

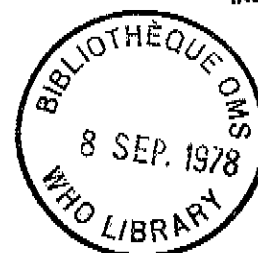


*Meeting of Investigators on Chronic Liver Disease,*

INDEXED

CHRONIC LIVER DISEASE: GLOBAL ASPECTS,  
EPIDEMIOLOGY AND INTERVENTION

Report of a WHO Meeting  
Geneva, 21-25 November 1977



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## INTRODUCTION

A Meeting of Investigators on Chronic Liver Disease was held at WHO Headquarters in Geneva from 21 to 25 November 1977. The meeting was opened by Dr CH'EN Wen-chieh, Assistant Director-General, who stressed that chronic liver disease, especially liver cirrhosis of various types and liver cancer, was known to be a significant and increasing cause of ill health and untimely death all over the world but that, for many reasons, reliable data on the epidemiology of chronic liver disease were lacking. The meeting had been convened to consider present knowledge, and the reasons for its limitations, to identify areas where new knowledge was most crucially needed, and to make recommendations on how to obtain it.

Selection of the most cost/effective precautions and/or therapeutic measures should be based on an epidemiological assessment of chronic liver disease as a health problem. Epidemiological data would provide guidance for investment in research and development, especially if collected in a way which permitted comparisons between different populations at one time or within one population at different times. The standardization of nomenclature, criteria and methodology remained a critical obstacle to obtaining comparable data and, therefore, attention was directed to the efforts of the International Association for the Study of the Liver to achieve such standardization.

A particular aim of the meeting was to draw attention to the global importance and magnitude of the health problems associated with chronic liver disease.

### 1. NOMENCLATURE AND DEFINITIONS IN CHRONIC LIVER DISEASE

The following chronic liver diseases are considered to be of global importance. Names and definitions of entities are given in accordance with the recommendations of the International Association for the Study of the Liver<sup>1</sup>. The clinical, functional, morphological and etiological criteria adopted are given in an appendix to this report.

#### 1.1 Hepatitis

##### 1.1.1 Chronic hepatitis

Definition: inflammation of the liver continuing without improvement for at least six months. In some instances the condition is relatively benign (chronic persistent hepatitis), whereas other patients have chronic active hepatitis which may progress to cirrhosis. These types of hepatitis may be associated with hepatitis B antigen (HBV) in the serum and are then considered to represent sequelae of acute B-virus hepatitis. In other instances, the putative A virus (or others)<sup>2</sup> may be responsible, especially when the disease follows an episode of acute epidemic hepatitis<sup>3</sup>. An autoimmune basis has neither been excluded nor confirmed in other cases; some consider the presence of non organ-specific immunoserological markers, such as smooth-muscle antibody, in appropriate titres to indicate a specific etiology. Identical clinical, functional and morphological features may be found in some instances of drug-induced hepatitis, alcoholic liver disease or in some other diseases such as Wilson's disease.

##### a) Chronic persistent hepatitis

Definition: a non-specific morphological liver lesion. The long-term sequelae have not been established. Rarely, patients may progress to chronic active hepatitis, whereas other

<sup>1</sup> Diseases of the Liver and Biliary Tract. Standardization of Nomenclature, Diagnostic Criteria and Diagnostic Methodology. Fogarty International Center Proceedings No. 22, 1976 (USA Department of Health & Welfare Publication (NIH) 76-725)

<sup>2</sup> Chronic liver disease rarely follows acute hepatitis type A

<sup>3</sup> Some workers consider autoimmune chronic active hepatitis (ANA and SMA-positive) as a separate etiological entity

examples of the condition may represent the inactive phase (occurring spontaneously or induced by treatment) or more active disease. Differentiation from chronic active hepatitis is difficult in some instances.

b) Chronic active hepatitis

Definition: a continuing inflammatory lesion of the liver which may progress to more severe disease, including cirrhosis, continue unchanged or subside (spontaneously or with treatment).

1.1.2 Toxic hepatitis

a) Due to chemicals and poisons

Definition: injury of hepatocytes with little or no inflammatory response caused by ingestion or inhalation of a hepatotoxic agent, usually accidentally or suicidally, and often as a result of domestic or industrial hazard. The toxic agent may be of mineral, synthetic or botanic origin.

b) Drug-induced hepatitis - toxic (predictable)

Definition: acute hepatic necrosis or steatosis or chronic hepatic injury with fibrosis due to direct toxic effect of a drug or toxic effect of metabolites of drugs. Toxicity is determined by the dose of the drug and status of hepatic drug metabolizing mechanisms.

c) Drug-induced hepatitis - idiosyncratic (not predictable)

Definition: an acute degeneration or necrosis of hepatocytes with or without inflammatory response or a chronic necroinflammatory lesion with fibrosis which is caused by an adverse reaction to a medicinal agent because of hypersensitivity to, or aberrant metabolism of the agent. A hypersensitivity reaction may be due to a drug acting as an antigen or to the formation of chemically-reactive metabolites covalently bound to tissue molecules.

1.1.3 Alcoholic hepatitis

Definition: an acute or chronic degenerative and inflammatory lesion of the liver in the alcoholic which is potentially progressive or reversible; it does not necessarily include steatosis, fibrosis or alcoholic cirrhosis, although it is frequently associated with these conditions.

1.2 Fibrosis and cirrhosis

1.2.1 Hepatoportal sclerosis

Definition: portal, and frequently septal fibrosis associated with portal hypertension, occurring predominantly in adults, mostly males, in tropical zones.

1.2.2 Chemical-induced fibrosis without necrosis

Definition: an irregular fibrosis varying in degree throughout the organ and encroaching upon portal vein tributaries associated with thickening of and beneath the surface capsule and focal perisinusoidal fibrosis.

1.2.3 Alcoholic cirrhosis

Definition: cirrhosis develops in about 10% of persons taking alcoholic beverages in excess; alcoholic hepatitis (1.1.3) is its precursor. Alcoholic hepatitis and cirrhosis frequently coexist.

1.2.4 Cirrhosis following viral hepatitis B

Definition: cirrhosis developing as a result of viral hepatitis B. Chronic active hepatitis or hepatitis with bridging or multilobular sclerosis are the usual precursors.

### 1.2.5 Cryptogenic cirrhosis

Definition: cirrhosis where the etiology is not established.

### 1.2.6 Primary biliary cirrhosis

Definition: a form of intrahepatic disturbance of bile secretion, affecting predominantly middle-aged women, with segmental destruction and, later, absence of septal bile ducts.

## 1.3 Focal lesion of liver

### 1.3.1 Tuberculosis of the liver

Definition: infection of the liver with tubercle bacilli with production of localized granulomata, miliary lesions or tuberculoma. Non-specific alterations attributable to the effects of prolonged infection, malnutrition, or concomitant disease are not included.

### 1.3.2 Schistosomiasis of the liver

Definition: involvement of the liver with species of human *Schistosoma*. Acute and chronic forms are recognized.

### 1.3.3 Hydatid cyst of the liver

Definition: involvement of the liver with the larval form of *Echinococcus granulosus* or *E. multilocularis* (*E. alveolaris* produces a fibrosing lesion).

### 1.3.4 Amoebic abscess of the liver

Definition: infection of the liver with *Entamoeba histolytica*, which results in abscess formation.

## 1.4 Vascular lesions of the liver

### 1.4.1 Veno-occlusive diseases

Definition: a disease characterized by acute and/or chronic occlusion of the centrilobular and sublobular hepatic veins. The larger hepatic veins are not affected. Thrombosis of the larger veins is not a feature.

## 1.5 Metabolic disorder

### 1.5.1 Iron-storage disease

#### a) Idiopathic haemochromatosis

Definition: a presumed inborn error of metabolism with increased concentration of iron in liver cells associated with cirrhosis. A history of iron or alcohol ingestion does not necessarily exclude this form of disease.

#### b) Haemochromatosis of the alcoholic

Definition: iron overload developing in the liver in association with chronic liver disease in the alcoholic related to increased absorption or ingestion of iron.

#### c) Bantu haemochromatosis

Definition: hepatic siderosis which develops in the Bantu and is related to high ingestion of alcoholic beverages and to the use of acid foods prepared in iron cooking utensils.

## 1.6 Tumours of the liver and intrahepatic bile ducts

### 1.6.1 Hepatocellular carcinoma

Definition: a malignant tumour composed of cells, somewhat resembling hepatocytes, often in the setting of cirrhosis. It may exhibit local vascular or lymphatic metastases.

### 1.6.2 Cholangiocarcinoma

Definition: an intrahepatic malignant tumour composed of cells resembling those of biliary epithelium.

## 1.7 Diseases of extrahepatic bile ducts.

### 1.7.1 Parasitic invasion of the bile ducts

#### a) Bile duct flukes

##### Fascioliasis

Definition: infestation of the bile ducts with the adult trematode Fasciola hepatica or gigantica (other species in domestic animals) often causing partial obstruction of the bile ducts with cholestasis and cholangitis, which may become chronic.

##### Chlonorchiasis or Opisthorchiasis

Definition: infestation of bile ducts with the adult trematode Chlonorchis or Opisthorcis sinusis (or, less commonly, other species) often causing obstruction of the bile ducts, with cholestasis and cholangitis that may become chronic and lead to intrahepatic bile duct carcinoma.

#### b) Ascariasis

Definition: obstruction of the common bile duct, often with acute cholangitis caused by the migration of adult Ascaris lumbricoides from the intestine through the sphincter of Oddi.

## 2. EPIDEMIOLOGY - GLOBAL ASPECTS OF PREVALENCE, INCIDENCE AND MORTALITY

The actual incidence and mortality from chronic liver disease is not known with any degree of precision in many countries and continents. It is evident that there are gross underestimates of the magnitude of liver disease due to lack of proper and uniform reporting of either morbidity or mortality statistics.

### 2.1 Africa

The incidence of cirrhosis is approximately 23 per 100,000 population in Uganda.

Hepatocellular carcinoma varies from 5.8 per 100,000 in Nigeria to 98.2 per 100,000 in Mozambique. 90% of patients with hepatocellular carcinoma have cirrhosis.

Schistosoma mansoni is still an important cause of chronic liver disease along Lake Victoria and the Nile basin. Amoebic hepatitis and hepatic abscess are also problems.

### 2.2 Asia

Chronic hepatitis, cirrhosis and hepatocellular carcinoma are common in various countries. The incidence of chronic hepatitis is 30 per 100,000, and of cirrhosis 11.5 per 100,000 in Japan. The mortality from cirrhosis is 13.6/100,000 (19.9 male and 7.5 female), and from hepatocellular cancer 12.4/100,000. The incidence of hepatocellular cancer is 49% in cirrhosis following viral B hepatitis and 12% in cirrhosis following alcohol intake.

Schistosomiasis japonicum is found in southern China, the Philippines and several regions of Japan. The actual incidence of and mortality from schistosomiasis in these regions is not known. Approximately 35% of all cases of chronic active hepatitis in Japan have HBsAg.

There is evidence to indicate that in South-East Asia chronic active hepatitis, cirrhosis and primary carcinoma of the liver are problems of public health importance but there are interesting geographical differences between the countries of the Region and even within the same country. In Burma, 9% of blood donors are HBsAg positive, 9% of all autopsies are accounted for by primary carcinoma of the liver and 90% of these patients have associated cirrhosis. In Thailand, the HBsAg carrier rate in the population varies from 6 to 10%, 2.3% of all autopsies are due to primary liver cancer; 7% are cholangiolar. In 70% of primary liver cancers, there is an associated cirrhosis. In Sri Lanka, less than 1% of the population are HBsAg carriers, 50% of all cirrhosis are due to chronic alcoholism. In India, 66% of chronic active hepatitis, 40% of cirrhosis and 55% of cases with primary liver cancer are positive for HBsAg in the blood. In 100% of all cases of primary liver cancer, HBsAg can be demonstrated in the liver cells surrounding the carrier. In India, in addition to chronic active hepatitis, cirrhosis and primary liver cancer, two other forms of chronic liver disease exist, viz non-cirrhotic portal hypertension (hepatoportal sclerosis) and Indian childhood cirrhosis.

