

# Chapter 6

## Medical Diagnosis in Hepatology

In the previous chapters, the theoretical aspects of diagnosis have been discussed in much detail. This second part of the thesis focusses on the application of some of these principles to the medical diagnosis of disorders of the liver and biliary tract.

In this chapter, an overview of the problem of diagnosing disorders of the liver and biliary tract is presented from a medical perspective. This chapter may be viewed as a summary of the knowledge acquired to build the HEPAR system. First, some anatomical and physiological principles concerning the liver and biliary tract are briefly discussed. Next, the clinical approach to the patient with a disorder of the liver or biliary tract is reviewed. The general diagnostic strategy followed for these patients is outlined. Furthermore, some of the more frequently applied laboratory tests and procedures in diagnosis are briefly described. A small number of disorders of the liver and biliary tract are described in some detail.

### 6.1 The liver and the biliary tract

The liver is the largest solid organ in the human body, weighing about 1.5 kg. This organ has an enormous number of different functions, including the formation of bile and urea, carbohydrate and fat metabolism, reduction and conjugation of steroid hormones, and the production of plasma proteins. Most of these functions are metabolic in nature. The liver consists of three major cell types: the *hepatocyte*, the *biliary epithelial cell* and the *Kupffer cell*. The hepatocytes are responsible for most of the metabolic functions mentioned above. The liver is supplied with oxygen by the common hepatic artery, a side-branch of the aorta. The portal vein carries blood that is saturated with nutrients from the gastrointestinal tract to the liver. The blood leaves the liver by the hepatic veins.

The bile, a complex solution composed of water, bile acids (among others cholic acid), bile pigments (biliverdin glucuronide, bilirubin glucuronide), fatty acids, cholesterol, etcetera, is excreted by the hepatocytes through a complicated mesh of small bile ducts into the common bile duct, which drains into the duodenum. Between meals, bile is stored in the gallbladder, a pouch emerging from the common hepatic duct.

Studies show that the liver's reserve capacity to damage is large; recovery of patients has been reported following 80 to 90 per cent resection due to the large capacity of the liver

to regenerate [Karran & McLaren, 1985]. In view of the central role the liver plays in bile metabolism, liver damage is often associated with bile excretion derangements, frequently resulting in jaundice. *Jaundice*, which is characterized by, among others, yellow eyes and skin, is due to increased plasma levels of bilirubin. These and other similarities between the symptoms and signs of disorders of the liver and those of disorders of the biliary tract are the main reason to treat these two systems as a single entity. The duodenum and pancreas are considered additional potential sources of disorders of the liver and biliary tract, due to their close anatomical relationship to the common bile duct.

Although a large variety of laboratory tests are available to assess the liver function, there is no single combination of tests that is informative for all patients. As a consequence, the principal approach to the patient with a disorder of the liver and biliary tract is strongly clinical in nature, i.e. information from history and physical examination is an essential ingredient for the proper diagnostic management of these patients.

## 6.2 Clinical diagnosis in hepatology

In this section, a review of diagnosis in hepatology is presented.

### 6.2.1 Approach to the patient

The central problems in the diagnosis of disorders of the liver and biliary tract in the patient are [Karran et al., 1985]:

- (1) To determine whether the disorder is primarily affecting the hepatocytes (*hepatocellular disorder*) or primarily affecting the biliary tract (*biliary obstructive disorder*);
- (2) To establish whether the disorder is acute or chronic in nature;
- (3) To recognize whether the disorder has benign or malignant features.

Based on this information, it is often possible to develop a plan for further diagnostic assessment to reach an acceptable *differential diagnosis*, i.e. a small set of disorders where each disorder more or less fits the findings observed in the patient. From this differential diagnosis, a single disorder with strongest evidence, often called the '*final diagnosis*' or '*definite diagnosis*' may be selected if sufficient evidence is available.

As a matter of terminology, in the medical literature the collection of derangements associated with the diseases in the group of hepatocellular disorders is sometimes referred to as intrahepatic cholestasis, whereas the set of derangements associated with the diseases in the group of biliary obstructive disorders is sometimes referred to as extrahepatic cholestasis. It should, however, be noted that disorders with extrahepatic cholestasis may also involve, or even be limited to, the intrahepatic parts of the biliary tract. Other authors, therefore, use the terms intrahepatic and extrahepatic cholestasis in another sense, namely to signify a distinction at the anatomical level (inside the liver – intrahepatic – versus outside the liver – extrahepatic). Another possible source of confusion is the use of the term 'cholestasis' in the literal sense of stagnation (stasis) of bile; it has traditionally been used to describe the accumulation of bile as seen under a light microscope. In this

thesis, the terms hepatocellular disorder and biliary obstructive disorder are used instead, because of their less ambiguous meaning. When the connotation implied by the term 'disorder' seems undesirable, the pathophysiological terms *hepatocellular derangement* or *hepatocellular damage* and *biliary obstruction* will be used instead.

The aetiology of hepatocellular disorders varies widely. Some causes of disease belonging to the class of hepatocellular disorders are:

- Alcohol abuse, which may give rise to alcoholic hepatitis, alcoholic cirrhosis, steatosis hepatis, Zieve's syndrome.
- Viral infection; examples of viral disease which affects the liver are hepatitis A, B and C, and cytomegalic inclusion disease.
- Autoimmune disease, such as causing autoimmune chronic hepatitis.
- Inborn errors of metabolism, such as in Gilbert's syndrome, which is caused by a deficiency of the enzyme glucuronyl transferase in the hepatocyte, or Wilson's disease in which a lack of the copper-binding  $\alpha$ -globulin caeruloplasmin is found.

