Diagnostics in Liver Diseases

4 Clinical findings

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1 Elements of liver diagnostics

In the case of a disease, the basic requirement for systematic and appropriate therapy is the diagnosis. (34)

► When translated, the Greek word **"diagnosis"** means *"decision"*, *"differentiation"* or *"assessment"*. • A disease is identified by the information gained from the patients themselves *(= auto-anamnesis)* or their personal environment (= *external anamnesis*) as well as from diverse examination results (= *findings*).

The term **diagnosis** includes the nosological and systematic designation of a clinical picture and the sum total of the results, which provide a basis for medical action and therapeutic success.

The term **diagnostics** covers all measures aimed at identifying the development of a disease and ultimately producing a diagnosis.

A diagnosis should be *rational* (= *in terms of intellect*), that is to say logical and targeted. At the same time, however, the way it is arrived at must be *efficient and economical* (= *expedient*), i.e. financially viable (cost effective for the health service) as well as acceptable in terms of the strain it puts on the individual patient. • For this reason, economical and efficient diagnostics is by definition rational.

A rational diagnostic procedure is always economical and efficient when carried out at the hospital or in the doctor's surgery – even though it may be more expensive in individual cases. • Economical and efficient diagnostics must never become irrational!

These two basic requirements for rational and economical diagnostics are likewise true for detailed diagnosis (19) – even if a **detailed diagnosis** understandably entails greater reflection and higher costs. With a detailed diagnosis, however, particularly an **early diagnosis**, the therapeutic measures applied can be better targeted, more appropriate and indeed more successful – and ultimately less cost-intensive. (s. fig. 4.1)

► Each diagnostic step and each detailed diagnosis presents certain **difficulties** in terms of methodology and theory:

1. Emergency therapy may be urgently required **prior to** diagnosis.
2. Diagnostics may be **limited:**
   a. because examination techniques are (still) insufficiently developed,
   b. because of inadequate equipment for examination purposes,
   c. because they are refused by the patient.
3. All too often there is, unfortunately, a tendency to apply examination techniques on a broad and cost-intensive scale, and indeed "irrationally".

► In 1979 J.E. Hardison drew up a *list of arguments* that are used to explain this kind of behaviour in medical practice, and which are equally applicable today (14):

1. the excuse that "everything has been done";
2. the excuse that if something is not done immediately, it will never be done at all;
3. the excuse that more has to be undertaken under inpatient conditions than at the doctor's surgery;
4. the academic excuse – as if there were such a thing as an academic or a non-academic diagnosis;
5. the father-mother excuse: "If it were my father or mother, I would do it like that";
6. the precluding excuse: "Well, perhaps we'll find something we never even thought of";
7. the legal excuse: "If we don't carry out the examination, we could be sued".

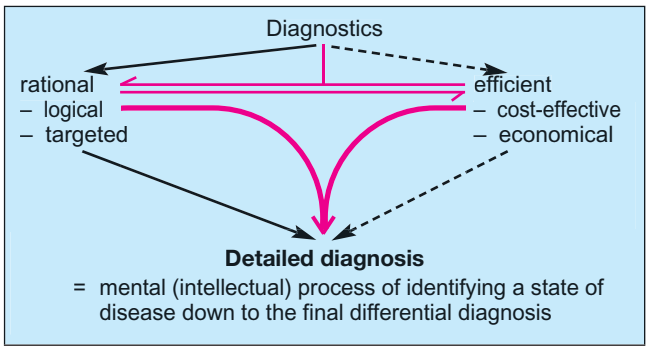

Fig. 4.1: Elements of diagnostics

In his textbook on „Funktionelle Pathologie" (1932) Gustav von Bergmann coined the term **hepatopathy,** since more detailed liver diagnostics was not possible at that time.

Diffuse (and circumscribed) liver diseases commencing in mesenchymal and epithelial tissue (inflammatory and degenerative)

manifestly icteric ↔ latently icteric ↔ anicteric

hepatopathy

acute, subacute liver atrophy

cirrhoses (haematogenic, biliary) as inflammatory reaction forms, intermittent

fatty liver (often glycogen deficiency)

cholangitis, cholangiolitis

1st hepatological principle

The term "hepatopathy", coined by Gustav von Bergmann in 1932, and the expression "liver parenchymal damage", which has also been employed occasionally, should only be used to describe the so-called "prediagnostic stage" of liver disease.

In any form of suspected "hepatopathy", the preliminary steps towards reaching a **diagnosis** and ultimately the **detailed diagnosis**, whether at the doctor's surgery or at the hospital bedside, should always proceed rationally and economically by means of step-by-step systematic examination.

The impressive, almost "99%" certainty of present-day liver diagnostics is the outcome of the coordination of all available examination techniques that have meanwhile been perfected – in conjunction with the further development of sensitive and specific procedures.

1.1 Diagnostic targets

The seven main diagnostic questions (s. tab. 4.1) can be answered in nearly all cases using four sets of examinations (s. fig. 4.2) – provided all the necessary diagnostic channels can be applied. By repeatedly reviewing the activity and the function of the liver, it is possible to make reliable statements on the course of the disease, the success of therapy and the prognosis.

► In this context, **check lists** simplify and accelerate the examination procedure. It is most important that no key factors are forgotten and nothing is undertaken unnecessarily. (19) (s. figs. 4.22; 5.2; 15.3; 35.10) (s. tab. 29.7) • In addition, a **step-by-step programme** subdivided into minimum, necessary and maximum requirements (s. tab. 5.23) together with logically constructed **flow diagrams** (s. figs. 9.4; 13.7; 16.10, 16.17; 19.15; 22.9–12) facilitate the required rational and economical *"step-by-step diagnostics"*.

2nd hepatological principle

It is not **"what is done"** in terms of numerous examinations and chemical laboratory parameters that is ultimately decisive, but the clinical **interpretation** of the findings and the clinical consequences which result from that.

Hepatopathy
= prediagnostic stage

Diagnosis

Detailed diagnosis

1. **Determining liver damage**
   - primary liver disease
   - secondary (reactive) liver disease
2. **Classifying liver disease**
   - diffuse
   - localized
3. **Differential diagnosis of jaundice**
   - prehepatic
   - intrahepatic
   - posthepatic
4. **Determining the type and aetiology of liver disease**
   - hepatitis
   - cholestasis
   - fibrosis
   - cirrhosis
   - focal lesions
   - tumours
   - infections
   - parasitic
   - vascular
   - immunologic
   - metabolic
   - toxic
   - genetic

   etc.
5. **Determining the stage of disease**
   - prodromal
   - acute
   - chronic
   - cured

   ⟷ compensated / decompensated
6. **Determining the activity**
   - enzymatic activity
   - mesenchymal activity
   - immunological activity
   - histological activity
7. **Testing the liver function**

Statements concerning

1. **Course of the disease**
   - regressive
   - stationary
   - progressive
2. **Success of therapy**
3. **Prognosis**

Tab. 4.1: Diagnostic targets and other relevant aspects in liver diseases

1.2 Diagnostic pillars

The target of a detailed diagnosis is generally achieved using various and mutually complementary examination techniques. Diagnostic methods in liver disease are founded on four diagnostic pillars, which are applied stepwise and nearly always provide the basis for an exact and detailed diagnosis. Complex or invasive techniques are only used in cases where they are clearly indicated. If the various examination procedures are inadequately coordinated and the results improperly interpreted, it is, unfortunately, all too easy to obtain "false-positive" or "false-negative" results. (19) (s. fig. 4.2)

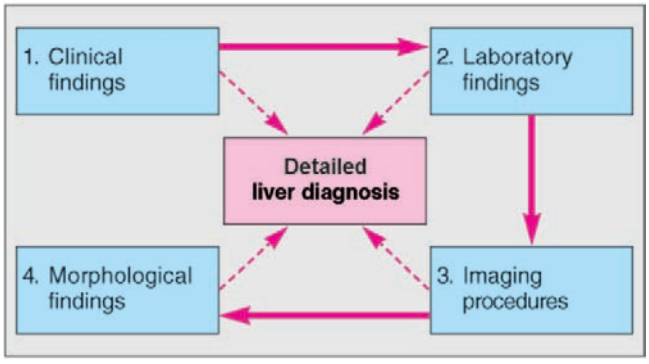

Fig. 4.2: Diagnostic pillars for detailed diagnosis in liver diseases

3rd hepatological principle

In the diagnosis and assessment of liver disease, the clinical, laboratory and ultrasound findings must always be interpreted integratively and simultaneously, together with the histology and any additional imaging procedures (insofar as these are indicated).

► A *detailed diagnosis* should be the ultimate aim, so that in each case:
(*1*.) the cause of the liver disease is identified and perhaps eliminated by successful therapy;
(*2*.) the therapeutic possibilities for the treatment of liver disease can be applied more specifically and hence lead to greater success;
(*3*.) both the effect and efficacy of therapeutic measures can be statistically evaluated in those patients who are clinically comparable.

The hepatological issues in question, differential diagnostic considerations and possible therapeutic outcome determine the scope of the diagnostic measures undertaken. This calls for systematization and rationalization at all times.

1.3 Diagnostic accuracy

Even with normal bioptic histology, it is possible to detect liver damage with an adequate degree of probability by means of laboratory parameters. • By contrast, even pathological liver biopsy findings can be accompanied by normal laboratory values. In individual cases, this can mean that a liver disease is "mute" under chemical laboratory conditions, but at the same time histologically "false-normal". Combining the clinical and chemical laboratory findings with the results of sonography and morphology makes it possible to achieve a hepatological diagnosis or detailed diagnosis of almost **"99%" certainty**.