### 2.3 Australia

The frequency of chronic HBsAg carriers and chronic HBsAg positive hepatitis is relatively low as compared with other areas of the world. Mortality from cirrhosis is 1.1% in males and 0.6% in females. Among all cases of cirrhosis, alcohol accounts for 55%, chronic hepatitis for 20%, haemochromatosis in 5-10%, biliary tract disease 5-10%, and the remainder represent cryptogenic cirrhosis. Hepatocellular carcinoma is very rarely seen in Australia.

### 2.4 Europe

Biochemical screening has been conducted to determine the frequency of liver disease. Although such biochemical screening in one instance (German Democratic Republic (GDR)) revealed as high an incidence as 24.6%, only 1.4% of 2,908 inhabitants of a rural village had morphological manifestations of liver disease. Studies of carriers of HBsAg revealed 39% with chronic hepatitis.

The incidence of chronic hepatitis and cirrhosis is increasing. 3.4% per 1,000 hospitalized patients in GDR have cirrhosis. The peak of chronic hepatitis is between ages 24 and 25 and the peak of cirrhosis is in those over 50 years. The mortality rate from cirrhosis in Europe over the past 15 years has increased and at present it is reported as up to 10 per 100,000 in Bulgaria, Finland, Netherlands, Norway, Poland and UK. It is between 10 and 20 per 100,000 in Czechoslovakia, Denmark, Greece, Hungary and Switzerland and it is above 20 per 100,000 in Austria, France, Italy, Luxembourg, Portugal and Spain.

### 2.5 Latin America

Cirrhosis is observed in 7.2 to 13.4% of autopsies. In males, an alcoholic antecedent is found in 75 to 88%, in females the alcoholic antecedent is unusual. In females there is the antecedent (clinical) of chronic active hepatitis in 25% of cases.

Hepatocellular carcinoma is found in 2.6 to 16% of all autopsies. There is associated cirrhosis in 62 to 90% of hepatocellular carcinomas.

Schistosoma mansoni is present in many Latin American countries. Granulomata with ova and/or mild hepatic fibrosis are found in up to 40% of autopsies. Severe hepatic fibrosis is present in 0.2 to 1% of population exposed for long periods of time. The incidence of the disease has decreased in areas where treatment of infected patients is combined with intensive control of the vector and adequate faeces disposal.

### 2.6 USA and Canada

In the united States of America and Canada chronic hepatitis and cirrhosis are common chronic liver conditions. An increasing number of patients are developing cancer and patients who immigrate from areas where schistosomiasis and amoebic diseases are endemic are seen with these diseases. Approximately 1% of the total population have had viral hepatitis B; there is an increase in this disease in slum or urban areas. There is a very high incidence (85%) in

patients who are drug addicts or prostitutes. Histological studies of biopsies of patients in the latter group reveals that approximately one-third have normal liver, one-third hepatitis, and one-third fibrosis. The most common liver disease in both the USA and Canada is that related to alcoholism. There are approximately 8,000,000 alcoholics in the USA of whom one-third have hepatitis, one-third fibrosis or cirrhosis and a further third have no histological abnormalities.

In the USA mortality from cirrhosis and its complications has increased more than from any other disease during the past ten years. The overall mortality from cirrhosis is 14.8 per 100,000 and from primary liver cancer five per 100,000. In urban slum areas the mortality from cirrhosis is 25.3 per 100,000 and from primary liver cancer seven per 100,000. The most common cause of the underlying disease is alcoholism. In young people the mortality is 14 per 100,000 in the most populous states in the USA. The principal problems are metabolic disorders and hepatitis.

## 2.7 Summary

There is marked variation in the reported statistics; this is due to the fact that there are very few satisfactory mechanisms for the collection of information on the prevalence of liver disease. Available data are based on clinical findings which are unreliable, biochemical tests which lack specificity and autopsy studies which are satisfactory but infrequently performed. Nevertheless it is evident that there is a significant increase in the reported incidence of and mortality from chronic liver disease.

## 3. CURRENT CLINICAL PROBLEMS

The relationship of many of the following etiological factors to each disease state may be modified by nutritional factors, by coincidental infection with micro-organisms which modify the function of the immune system, and by the ingestion of drugs which alter the host's metabolic processes. Thus, in many cases, the pathogenetic process may be multifactorial. The major etiological factors are however considered separately.

### 3.1 Chronic liver disease following viral hepatitis

There is now compelling evidence for the existence of additional hepatitis viruses apart from the type A and B viruses, which have been termed "non-A, non-B" or type C. The best data derive from the study of post-transfusion hepatitis: in some countries, after the exclusion by serological means of cases attributable to known viruses, 80-90% of cases remain unidentified and have been designated "non-A, non-B". The relative importance of the different viruses in each community remains to be fully elucidated.

#### 3.1.1 Antigenic structure of hepatitis B virus

Since the discovery of Australia antigen, the structural analysis of HBV has made remarkable progress. HBV, a 42 nm double-shelled virus, originally known as the Dane particle, is known to have three major components.

a) HBsAg: Hepatitis B surface antigen (Australia antigen) is found on the surface of the virus and on the 20-22 nm spherical and tubular forms. It is non-infective. HBsAg carries common determinants a and Re and four antigenically distinct subdeterminants, d, y, w and r exist. Four subtypes, adw, adr, ayw and ayr have been observed.

b) HBcAg: Hepatitis B core antigen is found within the core of the virus and is considered to be virion nucleocapsid. HBV-specific DNA polymerase activity and circular double-stranded DNA are associated with the nucleocapsid.

c) HBeAg: Although the topological relationship of HBeAg to HBV is not clear, the presence of HBe antigen in serum is closely associated with the presence of Dane particle, HBcAg- and HB-specific DNA polymerase activity in the sera. The presence of HBeAg is now considered to be a marker of infectivity of HBsAg containing material.

Techniques to measure these antigens and corresponding antibodies have been developed and have made possible both the clinical and epidemiological study of HBV infection.

### 3.1.2 Acute and chronic HBV infection

Two types of HBV infection can be identified by serial analysis of the HBs, HBc and HBe antigen/antibody systems.

a) Acute infection: After primary exposure to HBV in an immunologically mature host, transient HBs and possibly HBe antigenaemia is followed by the clinical manifestations of hepatitis with rather a long incubation period. Then, anti-HBc (possibly anti-HBe) and anti-HBs responses occur, resulting in resolution of the hepatitis. The titre of anti-HBc usually does not exceed  $2^{10}$  by the immune adherence haemagglutination method.

b) Chronic infection may arise following perinatal infection or infection in later life. Under these circumstances there may be persistent HBs antigenaemia and anti-HBc titres are usually greater than  $2^{10}$  by IAHA. These subjects may have normal liver histology, chronic persistent or active hepatitis or cirrhosis.

### 3.1.3 Chronic HBsAg carriers

There is substantial evidence that type B (and possibly type C) viruses can induce chronic liver disease whereas type A does not. The evidence is of two types. The first is the serial study of patients with acute hepatitis in adult life or of perinatal infection who have progressed to chronic persistent or to chronic active hepatitis, with or without cirrhosis. The second line of evidence stems from studies of the prevalence of HBsAg positivity in patients with established chronic liver disease. Examination of data in the literature reveals that in certain areas 30-40% of cases of chronic persistent and chronic active hepatitis and 40% of cases of post-necrotic cirrhosis are carriers of the HBsAg. These prevalence rates are significantly greater than the carrier rate for HBsAg in the general population and in diseases of known or presumed non-B etiology. The highest prevalence of HBsAg positivity in chronic liver disease occurs in subjects from countries with a high carrier rate in the general population. This led to the suggestion that the association of the HBsAg with chronic liver disease was merely a reflection of the depressed immune status of these subjects and not necessarily indicative of a causal relationship between the virus and the disease state. This thesis may account for the existence of some HBsAg carriers amongst subjects with established non-virus-related liver disease but the relatively lower incidence of HBsAg positivity amongst patients with immunosuppression associated with non-hepatic conditions suggests that coincidental persistent infection with this virus because of immunodepression accounts for very few cases of HBsAg-positive chronic liver disease.

The reason for the failure to eliminate the type B (and possibly the type C) virus is uncertain. At the moment most emphasis has been laid on host factors, particularly the immune response to the virus. The host's defence system must eliminate the virus from intracellular sites as well as neutralize extracellular spread. These defence systems are complex and it seems possible that different factors may operate in each case. The importance of host factors has been deduced from the demonstration of an association of the carrier state with certain HLA phenotypes. The effect of nutrition and concurrent infections on the immune response to the hepatitis viruses may also influence the ultimate outcome of the infection. The part that this plays in developing countries remains to be determined.

The source and method of infection is of considerable importance. In most countries the reservoir of infection lies in the chronic carriers and in some areas primate carriers may also exist. The parenteral route of infection, either during medical therapeutic measures or close personal contact, is well established. Whether true non-parenteral transmission exists or merely represents the less obvious forms of parenteral exposure remains to be determined. Certainly many body fluids (semen, vaginal fluid, urine, saliva) contain HBsAg, but whether they are infective, and whether the virus can break epidermal and mucosal surfaces is unknown. Direct spread is of major importance and in tropical areas vector transmission may also constitute a problem. The HBsAg has been demonstrated in mosquitos and bugs but the infectivity

remains to be established. Finally, perinatal transmission has been shown to be of major importance in Japan, China and Indonesia. The mother who has acute B hepatitis in the last trimester of pregnancy or who is an HBeAg positive carrier, will almost certainly infect her child in the perinatal period, and these infants become chronic carriers. This mode of transmission will maintain the human reservoir of infection. In some cases the virus may continue to express itself, the patient will be HBsAg- and HBeAg-positive, but in others the viral DNA may be integrated into the host-cell genome and not express viral antigens. These patients may run the risk of developing both chronic liver disease and hepatocellular carcinoma, and further studies are required to define these probabilities.

In general, HBeAg becomes negative soon after primary exposure to HBV. However in the orient, where the prevalence of HBsAg positivity is more common, HBeAg persists longer. The percentage of HBeAg-positive carriers is therefore higher. For example, among 15,078 HBsAg-positive blood donors in Japan, HBeAg was detected in 22%, whereas the rate is extremely low in western Europe. Persistence of HBV infectivity (HBeAg positivity) in asymptomatic carriers up to the reproductive age may increase the risk of perinatal transmission and cause the higher prevalence of HBV carriers in some areas.

Treatment should be directed at the stage before integration of viral DNA into the host cell. Possibly, therapeutic targets should be neonatally infected infants and cases of acute hepatitis which are in the early stages of evolution into chronic active hepatitis. The use of any form of therapy in carriers of the virus who have normal liver function or minimal inflammatory activity needs further study. The aim in these subjects must be the reduction of infectivity or even elimination of the virus.

There are two possible approaches to therapy; one is with anti-viral drugs and the other is manipulation of the host's immune response.

In the former category, interferons may in some cases be effective in reducing the rate of viral replication and this should reduce infectivity but the effect of this on the progression of the liver lesion is poorly documented. Further studies of the value of this therapy are required, but the restricted availability of interferon and expense may limit its potential usefulness. The evaluation of inducers of endogenous interferon production has been limited to animal studies because of the toxicity of these agents. At the moment the available anti-viral agents are potentially toxic and the risks of therapy cannot be balanced against the risks of the disease until further knowledge of the natural history of these diseases is available. In particular, knowledge is required about the probability of progression to cirrhosis and to carcinoma.

The alternative approach lies in the manipulation of the immune system (immunopotential) to allow the host to eliminate the virus. At present this is only of hypothetical interest, and its clinical use remains to be evaluated. The use of suppressive regimes to reduce inflammatory activity in chronic active liver disease (HBsAg-positive) remains to be established and will not aid the patient to eliminate the virus: the danger of developing liver-cell cancer and of infecting others still remains and further studies are required to determine the size of these risk factors.

#### 3.1.4 Prevention

Our understanding of the method of spread of this virus suggests that prophylactic intervention may be possible in the following situations:

- a) "perinatal" transmission
- b) "post-transfusion" transmission (including accidental "needle-prick" exposure)
- c) "co-habitation" transmission.

In the context of developing countries with high carrier rates, a major advance might be anticipated by screening blood products for HBsAg by the most feasible sensitive technique (see WHO Technical Report Series No. 602, p.28). Screening of antenatal and surgical patients

for HBsAg may be desirable in alerting attendant medical personnel to potentially-infective cases but, until effective methods of reducing the infectivity of the mother or of immunizing the child are established, this is not recommended as a routine procedure. The effectiveness of both passive and active immunization in protecting exposed medical and non-medical personnel is under active evaluation (WHO Technical Report Series 602).

