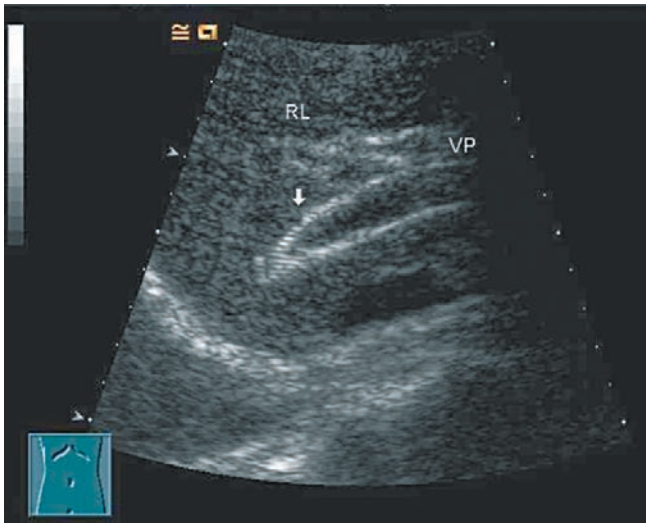

Fig. 16.16: Sonographic evidence of a TIPS (arrow) in a hypoechoic hepatic mass with the typical texture of cirrhosis (VP = portal vein; RL = right liver lobe)

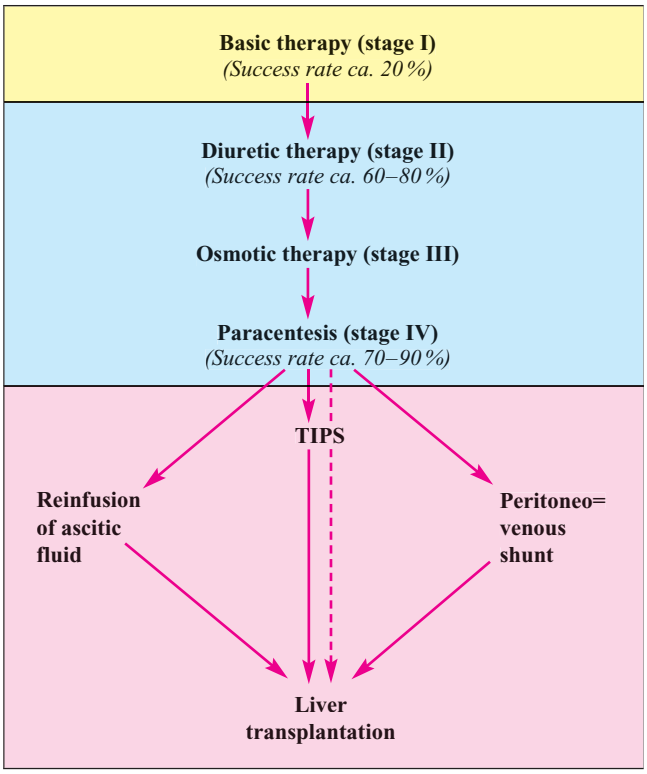

Fig. 16.17: Steps in conservative and invasive or surgical treatment for hepatogenic ascites

► **Underlying disease of liver cirrhosis**: This conditions does not remain stable "in itself". Actually, it causes a multitude of dysfunctions as well as disease-related conditions of deficiency and malnutrition, which impair the entire organism biochemically in a variety of ways. These factors, however, can often be permanently influenced by supporting the patient with various **therapeutic measures.** The survival time is restricted by the underlying disease. • For this reason, decision focuses on the alternatives of "optimal" conservative treatment or liver transplantation. On reviewing all clinical reports from over 100 publications available to us, it can be concluded that it is most definitely possible to improve the mortality rate and reduce the complications as well as to achieve a genuinely better quality of life while slowing down the course of disease and thus lengthening survival time. (152, 153, 210–216) (s. fig. 16.17)

11 Surgical treatment

Formerly, the possibilities of treatment were limited. At one time, 80 (–90)% of all ascites cases were considered to be refractory to therapy. Death could be expected within a short space of time. This explains the development of a multiplicity of surgical techniques – which seemed justifiable in spite of the high mortality rate (30–60%) – in order to achieve a longer survival time with a better quality of life for the individual. Despite sophisticated ideas, which indeed appeared to be logical at the time, these techniques generally proved inadequate and unfeasible in the long run. (s. tab. 16.19)