► The **specificity** and **accuracy** of individual laboratory parameters used to be assessed almost solely on the basis of morphological findings. • Today, exact procedures are available for hepatological detailed diagnosis which provide excellent sensitivity and specificity (especially in the fields of serology and immunology). But they have by no means ousted the histological examination of the liver. On the contrary, **histology** has gained enormously in significance, particularly due to more advanced methods and a better interpretation of results. The same is true of **electron microscopic** assessment of hepatocellular organelles and biological membranes, which constitute the morphological substrate for the many functions of the liver. • Hence, the **visionary target** of *"organelle pathology"* and *"organelle diagnostics"* has proved feasible.

In reviewing the accuracy of diagnostic procedures in 520 of our own patients with different liver diseases, varying results (depending on the severity of the disease) were found. (s. tab. 4.2)

Clinical findings	**30%**
Laboratory parameters	**81–96%**
Ultrasonography	**60–75%**
Histology	**82–95%**
Laparoscopy	**78–88%**
Laparoscopy + histology	**97%**

Tab. 4.2: Accuracy of diagnostic procedures in various liver diseases (E. Kuntz, 1987) (s. tab. 5.11)

4th hepatological principle

Up to now, no single examination method exists (be it a clinical, laboratory chemical, morphological or imaging procedure) which, in itself, allows a global statement to be made regarding a particular type of liver disease or liver dysfunction.

2 Clinical findings

At the forefront of liver diagnostics are the tried and tested methods of *anamnesis*, *inspection*, *palpation* and *percussion* or even *auscultation*. These specific medical examinations can be regarded as a safety net in daily routine diagnostics. Within the scope of the many examinations that take place at the doctor's surgery, these basic medical skills help to filter out patients with "suspected hepatopathy". Ascertaining the clinical findings is deemed to be the *1st diagnostic pillar* and, as such, constitutes the commencement of any diagnostic procedures focused on the liver. (s. fig. 4.2)

2.1 Anamnesis

The anamnesis is of particular significance for the clinical findings – and *is usually the first step towards establishing a diagnosis.*

Determining whether there has been any history of hepatobiliary disease in the *family* and establishing the geographic and ethnic origin of the patient are both key anamnestic factors. • It must be ascertained whether the *disease* has occurred suddenly, developed gradually, or simply not been noticed up to now. • It is also important to determine whether this is a *primary* or *secondary* liver disorder (the latter is a concomitant reaction which has occurred during a systemic illness or other organic disease). The anamnestic search for the cause of the infection in the patient should take into account viral, bacterial, parasitic and mycotic diseases. *(see chapters 22–26)* (s. tab. 4.1)

Anamnestic evidence of *alcoholism* or *drug abuse* and also personal questions relating to *sexual habits* should be handled with extreme care and sensitivity. Once one has gained the patient's trust, it is considerably easier to obtain the relevant details. • It is essential to establish whether the patient has been exposed to any *foreign sub-*

stances (medicines, herbal remedies, aphrodisiacs, chemicals). This can be done with the aid of the **check list** which we have been using for many years. (s. tab. 29.7) *(see chapters 29 and 30)*

It is mainly "targeted" **questioning** which sheds light on the possibility of liver disease.

► **Questions:**
"Targeted" (i. e. specific) questions are most likely to lead to the *"target"*:
- previous diseases of the liver or biliary tract?
- previous operations?
- previous blood transfusions (blood products)?
- particular eating habits?
- metabolic diseases (diabetes, gout, hyperlipidaemia, etc.)?
- consumption of alcohol?
- intake of medicaments?
- occupation- or hobby-related liver noxae?
- drug abuse?
- journeys abroad?
- sexual habits?
- hereditary liver diseases?

Another group of anamnestic findings is based on the patient's subjective **complaints**. However, patients suffering from liver disorders frequently fail to recognize symptoms by themselves.

► **Complaints:**
- Fatigue (*"pain of the liver"*), decline in performance and productivity, weariness, affective lability, nervousness, lassitude, sleeping disorders, lack of concentration (s. p. 91)
  = *such as can be witnessed in many harassed people today as "neurasthenic syndrome".*
- Abdominal pain, repletion, flatulence, nausea, loss of appetite, indigestion, food intolerance, loss of weight
  = *such as are found in various abdominal diseases.*
- Epigastric pain, nausea, vomiting, intolerance regarding fatty foods or smoking and alcohol, pruritus, constipation, meteorism
  = *such as occur in cholecystopathy.*
- Stenocardia, vertigo, tachycardia, hypotonia, circulatory disorders
  = *such as are found in cardiovascular diseases.*
- Fever, arthralgia, myalgia, muscle cramps
  = *such as are often witnessed in infectious diseases.*
- Impotence, amenorrhoea, nosebleeds, bleeding gums, tendency to haematoma, night blindness
  = *which can also lead to a wrong diagnostic conclusion.*

This wide range of very different subjective ailments makes it clear that there are no typical symptoms and that it is not possible to draw any conclusions on the basis of such complaints as to the severity of the liver disease. Here the constellation of the symptoms and findings (as well as the time when they first appeared and their duration) can provide more information than is available from merely one symptom or finding.

The most frequent, yet **non-specific complaints** mentioned by liver patients are fatigue, languor, repletion, flatulence, epigastric pressure, lack of appetite, nausea, various forms of intolerance, pruritus and impotence. • *Information* on dark-coloured urine, discoloured stools, haematemesis, cutaneous haemorrhages or tarry stools are important signs of hepatobiliary disease. (s. fig. 4.22)

2.2 Palpation

2.2.1 Palpation of the liver

"One good feel of the liver is worth any two liver function tests" (F. M. Hanger, jr., 1971).

Determining liver size is the *"simplest"* and *"cheapest"* liver function test and, chronologically speaking, also the *"first"*. (s. fig. 4.3) (9, 21, 26–29, 31, 32, 35–37)

► Every enlarged or hard liver must be considered pathological – until counter-evidence is produced by laboratory values and ultrasonography and, if necessary, by means of histology or laparoscopy.

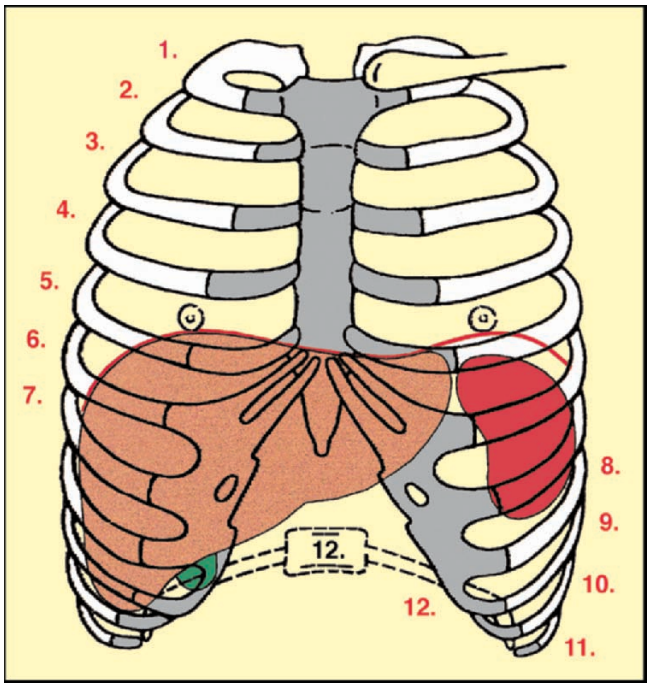

Fig. 4.3: Contours of the liver (brown) and spleen (red) and part of the gall bladder (green) in the right and left hypochondrium (costae verae 1–7; costae spuriae 8–10; costae fluctuantes 11–12)

Sliding palpation: Liver size, consistency and surface as well as tenderness on pressure can be determined by sliding palpation. The lower edge of the liver is perceptible by touch at the costal arch in the mid-clavicular line. It crosses the epigastrium and ends at the left costal arch on the level of the parasternal line. Under palpation, the liver edge was felt to be deeper than shown by the scan, and only in 60% of all cases did palpation of the liver edge correlate with the scan. (32)

Bimanual ventral palpation: The finger tips of both hands are pressed inwards 1–2 cm, flat and parallel to each other below the costal arch. Upon deep inspiration, the size of the liver can be determined by the caudal shift of the liver margin. (s. fig. 4.4)

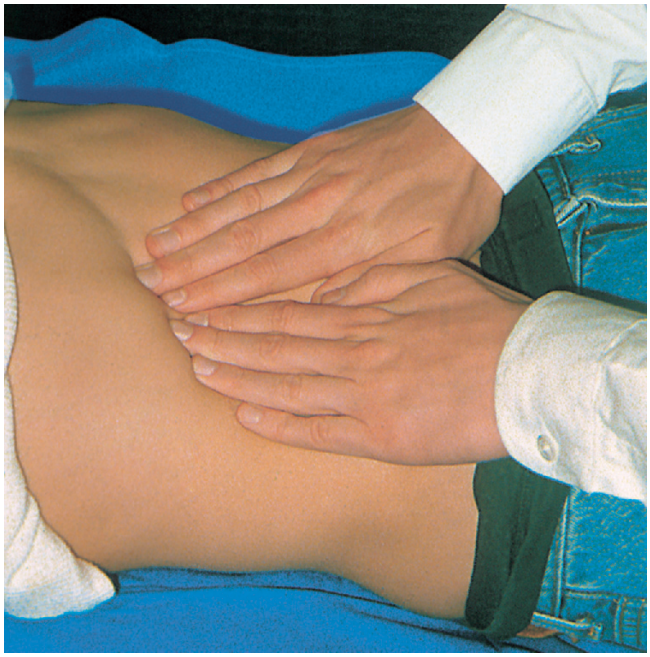

Fig. 4.4: Palpation of the liver: bimanual ventral palpation (Gilbert´s technique)

Bimanual ventrodorsal palpation: The palpating right hand presses deep into the right costal arch during the expiratory phase and moves upwards during the inspiratory phase – taking the skin and tissue layers with it. Because it moves downwards on inspiration, the liver can be better felt by the left hand when pressing up from behind in a ventral direction. (s. fig. 4.5)