The problem of the supply of reagents and the standardization of techniques to screen for HBs antigenaemia is the concern of the WHO collaborating centres for viral hepatitis (see recommendations).

### 3.2 Chronic liver disease and autoimmunity

Chronic active hepatitis (CAH) is probably heterogeneous with possible subtypes related to autoimmunity, the hepatitis B virus and adverse drug reactions, with other cases remaining "cryptogenic". Primary biliary cirrhosis (PBC) is clinically distinct but also has autoimmune features.

In global terms, autoimmune liver diseases (CAH and PBC) are not numerically important, being infrequent in Northern Caucasian populations. However, if, as is now suspected, autoimmune reactions potentiate damage associated with other causal agents e.g. hepatitis B virus, alcohol or hepatotoxins, then the understanding of autoimmune reactions in the liver assumes greater importance. The reasons for implicating autoimmunity as one of the several possible causes of CAH and the ensuing cirrhosis, and of PBC, are as follows:

- (1) the continuing hepatocellular destruction and profound lymphoid response (excess gammaglobulin in blood, excess immunocytes in liver) with no obvious extrinsic cause;
- (2) the readily-demonstrable autoimmune serological markers in blood, with high specificity for CAH or PBC, indicative of failure of normal self-tolerance: there is no consensus as to the presence of any liver-specific autoimmune process;
- (3) modification of the course of presumed "autoimmune hepatitis" by corticosteroid drugs, indicating that liver-cell damage depends more on the response of the host than the activity of any extrinsic pathogen;
- (4) genetic considerations, including coexistence of "autoimmune CAH" with other immunopathology and with the phenotype HLA-B8.

The non-demonstrability of a viral agent in "autoimmune" hepatitis does not imply that the disease occurs wholly independently of an extrinsic cause. A virus such as that of hepatitis A, B or C could initiate the disease, and/or be present in a defective form in the liver and create a neoantigen which evokes a host response. Hence there is need for application of modern techniques in virology to examine this question.

The therapeutic use of corticosteroid drugs, combined or not with azathioprine, is now well accepted, but further studies are required to establish policies for duration of treatment and to assess long-term adverse effects of current disease-suppressive regimes.

Further studies on genetic aspects of "autoimmune" hepatitis are desirable. The already published studies (which could be supplemented) on occurrence of disease, or autoimmune serological markers in families of probands with autoimmune hepatitis do not suggest any substantial inherited predisposition. However extension of studies on HLA determinants in chronic hepatitis to ascertain associations of loci for D region antigens (DW 3) and B cell alloantigens will further understanding of susceptibility, and could help in diagnosis and classification.

### 3.3 Chronic liver disease in parasitic infection

A few important elements have been chosen from an extensive list of parasites which affect the liver.

### 3.3.1 Schistosomiasis

Infection with Schistosoma japonicum may provoke liver changes that range from mild portal fibrosis to severe cirrhosis, depending upon the number of harbouring trematodes and the duration of infection. Schistosoma mansoni infection provokes changes ranging from mild to severe portal fibrosis.

In Japan and Latin America, the incidence of schistosomiasis has been significantly reduced as a result of intensive snail eradication, adequate faeces disposal, education of the public and treatment of patients. International agencies have played an important role in achieving these results.

In Africa S. mansoni is still an important cause of chronic liver disease, particularly in the Nile basin and around Lake Victoria.

### 3.3.2 Amoebiasis of the liver

Chronic amoebic infection (more than three months) represents less than 10% of amoebic involvement of the liver. Clinically, the patient has firm hepatomegaly, simulating tumour of the liver or chronic active hepatitis. There may be severe loss of weight and little or no fever. Other clinical features are anaemia and abdominal pain. Diagnosis is done by scanning, ultrasound, and immunological tests.

There is controversy on treatment (surgical, drainage through needle or drugs).

### 3.3.3 Echinococcosis

The echinococcosis granulosa is a small tapeworm for which the primary host is the dog and the intermediate host is the sheep. The parasite dwells in the small intestine of the dog and discharges the ova onto pastures, they may be ingested by sheep (or man) and these develop into cysts. Ingestion of infested livers by dogs completes the cycle.

Echinococcosis is important medically in that man can be infested as an intermediate host with cyst formation in the liver and other sites. Economically it is important in that meat production is jeopardised. Control of echinococcosis is relatively simple, primarily by detection and treatment of parasitized dogs and by preventing the access of dogs to infested offal.

### 3.3.4 Tuberculosis of the liver

Hepatomegaly and fever may be the first clinical manifestations of disseminated tuberculosis. Occasionally splenomegaly and pancytopenia are the chief features.

Liver dysfunction due to the disease must be differentiated from that caused by hypersensitivity to chemotherapeutic agents used to treat tuberculosis. Liver biopsy is very helpful to establish diagnosis and the sensitivity to antibiotics of the tubercle bacilli. Positive tuberculin tests may be useful in countries where prophylactic immunization has not been undertaken.

## 3.4 Chronic liver disease and alcohol

### 3.4.1 Identification

There is ample statistical evidence of an association between alcoholism and chronic liver disease and it is reasonable to conclude that ethyl alcohol has been identified as an etiological factor in chronic liver disease. Surveys have shown that about ten per cent of alcoholics suffer from chronic liver disease, indicating that in most cases alcohol does not damage the liver. However, more detailed studies, taking the quantity and duration of alcohol consumption into consideration, demonstrate a considerably higher frequency. Thus the evaluation of alcohol as an etiological factor requires better quantitative assessment.

### 3.4.2 Risk factors

These can be considered at the levels of individuals and populations.

Individual factors may include: (i) age at onset of drinking, and sex; (ii) amount of alcohol consumed, there being general agreement that a "prolonged" daily intake of 80 gms places an individual "at risk" and that 120 gms is definitely noxious; (iii) duration of exposure; (iv) the influence of the type of alcohol consumed (suspicions that wine may be more toxic than other forms of alcohol are not generally accepted); (v) drinking habits (the effect of continuous or intermittent drinking has not been evaluated); (vi) the mode of preparation of the alcohol (possibilities of contamination by excess of iron, other trace metals and, in some areas, aflatoxins and pesticides); (vii) accentuation of the effect of alcohol by co-factors which include (a) nutritional status, (b) hygiene, living conditions and socio-economic class, (c) industrial toxins, (d) co-existing diseases such as diabetes mellitus, tuberculosis, or other liver diseases, (e) drugs taken concurrently or other components of "dependence behaviour" such as smoking and consumption of caffeine-containing beverages; (viii) knowledge of genetic and/or ethnic predisposition to alcohol-toxicity is lacking, although this could influence the metabolic disposal of alcohol and its breakdown products, or the host response to products of tissue damage.

Alcohol could well be studied in populations as an epidemiological model of "host-parasite" relationship. In such a model, important population considerations would be: (i) amount of alcohol available; (ii) roles of education and advertising; (iii) drinking habits; (iv) type of alcohol consumed and mode of preparation; (v) influence of family, tradition and culture and (vi) nutritional status of the population.

### 3.4.3 Morphological responses of liver to alcohol

There are a number of differing morphological changes seen in the liver as a result of alcohol abuse, with the following listing not implying that the changes are necessarily sequential: (i) fatty liver, which is reversible; (ii) alcoholic hepatitis with inflammatory changes, fat, possibly alcoholic hyaline, and centralobular and portal fibrosis - whether or not alcohol abuse continues or ceases, these changes may remain static for long periods, heal with scarring or show progression; (iii) cirrhosis, micronodular or macronodular, is the typical "end stage".

### 3.4.4 Pathogenesis of alcohol-related disease of the liver

#### a) Role of ethanol toxicity in initiating and perpetuating hepatocyte injury

Studies have shown that acetaldehyde causes mitochondrial damage, altered glycoprotein metabolism and altered immunological activity, each of which may contribute to injury. The amount, duration and type of alcohol have been incriminated as major factors, but individual susceptibility varies.

#### b) Role of nutritional factors

It has been shown that alcohol in the presence of a nutritious diet may produce fatty liver; however, this does not exclude the possibility that malabsorption or malutilization of foodstuffs is a factor contributing to CLD in alcoholics. Recent evidence that pyridoxal-5-phosphate, cystein and other chemicals may inhibit acetaldehyde cytotoxicity and that folate depletion may interfere with repair of liver damage suggests an important role for nutrition in both the development and perpetuation of chronic liver disease in alcoholics.

### 3.4.5 Treatment of chronic liver disease in alcoholics

#### a) Abstinence

Psychosocial (Alcoholics Anonymous) and medical follow up programmes have lead to abstinence in up to 50% of patients in some studies. Psychotherapy, drug therapy (disulfiram) and other measures to achieve abstinence have proved successful in selected alcoholics with CLD.

b) Nutrient therapy

It has been shown that most alcoholics with liver disease have deficiencies of vitamins, minerals and protein. Controlled studies have demonstrated the value of correcting deficits of the following nutrients in facilitating repair of liver injury: folic acid, vitamin B6, vitamin B12, zinc, phosphate.

c) Hormonal therapy

Corticosteroids and androgenic anabolic steroids have been used in the treatment of alcoholic hepatitis but their value is not established and additional controlled studies are needed.

3.4.6 Preventiona) Identification of high-risk groups

High-risk occupations. There is a widespread belief, not sufficiently well supported by survey data, that certain occupations may be associated with high rates of alcoholism. The most obvious is the alcohol industry itself, be this the wine, spirits or brewing industries. Other industries in which there is claimed to be a high rate of alcohol abuse include transport and advertising.

b) Individual predisposition to alcohol-induced disease

The genetic and other predisposing factors in alcohol-induced tissue damage are unknown, although there is clearly a wide range of tolerance to alcohol amongst individuals. The known familial predisposition to alcoholism could be equally explained by a genetic component or by early conditioning within the family to acceptance of alcohol. Genetic factors under examination include histocompatibility (HLA) phenotypes with the suggestion from some groups that HLA-B8 has a slight positive effect in the development of alcoholic hepatitis.

c) The "high-risk" effects of alcoholic hepatitis

Once individuals have been identified as suffering from alcoholic hepatitis, it is accepted that they are at high risk for progressive alcoholic liver disease culminating in cirrhosis. This fact carries the important implications that doctors should be aware of this sequence of events, that persons suspected of having alcoholic liver disease should be admitted to hospital for liver biopsy to determine whether alcoholic hepatitis is histologically evident and, if so, every effort should be made to induce such "at risk" individuals to cease consumption of alcohol.

3.5 Chronic liver disease and malnutrition

The liver has long been the object of study in protein-energy malnutrition. Fatty liver of varying grades of severity is seen in protein depletion when the calorie supply is relatively adequate. This is accompanied by a series of complex changes in the activities of various enzyme systems and in the synthesis of various proteins in the liver. All these changes are reversible by protein supplements. There is no evidence that protein-energy malnutrition per se leads to fibrosis, cirrhosis or liver carcinoma.

There is, however, a distinct possibility that protein-energy malnutrition may alter significantly the response of the liver to injuries of various kinds. The regenerative capacity of the liver and collagen formation are significantly affected by the state of protein nutrition. The various alterations in the enzyme activities of the liver, including the drug metabolizing enzyme systems, may lead to either potentiation of or protection from hepatotoxic agents - depending upon the pathway of metabolism of a given agent.

There is also the question of the effect of protein-energy malnutrition on immunological reactivity and how this may alter the response of the liver to various infections, including hepatitis viruses. It is now well established that protein-energy deficiencies significantly depress cell-mediated immune responses, although their effect on humoral responses is variable and less well defined.

In view of the widespread prevalence of protein-energy malnutrition, especially of the mild and moderate forms, there is an urgent need to study the role of protein-energy malnutrition in influencing the response of the liver to hepatotoxic substances, drugs and hepatitis viruses and in determining the pattern and evolution of CLD in different parts of the world. One particular aspect would be to determine the relative HBsAg carriage rates in well- and poorly-nourished groups within the same community.

### 3.6 Chronic liver disease and mycotoxins

The possibility that contamination of dietary staples by aflatoxin could be an etiological factor in liver cancer in man stems from several sources. A significant correlation between the homes of patients with hepatocellular carcinoma and the distribution of groundnut cultivation in the West Nile District of Uganda has been demonstrated. More recently, in a study carried out in the Muranga District of Kenya, a statistically-significant association between ingested levels of aflatoxin and liver cancer was observed. Correlation does not necessarily prove causation and these data at best merely demonstrate association between aflatoxin and hepatocellular carcinoma.