Probably the first surgical step was **hepatopexy,** as performed by Ch. Th. Billroth in 1894. After the first **omentopexy** (or epiplopexy) was carried out by D. Drummond et al. in 1896 (223) and by S. Talma in 1898 (239), attention continued to focus on surgical ways to treat ascites. With regard to the pathophysiological aspects, the techniques can be categorized into six groups:

1. Interventions in the portal vein system
2. Interventions in the abdominal arterial system
3. Interventions in the endocrinium
4. Coating of the liver
5. Drainage operations
6. Liver transplantation

• By means of **visceropexy** (e. g. hepatopexy, omentopexy, splenopexy, rectus wick operation), an attempt was made to relieve the portal vein circulation by the gradual spontaneous development of venous collaterals and to improve the collateral circulation at the same time. (218, 223, 226, 227, 229)

• Following the first **portacaval anastomosis** on a human being carried out by E. Vidal in 1910 (this operation had already been successfully performed on an animal by N. V. Eck in 1877), the technique was then used to treat ascites. Here, side-to-side anastomosis proved superior to end-to-side anastomosis. With the help of portacaval as well as mesocaval or splenorenal anastomosis, it was possible to achieve a sustained reduction in the portal blood flow to the liver, yet success was poor in terms of eliminating the ascites. (219)

• Likewise, an attempt was made to eliminate ascites surgically by reducing the portal and arterial blood flow to the liver. This was achieved by **arterial ligation** in the root zone of the portal vein as well as by ligation of the hepatic artery. The results were disappointing.

• In 1953 animal experiments demonstrated that bilateral **adrenalectomy** culminated in clear natriuresis, causing the ascites to disappear (J. O. Davis et al., 1953). This observation was confirmed in 1954 in a patient with portal ascites and bilateral adrenalectomy.

I. Interventions in the portal vein system
1. Hepatopexy (Ch. Th. Billroth, 1884)
2. Omentopexy (D. Drummond et al., 1896; S. Talma, 1898)
3. Splenectomy (I. N. Rafferty, 1900)
4. Splenopexy (Bunge, 1902)
5. Rectus wick operation
6. Anastomosis operation:
   − portacaval (E. Vidal, 1910);
   − mesocaval; splenorenal
7. TIPS (R. F. Colapinto et al., 1983)

II. Interventions in the arterial system
1. Ligature of the hepatic artery (A. Narath, 1909)
2. Ligature of the splenic artery (R. M. Moore et al., 1950)
3. Ligature of the left splenic-hepatic-gastric artery (J. K. Berman et al., 1952)
4. Ligature of the splenic-hepatic artery (J. L. Madden et al., 1953)
5. Ligature of the coeliac artery (R. Wanke, 1956)

III. Interventions in the endocrinium
1. Total adrenalectomy (F. G. W. Marson, 1954)
2. Thyroidectomy (J. W. Canter et al., 1959)

IV. Coating of the liver
1. Hepatodematosis (G. Oselladore et al., 1963)

V. Drainage operations
1. Sapheno-peritoneostomy (M. Ruotte, 1907)
2. Tissue, skin (P. Patterson, 1910)
3. Retroperitoneum
4. Ureter, renal pelvis (C. Ferguson, 1943)
5. Urinary bladder (D. Mulvany, 1955)
6. Ileoentectropy (C. G. Neumann et al., 1956)
7. Pleuroperitoneostomy (I. El-Toreai, 1961)
8. Peritoneovenous shunt (H. N. Smith, 1962)
9. Thoracic duct − azygous vein (A. E. Dumont et al., 1963)
10. Hepatophrenopexy (A. L. Meier, 1970)
11. Hepatospleno-pneumopexy (H. Akita et al., 1980)
12. Thoracic duct − subclavian vein (E. L. Coodley et al., 1980)

VI. Liver transplantation

Tab. 16.19: Surgical attempts to eliminate refractory ascites (s. also tab. 19.7!)

