The morphology of cirrhosis¹

Recommendations on definition, nomenclature, and classification by a working group sponsored by the World Health Organization

P. P. ANTHONY, K. G. ISHAK, N. C. NAYAK, H. E. POULSEN, P. J. SCHEUER, AND L. H. SOBIN

From the Bland-Sutton Institute of Pathology, Middlesex Hospital Medical School, London, the Armed Forces Institute of Pathology, Washington, the All India Institute of Medical Sciences, New Delhi, Hvidovre Hospital, University of Copenhagen, The Royal Free Hospital School of Medicine, London, and the Cancer Unit of the World Health Organization, Geneva

SUMMARY This memorandum provides guidelines on the definition, nomenclature, and classification of cirrhosis, chronic hepatitis, and hepatic fibrosis. These are considered according to morphological characteristics and aetiology. It is hoped that this system will serve as a standard for diagnostic, research, and epidemiological purposes. The relationship of cirrhosis to liver cell carcinoma is briefly discussed and the possible morphological markers of an increased risk of malignancy are defined.

The aim of this paper is to provide guidelines for the pathologist on the definition, nomenclature, and classification of hepatic cirrhosis and related conditions. The many systems of classification in current use (Table 1) hinder rather than help comparisons of published data and the evaluation of relationships between cirrhosis and liver cancer. Different words have been used to describe essentially similar features, and a single word is sometimes applied to a variety of forms. The terminology of many classifications is based on a mixture of pathogenesis, morphology, and aetiology (for example, 'post-necrotic', 'portal', and 'biliary' cirrhosis). There is, therefore, a need for a logical and readily reproducible system.

In the preparation of these guidelines, comments and criticisms from a number of other pathologists and hepatologists throughout the world have been taken into account. An attempt has been made to study a wide variety of material from different geographical areas.

Cirrhosis

DEFINITION

It is generally agreed that cirrhosis is best defined in

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morphological terms but, in spite of many attempts, no single definition exists that does not require further elaboration or qualification. The essential features are considered to be parenchymal necrosis, regeneration, and diffuse fibrosis, resulting in disorganisation of the lobular architecture throughout the whole of the liver. There are many who consider that the altered vascular relationships are an equally or even more important feature. All would agree, however, that cirrhosis is a chronic, progressive condition that results in liver cell dysfunction and portal hypertension. Instances of regression from established cirrhosis to normal liver architecture are rare and open to doubt.

In this article *cirrhosis is defined as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.*

The process is *diffuse* in the sense that it involves the whole organ. Focal lesions, eg, focal nodular hyperplasia, do not constitute cirrhosis. Diffuse nodularity without fibrosis, eg, the nodular hyperplasia associated with Felty's syndrome or induced by drugs and chemicals, is not cirrhosis, nor is diffuse fibrosis without nodularity, eg, hepatoportal sclerosis. There are conditions in which both generalised fibrosis and nodularity are present, eg, congenital hepatic fibrosis, but which are not considered to constitute cirrhosis because the lobular architecture is largely maintained.

It is generally assumed that *fibrosis* is the result of

Table 1 *An approximate comparison of terms used to designate various types of cirrhosis*

Nutritional	Septal	Laennec's types A, B, C, D	Regular	Micronodular	Type C	Laennec's, fatty, alcoholic, portal, monolobular, diffuse, uniform, finely nodular, florid Nonalcoholic, toxic, multilobular, atrophic, trabecular, variform, coarsely nodular, healed yellow atrophy
Postnecrotic	Postcollapse	Postnecrotic	Irregular	Macronodular	Type A	
Posthepatitic	Incomplete septal				Type B	

necrosis, and some definitions of cirrhosis include the presence of necrosis as a criterion. Whatever the mechanism of fibrosis and whatever the initial lesion may have been, evidence of necrosis may no longer be apparent by the time a cirrhotic liver is examined. Necrosis is, therefore, omitted from the morphological definition of cirrhosis. Fibrosis is generalised throughout the liver, but it is variable in extent and distribution, eg, focal, diffuse, multilobular (see Glossary, pages 411-412).