Hepatomegaly can easily be mimicked under palpation by phrenoptosis in lung emphysema, ptosis of the liver, asthenic habitus and an enlarged Riedel's lobe. (s. p. 18) • It is difficult to state the extent of liver enlargement exactly in terms of "finger breadths" below the costal arch: when 120 "finger breadths" were compared, they were found to range from 1.3 to 2.4 cm. (32) *(see chapter 11)*

Liver atrophy can be assumed when the edge of the liver is elevated due to meteorism or in the Chilaiditi syndrome. • However, the liver may also shrink or no longer be palpable due to increasing liver atrophy in acute viral

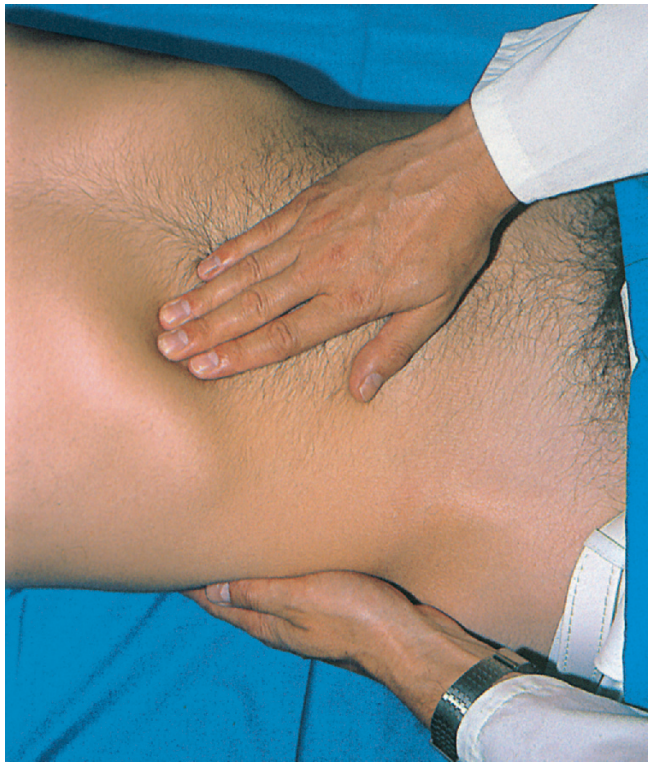

Fig. 4.5: Palpation of the liver: bimanual ventrodorsal palpation (Chauffard´s technique)

hepatitis or liver cirrhosis. Thus, a diminished liver can be a more severe condition (generally with a poorer prognosis) than an enlarged liver (e. g. fatty liver).

During palpation, the **liver surface** proves to be smooth, humped or roughly noduled. The consistency of the liver is perceptible as soft, firm or hard. It is important to point out that the firmer the liver, the larger it appears to the palpating hand.

In a normal liver, the **liver edge** feels relatively sharp and insensitive to pain; the surface is smooth and the consistency is soft. In liver cirrhosis, the edge of the liver is sharp and hard; the consistency is firm. In acute hepatitis, the edge of the liver, which tends to be rounded, and the clearly enlarged liver are painful under pressure. • *Hepatomegaly*, caused for example by a fatty liver, displays a rounded liver edge with little or no sensitivity to pressure, whereas in congestive liver, the blunt liver edge proves to be very painful on palpation. • There is admittedly a slight chance of confusing the edge of the liver with *tendinous inscriptions*, but the latter are not displaced in relation to the skin and tissue layers during respiration.

Pain on palpation mainly points to capsular tension as a result of an enlarged liver (acute viral hepatitis, fatty liver, congested liver). In general, the metastatic liver is likewise painful. *Liver abscesses* may cause (frequently severe) pain on tapping. The liver parenchyma itself is insensitive to pain, although pain receptors are found

sporadically in the walls of the portal and arterial vessels or in interlobular connective tissue.

2.2.2 Palpation of the spleen

Palpation of the spleen should always accompany palpation of the liver. It is carried out with the patient in a semidextral recumbent position, the knees bent and the arms lying flat at the sides of the body. Normally, the spleen is not palpable.

Splenomegaly is perceptible by touch at the costal arch in the inspiratory phase. This can be accomplished in particular during ventrodorsal palpation when the physician's right hand works from the back towards the (not too deeply) palpating left hand. An enlarged spleen is easily perceptible due to its "downward and inward" movement (in contrast to the left lobe of liver). • *Sensitivity to pressure* of the enlarged spleen points to an inflammation. *(see chapter 11)*

The following **technique** can also be used to detect an enlargement of the spleen: the examining physician, standing to the left of the patient (who is positioned as described above), palpates with the finger tips of the left hand below the costal arch in order to detect the enlarged spleen during the inspiratory phase.

2.3 Percussion

2.3.1 Percussion of the liver

Percussion also enables the size of the liver to be established; hepatic dullness (in cm) is determined by the localization of the so-called liver-lung margin and the lower liver edge, as measured on the right mid-clavicular line (MCL). During this procedure, the lower lung margin is subjected to light percussion, whereas the upper margin, i.e. lung-liver margin, is determined by heavy percussion. This gives the superficial dullness, i.e. *absolute liver dullness*, which is usually deemed to represent the *size of the liver*. Experience shows that the rounded top of the liver can be assumed to be about 5 cm higher than revealed by percussion. The size of the liver seems to be smaller with percussion than with ultrasound. Determining the liver size upwards is, however, of no genuine clinical significance, since hepatomegaly develops "downwards" in the area of least resistance. • Percussible determination of the **normal liver size** has produced mean values of 10–12 cm (9 ± 2 cm in women, 11 ± 2 cm in men) (E. Hafter, 1962; J. Naftalis et al., 1963; H.A. Kühn et al., 1979). (7, 21, 26–29, 31, 32, 35–37)

Once the percussion technique has been mastered, the **relative liver dullness** can also be more closely defined within the area of superficial dullness as a zone with a resonance on percussion resembling that of the thigh, i.e. the cranial part of the liver covered by the lung. This is the only way of determining the true size of the liver "upwards". • The size of the **left lobe of liver** is determined by percussion above *Traube's space*, which is narrowed in terms of percussion from the right due to an increase in size of the left lobe of liver.

Scratch auscultation is another way to determine the liver size or the lower liver edge. The stethoscope is placed on the epigastrium, i.e. above the liver; the finger tip strokes ("scratches") the mid-clavicular line in a cranial to caudal direction at intervals of approx. 1 cm parallel to the presumed edge of the liver; when the liver margin is crossed, the scratching noise in the stethoscope fades and finally disappears. However, this technique is not deemed to be reliable. (18, 42)

2.3.2 Percussion of the spleen

Percussion of the spleen is difficult and is carried out by tapping gently at various points on the anterior axillary line. The upper spleen margin lies about 10–15 cm above the left costal arch. The **absolute splenic dullness** (so-called spleen width) is about 6 to 7 cm; it lies between 9th and 11th rib. The splenic width established by percussion corresponds to the anterior lower two thirds of the spleen, i.e. adjacent to the thoracic wall. The upper third of the spleen is covered by the lung. When the spleen is subjected to percussion, variations in the shape of the thorax, diaphragm status and intestinal loops are evident (cf. liver percussion).

2.3.3 Ascites

Ascites can be recognized by the wide protuberance of the abdomen with moderate bulging of the abdominal flanks and spreading of the navel. Examination by percussion produces *tympanic intestinal resonance* in the upper area and typical *dullness in the flanks*. Small ascites (about 1 litre) is determined in the *knee-elbow position*, whereby dullness is detected in the lower abdominal region. The *fluctuation wave* is an impressive sign: a short hard surge of the fluid swell against the palpating hand is virtually conclusive. *(see chapter 16)*

2.3.4 Meteorism

Meteorism presents as a pointed arching of the abdomen at navel level. This condition is likewise associated with tympanic resonance; however, the dullness in the flanks is missing.

► It would be a tremendous loss if, on account of ultrasound methods, palpation and percussion of the liver and spleen were inadequately learned, inappropriately performed and no longer mastered as a basic examination technique for interpretative purposes.

2.4 Inspection

"Even though you read and learn so much, your learning does not mean that you know; let your eyes be your professors!" Paracelsus (s. pp XIX, 9, 923)

Hardly any other organ of the body causes such a wide variety of externally discernible changes to the skin and mucosa as the diseased liver. Inspection of the body gives

diagnostic clues regarding the presence of a liver disease or special maladies of the liver. Examination of the liver-diseased patient produces various findings concerning the whole body and the skin as well as the mucosa, nails and eyes. These signs are summarized under the term **skin stigmata in liver diseases** (German: *Leber-Haut-Zeichen"*; H. Kalk, 1955, 1957). (4, 16, 17, 25) (s. tab. 4.3)

1. Chvostek's body type	**14. Liver tongue**
2. Facies cirrhotica	**15. Lacquered lips**
3. Parotid enlargement	**16. Gynaecomastia**
4. Hair changes	**17. Dupuytren's contracture**
5. Jaundice	**18. Pigmentation and striae**
6. Spider naevus	**19. Erythematous stigmata**
7. Palmar erythema	**20. Xanthelasmas and xanthomas**
8. Telangiectases	**21. Scratch marks in pruritus**
9. White nails	**22. Eye changes**
10. Muehrke's nail lines	**23. Drumstick fingers**
11. Paper money skin	**24. Testicular atrophy**
12. White spots on the skin	**25. Cutaneous haemorrhages**
13. Smooth red tongue	**26. Vein dilatation**

Tab. 4.3: Skin stigmata in liver diseases (check list: s. fig. 4.22)

2.4.1 Chvostek's body type

The habitus described by F. Chvostek (1922) is frequently found in alcohol-related cirrhosis. In the male, it is characterized by the absence of secondary hair on the chest and abdomen as well as of axillary hair, and by a horizontal, female-like boundary of the pubes and a lengthening of the distance between xiphoid process and navel. *"Abdominal baldness"* (which means *effemination* with changes in the pattern of body hair) is a typical finding. The incidence is given as approx. 70%. These changes are often accompanied by thick hair-covering of the head growing down onto the forehead, and bushy eyebrows. • In women suffering from alcoholic cirrhosis, the pubic and axillary hair may also be largely absent, and the mammae may be atrophic.