► *An explanation for this success was found in the normalization of increased aldosterone values observed in ascitic dogs after adrenalectomy was performed.* (217, 228, 232) • **Thyroidectomy** (J. W. Canter et al., 1959) proved similarly favourable in terms of its effect on ascites. (217, 220)

• **Hepatodematosis:** Both in animal experiments and in human beings, it was demonstrated that hepatodematosis can prevent the development of ascites. This coating of the liver was effected using a plastic adhesive or polyvinyl sponge. Yet this procedure had no clinical significance.

• **Other methods:** There were various attempts to **drain the ascitic fluid.** Repeated paracentesis was carried out, in which knobs or tubes with closing caps were inserted into the abdominal walls. It was recommended to channel the ascitic fluid into the skin, tissue or retroperitoneal spaces. Drainage was laid to allow the ascitic fluid to run off into the renal pelvis, ureter or urinary bladder, a procedure which was complicated, dangerous and useless. Lymphovenous anastomoses between the thoracic duct and the azygous vein or subclavian vein likewise yielded no satisfactory results. Other techniques (e. g. pleuroperitoneostomy, ileoentectropy, hepatospleno-pneumopexy, hepatophrenopexy) were interesting as regards their methodology, yet proved to be of no clinical benefit. (221, 222, 224, 225, 230−232, 233−240)

12 Liver transplantation

Transplantation of the liver essentially gives patients with refractory portal ascites a chance to start a new life. However, in the presence of large-scale ascites, the surgeon is faced with a number of specific *problems* such as overdilated and thin abdominal walls, existing hernia, spontaneous bacterial peritonitis, significant volume displacement and hypotension as a result of the complete removal of ascites, large protein losses, restricted renal function or higher consumption of erythrocyte concentrates due to more pronounced collateralization. Nevertheless, the *survival rate* of patients with refractory ascites was 91.7% after one year and 84.3% after three years, which was identical to the survival rates of patients without detectable ascites or with intraoperatively minimally detectable ascites. These good results in the treatment of refractory ascites are achievable after orthotopic as well as heterotopic liver transplantation. (s. fig. 16.17) • Nevertheless, mention must be made of the fact that ascites can even occur for the first time after liver transplantation. (234) Causes of **postoperative ascites** include (*1.*) intraoperative disruption of the perihepatic lymph discharge, (*2.*) stenosis of existing caval anastomoses, (*3.*) hypalbuminaemia, (*4.*) relapse of the underlying disease, and (*5.*) chronic rejection of the transplant. *(see chapter 40.7)*

Synopsis

This resumé of the possibilities open for the treatment of hepatogenic ascites presents a successful **step-by-step therapy programme.** (s. fig. 16.17)

In all patients, **conservative therapy** is initially founded on basic and diuretic therapy, which is successful in 60−80% of cases. In individual instances, the therapeutic measures of stage III are recommended. Apparent refractory forms of ascites call for paracentesis (stage IV), unless there are reasons against this. Some 80−90% of all patients with portal ascites can be successfully treated conservatively. Given the appropriate indication, reinfusion of ascitic fluid is also feasible.

If the results of conservative therapy (stages I−IV) are unsatisfactory, **invasive treatment** should be considered. The decision in favour of a particular procedure is determined by hepatological factors such as (*1.*) general condition and age of the patient, (*2.*) underlying disease of the ascites, (*3.*) severity of the liver disease, (*4.*) complications of the ascites, and (*5.*) secondary findings as well as additional diseases.

The above mentioned factors yield clear hints as to the indication or contraindication for a specific invasive procedure. Following this preliminary decision, an indication is evaluated together with the surgeon or radiologist. In the light of the probable three-year survival time – a period which cannot be achieved by any other surgical technique – the indication for *liver transplantation* should be a primary consideration. The problem, however, is that, given the inadequate number of donor livers available, a suitable liver cannot always be obtained, and usually not in the time required. This is why a liver transplantation should always be planned in advance, if possible.

It may indeed be necessary to postpone the transplantation or to bridge the period prior to the transplantation owing to ascites factors or other particular difficulties, including the absence of a suitable liver transplant. To this end, the *peritoneovenous shunt* and *TIPS* are suitable temporary operative steps. Indeed, it is these techniques which actually make subsequent liver transplantation possible.

Thus PVS and TIPS are principally indicated if it is not (or not yet) possible to carry out a liver transplantation.

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