The *nodules* of a cirrhotic liver lack normal lobular organisation and are surrounded by fibrous tissue. They are often referred to as 'regenerative' or 'hyperplastic', terms that imply concepts of pathogenesis rather than serve morphological definition. They cannot be truly regenerative in that restitution to normal liver tissue does not occur. Histological evidence of growth is commonly seen in the form of liver cell plates more than one cell thick, and pressure on surrounding structures may be evident. Some nodules may contain portal tracts and efferent veins abnormally related to each other. These structures may be either pre-existing or newly formed. It is not known for certain just how the nodules of cirrhosis do arise but it is likely that several mechanisms take part. Regrowth after necrosis, dissection of lobules by fibrosis, and remodelling associated with altered vascular relationships are probably all operative.

CLASSIFICATION

In the past, cirrhosis has often been classified on the basis of a mixture of pathogenesis, morphological appearances, aetiology, and eponyms (Table 1). Such mixtures are confusing and undesirable, and any one classification should be restricted to a particular base or axis. Pathogenetic terms (for example, post-hepatitic) are often difficult to apply because the pathogenesis of a particular cirrhosis may no longer be evident at the time of examination. Morphological and aetiological classifications should be regarded as complementary rather than as alternative, and both should be separately applied to the individual example, as outlined in the sections that follow. There is evidence that the same morphological pattern can be produced by a variety of causal agents and that a single agent can produce a variety of morphological

appearances, sometimes in the same patient. The complete characterisation of cirrhosis in an individual case should take into account the morphological features, aetiology, stage of evolution, activity, and complications of the disease.

Morphology

Subdivision of cirrhosis into different morphological categories is better described as characterisation rather than classification, for the reasons already noted. These categories do not represent different diseases but are stages in the development of a single disease process. The morphological characteristics of any one cirrhotic liver result from the operation and interplay of a number of independent factors, such as liver cell necrosis, hyperplasia, and fibrosis. There is thus a range of morphological patterns rather than a small number of rigid categories.

There are nevertheless reasons for subdividing cirrhosis on a purely morphological basis. It enables patterns to be studied epidemiologically, and may allow their correlation with aetiological agents. Morphological patterns may reflect aetiology and stage of evolution and prognosis, and also affect the ease or difficulty of histological diagnosis. This is usually easy when nodules are small, regular, and closely set but can be extremely difficult when the nodules are large in relation to the sample. Liver cancer is found more often in cirrhotic livers with large nodules.

Among the systems of morphological categories currently in use, the division of cirrhosis into micronodular and macronodular forms is preferred. This is a simple system, readily understood, and already used in many parts of the world. It can be applied at both a macroscopic and microscopic level.

(a) *Micronodular pattern* (Figs 1, 3, 6). A cirrhotic liver in which *nearly all* the nodules are less than 3 mm in diameter. This somewhat arbitrary figure has been chosen deliberately in order to avoid forcing the majority of cirrhotic livers into a macronodular category; this is what happens when a maximum diameter of 1 or 2 mm is chosen. A striking feature is the regularity of the nodule size. Micronodules may rarely contain portal tracts (for example, in cirrhosis

due to venous outflow obstruction) or efferent veins (for example, in biliary obstruction) but generally they lack any normal structures. Many examples of cirrhosis associated with alcoholism, biliary obstruction, venous outflow obstruction, haemochromatosis, and Indian childhood cirrhosis fall into the micronodular category. There is a tendency for the micronodular pattern of cirrhosis to be seen relatively early in the course of the disease and for larger nodules to develop later, but there are exceptions to this rule.