A recent report from India incriminated heavy aflatoxin contamination of maize meal as the cause of severe hepatitis in adult humans and domestic animals. The syndrome was characterized by icterus, ascites, rapid development of portal hypertension and a high mortality rate.

#### 3.6.1 Preventive measures

The importance in certain parts of the world of food-associated toxins (aflatoxins and the toxic alkaloids of the Senecio, Crotonaria and Heliotropinum group) in the pathogenesis of CLD has already been mentioned. Mycotoxin production is mainly a post-harvest phenomenon in which the moisture content and temperature of the grain are important factors. Improved harvesting practices, including improved methods of drying and storage, which are economical and within the easy reach of the farmer in developing countries are urgently needed. In the case of contamination of food grains with Senecio, Crotonaria or Heliotropinum, simple methods such as weeding the latter plants from the fields where food crops are being grown and removal of contaminating seeds from the grain should help considerably in reducing the problem. Educating the public about the hazards of mould-infested and contaminated food grains should be an essential part of the preventive strategy.

### 3.7 Chronic liver disease and industrial hepatotoxins

There is concern that liver damage due to industrial toxins may be increasing, although definite evidence is lacking. Attention has been directed to this problem by the recognition of angiosarcoma of the liver due to vinyl chloride. Although the number of cases is relatively low it serves as an example of the problem: there may well be many other unrecognized industrial hepatotoxins and carcinogens. In many cases liver damage and/or neoplasia will not be the only, or primary manifestation of toxicity. Those tissues with rapid cell "turnover", e.g. bone marrow, intestinal mucosa, would be highly vulnerable and be predictors of possible hepatotoxicity.

#### 3.7.1 Known hepatotoxins

Organic solvents and pesticides are the best recognized of the industrial toxins. To these must be added halogenated hydrocarbons exemplified by vinyl chloride. There are probably many other substances with toxic effects towards which further research should be directed, metallic trace elements being one example.

List of known toxic substances have been compiled under the auspices of the United Nations Environment Programme (International Registry of Potentially Toxic Chemicals). A further listing of carcinogenic and mutagenic substances has been prepared by the International Agency for Research on Cancer, Lyon, France. Also national reference institutions, such as the National Institutes of Health, USA, provide relevant information (Registry of Toxic Effects of Chemical Substances, US Department of Health, Education and Welfare, National Institute for Occupational Safety and Health, CDC, Maryland, (1976)).

#### a) Scope of the problem

The toxicity of most noxious industrial substances cannot be assessed only by experiments in animals. There is need of epidemiological information based on accurate and comprehensive registration. Notification of suspected and proven cases should therefore be made at national and international levels.

Toxicity may be modified by various factors, either genetic and endogenous factors or exogenous factors such as foodstuffs, medicinal drugs, alcohol, the physical environment and chemical pollutants. Research is needed to clarify mechanisms of action and interaction, metabolism and mutagenic and cancerogenic dangers.

With regard to diagnostic and survey methods for liver toxicity, a programme of health surveillance has already been proposed (see WHO Technical Report Series, 571, 1975). In general, surveillance should include health record cards for each worker indicating possible toxic exposures, regular medical checks for symptoms of hepatotoxicity, evidence of hepatomegaly and selective biochemical screening using levels of aminotransferases and alkaline phosphatase in the first instance. Comprehensive biochemical tests should be performed at the first examination. Attention is directed to the likelihood that possible hepatotoxicity may be signalled by toxic effects on other tissues. If there is evidence of pre-existing liver damage, disease of other systems or alcohol or drug use, a worker should be withdrawn from a site of exposure to potential industrial toxins (Occupational Diseases: A Guide to Their Recognition. USDHEW (NIDSH) Publication No. 77-181, June, 1977).

#### b) Protection of workers

The protection of workers from noxious chemicals is primarily the responsibility of industry and should follow the guidelines developed for the industry concerned. Particularly important is monitoring of the atmosphere and working places so that levels of noxious substances are kept to permissible limits. If any sign of intoxication is found, a worker should be withdrawn and evidence of breakdown in precautions should be sought. A worker affected by an industrial toxin should receive prolonged medical follow up for detection of late toxicity including neoplasia.

Education is essential not only for managers but also for union representatives and especially for the workers themselves. They should be convinced of the importance of protective regulations and of the necessity for permanent surveillance and be invited to cooperate in the development of the best conditions and methods for protection.

Centralization and dissemination of information is needed to:

- a) protect without delay workers under similar conditions in all part of the world,
- b) collect relevant epidemiological information,
- c) promote research and improvement of protective measures,
- d) advise government and international bodies on appropriate legislation.

Legal aspects should include standards for safety limits of potential toxins. Regulations for protective measures should continuously be revised and improved under the guidance of national and international institutions.

#### 3.7.2 Unknown hepatotoxins

Although the existence of various unknown hepatotoxic substances is likely, this is extremely difficult to prove because of the masking effect of other factors, especially alcohol, and the unrecognized influence of trace elements present in extremely low amounts. The best possibility for the discovery of new hepatotoxins depends upon the specialized knowledge and intuition of the physician skilled in the study of occupational diseases.

### 3.7.3 Standard procedures for the evaluation of hepatotoxicity

Minimum requirements would be the following:

- a) A work-history record should be maintained for each employee, identifying each class of job which he or she occupies for one month or more, and job classifications should be made as uniform as possible on an industry-wide basis.
- b) Exposure data for each job classification should be maintained by all industries/occupations and should include
  - (i) identification of all chemicals utilized in a particular job classification or occupation,
  - (ii) analysis and characterization of all unknown chemicals or proprietary agents utilized in each job classification or occupation where such information is not available,
  - (iii) maintenance of yes/no exposure data for each chemical or groups of chemicals utilized by each job classification and/or occupation.
- c) A medical history and results of a physical examination should be obtained for each employee before employment.

A standardized employee history record-keeping form should include (i) previous or other occupations; (ii) previous chemical exposure; (iii) alcohol consumption (estimated ounces or ccs per unit time); (iv) smoking history (estimated packets/years); (v) history of prescribed and non-prescribed drugs; (vi) hobbies; (vii) a system-review related to gastrointestinal function, nausea, vomiting, diarrhoea, jaundice, and hepatobiliary disease and (viii) a family history including biliary tract disease, liver disease, cancer and diabetes.

The physical examination should be detailed with particular reference to the presence of liver disease.

All laboratory baseline or initial studies should be performed after a 10 to 14 hour fast and should include complete blood count, serum bilirubin, alkaline phosphatase and one or more of the alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT) or gammaglutamyl transpeptidase (GGPT) tests.

d) There should be continuous surveillance of all workers using the above programme at yearly or other specified intervals. The industrial physician may consider it wise to continue surveillance even after a worker leaves a particular occupation in certain circumstances and should inform the family doctor.

### 3.8 Chronic liver disease and drugs

An increasing number of widely-used and generally well-tolerated drugs, including traditional medicines, can cause hepatic injury. This may range from a transient asymptomatic elevation of serum transaminase or alkaline phosphatase, to clinically-overt acute and chronic hepatocellular or cholestatic liver disease. These drug-induced states are often clinically, biochemically and histologically indistinguishable from other forms of liver injury and this makes the establishing of a causal relationship between the drug and disease difficult. For this reason the list of drugs which are suspected of inducing liver injury is much longer than that of drugs which are of proven relationship.

Most drugs that injure the liver do so by one of two mechanisms. Some drugs or their metabolites are hepatotoxic by a chemical interaction with an essential structural component or metabolic enzyme system of the liver cell, whereas others involve a hypersensitivity reaction. In both cases host factors may influence the probability of a significant adverse reaction. The rate of generation and detoxification of a toxic metabolite will influence both types of reaction and the immune response genes may be involved in determining whether a patient manifests an idiosyncratic hypersensitivity response. The induction of benign and

malignant liver tumours by steroid hormones is important but is relatively uncommon and will not be considered further.

### 3.8.1 Direct hepatotoxins

These may cause acute hepatitis. The prolonged administration of a directly hepatotoxic drug, causing prolonged or repeated episodes of hepatitis, is a possible mechanism for the development of chronic liver disease. In this context salicylates and acetaminophen are suspect. When this is the mechanism of liver damage, it occurs in all subjects exposed in sufficient dosage. The drug in question will also produce liver damage in animals and will usually be identified as hepatotoxic in the preliminary animal toxicological studies to which most drugs are subjected. A causal relationship between the drug and the adverse reaction is readily established in an individual case by studying the effect of drug withdrawal.

Another approach to establishing a causal relationship between hepatotoxin and disease has been to relate plasma concentration of the drug or metabolite to the severity of the lesion. This is unreliable because of the numerous genetic and environmental factors which influence a subject's susceptibility. In most cases, metabolic activation of the drug, usually by microsomal mixed-function oxidases, is necessary to produce reactive metabolites which covalently bind to tissue macromolecules and thereby induce cellular malfunction. These activation systems are genetically controlled (fast and slow acetylation status) and are also affected by enzyme inducers (phenobarbitone, alcohol, rifamycin).

### 3.8.2 Indirect hepatotoxins (idiosyncratic)

A drug or its metabolite may induce liver damage by immunological mechanisms. The drug may alter either the regulatory system of the immune response so that reactions to "self-antigens" are no longer suppressed, or it may alter hepatocyte antigens so that they are no longer recognized as "self-components". In the former case, the ensuing disease state may be multi-systemic whereas the alteration of liver antigens would be expected to produce an autoaggressive assault solely on the liver.

One can approach the problem from two directions: by defining the host factors that determine susceptibility; by defining the mechanism by which the drug produces liver damage.

The involvement of host factors is suggested by the observation that only a small minority of exposed subjects develop hepatic injury. This is in contrast to the high susceptibility rates to hepatotoxins. The factors involved are poorly understood. Genetic factors may influence the rate and form of metabolism of the drug, thereby influencing the rate of formation of immunogenic complexes of drug metabolite with cellular macromolecules. Further advances in this field will stem from a more detailed knowledge of the genetics of drug metabolism and of the control of the immune system. Some progress has been made by the demonstration that microsomal enzyme activity is genetically determined and in the field of immunology, evidence suggests that HLA phenotypes may be linked to the immune response genotypes.

The mechanism by which a drug initiates an autoaggressive immune response is unknown. The drug may act as a hapten and combine with a membrane component of the hepatocyte, or may denature a self antigen. There will be a response to the drug-carrier complex or to the denatured liver cell antigen. Successful attempts to demonstrate these humoral and cellular responses are rare. The paucity of positive data may stem from failure to test with both the drug and its metabolites complexed to the appropriate carrier molecule.

Although it is theoretically possible that the autoimmune reaction may continue after removal of the initiating drug, this does not usually occur. Thus, for chronic liver disease to develop, prolonged exposure over several months would be expected. To establish a causal relationship of the drug to the liver lesion is a major problem. Withdrawal of the suspected drug usually results in clinical and biochemical improvement and in a clinical setting this is all that can be done. Re-challenge may be permissible in mild reactions but in more severe cases carries the risk of severe exacerbation. Very little help can be derived from biochemistry, histology or serology. For example, methyl dopa-, oxyphenisatin- or isoniazid-induced forms

of chronic active hepatitis are indistinguishable on biochemical and histological grounds from other forms of the disease.

Once chronic liver injury is established, whether it be related to drug exposure or other factors, the pharmacokinetics of additional toxins and drugs will be altered and a continued awareness of the metabolic fate of these materials is essential to prevent further problems arising. This problem requires continued study because of the introduction of new therapeutic agents.

The establishment of a causal relationship between a drug and chronic liver disease is dependent on the reporting of adverse drug reactions to national drug regulatory boards. The interpretation of these data is difficult because of limited knowledge of the population at risk and of compliance in reporting. The international collation of data by WHO would permit a more rapid recognition of potentially toxic drugs and the organization of multinational controlled studies.