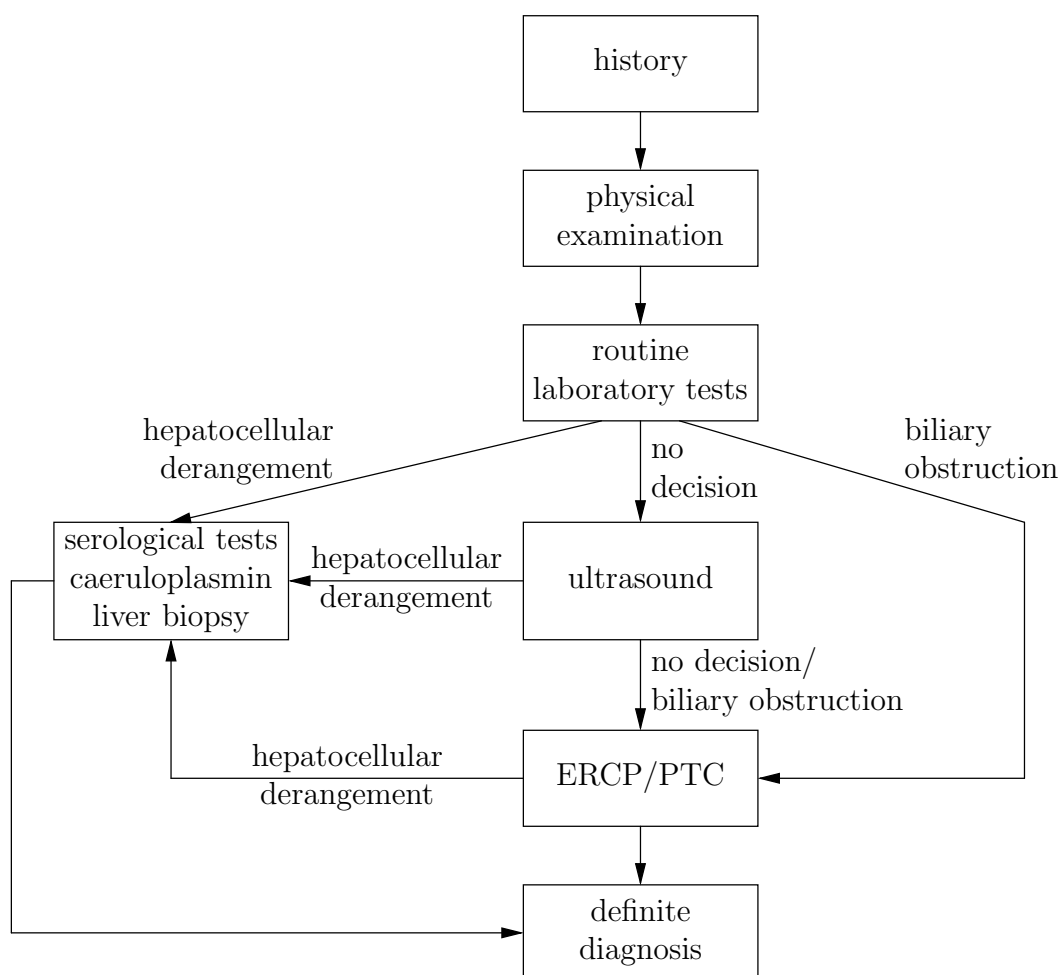
Since in all these disorders, the hepatocyte is affected, they share several symptoms and signs.

In biliary obstructive disorders, some form of obstruction always exists in the small, intrahepatic bile ducts or in the large bile ducts, i.e. the left and right hepatic ducts and the common bile duct. Obstruction of the biliary tract may be caused by:

- The presence of gallstones in the common bile duct.
- A benign or malignant tumour, such as pancreatic carcinoma, which may obstruct the common bile duct, bifurcation carcinoma, which may cause obstruction of the hepatic ducts and common bile duct at the porta hepatis, or a metastatic tumour in the liver, which may cause obstruction of the intrahepatic biliary tract due to compression of the surrounding tissue.
- Destruction of the small bile ducts, as found in primary and secondary biliary cirrhosis.

In advanced liver disease, there is often destruction of both the hepatocytes and the bile ducts, and the two clinical pictures will merge. Several of the disorders mentioned above will be treated in more detail in Section 6.7.

One of the interesting features of the area of hepatology is its strong clinical basis. Although a rapidly increasing number of diagnostic tests have become available in the past two decades, a careful and thorough history and physical examination, supplemented with a small number of laboratory tests, are still of overriding importance in the diagnosis of disorders of the liver and biliary tract. Clinical information often provides sufficient evidence concerning the underlying pathology and aetiology of the disease, and may even indicate a definite diagnosis. Supplementary diagnostic investigations, such as endoscopic retrograde cholangio-pancreaticography (ERCP), need therefore only be performed in a limited number of carefully selected patients. To this end, a clear plan of investigation



**Figure 6.1:** Diagnostic plan in patients with liver or biliary tract disease.

is of the utmost importance. The diagnostic plan that has been taken as the basis for the development of the HEPAR system is depicted in Figure 6.1. This diagnostic plan is commonly followed by the clinician in dealing with a disorder of the liver or biliary tract. This same structure has been adopted in the HEPAR system (cf. Chapter 7). We shall first review the process of history taking and physical examination in hepatology, and discuss some of the most frequently applied laboratory tests, before discussing some of the diagnostic procedures in more detail.

### 6.2.2 Patient history

A patient with a disease of the liver or biliary tract will typically have jaundice, i.e. yellow sclerae, dark urine and pale, clay-coloured stools. However, in some patients none of the features may be present, and the suspicion of the presence of a liver disease may only be based on coincidentally detected abnormal laboratory findings. Information from the patient history may point to a specific disease. For example, if a patient has been in contact with a jaundiced subject, has visited a (sub)tropical area, has been transfused with blood products or is a heroin addict, some form of viral hepatitis may be suspected.