2.4.2 Facies cirrhotica

Patients with liver cirrhosis often show typical facial skin stigmata: the colour is a pallid yellowish grey, mostly with patchy pigmentation due to the greater deposition of melanin. Spider naevi and reticular telangiectases are found. The skin frequently appears shrivelled, wrinkled and prematurely aged.

2.4.3 Parotid enlargement

Parotid enlargement is occasionally found in cirrhotic patients, especially in alcohol-related cirrhosis (M. Sposito, 1942). An enlarged parotid is not painful. (11, 48)

2.4.4 Hair changes

Apart from the *hypotrichosis* of primary and secondary pubic hair, already described in Chvostek's body type, cirrhosis patients occasionally show an absence of frizziness in pubic hair. • In kwashiorkor, the hair becomes light in colour and straggly, and loses its frizzy appearance with simultaneous hypotrichosis.

Localized *hypertrichosis* is found in Chvostek's body type in the form of noticeably bushy eyebrows. It is also, however, found in porphyria cutanea tarda in the area around the zygomatic arch and lateral to the eyes, as well as on the forearm and lower leg, mostly in the form of short, compact hairs.

► Hypertrichosis (particularly of the lanugo type) is also described as the **paraneoplastic syndrome**, above all in cases of carcinoma of the intestinal tract or the digestive organs (*Herzberg-Potjan-Gebauer syndrome*, 1969).

2.4.5 Jaundice

In the case of increased serum bilirubin levels of 1.8–2.0 mg/dl, diffusion is effected through the blood capillaries, and bilirubin accumulates in the connective tissue, mainly in elastin. (s. p. 37) In its subsiding phase, jaundice is therefore still visible for longer periods even when serum bilirubin values are normal. • Initially, *scleral icterus* develops, which is easily recognizable in daylight when serum bilirubin values are > 2 mg/dl. (s. p. 89) This subicterus is likewise witnessed in the conjunctiva and occasionally on the oral mucosa at the boundary between the soft and hard palate as well as on the periumbilical abdominal skin. (33, 42) • In fully developed *jaundice*, colours range from straw-coloured yellow through bright yellow to greyish yellow as well as reddish yellow and greenish yellow. Icteric discoloration of the skin is frequently darker in the upper than in the lower part of the body. *(see chapter 12)*

Verdin icterus is deemed to be the prototype of obstructive jaundice, particularly in long-standing courses of the disease; **melas icterus** displays a greyish green hue; **rubin icterus** (rust-coloured) is mainly regarded as a sign of hepatocellular jaundice, whereas **flavine icterus** is more likely to occur in cases of haemolysis (Th. Brugsch, 1930). Such systematization of the icteric forms in terms of pathogenesis is, however, unreliable and obsolete, since the differences in colour mainly correlate with the duration of the jaundice and the level of serum bilirubin.

2.4.6 Spider naevus

► These arterial telangiectases were observed in liver disease by V. Hanot and A. Gilbert in 1890, by A. Gilbert and M. C. Herrscher in 1903 and by F. Parkes-Weber in 1904. • Such spiders were first described in pregnant women by D. Corbet in 1914. Spiders evident in liver disease were the focus of renewed attention in the nineteen-thirties (J. Steinmann, 1935; N. Fiessinger, 1936; H. Eppinger, 1937).

The term spider naevus (Latin: naevus araneus) is also known as liver star, liver spider, vascular spider or spider naevi. (17, 20, 25, 30)

Spider naevi consist of a central arterial vessel, about the size of a pinhead, from which minute, steadily narrowing capillaries, similar to a spider's legs, lead off ra-

dially. A passage into the veins, however, cannot be discerned. The central artery winds its way upwards out of the subcutis with an ampulla-like dilatation directly under the epidermis. From the morphological point of view, the course of the vessel can be divided into five sections (G.A. Martini, 1964). The central arterial telangiectasis, often button-like and occasionally even clearly protruding, can be seen to pulsate. Spiders occur as solitary or multiple stigmata. (s. fig. 4.6)

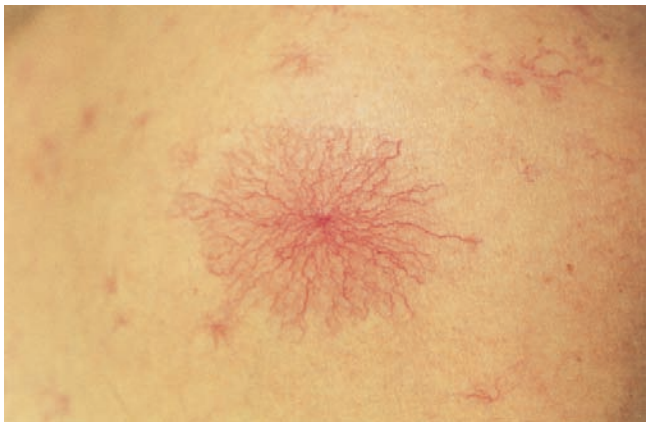

Fig. 4.6: Spider naevus in liver cirrhosis in the ventral side of the left shoulder

The size of the areola of spiders ranges from just a few millimetres up to 2 cm, or even more. When pressed with a glass spatula, the radiating areola disappears and the small pulsating central vessel remains visible, but also disappears if more pressure is applied. Removing the pressure leads to a swift filling of the central vessel and the peripheral vascular areola. The spider can have a narrow white marginal rim. • The most common sites are nose, forehead, zygomatic arch, neck, throat, shoulders, chest and back as well as the extensor sides of the arms and dorsum of the hand. Hence, this localization of the spider naevi corresponds to the area of influence of the superior vena cava, the region of the excitation erythema, the projection fields of the trigeminus core region as well as the phrenic dermatomes (C_3 and C_4) and the neighbouring dermatomes (C_5 to C_8).

The spider naevi occur as segmental reflexes, depending on visceral affections. This would explain why they "blossom" and reoccur when the liver condition deteriorates, and fade when the liver condition improves. The occurrence and rapid appearance of fresh spiders can be considered as an unfavourable sign, such as is observed, for example, in serious virus hepatitis or in the development of primary liver cell carcinoma.

Aetiopathogenesis: W.B. Bean (1942) assumed the cause of spiders was increased oestrogen blood levels. Other aetiopathogenic factors include the activation of vasoactive ferritin and vasoactive histamine or the presence of bradykinin and endotoxins. Consequently, the altered haemodynamics in chronic liver disease in the sense of a hyperdynamic circulation would also affect the dermatome areas, specified above as preferred sites. • Spider naevi are found not only in liver disease, but also in pregnancy, collagen disorders, hyperthyroidism as a paraneoplastic symptom, lead poisoning, vitamin deficiency conditions or following the intake of oestrogen and similar hormone preparations.

2.4.7 Palmar/plantar erythema

Palmar erythema (erythema palmare symmetricum, "liver palms"), frequently observed (60–75%) in chronic liver disease, was initially described by H.J. Chalmers in 1899. It becomes manifest as diffuse or patchy reddening of the palms up to the start of the wrist joint; it is particularly evident on the balls of the small finger and thumb as well as on the finger tips and finger joints. The affected area is clearly outlined against the rest of the hand surface. The centre of the palm is generally free of erythema. The hands are warm – corresponding to the vasodilatation and increased circulation. Palmar erythema varies in its intensity: during sporadic deterioration in the course of the disease, it can be more pronounced, and when the liver findings improve, it can fade. (s. fig. 4.7) • Occasionally, the soles of the feet are also affected and show *plantar erythema*. (16)

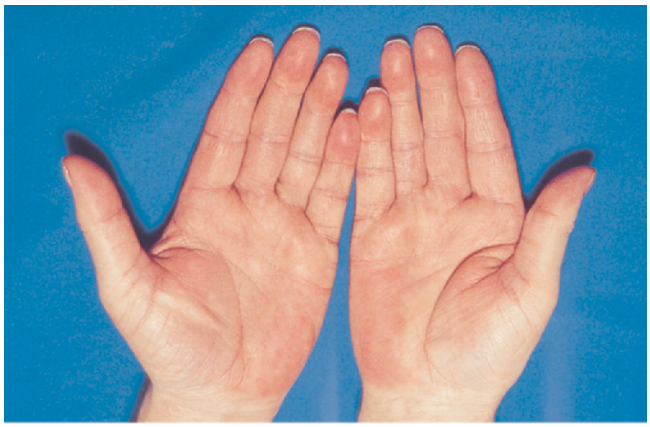

Fig. 4.7: Palmar erythema in liver cirrhosis

Morphology: No morphological changes of the cutis are witnessed. The blood capillaries are irregularly distributed and of differing length; however, they meander greatly in their path with arch-shaped dilatation of the final loop. The blood flow is rapid and jerky.

► **Differential diagnosis:** Palmar erythema is also found in pregnancy, in hyperthyroidism, collagen diseases, endocarditis, long-standing feverish conditions, tuberculosis, diabetes mellitus, malignant tumours, chronic polyarthritis and in cases of malnutrition – as well as in healthy people.

Aetiopathogenesis: As with spider naevi, the capillary dilatation causing palmar erythema is attributed to an increased oestrogen content of the blood, a rise in bile acids or endotoxins and an activation of vasodilating substances with more numerous arteriovenous shunts as well as a hypercirculatory syndrome. Portal hypertension is seen as an important codeterminant. • The "blossoming" of spider naevi and palmar erythema is also observed in the phenomenon of *haemodynamic-related resistance to diuretics.*

Incomplete spider naevi are known to develop within a palmar erythema: they do not possess a central artery. The combination of these two liver skin stigmata is fre-

quently found in decompensated liver cirrhosis and in highly active chronic hepatitis.