### 3.9 Chronic liver disease - hereditary factors

#### 3.9.1 HBV-related liver disease

Studies on families point away from strong hereditary influences in chronic liver disease. The well-documented clustering in families of HBsAg, with and without evidence of chronic liver disease, appears to depend more on intra-familial infection than a susceptible phenotype. Although the earlier concept of HBsAg as an inherited serum polymorphism lacks supporting evidence, genetic determinants of carrier status may exist and should be sought among populations in which the carrier rate is high. In one such study, there was a weak association of the carrier state with HLA-A3, and BW35 and in another there appeared to be more effective clearance of HBsAg in HLA-B8-positive subjects.

#### 3.9.2 Autoimmune liver disease

Reported studies on families of propositi with autoimmune liver disease (CAH and PBC) show some excess of subjects with liver disease or serological markers of autoimmunity, but the frequency is low. That inheritance plays some part in "autoimmune" hepatitis is supported by the highly-significant association of some HLA phenotypes with this disease (HLA-B8 and, according to one study, with HLA-DW3). The "relative risk" of chronic hepatitis for carriers of HLA-B8 is moderate (up to 20-fold). HLA-B8 is associated more with the disease CAH itself than with the associated autoimmune serological markers, or with hypergammaglobulinaemia. Autoimmune CAH existing in B8-positive subjects shows some but not impressive differences from CAH in B8-negative subjects including a greater tendency for relapse after cessation of suppressive treatment.

#### 3.9.3 Alcohol-induced disease

Early studies suggest an association of the HLA-B8 phenotype with alcohol-induced hepatitis but further studies are required before a genetic component can be incriminated in this disease.

#### 3.9.4 Haemochromatosis

This is a liver disease in which the genetic component is known to be strong, and there has been recent recognition of a highly significant association of HLA-A3 and B14; the relative risk for subjects with A3 and B14 is 90-fold. HLA typing could be of value in screening male relatives of haemochromatosis subjects for recognition of susceptible subjects. They could be advised as to avoidance of iron-containing foods and alcohol. They should be monitored for rising levels of serum iron and, where the level is abnormally high, they should be assessed for incipient disease by liver biopsy.

#### 3.9.5 Alpha-1 antitrypsin (AAT) deficiency in chronic liver disease

This is one important cause of intrahepatic cholestasis in infancy. AAT is a glycoprotein

synthesized by the liver and which functions as an enzyme inhibitor of trypsin, elastase, collagenase, chymotrypsin, plasmin and Hageman factor cofactor. AAT shows an extensive polymorphism. Twenty-four alleles of the AAT gene have been identified, the inheritance of which is codominant. Phenotypes are designed by the initials Pi (protein inhibitor) followed by letters referring to electrophoretic mobility. PiM is the predominant phenotype. Individuals with the PiZZ, PiPZ, PiSZ show an increased incidence of cirrhosis and emphysema. The same holds true for the phenotype Pi - where there is little or no AAT. Depending on the frequency of the PiZ gene, the frequency of the PiZZ phenotype (where the AAT function is most impaired) in children with neonatal intrahepatic cholestasis is around 15-30%.

Some 10-15% of children with the PiZZ phenotype seem to develop liver disease in infancy. Later on, at three and six months of age, 41% show biochemical evidence of liver disease but most of these children are clinically well. However, portal hypertension may occur. Patients who do have a subclinical obstructive jaundice may develop cirrhosis.

Since AAT-deficiency is rarely found in young adult cirrhotics with no history of neonatal cholestasis, it is assumed that the prognosis of patients who show only biochemical signs of liver disease is good. The danger of emphysemics developing, liver cirrhosis and/or a liver cancer in late adulthood is about 10-15%.

### 3.10 Chronic liver disease and primary hepatocellular carcinoma

The early detection and treatment of hepatocellular carcinoma would be aided by the definition of high-risk groups and the development of screening methods to detect the tumour at an early stage. CLD will be discussed in a later section.

The fact that this carcinoma is more common in males than females and occurs at a significantly increased incidence rate in certain types of chronic liver disease, particularly those associated with cirrhosis, helps define a high risk group.

#### 3.10.1 Association with HBV markers

In Asia, Africa and the Pacific areas, where primary hepatocellular carcinoma (HCC) is common, a greater incidence of HBV markers, particularly HBsAg and anti-HBc, has been demonstrated in patients with HCC than in matched controls (including other cancer patients or the general population). A higher prevalence of persistent HBs antigenaemia and high titre of anti-HBc, over 2<sup>10</sup> by immune adherence haemagglutination, has shown that large proportions, ranging from 60 to 90% of HCC, have evidence of chronic HBV infection.

The relative risk of the HBsAg-positive group for HCC is calculated as 24 to 80 times higher compared to the HBsAg-negative group, while the relative risk of the anti-HBs-positive group is as low as 0.3 compared to the HBsAg-negative group.

The sum of the HBsAg-positive rate and anti-HBs-positive rate as determined by a highly sensitive technique will give the exposure rate to HBV among the population. The HBs antigenaemia rate is calculated as the HBs antigen-positive rate among the population exposed to HBV. HBs antigenaemia rate in HCC patients is 80-100% in different countries throughout Asia, Africa and the Pacific areas while that in the general population is 10-30%.

The above data show a close association between chronic HBV infection and HCC in HCC-prevalent areas.

It may be postulated that HBV may infect a variety of cancer patients who have an antecedent condition with immunological deficiency resulting in high susceptibility to acute HBV infection and the development of the chronic carrier state. However, among other cancers tested, HCC is the only cancer with strong association with markers of chronic HBV infection. Further evidence comes from a follow-up study of liver cirrhosis patients for over four years. The highest frequency of the development of HCC among liver cirrhosis patients was observed in those with HBsAg in the serum and a high titre of anti-HBc. The clinical manifestations of HCC have not yet been found in a liver cirrhosis group with positive anti-HBs. In all these

follow-up cases, HBsAg was demonstrated in the serum and liver cells before the clinical manifestation of HCC, as revealed by angiography and measurement of serum alphafetoprotein.

Another possibility is that chronic HBV infection is responsible for cirrhosis and that HCC then arises from regenerative nodules by mechanisms in which HBV is not involved. This sequence may explain HCC developing in patients with alcoholic cirrhosis but this is much less frequent. It is not supported by the fact that a number of HCC cases associated with chronic HBV infection develop in patients with chronic active hepatitis but without evidence of cirrhosis.

The accumulated evidence discussed above shows the strong possibility that chronic HBV infection which is caused by primary exposure to HBV at neonatal or infant stages is a significant oncogenic factor in the induction of HCC. Therefore the prevention of HBV infection in the newborn stage or childhood should reduce the incidence of this neoplastic disease.

Three measures against primary exposure in the highest risk groups have been considered:

application of high-titre anti-HBs human gammabloulin to infants born of HBeAg-positive mothers immediately after birth;

reduction of infectivity of HBsAg-carrier mothers who are HBcAg-positive at the time of delivery - this may be possible by the administration of large quantities of human interferon and its effect can be measured by HBeAg or HBV-specific DNA polymerase activities;

(These two measures are applicable upon assessment of safety for newborn babies)

application of HBsAg as a vaccine for active immunization of infants or children who have close contact with HBeAg-positive HBV carriers - for this purpose, HBsAg free from HBV DNA is considered to be the most valuable source since a possible "oncogenic" virus DNA is excluded from vaccine preparations.

### 3.10.2 Alcohol-related disease

Alcoholic patients with established cirrhosis are at risk of developing HCC and 10% will die of it.

### 3.10.3 Metabolic liver disease

Alpha-1-antitrypsin (AAT) deficiency (PiZZ) has been described in a few HCC patients. The determination of AAT phenotypes in a large series of patients in Africa seems to extend the association to heterozygotes (PiMZ). Further controlled studies are needed before this can be ascribed as a significant risk factor.

Patients with tyrosinosis also have an increased risk of developing HCC.

### 3.11 Summary

Although some associations have been described, the causal relationship and pathogenetic mechanism in many cases of CLD is unknown. The contribution of genetic factors, other than those already mentioned, should be further studied (HLA typing). Furthermore, the continued search for additional environmental carcinogens is essential (the role of mycotoxins has been dealt with in section 3.6) and the possibility of multifactorial etiology recognized. The combined study of host and environmental factors should be undertaken in several countries so that the significant geographical variations in incidence may be explained and possibly yield insight into pathogenesis as the basis for therapeutic intervention.

## 4. DETECTION OF CHRONIC LIVER DISEASE

The methods used to screen for CLD must be sensitive and must be tailored to the medical facilities of the community being studied. In general, the diagnostic capacity of screening techniques will be low, and a second line of investigation, using additional techniques will be

needed to provide a detailed knowledge of the pattern of CLD in any community. This second stage requires more sophisticated medical resources at a hospital institution rather than a field station. The value of various methods is discussed.

Screening for CLD may therefore be done at three levels:

- 1) by population studies (house-to-house visits, occupational screening or screening of blood donors);
- 2) by primary health care physicians screening subjects with or without symptoms and signs of liver disease;
- 3) by hospital investigation of symptomatic subjects (in-patient resources);

In general, the most detailed knowledge of the spectrum of disease will accrue from hospital investigation.

4.1 History and physical examination: may be used by the primary care physician to determine the presence of CLD. In many cases, the development of CLD is insidious and symptoms occur late in the natural history. The first are vague and only when the late manifestations of liver failure and portal hypertension occur do symptoms point specifically to the liver. Once the presence of chronic liver disease is established, the problem of determining etiology arises. The contribution of environmental and inherited factors may be suspected from the history. An occupational and family history may be helpful in this respect. Although suspicion of a particular etiology may arise from the history, the diagnosis and possible screening of other family members (Wilson's disease, haemochromatosis and HBV-associated disease) is biochemically and serologically based.

Physical examination suffers from the same limitations both in establishing the presence of chronic liver disease and in determining etiology. The major signs are those of the complications of late CLD, namely portal hypertension and liver failure (deficient synthetic and excretory functions). The liver is palpable in most cirrhotic patients and in some cases (e.g. alcohol-induced disease) may be markedly enlarged in the early stages. At the end-stage of chronic active hepatitis the liver is often small and cirrhotic. The spleen is palpably enlarged in many subjects who have cirrhosis. The presence of spider naevi, palmar erythema, gynaecomastia and testicular atrophy also indicate severe disease and, although each may occur in other conditions, together they are a clear indication of the presence of CLD. Certain signs are specific for individual types of liver disease: Kayser-Fleischer rings in Wilson's disease and pigmentation in haemochromatosis, but these are rare and the major value of physical examination is to establish the presence of CLD. Further biochemical serological and histological tests are then necessary to determine etiology.

In general, history and physical examination are of low sensitivity, detecting mainly established CLD, and of poor diagnostic capacity, except in a few situations where environmental and familial factors may be suspected. At the simplest level the detection of hepatomegaly by trained personnel may give a crude measure of the incidence of liver disease in a community, and will serve to focus more detailed studies on the geographic areas of greatest need.

4.2 Basic liver function tests: require technical facilities which therefore restricts their use to areas within a small radius of a hospital. Most of these tests have the purpose of detecting or quantifying a) hepatic synthetic functions (example: prothrombin time, serum-albumin concentration), b) hepatic excretory functions (example: serum bilirubin concentration, alkaline phosphatases), c) hepatocellular disintegration or membrane damage (example: serum alanin aminotransferases), and d) immunological responses to (or causes of) liver damage (example: serum IgG levels).

Chronic liver disease due to specific, detectable pathogens (e.g. schistosomiasis, hydatid cysts) normally should be identified by specific markers of the pathogen. Other chronic liver disease may cause abnormality in all of the above respects but none of them is specific. The diagnostic specificity (predictive value of a positive test) and sensitivity (predictive value of a negative test) of individual tests depend on:

- 1) which type of patient should be identified by the test?
- 2) what is the frequency of this type of patient in the population studied?
- 3) what is the composition of the background population (prevalence of other diseases which may cause abnormal test results)?
- 4) which methodology is used (accuracy and precision of the test)?

All of these four factors are assumed to vary greatly from one geographical area to another. A certain knowledge of this variation is necessary for the planning and evaluation of screening procedures and cooperative pilot studies should be performed with this purpose.

There are few data available on which to assess cost-effectiveness of each test and efficiency (false positives and negatives) and comparative studies should be initiated. Matters to be decided before protocols are prepared include:

- 1) target population,
- 2) tests to be used,
- 3) chemical methodology,
- 4) cut-off point,
- 5) consequences of positive test result.

For example, the following study could be made in different geographical areas.