A patient with jaundice due to a biliary obstructive disorder (cholestatic jaundice) will typically have dark urine and pale stools. A history of biliary colics is strong evidence that the jaundice is caused by stones in the common bile duct. A dry mouth and burning eyes may indicate the disorder to have an autoimmune origin. If the patient is suffering from pain, its nature (paroxysmal or continuous), location, possible radiation to other parts of the body, and the relation to food intake is important information to differentiate between various disorders. Information from the *family history* may provide evidence for a genetic origin of a disorder.

### 6.2.3 Physical examination

Physical examination of the patient may yield important information about the severity and aetiology of the disorder, and may sometimes even yield a definite diagnosis. For example, the presence of Kayser–Fleischer rings on inspection of the patient’s eyes leads immediately to the conclusion that the patient probably has Wilson’s disease. Certain cutaneous stigmata, such as erythema of the palm of the hands (palmar erythema), indicate the presence of a chronic dysfunction of the hepatocytes. Splenomegaly (enlarged spleen) and caput medusae (tortuous veins around the navel) indicate portal hypertension, i.e. increased pressure in the portal venous system usually associated with cirrhosis of the liver. A palpable gallbladder in a patient without pain (Courvoisier’s sign) or an epigastric mass discovered by palpation, may be explained by the presence of a pancreatic carcinoma. Percussion of the abdomen may yield evidence about the presence of ascites (abnormal protein-rich fluid in the abdominal cavity).

### 6.2.4 Diagnostic tests

The routine laboratory tests to investigate the nature of a disease of the liver and biliary tract are the serum levels of conjugated and unconjugated bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, 5′-nucleotidase, and  $\gamma$ -glutamyl transferase. These laboratory tests are used to differentiate between hepatocellular derangement and biliary obstruction.

Unconjugated bilirubin is a break-down product of haemoglobin, an oxygen-carrier metalloprotein present in erythrocytes. Most of this unconjugated bilirubin is reversibly bound to plasma albumin. It is taken up by the hepatocytes by a carrier-mediated transport mechanism, and inside the cell conjugated to bilirubin glucuronide by the enzyme glucuronyl transferase. Conjugated bilirubin is actively excreted in the bile. The serum level of conjugated bilirubin is elevated in most diseases of the liver and biliary tract. The serum level of unconjugated bilirubin is increased in haemolytical anaemia (not covered in HEPAR), and in several liver diseases such as Gilbert’s disease and Zieve’s syndrome.

Urine is usually examined on the presence of urobilin and conjugated bilirubin. Conjugated bilirubin is partially oxydated to urobilinogen in the intestines, part of which is reabsorbed to the blood. As a water-soluble substance, some urobilinogen is excreted into the urine where it is oxydated to urobilin. The absence of urobilin in urine indicates that the transport of conjugated bilirubin to the intestines is blocked, due to biliary obstruction. Since biliary obstruction leads to the accumulation of conjugated biliru-

bin in the blood, again a water-soluble substance, increased amounts of bilirubin can be found in urine. Unconjugated bilirubin is not excreted in the urine due to its binding to plasma albumin; under normal conditions albumin cannot cross the glomerular basement membrane in the kidney.

The tests mentioned above belong to a wide range of biochemical tests of liver function and presence of hepatocellular damage or biliary obstruction, commonly called '*liver function tests*'. More about these tests will be said in Section 6.3. It should be noted that the outcomes of the routine laboratory tests merely guide the selection of further diagnostic tests as indicated in Figure 6.1; they do not offer conclusive evidence.

If the evidence indicates hepatocellular damage, several supplementary laboratory tests are available to differentiate between various hepatocellular disorders. In particular serological tests, such as hepatitis B serology, and the presence of hepatitis A IgM, cytomegalovirus, smooth muscle, nuclear, or mitochondrial antibodies provide important evidence for a particular disease. Section 6.4 reviews the most important serological tests.

If insufficient evidence concerning the hepatocellular or biliary obstructive nature of a disorder has been gathered for a patient, ultrasonography may be carried out, providing more specific evidence regarding disease of the biliary tract and the pancreas. Ultrasonography of the liver and biliary tract, and of anatomical structures in their direct neighbourhood, is discussed in Section 6.5.

## 6.3 Biochemical hepatobiliary assessment

In this section, the most important biochemical tests used in the assessment of liver function in general, extent of hepatocellular damage, presence of biliary obstruction or hepatocellular malignancy are reviewed. For a more detailed treatment of the subject, the reader is referred to [Price & Alberti, 1985].

### 6.3.1 Assessment of liver function

Hepatocytes play an important role in the synthesis of plasma proteins. The  $\alpha$ - and  $\beta$ -globulins are only produced in the liver. Quantitatively the largest amount of protein synthesized by the liver is albumin, the protein that is responsible for a significant part of the colloid osmotic pressure of plasma. A low level of albumin, hypoalbuminaemia, is often found in chronic liver disease. However, there are several other conditions that may give rise to hypoalbuminaemia, such as malnutrition, which therefore should be ruled out.

The liver also plays an important role in the metabolism of steroid hormones, such as progesterone and the oestrogens, and the androgenic hormone testosterone. Although the precise endocrinological basis is unclear, in male patients chronic liver disease may result in gynaecomastia (female-like breast development) and testicular atrophy; disturbance of the steroid metabolism may be causally related to these signs.

In addition to metabolic functions, the liver also has a function in the storage of several compounds. Only the functions that are important for the diagnosis of liver disease, i.e. the storage of iron and copper, will be mentioned. Iron is bound to transferrin, a protein that transfers iron to the tissues. Excess of iron is stored in the liver as ferritin and

haemosiderin. A chronic overload of iron may result in a form of liver damage called haemochromatosis. Copper is another compound stored in the liver. In the recessively inherited liver disease, Wilson's disease, there is an excess of copper deposits in the liver, especially in homozygous patients, eventually causing symptoms and signs of liver disease. Furthermore, the levels of the copper-binding protein caeruloplasmin, that is produced by the liver, is reduced. The serum level of caeruloplasmin may be determined if Wilson's disease is suspected in the patient.