(b) *Macronodular pattern* (Figs. 2, 4, 5, 7). Many nodules are over 3 mm in diameter but the size varies considerably and some nodules measure several centimetres. They may contain portal structures and efferent veins, but these are abnormally related to each other. Two subcategories can be recognised. In one, the macronodules are divided by slender, sometimes incomplete septa, which link mainly portal tracts. The fine, reticulate pattern of fibrosis makes nodularity unapparent to naked-eye examination and renders histological diagnosis difficult. This seems to

be a common pattern in the tropics and subtropics ('incomplete septal' or 'posthepatic' pattern). In the other subcategory, the liver is more coarsely scarred, with obvious macronodules surrounded by broad fibrous septa. These may contain several portal tracts. This pattern has been assumed to result from necrosis of large areas of parenchyma ('postcollapse' or 'postnecrotic' pattern).

(c) *Mixed pattern*. When micro and macro nodules are present in *approximately* equal proportions the term 'mixed' may be applied.

The size of the liver, as seen *post mortem*, is of some additional interest. Micronodular cirrhotic livers are often normal in size or enlarged, particularly when fatty. Macronodular cirrhotic livers may be normal but are often reduced in size, especially when coarsely scarred.

Aetiology

The first of the three categories listed below includes established associations between aetiological factors and cirrhosis, but the precise nature of the associa-

Fig. 1

Fig. 1 Cirrhosis with a micronodular pattern in a middle-aged male alcoholic; nearly all the nodules are less than 3 mm in size (indicated by scale).

Fig. 2

Fig. 2 Cirrhosis with a macronodular pattern in an elderly man with a history of hepatitis many years before, but tests for hepatitis B antigen negative; many of the nodules are larger than 3 mm in diameter (indicated by scale).

Fig. 3

Fig. 3 Cirrhosis with a micronodular pattern in an alcoholic; the nodules are almost uniform, lack any normal structure, and are roughly lobular or sublobular in size. Reticulin $\times 24$.

Fig. 4

Fig. 4 Cirrhosis with a macronodular pattern; no history of hepatitis, but hepatitis B antigen present on testing; the macronodules are divided by slender, sometimes incomplete septa ('incomplete' or 'posthepatitic' pattern). Reticulin $\times 24$.

tions and of the pathogenetic mechanisms involved is often far from clear. Aetiological diagnosis is usually reached by a combination of epidemiological, clinical, biochemical, immunological, and histological investigations.

In the second category the association between an aetiological agent and cirrhosis is debatable or controversial. The role of autoimmunity as an initiating cause of cirrhosis remains unproven, although it is likely that immunological mechanisms play an important part in the perpetuation of chronic liver disease due to a variety of causes. It is doubtful if malnutrition by itself is ever a cause of cirrhosis in man. Protein deficiency, as seen in Kwashiorkor, produces gross fatty change in the liver but it does not lead to chronic liver disease. Mycotoxins, of which aflatoxin is the best known, are a potent cause of liver cancer in animals, and can produce cirrhosis in some species. Their exact role in human cirrhosis is still uncertain. Several parasitic diseases can give rise to hepatic fibrosis. In the case of schistosomiasis,

this fibrosis may be diffuse, extensive, and clinically important. Whether cirrhosis can also result from schistosomiasis without the intervention of other aetiological factors is not proved.

The third category includes cirrhosis with a well-defined geographical, clinical, or morphological pattern but without an established cause. It also includes cirrhosis without a well-defined pattern and in which it has not proved possible to identify a cause. Such cases have been labelled 'cryptogenic', but this group presumably includes several different, potentially identifiable aetiologies and should not be regarded as a disease entity.

(a) *Cirrhosis with established aetiological associations.* The following factors are recognised:

Viral hepatitis

Alcoholism

Metabolic disorders (eg, haemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, type IV glycogenosis, galactosaemia)

Fig. 5 Cirrhosis with a macronodular pattern, aetiology unknown; the macronodules are separated by broad fibrous septa ('postcollapse' or 'postnecrotic' pattern). Reticulin $\times 33$.

Fig. 6 Characteristic fragmentation of a needle biopsy specimen in a case of cirrhosis with a micronodular pattern. Such fragments are wholly or partially surrounded by fibrosis, which may be recognised only with the help of reticulin or collagen stains. Reticulin $\times 50$.