2.4.8 Telangiectases

Apart from spider naevi, reticular telangiectases are frequently witnessed, particularly in alcoholic liver disease. They appear as tiny, bluish red vessels, in general symmetrically positioned on the cheeks, but also on the nose, forehead and neck. Those parts of the skin that are exposed to light are predominantly affected. The arterial and venous capillary loops are dilated.

2.4.9 White nails

White nails is the term, which is generally used to describe a light pink/silvery-white enlargement of the nail lunula. (41) Ultimately, the entire nail plate is coloured a diffuse lacklustre white, except for a narrow, normal-coloured rim. The lunula of the thumb, the colour of which resembles frosted glass, can also spread and eventually take up the entire nail. The nails frequently have *longitudinal grooves*. Fully developed white nails actually look as though they have been coated with mother-of-pearl nail varnish. In the majority of cases, white nails occur after long-standing liver cirrhosis (10 to 20 years); they are hence considered to be a late sign. The cause of the whitish discoloration is attributed to air bubbles in the nail resulting from a disorder in the metabolism of keratin. White nails are often combined with "paper money skin". (4, 25, 41) (s. fig. 4.8)

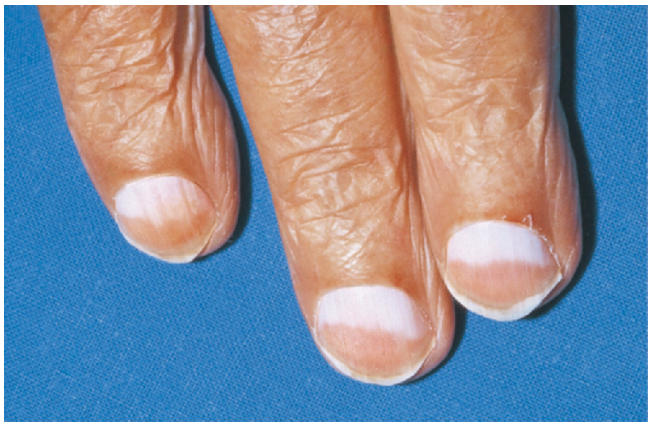

Fig. 4.8: White nails and paper money skin in liver cirrhosis

2.4.10 Muehrke's nail lines

These are white lines running across the nail plate parallel to the lunula. They were first observed by C.R. Muehrke (1956). Instead of being contained in the actual nail, the lines are set in the nail bed. This is thought to be caused by severe prolonged hypalbuminaemia (< 2.2 g/dl), especially in cases of cirrhosis or nephrotic syndrome. This finding is, however, relatively rare. (24)

2.4.11 Paper money skin

The skin of the chronic liver patient often resembles so-called *parchment skin*: it appears prematurely aged, shrivelled, wrinkled, dry and atrophic – mostly greyish yellow in colour. (s. figs. 4.8, 4.19; 20.1) In contrast, partially atrophic, slightly reddened skin areas that have the appearance of a fading exanthema can occasionally be seen. Within these areas of the skin, there are fine, linear telangiectases, scattered at random, resembling delicate fibres. For this reason, the term *paper money skin* was coined (W.B. Bean, 1945). These changes are mostly found around the neck down to the chest area, on the cheeks, behind the ears and on the surface of the hands and fingers. Exposure to sun and wind renders the appearance of paper money skin more pronounced. It is frequently combined with spider naevi.

2.4.12 White spots on the skin

Liver-disease patients often display white spots on the skin, which are the size of a lentil (sometimes as large as 0.5–1.0 cm in diameter). They can be detected chiefly in the area of the arms, on the back and on the buttocks. Upon cooling of the skin, white spots appear or become more pronounced, so that a cold-related vasocontraction is assumed to be the causative factor. In the predilection area of the spider naevi, the white spotting of the skin is usually deemed to be a preliminary stage of liver star: within the round white spot, a central red dot is formed, from which the typical spider naevus develops with a white areola.

Vitiligo: Vitiligo (caused by functional failure of the melanocytes) sometimes occurs in primary biliary cirrhosis or autoimmune hepatitis.

2.4.13 Smooth red tongue

A *smooth red tongue*, first described by H. Kalk (1955) (16), is raspberry-coloured. It is moist and more or less atrophic. There is no coating of the tongue, nor can any independent capillary changes or venous stasis be detected. The red colour is often in contrast to the yellowish or greyish yellow skin colouring. The tongue changes mainly develop parallel to the course of the cirrhosis: upon clinical improvement, the raspberry shade changes into the normal reddish grey colour of the tongue, which regains its coating. These changes of the tongue occur relatively rapidly as the condition improves or deteriorates. In cases with significant hepatic dysfunction, the smooth red tongue generally remains unchanged. Its cause is assumed to be metabolic cell dysfunction or hyperergic-allergic phenomena. (15) • There is often *angular cheilosis* with rhagades (perlèche, angulus infectiosus), such as can be witnessed in vitamin B_2 deficiency, diabetes mellitus, iron deficiency, infections, etc. (s. fig. 4.9)

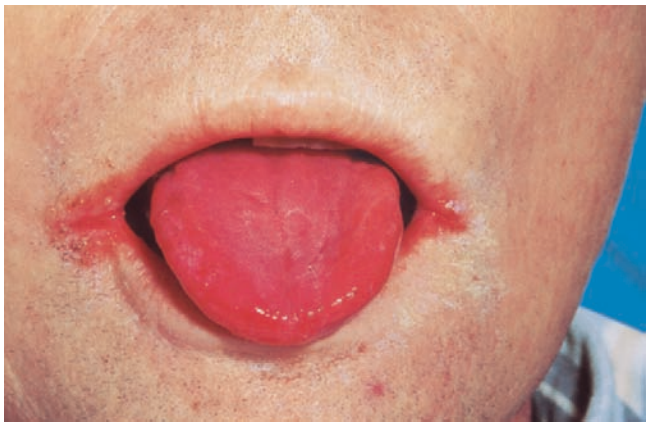

Fig. 4.9: Smooth red tongue with angular cheilosis in liver cirrhosis

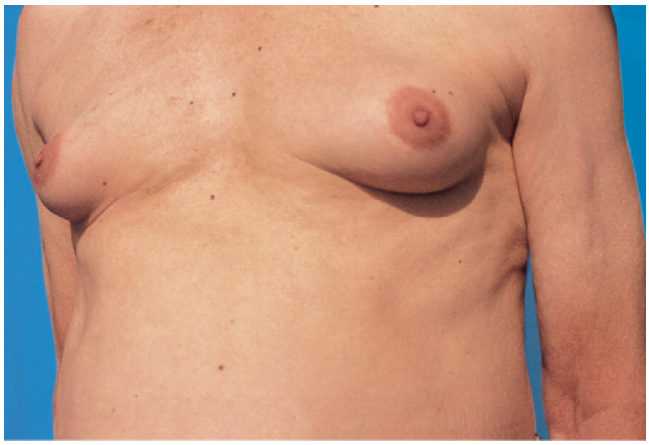

Fig. 4.10: Gynaecomastia in liver cirrhosis

2.4.14 Liver tongue

A so-called congested tongue or "liver tongue" (R. Pannhorst et al., 1957) is voluminous due to the accumulation of fluid and displays tooth marks at the edges. It often has a deep median vertical groove and several small furrows or fissures. Corresponding to its occurrence with (or due to) portal hypertension, it is bluish purple in colour and its undersurface displays greatly distended veins. (15)

2.4.15 Lacquered lips

A smooth red tongue is often combined with a peculiar reddish colouring and smoothness of the lips, known as lacquered lips. They are also one of the late signs of cirrhosis, mainly with a necrotic course of the disease.

2.4.16 Gynaecomastia

In cases of gynaecomastia, the male mammary gland is enlarged. Within the increased volume of the breast, a firm, circumscribed and relatively well-defined tissue mass can be felt, which is usually sensitive to pressure. Apart from the enlargement of the mammary gland, which causes the patient mental as well as physical distress, spontaneous and sometimes sharp pain occurs. Occasionally, a serous or milk-like secretion is discernible. Gynaecomastia can also be unilateral. It occurs most frequently in alcoholic cirrhosis. (s. fig. 4.10)

The **cause** of gynaecomastia is generally attributed to inadequate inactivation of oestrogen or decreased production of testosterone (e. g. due to a lack of zinc in chronic alcoholism). Likewise of causative significance are the increased prolactin plasma level and a greater degree of response on the part of the mammary gland tissue. (6, 8, 25)

Differential diagnosis: Gynaecomastia is also found as a persistent pubertal condition and in adiposity. It is always important to exclude other causes such as testicular tumours, hypogonadism, corticoadrenal tumours, bronchial carcinoma, etc. • Gynaecomastia can also occur as a result of treatment with *spironolactone*, which is often indicated in cirrhosis patients – however, when the medicament is no longer taken, this finding is reversible.