### 6.3.2 Tests of hepatocellular damage

The levels of the aminotransferases, aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT), are the tests most frequently employed by the clinician to assess hepatocellular damage. The information obtained by these tests is not very specific, i.e. which liver disease may be involved cannot be determined by these tests. Both enzymes are present in high concentration in the hepatocyte. The serum levels of these enzymes may be increased due to leakage of cytoplasm into the circulation, caused by increased membrane permeability or breakdown of the membrane. In acute liver disease, the concentrations of these enzymes may rise 20 to 50 times the upper limit of the normal range; in chronic liver disease, the elevation will be more moderate, about five times the upper limit of the normal range. In disorders that only lead to increased cell membrane permeability, such as acute hepatitis, the ALAT level is usually more increased than ASAT levels. Similarly, in biliary obstruction ALAT levels are usually more elevated than ASAT levels. On the other hand, for hepatic necrosis, the levels of ASAT may rise above those of ALAT. A possible explanation of these observations is that although both enzymes are present in the cytoplasm of the hepatocyte, in contrast with ALAT, ASAT can also be found in the mitochondria; only cytoplasm will leak through the cell membrane.

The levels of ASAT and ALAT are usually studied relative to the serum concentrations of alkaline phosphatase,  $\gamma$ -GT or 5'-nucleotidase, three compounds used in the assessment of biliary obstruction (cf. Section 6.3.3). In case of hepatocellular derangement, typically the levels of ASAT and ALAT are increased whereas the levels of alkaline phosphatase, 5'-nucleotidase and  $\gamma$ -GT are normal, or slightly increased. The elevation of alkaline phosphatase, 5'-nucleotidase and  $\gamma$ -GT can be explained by the fact that in many patients with a hepatocellular disorder, some features of biliary obstruction are present.

### 6.3.3 Tests of biliary obstruction

The biochemical tests of biliary obstruction are used to determine whether or not the bile flow is obstructed somewhere between the small bile canaliculi enclosed between the hepatocytes and the large common bile duct. The pathophysiological basis of biliary obstructive symptoms and signs is the (possibly partial) inability to excrete bile. As a consequence, several bile components appear in blood. One of these components is conjugated bilirubin discussed in Section 6.2.4. The most frequently employed laboratory test to investigate the presence of biliary obstruction in the patient is alkaline phosphatase (AP). The concentration of this enzyme is raised up to ten times the upper limit of normal range in patients with biliary obstructive disease. In particular, the concentrations are

high in extrahepatic obstruction, e.g. obstruction due to pancreatic carcinoma, but may also be high in intrahepatic obstruction.

A disadvantage of the alkaline phosphatase test is that the concentration may also be increased in the presence of bone disease. Whether increased alkaline phosphatase levels are related to liver or bone disease can be established by the serum levels of 5'-nucleotidase, an enzyme that is only raised in serum for liver disease. There are patients, however, for whom this does not hold: the concentration of 5'-nucleotidase does not follow that of alkaline phosphatase, even though liver disease is present. The enzyme  $\gamma$ -glutamyl transferase ( $\gamma$ -GT) is used in a similar way to 5'-nucleotidase; serum levels of this enzyme are particularly high in biliary obstructive disorders.

In summary, classical biliary obstruction causes increased levels of alkaline phosphatase, 5'-nucleotidase and  $\gamma$ -GT, and normal levels of ASAT and ALAT. However, in some biliary obstructive disorders features of hepatocellular derangement can be observed, as demonstrated by the fact that the concentrations of ASAT and ALAT are above the normal upper limits.

### 6.3.4 Tests for hepatobiliary malignancy

In hepatic malignancy, several biochemical tests discussed above may yield abnormal results, depending on the state of the tumour. For example, the tumour mass may, due to compression of surrounding liver parenchyma, give rise to intrahepatic biliary obstruction causing the concentration of alkaline phosphatase to rise. It has been shown that infiltration of liver parenchyma by tumour cells may also produce increased levels of the aminotransferases.

For primary hepatocellular carcinoma, a malignant tumour arising from the liver parenchyma, a frequently applied test is the detection of  $\alpha$ -foetoprotein in blood. The compound  $\alpha$ -foetoprotein is a protein normally present in the fetus but not in the adult; it is synthesized again by the tumour cells.

Tumours of the biliary tract and pancreas may give rise to disturbances of biochemical parameters as discussed above for biliary obstruction.

## 6.4 Immunological and serological tests

There are several disorders of the liver and biliary tract that have associated immunological disturbances. Below, the immunological changes that are directly relevant for diagnosis will be briefly reviewed.

### 6.4.1 Auto-antibodies in hepatobiliary disease

In a number of disorders of the liver and biliary tract antibodies directed against the patient's own cellular components can be detected. Antibodies directed against the components of the cell nucleus can be observed in autoimmune chronic hepatitis and primary biliary cirrhosis (cf. Section 6.7). These antibodies may give rise to the LE-cell phenomenon, i.e. polymorphonuclear leukocytes that incorporate engulfed nuclear material from lymphocytes as a large homogeneous mass.



Antibodies directed against smooth muscle cells, in particular binding to actin molecules in these cells, can be found in high titres in patients with autoimmune chronic hepatitis; these antibodies may also be present in primary biliary cirrhosis and viral hepatitis.

Antibodies directed against the mitochondria may be found in over 85 per cent of all patients with primary biliary cirrhosis. Because in other hepatobiliary disease mitochondrial antibodies are less frequently encountered, the demonstration of mitochondrial antibodies in blood is a valuable test in the diagnosis of primary biliary cirrhosis.