Fig. 7 Adjacent areas of liver parenchyma in cirrhosis may grow at different rates and produce nodular remodelling, shown in the right half of the field. Reticulin $\times 150$.

Biliary disease (intra- and extra-hepatic)
 Venous outflow obstruction (veno-occlusive disease, Budd-Chiari syndrome)
 Toxins and therapeutic drugs (eg, pyrrolizidine alkaloids, methotrexate, oxyphenisatin, alpha methyl dopa)
 Intestinal bypass operations for obesity

(b) *Debatable aetiological factors*. Examples are:

Autoimmunity
 Mycotoxins
 Schistosomiasis
 Malnutrition

(c) *Cirrhosis of unknown aetiology*

- (i) *With well-defined pattern*—Indian childhood cirrhosis
- (ii) *Without well-defined pattern*—'cryptogenic' cirrhosis

DIAGNOSIS

Recognition of cirrhosis

Recognition is usually easy at *necropsy*, although the incomplete septal variant of the macronodular pattern may present some difficulties, especially in the absence of stains for collagen and reticulin fibres. The micronodular pattern is sometimes difficult to

recognise with the naked eye. Surgical *wedge biopsies* can be misleading since there is sometimes increased fibrous tissue in the subcapsular area, and the appearances may mimic those of cirrhosis. The problem is usually resolved if the biopsy is sufficiently large, because the changes do not extend into the deeper part of the liver except in cirrhosis. The recognition of cirrhosis may be difficult in *needle biopsy specimens*, especially in those taken with a needle of the Menghini type. This needle tends to aspirate soft liver parenchyma preferentially, leaving the tougher connective tissue behind. This is a particular problem when nodules are large. Helpful features for the recognition of cirrhosis in a needle biopsy specimen include the following:

(a) *Presence of parenchymal nodules* separated by fibrous septa. When several well-defined nodules are seen the diagnosis of cirrhosis is virtually certain, but an occasional rounded area of parenchyma may be seen in any severe fibrotic liver.

(b) *Differences in liver cell size and appearance* between one area and another. This may be accompanied by liver cell dysplasia (see below) or by evidence of active growth (thickened liver cell plates, evidence of compression).

(c) *Fragmentation of the biopsy specimen* with or without fibrous tissue at the margins of the frag-

Fig. 8a Swollen, 'ground-glass' hepatocytes showing finely granular, eosinophilic cytoplasm due to the presence of hepatitis B surface antigen. Haematoxylin and eosin $\times 640$.

Fig. 8b 'Ground-glass' hepatocytes stained with Shikata's orcein technique $\times 400$.

Fig. 9 Alcoholic hepatitis: Inflamed fibrous septa dissect the liver into nodules; there is also extensive diffuse fibrosis within the parenchyma; liver cells show fatty change. H and E $\times 100$.

Fig. 10 Alcoholic hepatitis; note fibrosis extending from a portal tract (bottom left) to an area once occupied by a central vein which is now obliterated (top right). This change has been referred to as 'centrilobular hyaline sclerosis', as fibrosis is often rather hypocellular and may be quite dense. Masson's trichrome $\times 160$.

ments or partially surrounding them. If the fibrous tissue is scanty, it may be recognised only with the help of reticulin or collagen stains.

(d) *Fibrous septa* traversing the specimen, often with abnormal lobular architecture, for example, absence of portal tracts or of normal vascular relationships.

(e) *Altered architecture and vascular relationships* without septum formation.

The precise point at which pre-cirrhotic changes become established cirrhosis cannot always be determined.

Morphological pattern

This is easier to determine in necropsy material and in wedge biopsies than in needle biopsy specimens, because of the problem of sampling. It is not possible to deduce the morphological pattern in the whole liver with confidence from a small specimen. Apparent resolution of cirrhosis after treatment should be interpreted with great care, because the passage of time can lead to increase in nodule size and difficulty in biopsy diagnosis.

Aetiology

This paper does not set out to give a complete description of the characteristics of all forms of cirrhosis, but the following guidelines are offered to

highlight histological features which may help to determine some important causes (Table 2).