- 1) Patient seeking primary health care. For evaluation of the study the population serviced by the primary health care system should be characterized as to size, socio-economic background and general health problems.
- 2) Among the tests available alanin aminotransferases is assumed to be the most cost/benefit effective. Cost in this connexion means expenses for chemicals and technicians and inconvenience for probands, benefit means an appropriate sensitivity/specificity ratio.
- 3) In a cooperative study one method should be used. It should be feasible under the most difficult conditions expected in any of the participating units, and accuracy and precision should be matched with the purpose of the study. The International Federation of Clinical Chemistry has committees dealing with these problems.
- 4) Will depend on 3). As an estimate, twice the upper normal (95%) limit may be chosen.
- 5) Clinical examination and full battery of routine liver tests. If results of the routine tests are abnormal, non-routine tests and/or liver biopsy should be performed.

#### 4.3 Serology

##### 4.3.1 HBV antigens and antibodies

Testing for HBsAg and antibody (anti-HBs) will differ in applicability according to region, being highly useful for general screening in high prevalence areas of the world (with carrier rates for HBsAg of 15%) and useful only for the specific screening of blood donors, health-care personnel etc. in low prevalence areas (with carrier rates of 0.1%). Current radio- and enzyme-immunoassays for HBsAg are highly sensitive but in a small proportion of cases of CLD the test for HBsAg may be negative despite apparent persistence of HBV in the liver, evidenced by "induction cells" in the liver biopsy, immunofluorescence demonstration of HBsAg in liver or antibody to core antigen (anti-HBc) in serum.

The specificity of assays for HBsAg is extremely high in terms of detection of antigen but low in terms of detecting liver disease in that the test does not discriminate healthy carriers with a normal liver from those with lesions ranging from chronic persistent hepatitis to cirrhosis.

Detection of anti-HBc by immunoassay, at present a research procedure, may be applicable to cases of chronic active hepatitis and cirrhosis in which tests for HBsAg are negative, to assess whether HBV is present as an intrahepatic infection without release of excess viral coat material.

The presence of HBeAg is useful for predicting progression and chronicity of hepatitis in carriers of HBsAg, but this assay would not be a screening procedure. Along similar lines, there could be wider use of histochemical and immunofluorescence procedures to detect evidence of HBV in the liver biopsies of patients with chronic hepatitis and cirrhosis in whom tests for HBsAg are negative.

#### 4.3.2 Autoantibodies

Tests for autoantibodies, ANA, ASMA and AMA, are now routine in immunological laboratories throughout the world. The uncertain sensitivity and specificity of these tests for chronic liver disease could be resolved with the development and use of appropriate laboratory standards. ANA has already been accepted as an International Standard by WHO while a standard for ASMA and AMA should be developed. The availability of standards and free exchange of sera among laboratories would facilitate consensus on the diagnostic significance of positive tests, and need for titration. This could be done through various WHO collaborating centres.

Reactions to liver specific protein (LSP), as judged by in vitro tests for cell-mediated immunity, and humoral immune responses to liver membrane antigen, as judged by immunofluorescence, are research procedures directed towards the search for the specific target of attack in autoimmune liver disease.

#### 4.3.3 Alpha-1-antitrypsin (AAT) (see 3.9.5)

Tests for deficiency of AAT are sensitive, but not specific, in that absence of the inhibitor is not necessarily associated with liver disease, and hence screening cannot be recommended. The phenotyping of this protein may possibly be of value in relation to defining high risk groups for development of primary HCC. (see 3.10)

#### 4.4 Alphafetoprotein (AFP)

AFP is the major plasma protein in early foetal life. Its synthesis decreases thereafter and it exists only in trace amounts in the normal adult. Its increase is associated with the occurrence of primary liver cancer, some yolk-sac tumours and, more rarely, fore-gut derived carcinomata. The occurrence of these tumours may cause a considerable increase of AFP in the range of ng/ml and even mg/ml. AFP may be quantitatively assayed by radio- or enzyme-immunoassay. Mancini's and Laurell's techniques offer alternative but less sensitive methods of assay. An international standard is available from the International Agency for Research on Cancer, Lyon, France.

The follow up of patients with liver cirrhosis shows that increased levels (in the range of 20-100 ng/ml) may be observed in a minority of patients with alcohol-related cirrhosis or cirrhosis following HBV infection and, rarely, with primary biliary cirrhosis. Most elevations are transitory. Their significance is not clearly understood but may be related to liver regeneration. Persistent elevations with steadily increasing levels are almost always associated with the growth of HCC. Thus sequential quantitative AFP measurements give a highly-efficient method of detecting primary liver cancer in these patients. A small number of patients show long-term elevation of AFP (approximately 1%) not connected with primary liver cancer. The significance of such rises is still obscure.

The use of radioimmunoassay as a screening procedure in populations at risk is effective in detecting the early stage of development of hepatocellular carcinoma but, because of the cost of such screening procedures and the lack of effective therapeutic measures, screening is not generally recommended. This position should be reviewed when more effective treatment is available.

#### 4.5 Liver morphology

This is the most diagnostically discriminative procedure but requires hospital facilities and, in particular, trained histopathologists.

4.5.1 Autopsy frequently reveals unsuspected CLD. The decreased frequency of autopsies in certain developed countries has diminished greatly the ability to obtain valid statistical data on incidence. The growing morbidity and mortality from liver disease with increasing numbers of recognizable etiological factors make it desirable to reinstitute routine autopsies. This is an important device in assessing the frequency and type of liver disease in a given geographic area.

4.5.2 Liver biopsy usually detects CLD, although there may be a sampling error. It should be performed in all patients with suspected CLD unless contra-indicated by bleeding tendency, liver abscess, vascular tumours of the liver, absent area of dullness, acute cholangitis or severe illness or cachezia. Liver biopsy is a simple and relatively inexpensive procedure. Light microscopy is usually adequate for diagnosis but may be combined with immunofluorescence to detect HBsAg and HBeAg. Serial biopsy is indicated to assess the natural history of CLD or response to treatment. At present, biopsies are essential to confirm a diagnosis of CLD, to determine its activity and severity and to monitor therapy. Under some conditions (detection of abscesses and tumours) isotope scanning, ultrasonography, computerized tomography and arteriography may be necessary. Where these facilities exist their full utilization should be encouraged.

#### 4.6 Summary

Information on the prevalence of CLD may be obtained through:

- population studies;
- physicians giving primary care;
- hospital admissions;
- autopsies on accident victims.

At each level a different degree of sensitivity and specificity of the diagnostic process will be required and obtained. In population studies, information on the prevalence of hepatomegaly may be all that is obtainable and, at this level, the sensitivity and diagnostic specificity will be low. More detailed biochemical and serological studies will be possible when studying the problem at the level of the primary care physician and, in general, this will be associated with an increase in sensitivity but a lesser improvement in specificity. The acquisition of the greatest specificity, a histological diagnosis, will only be possible from in-patient study or autopsy and both require hospital facilities, including a trained liver histopathologist. The training and strategic placing of these personnel and the initiation of the above types of study might be aided by WHO (see recommendations). This would allow a better assessment of the geographical distribution of CLD.

### 5. RECOMMENDATIONS

5.1 More attention must be given to the importance of CLD as an increasing cause of morbidity and mortality. Programmes must be developed to identify in each country and continent the frequency, mortality and causative factors. Measures must be developed for better recognition, reducing mortality and morbidity, and the prevention of CLD.

5.2 The nomenclature and diagnostic criteria developed by the International Association for the Study of the Liver should be adopted in all countries. A working agreement between the World Health Organization and the International Association is desirable to facilitate the updating of nomenclature and diagnostic criteria.

5.3 It is recommended that data be collected from medico-legal autopsies so that the prevalence of CLD in different parts of the world can be estimated. This will require the nomination or establishment of regionally-based collaborating centres to examine the submitted material.

5.4 a) The capacity of hepatitis viruses to produce CLD underscores the urgent need for better information from different parts of the world. What are particularly required are precise estimates of the prevalence of these infections, the relative roles of perinatal and later infection and the natural history of the diseases caused by these viruses, with special emphasis on cirrhosis and carcinoma.

b) Every endeavour should be made to screen all blood donors in those regions where the HBsAg carrier rate is high and to register post-transfusional hepatitis. This would permit the assessment of the usefulness of such screening procedures in reducing post-transfusional hepatitis and its sequelae.

c) Attempts should be made to prevent the perinatal transmission of the hepatitis virus by use of passive or active immunization or antiviral agents.

d) In regions with high carrier rates of HBsAg the effect of malnutrition and concurrent infection on the course of hepatitis B infections (susceptibility, hepatic damage and oncogenicity) should be examined.

5.5 a) Patients with alcohol-related liver disease should be identified by clinical, laboratory and, when possible, histological studies and the resulting information should be the basis for an intensive programme of education and surveillance to interrupt alcohol dependence.

b) It is highly recommended that there should be an intensification of present educational approaches to emphasize the health hazards involved in alcohol. These should be directed at early age groups and should be accompanied by the reduction or cessation of the advertising of alcohol.

5.6 Schistosomiasis is recognized as a major public health problem and forms part of the WHO Special Programme for Research and Training in Tropical Diseases. Hepatic involvement is a significant feature of these infections and the meeting endorsed the activities of the Special Programme.

5.7 The role of nutrition should be clarified in relation to immunological dysfunction and susceptibility to CLD, including chronic viral hepatitis, cirrhosis and hepatocellular carcinoma.

5.8 Aflatoxin intoxication is recognized as a major public health problem and is at present the subject of special programmes conducted by FAO/IARC. Proper food storage, followed by a significant reduction of liver cancer in endemic areas, would provide the proof for the role of aflatoxin and eliminate the problem.

5.9 There should be universal awareness of the potential hepatotoxic effects of industrially-used chemicals and information made available on lists of known toxic substances compiled by various agencies. Prescribed testing for toxicity in animals and careful surveillance of workers must be undertaken when new chemicals are to be introduced into industry.

5.10 There should be scrupulous testing of all newly-developed medical drugs for hepatotoxicity, carefully monitoring for toxicity in clinical trials, and notification of possible hepatotoxic reactions by primary care physicians once drugs have entered clinical use. In this case also, facilities for the international exchange of data are desirable.

5.11 Typing for HLA specificities and other genetic markers should be undertaken in selected patients with CLD due to viral hepatitis, alcohol-related disease, and drug-induced liver injury in existing specially equipped centres.

5.12 Much needs to be done to develop special programmes for the recognition of existing sufferers, and for the identification of the many persons at risk for each of the various CLD considered in this report. Only then can there be effective preventive measures and interruption of the progression of these debilitating diseases. The appropriate education of primary care personnel would be a cornerstone of these special programmes.

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\*1.1.1 Chronic hepatitis

a) Chronic persistent hepatitis

Clinical criteria Patients may have no complaints. Fatigue, weight-loss or minor abdominal symptoms are present in some. Occasionally the liver is tender or slightly enlarged. There may be a previous history consistent with an episode of acute hepatitis.

Functional criteria Apart from a modest (less than fivefold) and variable elevation of serum aminotransferases, conventional liver function tests are normal. Serum gammaglobulin concentration is not conspicuously elevated.

Morphological criteria Inflammatory round-cell infiltration of portal areas with minimal or absent piecemeal necrosis of the limiting plate, sometimes associated with focal necrosis and ballooning of hepatocytes similar to the findings in acute viral hepatitis, but less pronounced.

Etiological criteria

1. Sequelae of acute viral hepatitis types A or B with serological evidence of etiological agent.
2. Other etiologies undetermined.

b) Chronic active hepatitis

Clinical criteria The onset may be insidious or apparently sudden. A previous history consistent with acute viral hepatitis may be present. Symptoms may be absent or nonspecific (anorexia, fatigue, abdominal discomfort, etc.), whereas jaundice, ascites, hepatosplenomegaly and other features of parenchymal liver disease or portal hypertension are observed in those who are severely afflicted. Such features characterize those with necrosis joining portal and central areas (bridging necrosis) or necrosis of contiguous whole lobules, or cirrhosis. Systemic manifestation (arthralgias, rash, fever, etc.) are common and some patients have inflammatory diseases of other organs (inflammatory bowel disease, thyroiditis, scleroderma, sicca complex etc.).