## 6.4.2 Antigens and antibodies in viral hepatitis

### Hepatitis A

Hepatitis A is a viral infection caused by a small RNA virus, called HAV (Hepatitis A Virus). In the presence of this infection, antibodies against HAV, consisting of IgG and IgM fractions, can be detected. A raised anti-HAV IgM titre is diagnostic evidence for acute infection with HAV. The total titre of anti-HAV remains high after hepatitis A infection, and actually is evidence that the patient is now immune to infection with the virus. However, anti-HAV IgM will not be detected after about ten weeks following the initial symptoms.

### Hepatitis B

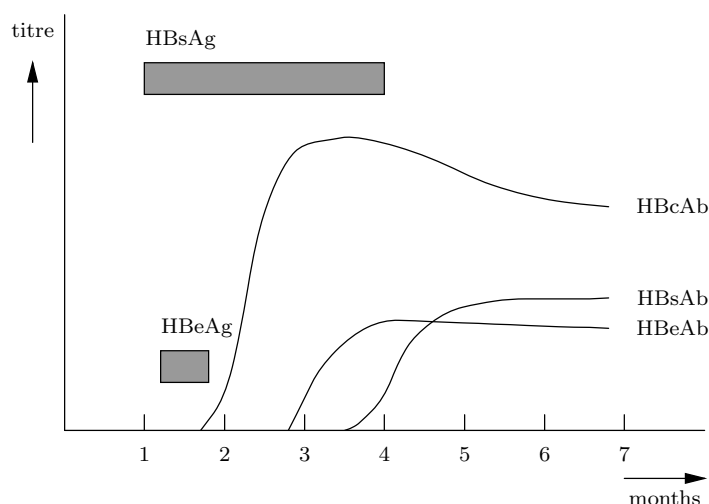
Hepatitis B is a viral infection of the liver, caused by a small DNA virus, called HBV (Hepatitis B Virus). Several components of the virus act as antigens. The complete virus is broken down to a core and an envelope. Core antigens are known as HBcAg and HBeAg; the envelope antigen is called HbsAg. The presence of these antigens in blood gives rise to the production of antibodies directed against these antigens. The antibodies are known as HBcAb, HBeAb and HBsAb, respectively. They are also referred to as anti-HBc, anti-HBe and anti-HBs, respectively. The HBV antigens and antibodies in blood are clinically of significant importance in diagnosing and monitoring the course of hepatitis B infection. The titres of the HBV antigens and antibodies vary during the course of the disease. Figure 6.2 depicts the titres of the HBV antigens and antibodies as a function of time.

In acute hepatitis B, there is an initial response consisting of HBcAb, even preceding the symptoms of the disease, together with the presence of HBsAg. In time following the detection of HBcAb in serum, HBeAb can be found. HBeAg is only detectable during the early phase of acute hepatitis B. HBsAb titres slowly increase after the disappearance of HBsAg from serum.

In chronic hepatitis B, the substances HBsAg, HBcAb and HBeAb can be detected in the patient's serum. (This cannot be read off from Figure 6.2, which assumes the virus to be nonpersistent.)

### Hepatitis C

In more than 90 per cent of the patients, viral hepatitis following blood transfusion is caused by HCV (Hepatitis C Virus), which is a small RNA virus [Alter et al., 1989;



**Figure 6.2:** Course of hepatitis B infection [Wright et al., 1985b].

Robbins et al., 1994]. It has been shown that hepatitis C also may be transmitted by organ transplantation [Pereira et al., 1991]. Hepatitis C was previously known as hepatitis non-A non-B. Symptoms and signs of hepatitis C are similar to those of hepatitis B, but jaundice is encountered less frequently in patients with hepatitis C than with hepatitis B. In general, symptoms and signs are milder than those found in hepatitis A or B. Antibodies to HCV can be demonstrated in about 85 per cent of patients having hepatitis C [Alter et al., 1989].

## Hepatitis D

Hepatitis D is an infection of the liver that can only occur when there is concomitant hepatitis B infection. It is caused by an RNA virus also called 'delta agent' or HDV. IgM anti-HDV antibodies are detectable in blood [Robbins et al., 1994]. This disease has not been included in the HEPAR system because of its strong relationship with hepatitis B.

## Infectious mononucleosis

Infectious mononucleosis is an infection caused by the Epstein-Barr virus (EBV). Although infectious mononucleosis is not primarily a liver disease, in the majority of patients with infectious mononucleosis, biochemical evidence of disturbed liver function can be demonstrated. Tests for infectious mononucleosis are therefore used to differentiate infectious mononucleosis from hepatitis A, B and C. By means of the Paul-Bunnell test, serological evidence for the presence of the disease can be collected.

## Cytomegalic inclusion disease

Cytomegalic inclusion disease is an infection due to the cytomegalovirus; inclusion of this virus in the hepatocyte and vascular endothelial cells can be demonstrated in about 20 per cent of cases. Elevated IgM antibodies against the virus can usually be demonstrated in

serum of patients with this disease. As for infectious mononucleosis, this tests is primarily used to differentiate this infection from hepatitis A, B and C.

### 6.4.3 Serological tests in bacterial and parasitic liver disease

Serological tests to demonstrate that a particular organism is the cause of a disorder of the liver or biliary tract, are usually specific for that organism. We therefore review the most important tests in relationship with the specific disorders caused by the organisms tested for.

#### Syphilis

Syphilis is a bacterial infection caused by *Treponema pallidum*. The liver may be affected in all forms of this disease. In particular, the disease may present itself in a way very similar to acute hepatitis. There are many different serological tests available, with varying sensitivity, to demonstrate the presence of syphilis in a patient. Tests that demonstrate the presence of antibodies to *Treponema pallidum*, such as the Fluorescent *Treponema* Antibody Absorption (FTA-Abs) test, have high sensitivity and specificity.