(a) *Viral hepatitis* (Figs 8a, 8b). Demonstration of the hepatitis B surface antigen in liver cells by empirical stains or immunohistological methods is helpful, but the antigen may also be found in carriers who have cirrhosis due to other causes. Failure to demonstrate the antigen does not exclude a viral aetiology. Its presence may be suspected by the finding of 'ground-glass' hepatocytes. At present, tests for other antigens such as core antigen or the 'e' antigen are not yet widely available.

(b) *Alcoholism* (Figs 9, 10, 11). A combination of fatty change, a micronodular pattern, and areas of relatively hypocellular fibrosis should suggest this cause. Later in the course of the disease cirrhosis is often macronodular, and fat may be scanty or absent. Features of chronic active hepatitis may be superimposed. The most helpful histological feature is the presence of alcoholic hepatitis, characterised by liver cell swelling with or without fatty change, pericellular fibrosis, Mallory's hyalin, and focal infiltration by neutrophils. Hyalin is not always identifiable and is also found in other conditions. Small, PAS-negative globules, which represent greatly enlarged mitochondria, may be seen at any stage. Siderosis is common.

(c) *Haemochromatosis* is characterised by increas-

Table 2 Morphological markers and aetiology of cirrhosis

Aetiology	Common morphological pattern*	Fat	Cholestasis	Iron	Copper	Acidophilic bodies	Xanthomatous change	PAS+ globules	PAS- globules	Mallory's hyalin	Ground-glass hepatocytes
Viral hepatitis	Macro or Micronodular	-	-	-	-	+	-	-	-	-	+†
Alcoholism	Micro or Macronodular	+	±	±	-	±	-	-	±	+	-
Haemochromatosis	Micronodular	±	-	+	-	-	-	-	-	-	-
Wilson's disease	Macronodular	±	±	-	±	+	-	-	-	+	-
α-1-Antitrypsin deficiency	Micro or Macronodular	±	±	-	±	±	-	+	-	±	-
Primary biliary cirrhosis	Micronodular ('Biliary')	-	±	-	+	-	+	-	-	±	-
Secondary biliary cirrhosis	Micronodular ('Biliary')	-	+	-	±	-	+	-	-	±	-
Venous outflow obstruction	Micronodular ('Reversed')	-	-	-	-	-	-	-	-	-	-
Intestinal bypass operation	Micronodular	+	-	-	-	±	-	-	-	±	-
Indian childhood cirrhosis	Micronodular	-	±	-	±	-	-	-	±	+	-

- usually absent; ± may be present; + usually present.

*Progression is generally from micro to macronodular.

†May also be seen in 'healthy' carriers.

ing portal fibrosis and septum formation with iron in liver cells, phagocytes, and bile-duct epithelium. Inflammation is usually slight, and, apart from the siderosis, the parenchyma is little altered.

(d) *Wilson's disease* (Fig. 12a). The morphological pattern of cirrhosis varies, but large nodules are common. Fatty change, nuclear vacuolation, and Mallory's hyalin may be prominent. The cirrhosis may show considerable activity, with piecemeal necrosis and inflammatory infiltration. Increased amounts of copper can sometimes be demonstrated, but copper is also found in some other conditions, notably primary biliary cirrhosis and other examples of chronic cholestasis.

(e) *Alpha-1-antitrypsin deficiency* (Fig. 12b). In homozygous (Pi ZZ) subjects the liver may be normal or abnormal, and a wide variety of disease patterns is found, ranging from hepatitis to cirrhosis. The latter sometimes resembles the cirrhosis which follows prolonged biliary obstruction. Intracytoplasmic globules of faintly eosinophilic material, which are positive with the PAS stain after diastase digestion, are characteristic. Similar globules have rarely been found in the absence of liver disease or emphysema.