2.4.17 Dupuytren's contracture

The term Dupuytren's contracture (F. Platter, 1614; G. Dupuytren, 1832) denotes a hardening of the palmar fascia in the connective tissue, with firm band-like connections extending as far as the periosteum and even into the outermost skin layers. The preferred site is the distal ulnar quadrant of the flat of the hand. Severe flexion contractures, especially of the 4th and 5th fingers, ultimately develop. (s. fig. 4.11)

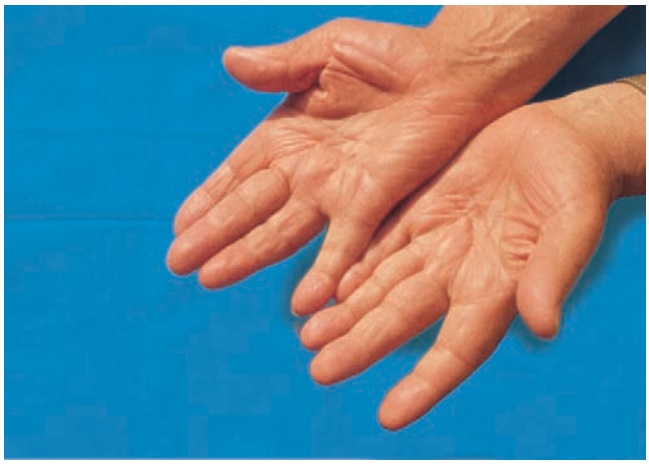

Fig. 4.11: Dupuytren's contracture in liver cirrhosis

Whereas Dupuytren's contracture is only found in about 2% of the population, it is detectable in about 30% of all cirrhosis patients, mainly bilaterally. Men are affected in 90% of cases and thus far more often than women. The disease generally commences unilaterally. Men are frequently affected in their younger years, whereas in women, the disease commences later and takes a more rapid course. There is a greater tendency towards recurrence of the disease after surgery than after radiological treatment. In cirrhosis patients, contracture occurs predominantly in combination with palmar erythema. There also seems to be a correlation between contracture and spider naevi. (2, 12, 23, 25)

At present, there are only hypothetical explanations for the **cause** of the contracture and its correlation with liver cirrhosis. A genetic factor probably plays a part, possibly also in combination with genuine epilepsy. Its more frequent incidence in alcoholic cirrhosis points to a disorder in collagen metabolism as a pathogenic factor. Evidently, the platelet-derived growth factor (PDGF) which is produced, causes the connective tissue to proliferate and contract. PDGF stimulates the formation of prostaglandin E., which likewise changes the fibroblast contractility. (40)

2.4.18 Pigmentation and striae

Patients suffering from **liver cirrhosis** frequently display a brownish discoloration of the skin, predominantly due to the deposition of melanin.

In **haemochromatosis**, a pronounced brownish pigmentation is found due to the deposition of haemosiderin and melanin in the skin (= *bronze diabetes*), particularly in the lines of the palm. (s. fig. 4.12) Other predilection sites with distinctive slate-grey pigmentation are the axillae and the inguinal or lumbar region. Occasionally, a brownish ring-shaped discoloration is seen on the proximal fraction of the nail plate.

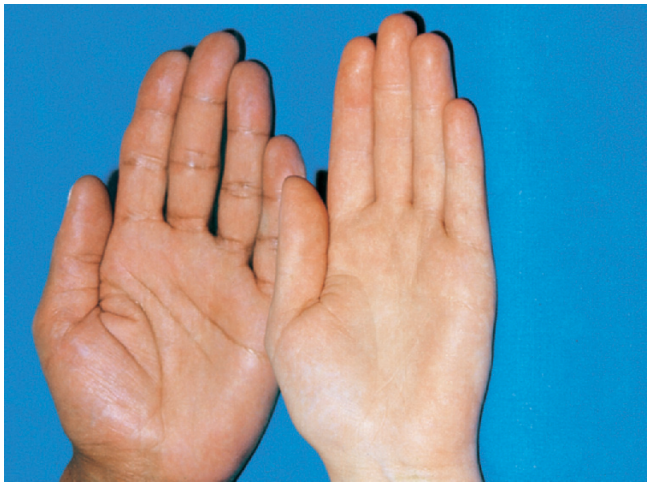

Fig. 4.12: Pigmentation of the lines of the palm in haemochromatosis (left) − in comparison with a normal hand

Wilson's disease is occasionally accompanied by an argyric-like discoloration of the *skin* (greyish brown to bluish grey). The fingernails often display skyblue-coloured lunulae (A.G. Bearn et al., 1958). (46)

Primary amyloidosis can cause the skin to turn reddish brown. • In **Gaucher's disease**, greyish brown pigmentation can develop, similar to chloasma uterinum. This symmetric pigmentation sometimes extends upwards from the foot to the knee. • In **kwashiorkor**, dark red blotches are sometimes found in the inguinal and periumbilical area. • In **hamartoma** of the liver, a greyish brown skin pigmentation of the acanthosis nigricans type has been described. In the axillae, the skin is thickened and its texture has a greater consistency; it is also more fissured. • **Juvenile cirrhosis** (= lupoid hepatitis) often produces dark purple stripes on the hips, gluteal region and thighs of the young women affected. These striae run parallel to the tension lines of the skin. They can fade due to skin atrophy and loss of pigmentation.

Where the skin is exposed to sunlight, **porphyria cutanea tarda** displays a greyish brown, maculate or even patch-like area of pigmentation, resulting from the deposition of melanin. The skin can be changed in the same way as in sclerodermatitis. Because of the photosensitivity of the skin, sporadic subepidermal blisters or pimples with encrusted skin lesions are formed, as a result of which the skin injures easily. The scars take the form of whitish, irregularly circumscribed blotches. (s. fig. 4.13) Periorbitally deposited melanin pigment is a typical feature.

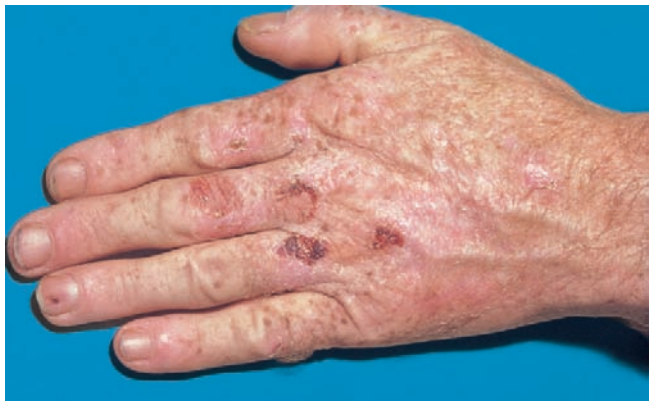

Fig. 4.13: Back of the hand in porphyria cutanea tarda

Butterfly sign: Hypopigmentation in the form of butterfly-shaped areas of skin on the back, located on either side of the spine, are sometimes seen in patients with cholestatic jaundice. (44)

2.4.19 Inflammatory erythematous stigmata

Erythema diffusum hepaticum can be observed in patients suffering from acute liver insufficiency. It is manifested as diffuse plate-shaped erythema of the face, extending up to the hair line. Occasionally, it can also be detected in the region of the jugulum and sternum. Minute red dots are frequently observed within the erythema. These become more prominent as the erythema fades away. Should reddish-coloured telangiectases occur in this area, the picture of paper money skin emerges. (s. figs. 4.8, 4.19)

Exanthemas are prodromal skin symptoms in acute viral hepatitis (5−20% of cases). They appear as urticaria, scarlatinoid or morbilliform exanthemas as well as varicella and erythematous multiform rashes.

Acrodermatitis papulosa eruptiva infantum (*Gianotti-Crosti syndrome*) can occur in children with acute viral hepatitis B. This is a lichenoid-papuloid skin rash on the face and limbs, which breaks out suddenly. The skin stigmata take 2−8 weeks to disappear. (s. p. 439)

2.4.20 Xanthelasmas and xanthomas

Xanthelasmas can be found at the corners of the eye or periorbitally, above all in cases of biliary cirrhosis due to primary biliary cholangitis (CDNC). (1) They display a yellow, reddish yellow to brownish yellow colouring and are sharply circumscribed, sometimes as large as a fingernail, sometimes arranged in stripes. They can be flat (*xanthelasma planum*) or, due to cholesterol deposits, appear as raised bulges or tubers (*xanthelasma tuberosum*). (s. fig. 4.14)

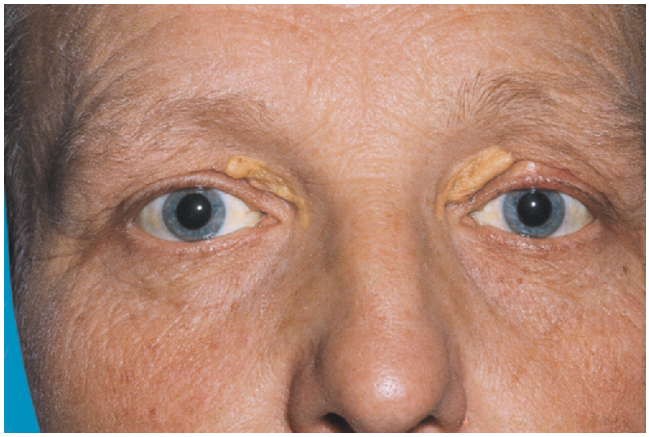

Fig. 4.14: Xanthelasmas in biliary cirrhosis as a result of primary biliary cholangitis

Xanthomas (*xanthoma tuberosum*) display a straw-like yellow through to greyish yellow hue. These are round, well circumscribed, plaque-like raised or papuloid deposits in the skin, which predominantly occur on the extensor sides of the extremities, the elbow and knee area, the external ear, parts of the buttocks and back, occasionally also on the hands and soles of the feet. They can appear in cholestatic liver diseases, particularly in biliary cirrhosis as a result of CDNC. Their occurrence depends on the lipid and cholesterol content of the blood. (1) These changes are considered to be late symptoms. (s. p. 243) (s. figs. 4.15, 4.16)

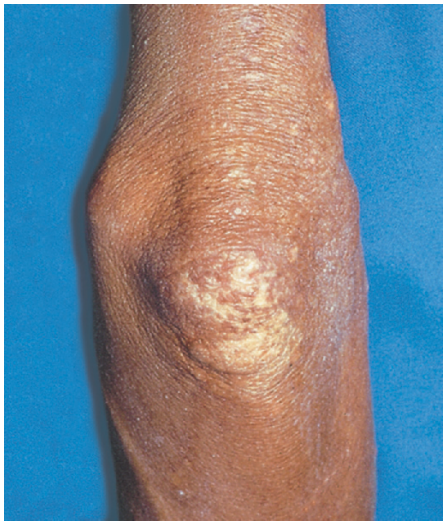

Fig. 4.15: Xanthoma on the elbow in biliary cirrhosis as a result of primary biliary cholangitis