#### Toxoplasmosis

Toxoplasmosis is a parasitic infection caused by the protozoa *Toxoplasma gondii*. The organism may affect all tissues in the body. The clinical presentation of toxoplasmosis may be very similar to that of viral hepatitis. A frequently applied serological test in the diagnosis of toxoplasmosis is the Sabin–Feldman test, a specific test to demonstrate the presence of antibodies directed against *Toxoplasma gondii* in the serum.

#### Amoebic liver disease

Amoebic liver disease is usually caused by *Entamoeba histolytica*, a protozoa that may give rise to intestinal ulcers (intestinal amboebiasis). *Entamoeba histolytica* may reach the liver through the portal vein, giving rise to the formation of liver abscesses of varying size. There are a number of serological tests available to demonstrate the presence of antibodies directed against *Entamoeba histolytica* in the serum.

#### Echinococcosis of the liver

Echinococcosis of the liver is caused by the flatworms *Echinococcus granulosus*, *Echinococcus multilocularis* or *Echinococcus oligarthrus*. In about 70 per cent of patients, these worms will give rise to the formation of cysts in the liver, known as hydatid cysts. Specific serological tests to demonstrate the presence of echinococcus antibodies in the patient are the immunoelectrophoresis test and indirect haemagglutination test.

## 6.5 Ultrasonographical and radiological investigation

In recent years, ultrasonography has become one of the major diagnostic techniques in the diagnosis of disorders of the liver and biliary tract. The conventional plain radiograph of the abdomen is therefore only of limited use.

### 6.5.1 Ultrasonography of the liver and biliary tract

Ultrasonography has the advantage that it is non-invasive in nature, and that it is easy to perform. A disadvantage is that its accuracy varies widely between various clinical centres. The lack of a standardized terminology hinders the communication between physicians on the results.

In general, ultrasonography of the liver and biliary tract is employed to investigate:

- The presence and cause of hepatomegaly (enlargement of the liver);
- The presence of hepatic metastases after diagnosis of primary malignancy at some other site;
- The cause of jaundice.

The main use of ultrasonography in hepatology is to differentiate hepatocellular causes of jaundice and disturbed liver function from biliary obstructive causes. As shown in Figure 6.1, ultrasonography of the liver and biliary tract is a diagnostic technique applied early in the diagnostic process.

Normally, the biliary tract cannot be visualized by ultrasonography due to its small diameter. In case of biliary obstruction, dilatation of the bile ducts can be demonstrated in almost all patients. Furthermore, it is often possible to localize the level of obstruction. In case of obstruction at the level of the left and right hepatic ducts or higher, only the intrahepatic bile ducts are dilated, whereas in case of biliary obstruction at the level of the common bile duct, e.g. due to pancreatic carcinoma or carcinoma of the papilla of Vater, both intrahepatic and extrahepatic bile ducts are dilated. Demonstration of the level of biliary obstruction can be hindered by the presence of gas in the duodenum or stomach, making it impossible to visualize the dilated common bile duct.

Some pathological conditions of the gallbladder, e.g. gallstones, or of the pancreas, e.g. pancreatic pseudocyst or carcinoma, can also be detected by ultrasonography.

Ultrasonography, being an important technique in the early assessment of hepatobiliary disease, has been incorporated as one of the tests in the HEPAR system (cf. Chapter 7). As stated above, one of the problems with ultrasonography of the liver and biliary tract is the lack of a standardized terminology to describe the findings observed. For the two validation studies of the performance of HEPAR, a systematic terminology was designed. The basic requirement for this terminology was that ultrasonography reports from Dijkzigt University Hospital and from Leiden University Hospital could be translated automatically to this standard terminology.

In the following sections, we briefly review the terminology used to describe the contents of ultrasonography reports in the HEPAR project.

### **Ultrasonography of the liver**

Findings of ultrasonographical assessment of the liver have been described using the following concepts:

- (1) Size of the liver (normal, enlarged, too small);
- (2) Density of the liver parenchyma (normal, hyperdense, hypodense);
- (3) Specific findings of liver parenchyma (normal, acoustic shadows, haemangioma, hypodense areas, hyperdense areas, multiple cysts, solitary cyst, solid mass(es));
- (4) The liver contour (smooth, nodular).

### **Ultrasonography of the biliary tract**

Assessment of the bile ducts:

- (1) Findings concerning the intrahepatic bile ducts (normal, dilated, hyperreflective);
- (2) Findings concerning the extrahepatic bile ducts (normal, dilated, stone, obstruction at the papilla of Vater, obstruction in the pancreas, common bile duct obstruction, stricture, tumour).

### **Other ultrasonographical findings**

A number of possible findings of ultrasonographical investigation have been classified under the heterogeneous heading of 'other findings':

- (1) Presence of ascites in the patient;
- (2) Description of the gallbladder (normal, acoustic shadows, dilated, polyp, shrivelled, signs of cholecystitis, sludge/debris, stone, thickening of wall, tumour);
- (3) Description of the hilar region (normal, shows cyst, solid mass);
- (4) Description of the hepatic veins (normal, thrombosis, without flow, not visible);
- (5) Description of the pancreas (normal, calcifications, cystic process(es), diffusely enlarged, dilated pancreatic duct, signs of pancreatitis, solid mass, visualized);
- (6) Description of the portal vein (normal, dilated, occluded, reversed flow);
- (7) Description of the vena cava inferior (not visible by ultrasound – which is normal –, thrombosis);
- (8) Description of the spleen (normal, enlarged, splenic vein occluded).

## 6.5.2 Radiological investigations

A plain radiograph of the abdomen may provide valuable information about the presence of calcified gallbladder stones, or demonstrate a sentinel loop sign which is typical for pancreatitis.