(f) *Primary biliary cirrhosis* (Fig. 13). Small and medium-sized bile ducts are hyperplastic or necrotic and are surrounded and infiltrated by plasma cells, lymphocytes, eosinophil leucocytes, and epithelioid cells. Ill-defined or well-organised granulomas form, usually near the damaged bile ducts. The lesions are focal and may be missed unless several sections are examined. Later, the damaged ducts are replaced by loose lymphoid aggregates, there is increasing fibrosis, and cholestasis is present at the periphery of the lobules. Mallory's hyalin sometimes is prominent and stains for copper are often positive. Lobular architecture remains intact for long periods. When cirrhosis is established paucity of bile ducts may suggest that it is primary rather than secondary to longstanding obstruction.

(g) *Secondary biliary cirrhosis* (Fig. 14). Portal fibrosis and septum formation predominate, and parenchymal alterations are often slight. There may be morphological cholestasis due to persisting obstruction to bile ducts, but this is not invariable or necessary for diagnosis. Lobular architecture survives for long periods, and groups of adjacent nodules form complex parenchymal islands resembling the pieces of a jig-saw puzzle.

(h) *Venous outflow obstruction* (Fig. 15). Helpful diagnostic features include a micronodular pattern with predominantly centrilobular fibrosis, which give the appearance of 'reversed lobulation'. Sinusoids around the fibrotic areas are markedly dilated. Collagen staining is necessary for accurate assessment of

lobular and vascular relationships and may reveal efferent veins with subintimal fibrosis, thrombosis, or fibrous obliteration.

(i) *Toxins and therapeutic drugs*. These can give rise to such a large variety of patterns and appearances that no brief outline can be given here. Drugs should be suspected as possible aetiological agents in all cases of cirrhosis.

(j) *Intestinal bypass operations for obesity*. Fatty change is common, and hepatic fibrosis may develop. Cirrhosis is rare, and the appearances may be identical with those seen in the alcoholic.

(k) *Indian childhood cirrhosis*. The cirrhosis is typically micronodular in pattern, and there is fibrosis around individual cells or small groups. Mallory's hyalin is prominent, widespread, and not recognisably centrilobular as it is in alcoholic hepatitis. Fatty change is usually absent.

Activity

This is measured by the degree of liver cell destruction and inflammatory infiltration, and its assessment is an important part of diagnosis. Piecemeal necrosis at the margins of septa is usually considered the most relevant form of necrosis in this respect, but other forms (eg, acidophilic bodies, focal necrosis) should also be taken into account. In cirrhosis due to alcoholism, for example, activity in the early stages may be largely in the form of alcoholic hepatitis, while later, perhaps after improved drinking habits, piecemeal necrosis and infiltration by lymphocytes and plasma cells may become more important. It is customary to grade activity in biopsy specimens as slight, moderate, or severe, but it should be remembered that activity may have been modified by treatment and that the sample of liver tissue may not be representative.

Complications and secondary phenomena

(a) *Ischaemic necrosis*. This may be focal, with coagulative necrosis of small groups of cells, or involve whole nodules or centres of nodules. It often, though not invariably, follows gastrointestinal bleeding.

(b) *Siderosis*. Intense liver-cell siderosis may be seen in alcoholic liver disease and it also follows portal systemic shunt operations.

(c) *Biliary obstruction*. This can develop as a result of cholelithiasis or distortion of intrahepatic bile ducts. Histologically visible cholestasis may also be due to drug therapy.

(d) *Infection*. There is an increased risk of viral and bacterial infections in cirrhosis, which may be evident on histology.

CIRRHOSIS AND CANCER OF THE LIVER
Available evidence indicates that cirrhosis is linked

Fig. 11 Alcoholic hepatitis: several hepatocytes contain clumps of Mallory's hyalin in their cytoplasm. Note the presence of neutrophil polymorphs, a characteristic feature. H and E $\times 640$.

with hepatocellular (or liver-cell) carcinoma but not with cholangiocarcinoma (intrahepatic bile duct carcinoma). The increased risk of malignancy may depend on the aetiology and the duration of the cirrhotic process.