Functional criteria Results of liver function tests are grossly abnormal, with serum aminotransferase and serum gammaglobulin concentrations being particularly elevated. Several nonorgan specific immunoserological tests (lupus erythematosus-cell test, antinuclear antibody, smooth muscle antibody and mitochondrial antibody) may be positive and elevated serum immunoglobulins (especially IgG) are frequent. In more severe disease, serum albumin concentration is reduced and prothrombin time is prolonged. Features of portal hypertension usually indicate cirrhosis.

Morphological criteria Round-cell infiltration involves the portal tracts, with moderate or severe piecemeal necrosis of liver cells extending outward into the parenchyma from the limiting plate. Changes similar to those present in acute hepatitis B may be seen in the lobule, together with features of cholestasis. Necrosis may bridge the lobule between portal triads or hepatic veins (bridging necrosis) or diffusely involve adjacent lobules causing collapse (multilobular necrosis). Later developments comprise the development of cirrhosis, with or without features of active hepatitis, continuing hepatitis of varying activity, complete resolution or residual scarring (septa formation).

Etiological criteria

1. Sequelae of acute viral hepatitis, types A or B with serological evidence of etiological agent.
2. Other etiologies undetermined.

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\* Numbers refer to numbers in section 1: Nomenclature and definitions in chronic liver disease.

### 1.1.2 Toxic hepatitis

#### a) Due to chemicals and poisons

Clinical criteria Manifestations are variable, depending on the nature of the toxic agent, the acuteness of the injury, and the susceptibility of exposed individuals. Acute toxicity of chlorinated hydrocarbons, elemental phosphorus and *Amanita phalloides* (or related species of poisonous mushrooms) have 1- to 2-day period of nausea, vomiting, diarrhoea and vascular collapse that precede evidence of hepatic disease. Liver injury characterized by jaundice, haemorrhagic phenomena and hepatic failure usually accompanied by renal failure. Mortality, which is modified by the dose of agent, circumstances of exposure and preceding state of patient (e.g. alcoholism), ranges from 10% (mainly from renal failure) for carbon tetrachloride poisoning to over 50% for elemental phosphorous or hepatotoxic mushroom poisoning.

Functional criteria Biochemical manifestations of acute hepatocellular necrosis include strikingly and often transiently elevated values of SGOT and SGPT, high bilirubin levels, depression of plasma clotting factors including prothrombin and relatively slight increase in alkaline phosphatase values.

Morphological criteria Hepatic necrosis is usually centrilobular in poisoning due to  $CCl_4$ , other hydrocarbons and *Amanita phalloides*, although it is occasionally massive. Often there is associated steatosis. In elemental phosphorous poisoning the predominant lesion is extensive steatosis often accompanied by necrosis. Necrosis may be associated with an inflammatory response.

#### Etiological criteria

1. History of exposure to known hepatotoxic agent.
2. Evidence of acute renal injury and failure.
3. Evidence of the noxious agent in biologic fluids or tissues of patient.

#### b) Toxic drug-induced hepatitis (predictable)

Clinical criteria Manifestations are variable, depending on the agent and the nature of the hepatic injury. Hepatic necrosis and degeneration induced by agents such as 6-MP or by large overdoses of acetaminophen are characterized by clinical manifestations of hepatocellular injury which include jaundice and hepatic failure. In the case of acetaminophen overdose, manifestations may occur two to three days after its ingestion. Acute steatosis such as that induced by tetracycline is manifested by mild jaundice and rapid debilitation. Chronic steatosis and cirrhosis such as that attributable to methotrexate presents with a clinical syndrome of hepatomegaly and other evidence of cirrhosis.

Functional criteria Biochemical manifestations of acute hepatocellular necrosis include elevated value of SGOT and SGPT, often strikingly so and hyperbilirubinaemia which may also be marked. Hypoprothrombinaemia is frequent and, when severe, indicates a poor prognosis. Biochemical abnormalities are usually mild with chronic steatosis and fibrosis.

Morphological criteria Hepatic necrosis resulting from medicinal agents may be diffuse or may consist of multiple focal areas and scattered acidophilic bodies, usually accompanied by relatively slight degrees of inflammatory response. Cholestasis may be prominent (e.g. 6-MP jaundice). Necrosis may be zonal, i.e. centrilobular as in the case of acetaminophen-induced injury, or peripheral, as in ferrous sulfate poisoning. Tetracycline toxicity is characterized by small droplet type of steatosis. Chronic hepatic disease due to the toxic effects of medicinal agents is characterized by steatosis, fibrosis, or cirrhosis and may be accompanied by prominent portal inflammation.

Etiological criteria Exposure to hepatotoxic agents known to cause hepatic injury or to overdoses of medicinal agents.

c) Idiosyncratic drug-induced hepatitis (not predictable)

Clinical criteria The syndrome of hepatic injury may resemble viral hepatitis with evidence of hepatocellular injury of varying severity including potential for hepatic failure and fatal outcome, or it may resemble obstructive jaundice with jaundice and pruritus the outstanding features (see intrahepatic cholestasis). Fever, rash, and eosinophilia preceding or accompanying the hepatic injury and prior exposure to drug or a relatively brief (<4 weeks) latent period between beginning administration of the drug and the development of hepatic injury provide circumstantial evidence of hypersensitivity. In absence of these features, aberrant metabolism rather than hypersensitivity may be the mechanism. It has been proposed that hepatic injury in these circumstances is due to production of hepatotoxic metabolites.

Functional criteria Biochemical manifestations of the acute hepatocellular form resemble those of acute viral hepatitis and include elevated levels of SGOT (aspartate aminotransferase) and SGPT (alanine aminotransferase), and more modest increases in alkaline phosphatase. Hypoprothrombinaemia is frequent and, when marked, indicates a poor prognosis. Chronic hepatocellular injury may resemble chronic active hepatitis. In cholestatic forms levels of transaminases are usually mildly increased while alkaline phosphatase may be markedly elevated.

Morphological criteria Drug-induced changes are not predictable and vary, giving rise to a spectrum of changes, including cholestasis, inflammation, and liver cell damage. The acute hepatocellular form is characterized by diffuse degeneration and necrosis, acidophilic bodies accompanied by varying degrees of inflammatory response of mononuclear cells and eosinophils. In some forms of injury (e.g. halothane) necrosis may be sharply localized and central or midzonal. Chronic forms of drug-induced hepatitis exhibit chronic portal and periportal aggregates of plasma cells, eosinophils, and lymphocytes. There is often hepatocyte degeneration, focal necrosis and acidophilic bodies.

Etiological criteria

1. History of exposure to one of a large number of drugs reported to cause hepatic injury especially halothane, isoniazid, antidepressant agents, oxyphenacetin, alpha-methyldopa, and others.
2. Absence of evidence of viral hepatitis or other cause of liver disease.
3. Systemic and histological evidence of hypersensitivity (fever, rash, blood or tissue eosinophilia) helpful diagnostic features but not necessarily present.
4. Administration of test dose to confirm role of suspected drug only considered when continued use of suspected agent is essential, and when initial lesion does not resemble viral hepatitis.

1.1.3 Alcoholic hepatitis

Clinical criteria Usual manifestations include jaundice, abdominal distress frequently associated with fever, leucocytosis, and ascites; in mild cases all of these features may be absent despite the presence of the histologic lesion.

Functional criteria Functional derangements characteristic of parenchymal hepatic injury. SGOT is slightly to moderately elevated (usually less than sixfold), but is characteristically higher than SGPT. Occasionally, serum alkaline phosphatase levels are disproportionately high. Hypoprothrombinaemia and hypoalbuminaemia are frequent, and when severe indicate a poor prognosis. Portal hypertension and its manifestations may be present, caused by centrilobular fibrosis or cirrhosis.

Morphological criteria Hyaline located in the central area of the lobule if there is no accompanying cirrhosis, otherwise diffusely distributed; ballooning of liver cells, liver cell necrosis with polymorphonuclear infiltrate; centrilobular fibrosis, usually but not always accompanied by steatosis. Lymphocyte cytotoxicity for autologous liver.

### Etiological criteria

1. History of acute and chronic alcoholism.
2. Absence of intestinal bypass surgery, primary biliary cirrhosis, hepatolenticular degeneration, and other conditions that may mimic morphological features of alcoholic hepatitis.
3. Serum antigen (AHAg) or antibody (AHAb) to alcoholic hyalin (AH) as determined by complement fixation or immune adherence haemagglutination tests in early phase or advanced phase of disease. Tests under evaluation are not generally available.

### 1.2 FIBROSIS AND CIRRHOSIS

#### 1.2.1 Hepatoportal sclerosis

Clinical criteria Insidious onset; massive splenomegaly without hepatomegaly, haemorrhage from esophageal varices; sometimes anaemia, leucopaenia and thrombocytopaenia.

Functional criteria On splenoportography the extrahepatic portion of the portal vein is dilated and tortuous with many collaterals, while intrahepatic radicals are narrow and tapering. The splenic blood flow is markedly increased. Hepatic blood flow is normal or sometimes elevated. Presinusoidal portal hypertension is present. Biochemical tests are usually normal except for BSP retention.

Morphological criteria In early stages the liver surface is smooth; histologically, wedge biopsies reveal multiple central veins close to portal tracts and multiple portal veins. In later stages the surface is wrinkled and there is stelate fibrosis without disturbance of architecture; intima thickening, sometimes with recanalized thrombosis of larger portal vein branches is seen in surgical specimens, while in needle specimens the smaller vein branches may hardly be altered.

Etiological criteria It is not known whether the changes in the portal vein branches are primary or secondary to the portal hypertension, the mechanism of which is not established since increased blood supply to the liver is improbable.

#### 1.2.2 Chemical-induced fibrosis without necrosis

Clinical criteria Often asymptomatic, may have splenomegaly, evidence of portal hypertension occasional cardiomegaly with high output.

Functional criteria Evidence of portal hypertension or peritoneoscopy and hepatic haemodynamic studies. Abnormal clearance of ICG.

Morphological criteria Periportal and subcapsular fibrosis, bile duct proliferation and peliosis hepatitis with atypical sinusoidal cells.

Etiological criteria Exposure to vinyl chloride (>8 years); arsenic and other noxious agents have been incriminated in this lesion which may also be associated with tumour formation (see Malignant Haemangi endothelioma).

#### 1.2.3 Alcohol-related cirrhosis

Clinical criteria Clinical features vary from none to signs and symptoms attendant to hepatic failure including jaundice, esophageal varices, ascites, coagulation defects and mental changes. Signs of nutritional deficiency including evidence of folic acid and thiamine deficiency are common. Myopathy, Dupuytren's contracture, palmar erythema, spider angiomas, gynecomastia, parotid gland enlargement, hair loss, and testicular atrophy are also often present.

Functional criteria Laboratory evidence of hepatocellular failure is usually due to coexisting alcoholic hepatitis or anoxic injury attendant to gastrointestinal haemorrhage or septicaemia. Serum SGOT is usually higher than the SGPT, but even in the presence of necrosis aminotransferase and activity is relatively low. Serum gammaglobulin is elevated but seldom above 2.5 g/dl. Haemodynamic studies show reduced total hepatic and portal blood flow and an elevated portal, wedged hepatic vein and transhepatic pulp pressure.

Morphological criteria The liver may be large or small. In the early stages the liver is large, with extensive steatosis and uniform involvement, nodules of uniform size (micronodular) and septa with few intact central and portal canals. Late stages are often characterized by an irregular (macronodular) cirrhosis, with portal tracts and central canals in nodules. Histological features of alcoholic hepatitis may be present.

Etiological criteria History of chronic alcoholism; previous criteria for alcoholic hepatitis; absence of other etiological factors.

#### 1.2.4 Cirrhosis following viral B hepatitis

Clinical criteria All manifestations of cirrhosis, from latent to decompensated forms of the disease occur. Signs of hepatic insufficiency and portal hypertension are prominent.

Functional criteria HBsAg may be present in serum. Serum gammaglobulin is frequently elevated above 2.5 g/dl but immune markers, such as smooth muscle antibody, are relatively rare.

Morphological criteria Regular and irregular micronodular and somewhat more often macronodular forms of cirrhosis are present. A markedly deformed liver is seen in approximately 10%; in these instances there is evidence of primary collapse in which the original spacing of portal and central canals is preserved.

Etiological criteria History of viral hepatitis, particularly if severe. May also follow anicteric hepatitis.

#### 1.2.5 Cryptogenic cirrhosis

Clinical criteria The entire spectrum from latent cirrhosis without clinical manifestations to active cirrhosis with features of secondary to portal hypertension and hepatocellular failure.