## 6.6 Other diagnostic techniques

Other frequently employed diagnostic techniques in hepatology are percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangio-pancreaticography (ERCP) and liver biopsy. These procedures are all invasive in nature, and are only used in the diagnostic process if no conclusion has been reached concerning the hepatocellular or obstructive nature of the disorder, or to confirm a particular diagnosis (See Figure 6.1). PTC and ERCP provide information about alterations in the biliary tract. For example, in carcinoma of the head of the pancreas, obstruction of the common bile duct and the main pancreatic duct can often be demonstrated. In primary sclerosing cholangitis, the typical findings of ERCP are multiple strictures (narrowings) with ‘beading’ of ducts between the narrow segments, and involvement of both the intrahepatic and extrahepatic duct systems.

PTC and ERCP are not usually carried out early in the diagnostic process; for this reason and because of the invasive nature of these diagnostic techniques, results of PTC and ERCP have not been incorporated in the HEPAR system.

## 6.7 Disorders of the liver and biliary tract

In this section, we briefly review the clinical features of a few disorders of the liver and biliary tract. This gives the reader an impression of the information with which the clinician starts when faced with the problem of establishing which disorder is responsible for the symptoms and signs observed in the patient. Eight of the about eighty disorders covered in HEPAR are briefly reviewed. We shall refrain from providing pathological and pathophysiological detail in describing these disorders, because such information is not essential in the very early stages of diagnosis. For a more detailed account on the subject, the reader may consult the standard textbooks, for example [Wright et al., 1985a]. The disorders are subdivided into four different categories, the meaningful combinations obtained from the diagnostic categories introduced in Section 6.2.1.

### 6.7.1 Acute hepatocellular disorders

An acute hepatocellular disorder generally develops within two weeks; they are associated with hepatocellular derangements.

#### Hepatitis B

Early symptoms in patients with hepatitis B are anorexia, nausea, malaise, weight loss, fever, dark urine and pale stools. Sometimes the patient has also generalized pruritus

(itch). After some time, the severity of these symptoms decreases, and jaundice develops in addition to abdominal (hepatic) pain. Jaundice and hepatomegaly may be the only findings detected by physical examination. All these symptoms and signs may also be found in other forms of viral hepatitis, malaria, amoebic liver disease and several other disorders.

There are several ways in which hepatitis B can spread through the population. Information from the disease history may sometimes indicate that the patient has been infected through one of these familiar routes. Several years ago, hepatitis B could be the result of transfusion with blood products, which is rare nowadays, due to improved quality control at the blood banks. Nowadays, hepatitis B is more commonly spread by close personal contact, contaminated syringes (such as used by heroin addicts). Personal contact as a cause is less common for hepatitis B than for hepatitis A.

### **Alcoholic hepatitis**

Alcoholic hepatitis is an acute liver disease in patients with alcohol abuse, in which the typical symptoms are anorexia, nausea, vomiting, abdominal pain. Physical examination may bring to light hepatomegaly and a painful liver on palpation. The biochemical findings are those of hepatocellular damage, with elevated total (conjugated and unconjugated) bilirubin in blood and a  $\gamma$ -GT/ALAT ratio lower than 5. By means of ultrasonography of the liver an enlarged liver that is hyperdense may be demonstrated, but in contrast to alcoholic cirrhosis the liver is not nodular.

## **6.7.2 Chronic hepatocellular disorders**

Chronic hepatocellular disorders develop over a period of several months. In the initial phase, symptoms and signs are primarily due to hepatocellular damage.

### **Autoimmune chronic hepatitis**

Autoimmune chronic hepatitis is a chronic liver disease of unknown origin, characterized by hepatocellular failure. Typically, the disease occurs in young women. On physical examination, the patient may have mild jaundice, spider angiomas (small blood vessel tumours), palmar erythema and butterfly erythema resembling the skin rash encountered in lupus erythematosus, an autoimmune disease affecting multiple organs. In young women, amenorrhoea and acne may be present; in the male patient one may observe cutaneous striae and gynaecomastia. Serum aminotransferase levels are almost invariably elevated. Immunological disturbances that may be demonstrated in the serum are smooth muscle antibodies, antinuclear antibodies and in about 15 per cent of the patients LE cells may be found (LE-cell phenomenon). The presence of these and other antibodies is also reflected by the hypergammaglobulinaemia (increased levels of  $\gamma$ -globulin in the serum) that is almost universally encountered in these patients.

### Wilson's disease

Wilson's disease (hepatolenticular degeneration) is caused by a genetic defect of copper metabolism, with a recessive inheritance pattern. Only homozygous patients develop the full clinical picture, although heterozygous patients may show some signs of the disease. The disease is slowly progressive; it usually takes until the patient is seven years old before symptoms and signs of hepatic disease become apparent. Somewhat later, neurological signs become manifest. These symptoms and signs are caused by the toxic effects of increased levels of copper on hepatic and neural tissue. Hepatic symptoms of the disease include fatigue, abdominal pain, spider angiomas, jaundice, oedema, ascites, oesophageal varices and splenomegaly. Deposits of copper in Descemet's membrane in the cornea cause brown rings at the peripheral cornea, known as Kayser–Fleischer rings.

Biochemical evidence for the disease can be collected by measuring the caeruloplasmin concentration, a copper-binding protein, in serum which is in 95 per cent of the patients below 200 mg/l. In addition, there is excess free (i.e. not bound to caeruloplasmin) copper in serum, and excretion of copper in urine is increased.

### 6.7.3 Benign biliary obstructive disorders

The principle feature of benign biliary obstructive disorders is obstruction to bile outflow, either at the level of the large, extrahepatic bile ducts or at the level of the small intrahepatic bile ducts.