Liver-cell hyperplasia in cirrhosis sometimes produces distinct, tumour-like nodules made up of double liver-cell plates with increased cytoplasmic basophilia. The term 'adenomatoid hyperplasia' has been applied to such appearances. There is no evidence that it is associated with an increased risk of malignancy.

Malignancy is often associated with, and may be preceded by, *liver cell dysplasia* (Fig. 16). The term refers to cellular enlargement, which affects both nucleus and cytoplasm, together with nuclear pleomorphism, multinucleation, and occasional mitoses. These changes may involve groups of liver cells or, less commonly, whole cirrhotic nodules. Liver-cell dysplasia is most frequently seen in macronodular cirrhosis, at an earlier age than hepatocellular carcinoma, and more commonly in males. It is also more frequently seen in areas where hepatocellular carcinoma is common, and its presence has been associated with the hepatitis B antigen.

Chronic hepatitis

DEFINITION

Chronic hepatitis has been defined as inflammation of the liver continuing without improvement for at least six months. Many examples of chronic hepatitis follow acute hepatitis, but in others no acute attack can be identified clinically. The transition of chronic hepatitis to cirrhosis is often difficult to define.

CLASSIFICATIONS

Morphology

Chronic hepatitis is normally classified according to histopathological features, although a complete diagnosis requires both histological and clinical data. Two main groups are recognised:

(a) *Chronic persistent hepatitis* (Fig. 17). This is a somewhat non-specific picture characterised by portal tract expansion and inflammatory cell infiltration. There is a variable and often slight degree of liver cell damage as shown by focal necrosis and acidophilic bodies. Lobular architecture remains intact, and piecemeal necrosis and fibrosis are very slight or absent. When more severe lobular changes of the type seen in acute hepatitis are present, the term

Fig. 12a *Wilson's disease: increased amounts of copper (dark granules) demonstrated by rhodanine. $\times 640$.*

Fig. 12b *Alpha-1-antitrypsin deficiency; heavy, intracytoplasmic, PAS-positive deposits in hepatocytes. PAS after diastase digestion $\times 640$.*

Fig. 13 Primary biliary cirrhosis; established cirrhosis with lamellar fibrosis surrounding a parenchymal nodule. Note absence of bile ducts and presence of lymphoid aggregates. H and E $\times 100$.

Fig. 14 Characteristic 'jigsaw' pattern of biliary cirrhosis, primary or secondary, in which outlines of parenchymal nodules appear to fit together as pieces in a puzzle. Masson's trichrome $\times 40$.

Fig. 15 *Venous outflow obstruction: atrophy, collapse, and fibrosis link centrilobular areas, giving rise to 'reverse lobulation'. Nodules of liver parenchyma contain portal tracts (top right). H and E $\times 100$.*

Fig. 16 *Liver cell dysplasia: a group of abnormal liver cells with large, hyperchromatic nuclei stand out in a field of cirrhotic macronodules. H and E $\times 160$.*

Fig. 17 Chronic persistent hepatitis: expanded portal tract infiltrated by mononuclear inflammatory cells. H and E $\times 250$.

'chronic lobular hepatitis' has been used by some authors. Chronic persistent hepatitis carries a good prognosis, and only a minority of patients progress to chronic active hepatitis.

(b) *Chronic active hepatitis* (Figs 18, 19). Inflammation affects portal tracts but is also seen in the lobules. The infiltrate is typically rich in lymphocytes and plasma cells. There is more fibrosis than in chronic persistent hepatitis, the lobules are involved, and lobular architecture is often altered. Piecemeal, bridging, and multilobular necrosis may be seen. Chronic active hepatitis has a worse overall prognosis than chronic persistent hepatitis and tends to progress to cirrhosis, but the milder forms may regress to chronic persistent hepatitis or fibrosis, especially after treatment. Chronic hepatitis and liver cancer rarely co-exist.