Functional criteria These depend on the stage, extent, and activity of the lesion. Serum gammaglobulin may exceed 2.5 g/dl and immune markers such as antinuclear antibodies (including positive LE reaction), smooth muscle, and mitochondrial antibodies may be found.

Morphological criteria All stages characteristic of cirrhosis are seen, both the regular, micronodular, and the irregular, macronodular form, with all transitions between them.

Etiological criteria Etiological factors are not established. In a fraction of the cases, especially in the western world, mostly in women at the beginning and the end of the reproductive period, prominence of the immunological reactions together with associated diseases, such as arthralgia, renal disease, and thyroiditis, have suggested a relation to chronic active hepatitis. In such cases "cryptogenic" would not be considered an applicable term by some workers.

#### 1.2.6 Primary biliary cirrhosis

Clinical criteria Most frequent in women between 35 and 65 years of age. Initially pruritus with or without jaundice, usually with hepatomegaly. Jaundice may become prominent, accompanied by xanthelasma and xanthomas. Presinusoidal portal hypertension is frequent. Bone thinning is common. In the late stages portal hypertension and hepatic failure may cause death. Average evolution takes years and always terminates in death.

Function criteria There is an increase in serum alkaline phosphatase activity. Hyperlipidaemia and hypercholesterolaemia are characteristic. Amonotransferases are only moderately increased. Mitochondrial antibodies are usually present. Macroglobulins are increased.

Morphological criteria The first stage is a nonsuppurative inflammation in the intra-lobular bile ducts, segmental in nature and associated with destruction of the ducts. In the second stage bile ductules proliferate and are destroyed with consecutive periductular fibrosis. Hyaline resembling alcoholic hyaline may be found on the lobular periphery. A third stage is characterized by scarring around the ducts, frequently associated with irregularly distributed peripheral cholestasis. The fourth stage represents true cirrhosis which is present only for a relatively short period during the evolution, but is the form often found at autopsy.

Etiological criteria Although the etiology is not established and either an immune reaction or an alteration of bile acid metabolism are strongly considered, drug-induced liver injury may be responsible. Drugs may cause or increase cholestasis in this disease and so unmask it. In earlier stages there is a reduced tendency to nonspecific delayed hypersensitivity, with sensitization of cultured lymphocytes to autologous liver tissue.

### 1.3 FOCAL LESION OF LIVER

#### 1.3.1 Tuberculosis of the liver

Clinical criteria Pulmonary, bone, or disseminated tuberculosis is present. In most instances of granuloma there are few clinical abnormalities. Miliary tuberculosis or tuberculoma are often accompanied by hepatomegaly, jaundice, and fever. Occasionally, splenomegaly with fever and pancytopenia are the chief features.

Functional criteria Dye retention, increased alkaline phosphatase, and altered electrophoretic protein patterns may be present. Liver dysfunction, including an increase in serum aminotransferases, must be differentiated from that caused by hypersensitivity to chemotherapeutic agents used to treat tuberculosis. Tuberculoma may be demonstrated by radionuclide scanning.

Morphological criteria The miliary tubercle consists of a mass of epithelioid cells, lymphocytes, and giant cells. Eosinophilic necrosis may be present and acid fast bacilli may be demonstrable. Tubercles may coalesce to form tuberculomas or spread along the intrahepatic bile ducts to produce tuberculous cholangitis. There may be a variety of nonspecific changes.

Etiological criteria Recovery of tubercle bacilli, a positive tuberculin test and lymphocyte hyperactivity to PPD.

#### 1.3.2 Schistosomiasis of the liver

Clinical criteria Spectrum of hepatic schistosomiasis includes: (a) an acute form, probably the result of a first massive infection in nonresidents of endemic areas, causing fever, urticaria and blood eosinophilia (over 20%) 35 to 45 days after exposure to contaminated water; (b) a mild or asymptomatic chronic form in over 90% of the infected subjects; and (c) a severe chronic form, that results in hepatosplenomegaly, esophageal varices, and other manifestations of portal hypertension. Pulmonary hypertension is occasionally present. Hepatocellular function is normal. Bleeding esophageal varices are a common cause of death.

Functional criteria Evidence of presinusoidal portal hypertension. Liver function tests may show elevated serum alkaline phosphatase, serum globulin, and blood eosinophils. Circulating immunoglobulins are usually increased.

Morphological criteria In the acute form there are many scattered periovular granulomas, with eosinophils and perivascular necrosis. In the mild chronic form periovular granulomas are few, small, and discrete both in portal spaces and in the liver parenchyma. Irregular fine septa are present and black dusty pigment is seen in portal macrophages. Advanced

chronic schistosomiasis (hepatosplenic) is characterized by pipe-stem fibrosis, portal fibrous enlargement, intrahepatic portal vein obstruction, hypertrophy of hepatic arterial tree, and egg granulomas in portal spaces. Liver parenchyma is usually preserved. Later it may show focal fibrosis and nodular regeneration, although a cirrhosis does not seem to occur. When present, another cause is suggested.

Etiological criteria Human schistosomiasis is caused by the three species of schistosome, S. mansoni, S. japonicum, and S. haematobium. Eggs (stool, urine, rectal and liver biopsy) and antibodies (skin test, complement fixation, immunofluorescence technique, and so forth) must be demonstrated to fulfill etiological criteria.

### 1.3.3 Hydatid cyst of the liver

### 1.3.4 Amoebic abscess of the liver

Clinical criteria Clinical manifestations are divided into acute and chronic abscess. Acute abscess is characterized by pain in the right hypochondria, fever, and leucocytosis with neutrophilia. There is tenderness to palpation in the liver area and intercostal spaces of the lower right chest and the right diaphragm is immobile. The chronic abscess causes some pain in the hepatic area, of more than two months duration, low fever, dry cough, anorexia, loss of weight, and asthenia. The liver may be tender.

Functional criteria The degree of functional impairment depends on the severity of the lesion, its chronicity, and the population involved. Liver function tests show minor changes in the direct bilirubin. Serum albumin and total cholesterol may be low, alkaline phosphatase may be high, aminotransferases and prothrombin time are usually normal, and the erythrocyte sedimentation rate is raised. Arteriography and liver scans (isotopic and ultrasonic) show filling defects.

Morphological criteria The typical lesion is an area of necrosis; the amoebas are found at the periphery. Most of the abscesses are bacteriologically sterile and inflammatory reaction is minimal. The pus is pinkish-brown (anchovy-colour), thick, and is of glutinous material. Liver substance, not involved by the parasite, shows little abnormality apart from some congestion and edema which explain the hepatomegaly so frequent in this condition. Healing, after therapy, leaves no distortion and no tendency to form scar tissue. Conclusive pathological proof of amoebic hepatitis, acute or chronic is lacking.

Etiological criteria Identification of Entamoeba histolytica.

## 1.4 VASCULAR LESIONS OF THE LIVER

### 1.4.1 Veno-occlusive disease

Clinical criteria Seen primarily in young children, but the disease has also been reported in older children and adults. The majority of cases have been seen in Jamaica. The acute stage is characterized by hepatomegaly, sudden onset of ascites, and usually pain. Splenomegaly may or may not be present. The subacute and chronic stages present much like other forms of cirrhosis.

Functional criteria Mild jaundice may be present in the acute stage. X-ray and endoscopic techniques demonstrate esophageal varices when portal hypertension is present.

Morphological criteria Obliteration of the centrilobular and sublobular hepatic veins with loose fibrous tissue. Early in the disease there is some centrilobular necrosis and sinusoidal congestion. Later on, centrilobular fibrosis, with dense collagenous tissue surrounding hepatic veins, develops. In the chronic stage, nonportal cirrhosis occurs. Further loss of parenchyma and secondary circulatory changes may obscure the original centrilobular fibrosis.

Etiological criteria History of exposure to pyrrolozidine alkaloids from crotalaria and senecio plants. Morphological evidence of a nonthrombotic obliterative lesion of the small hepatic vein.

## 1.5 METABOLIC DISORDER

### 1.5.1 Iron storage disease

#### a) Idiopathic haemochromatosis

Clinical criteria Usually occurs in middle-aged or elderly males (10% female) presenting with hepatomegaly, skin pigmentation, and hypogonadism; sometimes with diabetes mellitus. Testes are atrophied and body hair is scanty. Younger patients may show cardiac arrhythmias and failure. Arthritis is associated with the deposition of calcium siphosphate in synovia (pseudogant).

Functional criteria Serum iron levels are increased with 90% saturation of the serum iron-binding protein. Serum ferritin values are raised. Excessive body iron stores may be shown. Skin biopsy shows melanin and iron in the subderma. Pituitary hypofunction is responsible for the gonadal atrophy and occasional adrenal and thyroid failure.

Morphological criteria The liver is enlarged and reddish in colour. Early portal zone fibrosis is present and of "holly leaf" shape. Later cirrhosis develops. Increased concentration of iron in the liver biopsy. Hepatocellular carcinoma may be a late complication.

Etiological criteria The mode of inheritance could be dominant, intermediate, or recessive. Iron overload can be demonstrated in siblings, but overt disease is unusual in the second generation. The etiology is unknown, intestinal absorption of iron is increase, but the mechanism is unknown. Intestinal mucosal defect is suggested.

#### b) Haemochromatosis of the alcoholic

Clinical criteria Features of chronic alcoholic liver disease. At times, there is skin pigmentation. Diabetes mellitus is unusual.

Functional criteria Those of chronic hepatocellular disease. Serum iron level is raised. Body stores of iron are increased, but less so than in idiopathic haemochromatosis.

Morphological criteria Moderate deposits of hepatocellular and reticuloendothelial iron in association with features of chronic alcoholic liver disease.

Etiological criteria Increased iron absorption is related to chronic hepatocellular failure and, possibly, to pancreatic disease. There may be an increased ingestion of iron with alcoholic beverages.

#### c) Bantu haemochromatosis

## 1.6 TUMOURS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

### 1.6.1 Hepatocellular carcinoma

Clinical criteria The tumour occurs more frequently in males than in females and in greater frequency in certain parts of the world such as south east Asia and Africa. Association with cirrhosis is frequent but variable. Hepatomegaly, usually with a right upper quadrant or epigastric mass, and pain are present with anorexia and weight loss. Fever and jaundice may be present in about one-third or less of the patients. Ascites (frequently bloody) and other signs of portal hypertension may occur. Hepatocellular carcinoma should be suspected in any patient with cirrhosis showing clinical deterioration. Other unusual features may include signs of virilism and acute abdominal catastrophe due to haemoperitoneum,

signs and symptoms of hypoglycaemia, and hypercalcaemia.

Functional criteria Laboratory tests are abnormal and reflect underlying cirrhosis. Serum proline hydroxylase activity may be greatly increased. Hypoglycaemia, erythrocytosis, hypercholesterolaemia, hypercalcaemia and dysproteinaemia are rarely found. Elevated blood chorionic gonadotrophin is occasionally noted. Abnormally high levels of alphafetoprotein, present in 75% to 95% of patients, is virtually diagnostic when detected in the appropriate clinical setting. A liver scan may show areas of diminished uptake, which may be helpful but not diagnostic. Celiac angiography can accurately demonstrate vascular abnormalities suggestive of tumour.

Morphological criteria Trabecular, pseudoglandular, solid, cirrhosis, pleomorphic and clear cell tumours may be present.

Etiological criteria The exact etiology remains unknown, but the following conditions have been associated with a high incidence of hepatocellular carcinoma:

1. Cirrhosis
2. Haemochromatosis
3. Mycotoxins and plant toxins
4. Viral hepatitis (especially hepatitis B)
5. Certain androgenic steroids
6. Thorotrast
7. Alcoholism

#### 1.6.2 Cholangiocarcinoma

##### Clinical criteria

1. Relatively frequent in the Orient
2. No sex predominance
3. It is not uncommonly associated with cirrhosis
4. Usually occurs in adults and presents with an epigastric or upper right quadrant mass usually associated with jaundice.
5. Anorexia with weight loss and ascites may be present.
6. Haemoperitoneum is uncommon.

Functional criteria Functional impairment of the liver is not severe except late in the course. Angiography and liver scan may be helpful.

Morphological criteria Well-differentiated tumour composed of columnar to cuboidal epithelial cells with moderate amounts of clear or slightly granular basophilic cytoplasm.