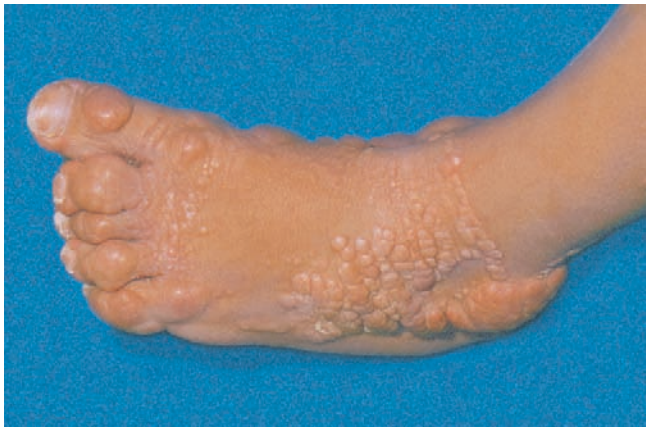

Fig. 4.16: Multiple xanthomas in chronic cholestasis due to congenital biliary tract atresia

2.4.21 Scratch marks in pruritus

Scratch marks as the outcome of an often unbearable pruritus are found in the form of stripe-like excoriations, blood-encrusted skin lesions, dot-like erosions or secondary papuloid dermatitis, lichenification and bacterially superinfected scratch wounds. There may still be some visible signs of scarring and pigmentation. (s. p. 243) (s. fig. 13.3)

When **pruritus** occurs in systemic disease without any initial changes of the skin, it is known as pruritus sine materia. This condition includes the cholestatic liver diseases and liver hamartoma that accompany pruritus in up to 70 % of cases. It is often in itself a cardinal symptom, with the itching mostly commencing in the palms of the hands and on the soles of the feet; in the evening and during the night, it is considerably more pronounced. Itching does not correlate with the degree of severity of cholestasis. In cases of unbearable itching, psychosomatic disorders and reactive depression or thoughts of suicide can appear. (3)

► The pathophysiology of pruritus has not yet been fully resolved. It can be assumed that the free nerve endings of the unmyelinated C-fibres in the dermis and epidermis serve as nocireceptors. These are activated directly by mechanical or thermal stimuli and indirectly via chemical, pruritogenic substances. The latter include: histamines, serotonin, proteases, prostaglandins (D2, E2), kinins, substance P, neurokinin A, etc. It is not known, which substances(s) can cause pruritus with cholestasis. The pathogenetic role of the bile acids is still in discussion (e. g. enhanced values of individual or combined bile acids, a shift in the relationship between bile acids). It seems certain that a greater opioidergic tonus prevails in cholestatic liver disease. Hence, pruritus could be caused by the epidural or intrathecal administration of opioids, but also eliminated by opioid-receptor antagonists.

2.4.22 Eye changes

Scleral icterus occurs from a serum bilirubin level of 1.6−1.8 mg/dl upwards. At the same time, the conjunctiva is icterially discoloured. Jaundice is based on the affinity of the elastic fibres for bilirubin. (s. fig. 4.17)

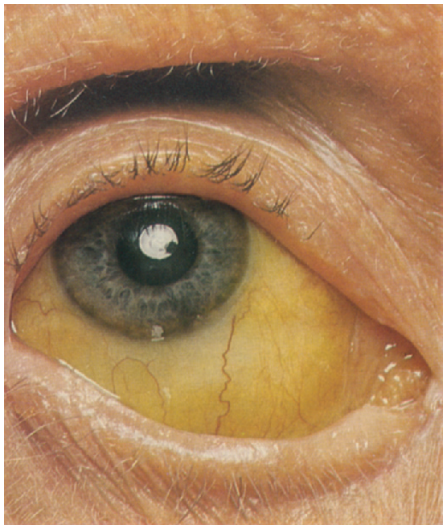

Fig. 4.17: Scleral icterus in akute viral hepatitis A

Kayser-Fleischer corneal ring (B. Kayser, 1902; B. Fleischer, 1903) occurs in Wilson's disease. It has also been observed in alcoholic liver disease. (47) Deposits of copper compounds form a brownish green corneal ring of 1–3 mm in width near the limbus. It can be identified at an early stage by slit-lamp examination. (s. fig. 4.18) • Individual radiating, greenish brown **sunflower cataracts** are sporadically detectable in Wilson's disease.

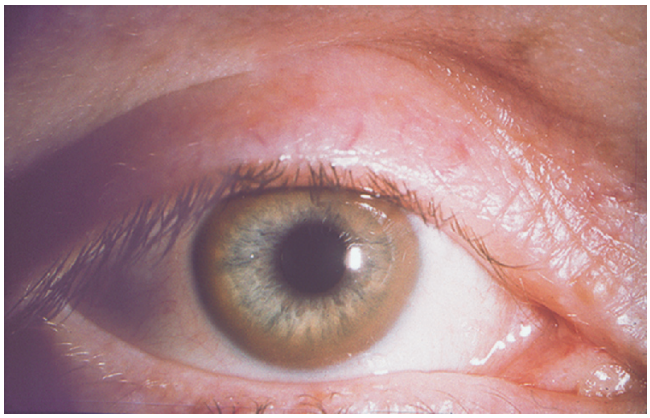

Fig. 4.18: Kayser-Fleischer corneal ring in Wilson's disease

Pingueculae present as wedge-shaped, yellowish deposits on both sides of the pupilla and are observed in Gaucher's disease. • **Retraction of the eyelid** (= Darlrymple's sign) and **infrequent blinking** (= Stellwag's sign), such as in hyperthyroidism, are also found in cirrhosis patients.

2.4.23 Drumstick fingers

Drumstick fingers can be observed in chronic liver patients with a hepatopulmonary syndrome. *(see chapter 18)* These changes are due to increased blood supply to the distal phalanges and the opening of arteriovenous anastomoses with relative hypoxia of the tissue as well as a more extensive formation of connective tissue between nail and bone. • The exaggerated convexity found in **hour-glass nails** can be a preliminary stage of drumstick fingers. Occasionally, a combined occurrence of finger clubbing and white nails is observed (= *hypertrophic osteoarthropathy*). (s. fig. 4.19) (s. p. 342)

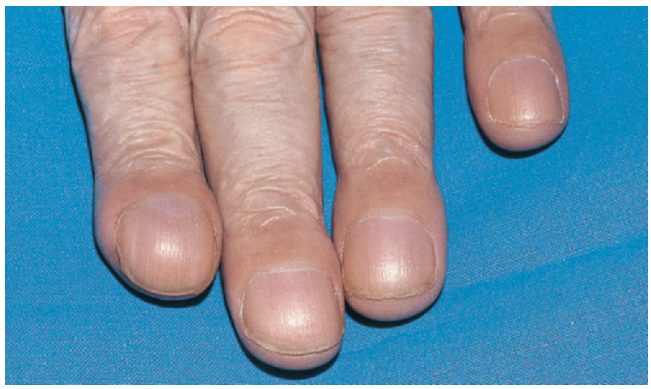

Fig. 4.19: Drumstick fingers and hour-glass nails in liver cirrhosis (and moderate paper money skin: s. figs. 4.8; 20.1)

2.4.24 Testicular atrophy

Considerable endocrine disorders may be present at times in cirrhosis patients. Progressive testicular atrophy with impotence and eunuchoidism (hypogonadism, "abdominal baldness", Chvostek's habitus) can occur. Fully developed testicular atrophy appears regularly in haemochromatosis.

2.4.25 Cutaneous and mucosal haemorrhages

Cutaneous and mucosal haemorrhages can occur in both liver insufficiency and liver cirrhosis. They appear as *suggilations* (coin-sized haemorrhagic foci) (s, figs. 4.20, 20.1), *purpurae* (small maculae) (s. fig. 20.2) or *vibices* (streak-like markings) as well as more extensive *ecchymoses* (circumscribed haemorrhagic foci >3 mm in size) and *petechiae* (pinpoint-sized capillary haemorrhagic foci) or as *suffusions* (confluent haemorrhagic foci, generally without sharp circumscription).

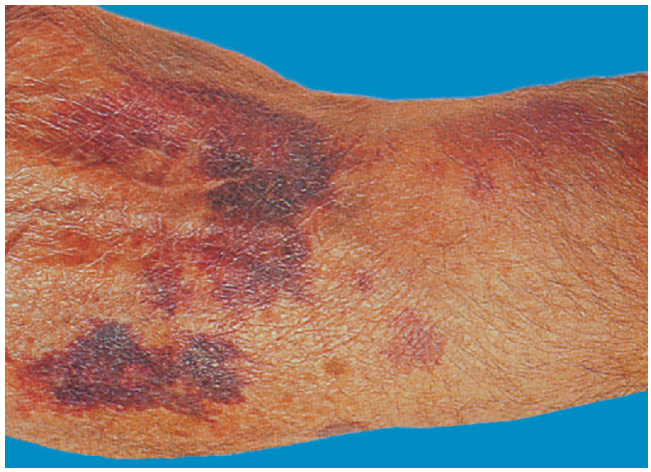

Fig. 4.20: Cutaneous haemorrhages (confluent and streak-like) on the lower part and wrist of the left arm in a patient with cirrhosis (s. figs. 20.1, 20.2)

The haemorrhages are spontaneous or occur as a result of skin punctures or traumatism. Causative factors include greater fragility of the vessels, defective anchoring of the smallest subcutaneous vessels, increased hydrostatic pressure when standing, and coagulaopathy.