#### Common bile duct stones

Symptoms and signs of common bile duct stones are caused by the mechanical obstruction of the common bile duct to the outflow of bile produced by the liver. It is believed that most of these stones originate in the gallbladder, although some stones have their origin in the bile ducts. Symptoms due to common bile duct stones include abdominal pain, often colicky (i.e. paroxysmal, spasmodic and severe) in nature probably due to the obstruction, jaundice, which is often associated with pruritus, dark urine and pale stools. If partial obstruction of the common bile duct is present, jaundice need not always develop. If obstruction is complete, urobilinogen cannot be detected in urine (cf. Section 6.2.4).

Accumulated bile is a good substrate for bacterial growth, causing infection of the common bile duct (acute cholangitis). The principal symptom of such an infection is fever associated with chills. Results of physical examination are tenderness at the right upper quadrant of the abdomen and signs of jaundice. Biochemical tests show an increase in alkaline phosphatase; if the concentrations of ASAT and ALAT are also elevated, hepatocellular damage due to raised biliary pressure should be suspected. Although jaundice is not always marked, total bilirubin concentration is usually increased.

#### Primary biliary cirrhosis

Primary biliary cirrhosis is a chronic liver disease in which the small intrahepatic bile ducts are affected. Its aetiology is unknown. Typically, the patient is a middle-aged woman; only about 10 per cent of the patients are male. An important early symptom



in this disease is generalized pruritus. In some patients, xanthomas may be present, as well as Kayser–Fleischer rings. Alkaline phosphatase is usually increased as are the levels of  $\gamma$ -GT and 5'-nucleotidase, indicating biliary obstruction. Immunological investigation shows mitochondrial antibodies in the serum in about 90 per cent of the patients. The cholesterol concentration is often elevated.

#### 6.7.4 Malignant biliary obstructive disorders

In malignant biliary obstructive disorders, obstruction of the small or large bile ducts is caused by the tumour mass of the malignancy. Obstruction of the small intrahepatic bile ducts is caused by compression of the surrounding normal hepatic tissue by tumour mass. When the tumour involves the biliary ducts, as it does in common bile duct carcinoma, or when the biliary ducts run through tumour tissue, as in pancreatic carcinoma, obstruction is more direct.

##### Pancreatic carcinoma

Carcinoma of the pancreas is usually localized in the pancreas' head. The average age of patients is about sixty years; the disease affects about twice as many males as females.

The patient experiences significant weight loss (often more than  $\frac{1}{2}$  kg per week), significant jaundice, pruritus, nausea and anorexia. Routine laboratory tests indicate biliary obstruction.

Ultrasonography may reveal a pancreatic solid tumour, and will almost always demonstrate dilatation of the intrahepatic and extrahepatic bile ducts.

##### Primary hepatocellular tumour

Primary hepatocellular tumour is a carcinoma that frequently develops in the patient with chronic liver disease, e.g. cirrhosis, haemochromatosis and chronic hepatitis B. In addition to the symptoms and signs caused by these chronic disorders, the patient may experience abdominal pain, jaundice, malaise, anorexia, weight loss, nausea and fever. Characteristic findings of physical examination are enlarged, tender liver and sometimes a palpable hepatic mass, ascites and sometimes distended abdominal veins. In about 25 per cent of the patient a bruit over the liver may be heard on auscultation. The routine biochemical tests show elevated concentrations of total bilirubin, as well as elevated levels of alkaline phosphatase, ASAT en ALAT. A useful and frequently applied test that is specific for primary hepatocellular tumour is the demonstration of  $\alpha$ -foetoprotein (cf. Section 6.3.4).

## 6.8 Discussion

It will be clear from the overview above that diagnosis in the field of hepatology is a complicated matter. The question now arises which of the diagnostic theories treated in the first part of this thesis is most suitable for diagnosing disorders of the liver and biliary tract.

When using a model of the normal structure and behaviour of the liver and biliary tract it is possible, at least in principle, to discover new, previously unknown disorders in patients. Unfortunately, this approach is not feasible in practice, because the information that would be required to drive such models is only available under laboratory conditions, and not in the clinic. This is certainly true during the early assessment of patients, when only information from history, physical examination and routine laboratory tests is available. But the most important limitation of this approach is that known disorders cannot be characterized sufficiently precisely in terms of normal structure and function of the liver and biliary tract. It was our aim to develop a diagnostic system, sufficiently accurate for real-life application. Therefore, knowledge about abnormal structure and function would be indispensable.

Malfunction of the liver and biliary tract is traditionally described in the medical literature in terms of disorders, which in turn are described as specific clinical patterns. Above, several disorders have been described in this fashion. Some of this knowledge is causal in nature; another part is empirical in nature. Thus, from a practical point of view, causal as well as empirical knowledge about disorders, as available from the literature and specialists in the field of hepatology, offer the best foundation for a diagnostic knowledge base in hepatology. In the terminology of our diagnostic framework, the evidence function  $e$  that is used to represent knowledge concerning disorders of the liver and biliary tract may be interpreted as denoting causal relations and empirical associations.

A complementary issue concerns the notion of diagnosis that best fits diagnostic problem solving in hepatology. Although co-occurring disorders in a patient are likely to interact with each other, it is unlikely that a patient suffers from more than one disorder of the same organ system at the same time. In particular, is it unlikely that a patient has more than one disorder of the liver and biliary tract at the same time, unless disorders are causally related to each other. Furthermore, in establishing a diagnosis, a physician tries to account for as many of the observed findings as possible. In a field like hepatology, it is often not possible to establish a diagnosis that accounts for all observed findings. Collecting disorders, each accounting for part of the observed findings, disregarding as few of the relevant disorders as possible, seems an acceptable approximation. Hence, the notion of diagnosis that underlies diagnosis in hepatology is similar to the notion of refinement diagnosis as discussed in Chapter 5; it is unlike notions of diagnosis such as strong causality diagnosis.