2.4.26 Vein dilatation

Clearly *recognizable veins* in the chest and abdominal area in approx. 40% of cases are a visible sign of portal hypertension with collateral veins. (s. fig. 4.21)

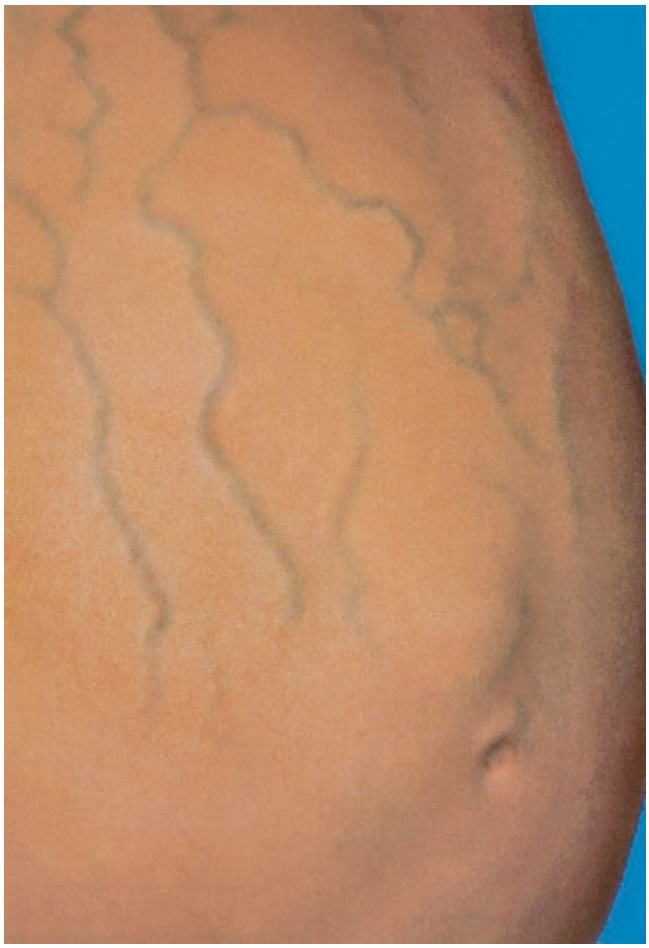

Fig. 4.21: Vein dilatation and tortuosity in the abdominal wall of a cirrhotic patient suffering from ascites and jaundice

Caput Medusae: Excessive forms of vein dilatation can develop in the abdominal skin, such as *vein convolutions* or *Medusa's head* (M. A. Severino, 1632); the latter is also known as *Cruveilhier's sign* (J. Cruveilhier, 1829). It develops in portal hypertension, with the result that after the obstructed umbilical vein has been reopened, collaterals are formed over the paraumbilical veins (so-called Sappey's veins). Subsequently, visible venectasiae radiate out from the navel, like the snakes on the head of the gorgon Medusa. • A similar venectasia can also be seen in the area of the epigastric and superficial thoracic veins (*Cruveilhier-von Baumgarten syndrome*). (s. fig. 7.4) • Caput Medusae is also formed as a result of a persistent and malformed umbilical vein with hypoplasia as well as in thrombosis of the intrahepatic branches of the portal vein. It even occurs in children and juveniles (*Cruveilhier-von Baumgarten disease*). With caput Medusae, the umbilical vein remains open or is reopened, or the paraumbilical veins are dilated without change in the blood pressure. • Thus a prehepatic block (portal vein or splenic vein thrombosis) can never cause a caput Medusae because it never affects the umbilical vein. (s. pp 254, 265, 861) (s. fig. 14.13)

2.5 Hepatic foetor

There can be a pronounced increase in methionine and its derivatives in acute liver failure or in serious cases of cirrhosis. From these substances, mercaptans are formed in the colon (e. g. methandiol, ethandiol, dimethyldisulphide). The cause of the *sweetish aromatic smell* of the expiratory air ("fresh-raw liver") known as hepatic foetor (F. Umber, 1926; L. Schiff, 1946) is deemed to be volatile *dimethylsulphide*, a derivate of methanethiol. (39) Its concentration does not correlate with the degree of encephalopathy or hepatic insufficiency, but with the intensity of the portosystemic shunts. • *Trimethylamine* is also suspected of being a causative factor. (22) (s. pp 275, 383)

2.6 Fatigue

In patients with liver disease, fatigue is the most commonly encountered symptom; it has a significant impact on the quality of life. This complex symptom encompasses a range of complaints, such as weariness, exhaustion, lack of concentration, lassitude, lethargy, malaise, drowsiness and sleeping disorders. The frequency of fatigue in patients with different forms of liver disease is variable; the highest incidence is actually found in cholestasis (65−85%), followed by autoimmune hepatitis, drug-induced liver diseases and chronic hepatitis B or C; it is observed less often in acute viral hepatitis. Remarkably, it has often been possible to detect antibodies to serotonin or gangliosides or phospholipids. • No specific therapies are currently available. CNS stimulants, including modafinil, have been discussed; sometimes, nocturnal therapy with low-dose amitriptyline or fluoxetine shows a slight response. In a recent clinical trial, the 5-HT3 receptor antagonist ondansetron appeared to have a limited effect on fatigue in PBC patients. (38)

► Central fatigue results from altered neutrotransmission within the brain and is, therefore, often associated with depression and anxiety. Experimental and clinical attention is focused on behavioural activation, arousal and locomotor activity; it would appear that basal ganglia, the brain stem and the limbic system, as well as higher cortical centres, are involved in central fatigue. The condition may result from a defective central release of CRH, which is the most potent activator of the hypothalamic-pituitary adrenal (HPA) axis. Serotonin plays an important role by activating a larger number of receptor subtypes. Interestingly, CRH and serotonin (probably 5-HT1.A) are intimately interrelated. The hypo-

function of the HPA axis has also been intensively discussed in relation to the development of central fatigue in liver disease. Other possible causes include the dopaminergic and cannabinoid system. In this context, increased cytokine levels may be a connecting link between liver disease and disorders of the neurotransmitter systems. (38)

2.7 Auscultation

Although auscultation of the abdomen is less important, this method of examination should be performed in certain diagnostic situations. Vascular sounds can occur in the form of arterial bruit or venous hum.

1. Arterial bruit: A systolic rushing sound synchronized with the heart beat indicates increased arterial blood flow. This often barely audible sound is easier to discern if one listens for arterial bruit and feels the patient's pulse at the same time. • It is sometimes heard where aneurysm or stenosis is present in large arteries (e. g. coeliac artery, hepatic artery) as well as in arteriovenous malformations, highly vascularized liver tumours, pronounced acute alcohol hepatitis, 1−2 days after liver biopsy resulting from temporary arteriovenous fistula, or in twisted arteries in cirrhosis. It is seldom found in healthy persons. (10, 13, 45)

2. Venous hum: Laennec (1819) was the first to describe the sound which one could hear coming from the veins of patients with cirrhosis. In France this sound phenomenon was termed "bruit de diable" (Bouillaud, 1835). The German term "Nonnensausen" is believed to have been introduced by von Mering (1901) in his textbook on internal medicine. It is derived from the noise made by a children's humming-top and is therefore best translated as "humming-top murmur". • Pronounced portal collateral circulation may cause a constant rushing sound due to increased blood flow. This hum mainly occurs between the navel and xiphoid. It is heard frequently and distinctly in the Cruveilhier-von Baumgarten syndrome as well as in venous convolutions on the surface of the abdomen and in the centre of the (extremely rare) caput Medusae. The noise increases when the patient inhales or is in a standing position. (5)

3. Friction rub: A respiratory friction sound above the liver is an indication of perihepatitis. This inflammation of the liver occurs in tumours, liver abscesses or bacterial perihepatitis (e. g. *Fitz-Hugh-Curtis syndrome*) and, in rare cases, temporarily after a liver biopsy. • Perisplenic rubbing is occasionally discernible after splenic infarction. When pressure is applied to the stethoscope, the rubbing sound increases.

3 Liver check list

A *liver check list* provides a swift and clear method of ensuring that all important **clinical findings** can be "ticked off" in the patient's file. This list comprises the ten most important subjective ailments, the twelve most important liver skin stigmata and the nine most important clinical findings. *One glance is enough to review the total findings of the liver patient; moreover, documentation itself involves a minimum of time and effort*. Over the years, such a check list has proved its value in numerous practitioners' surgeries and outpatient departments. It ensures that nothing is "forgotten" or "overlooked" and (particularly during the first check-up) enables a simple, yet extensive, documentation of hepatologic findings to be drawn up. (s. fig. 4.22)

Liver check list of clinical findings				**Name**				**Date**			
Anamnesis **10 most important complaints**				**Skin stigmata in liver diseases** **12 most important skin stigmata**				**Clinical findings** **9 most important clinical findings**			
	∅	+	++		∅	+	++		∅	+	++
1. Fatigue				1. Jaundice				1. Liver palpation			
2. Weariness				2. Spider naevi				2. Dark urine			
3. Repletion				3. Palmar erythema				3. Acholic stools			
4. Flatulence				4. Smooth red tongue				4. Bleeding			
5. Inappetence				5. Lacquered lips				5. Hepatic foetor			
6. Nausea				6. Gynaecomastia				6. Testicular atrophy			
7. Intolerances				7. Paper money skin				7. Splenic palpation			
8. Itching				8. White nails				8. Oedemas, ascites			
9. Impotence				9. Chvostek's habitus				9. Handwriting test (signature)			
10. Upper abdominal pressure				10. Dupuytren's contracture							
				11. Scratch marks							
				12. Haemorrhages							

Fig. 4.22: Liver check list of clinical findings (s. fig. 4.2) with the 10 most important subjective complaints, the 12 most important skin stigmata in liver diseases, and the 9 most important clinical findings (19) (s. fig. 5.2)

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