Aetiology

The lack of specificity of the picture of *chronic persistent hepatitis* has been referred to above, and similar appearances can be found in so-called non-specific hepatitis due to a large variety of causes. *Chronic active hepatitis* may follow acute viral hepatitis, often identifiable as type B. It may be due to drugs (for example, oxyphenisatin, alpha methyl dopa, isonia-

zid) or associated with chronic inflammatory bowel disease. In a minority of patients with Wilson's disease and in some alcoholics, the histological picture is predominantly that of chronic active hepatitis. In patients with no known aetiological factors but with high serum levels of abnormal antibodies (for example, against smooth muscle) and multisystem disease, a primary disturbance of immunity has been postulated ('lupoid hepatitis').

DIAGNOSIS

Certain difficulties should be borne in mind when needle biopsy specimens are examined:

1 The histological distinction between acute and chronic hepatitis is often difficult in the first months after an acute attack and tends to become easier with time.

2 The lesions of chronic persistent and chronic active hepatitis may be unevenly distributed throughout the liver, and an incorrect diagnosis may be made if the sample is small.

3 Treatment, for example with corticosteroids, can suppress manifestations of activity and lead to a falsely optimistic impression.

4 It may be difficult to assess whether cirrhosis is present or absent on the basis of a needle biopsy specimen in chronic active hepatitis.

Fig. 18 *Chronic active hepatitis: liver parenchyma is being destroyed by chronic inflammation and fibrosis, which spread out from portal tracts (bottom right). Liver cells are swollen and some are arranged in gland-like structures or rosettes. H and E $\times 250$.*

Fig. 19 *Bridging necrosis linking portal tract (left) with central vein (right) in a case of viral hepatitis B evolving into cirrhosis. H and E $\times 150$.*

Hepatic fibrosis

DEFINITION

Fibrosis is defined as the presence of excess collagen due to new fibre formation. It is to be distinguished from collapse of the pre-existing reticulin framework of the liver. Such collapse, however, may be followed by active fibroplasia. Used as a nosological term, fibrosis excludes the presence of cirrhosis or chronic hepatitis. Generally, fibrosis by itself causes little in the way of clinical symptoms or disturbances of liver-cell function, but portal hypertension can be produced by fibrosis alone, as in the case of schistosomiasis, hepatoportal sclerosis, or congenital hepatic fibrosis (Fig. 20).

CLASSIFICATION

Morphology

Fibrosis can be classified according to its location eg, diffuse, focal, bridging etc. (see Glossary.)

Aetiology

Fibrosis is a component of many forms of liver injury rather than a disease in itself. Aetiological classifications are, therefore, apt to be lengthy and somewhat

superfluous since they correspond closely to classifications of liver disease in general. It is pertinent, however, to state that, *in addition* to the causes of cirrhosis already outlined, the following causes of hepatic fibrosis can be recognised:

congenital, eg congenital hepatic fibrosis

metabolic, eg, mucoviscidosis

inflammatory, eg, sarcoidosis, tuberculosis, and other infectious disease

parasitic, eg, schistosomiasis

toxins and drugs, eg, vinyl chloride, Thorotrast, methotrexate

vascular, eg, hepatoportal sclerosis, veno-occlusive disease, infarcts

physical, eg, radiation

HEPATIC FIBROSIS AND CANCER OF THE LIVER

Several agents, notably vinyl chloride, arsenic, and Thorotrast, cause fibrosis and tumours of the liver. The latter have been mainly angiosarcomas, but rare instances of hepatocellular carcinoma and cholangiocarcinoma are also on record.

Glossary

acidophilic body, degenerate liver cell with rounded

Fig. 20 Congenital hepatic fibrosis: tortuous fibrous septa, containing many dilated bile ducts, separate nodules of liver parenchyma that have largely retained their normal lobular organisation. H and E $\times 95$.

outline and deeply eosinophilic cytoplasm in which nuclear remnants may be present.

ballooning degeneration, swollen liver cell with clear cytoplasm. Nuclear lysis is frequent and the cell may rupture.

collapse, condensation of the reticulin framework of the liver following necrosis.

feathery degeneration, *see* xanthomatous change.

fibrosis, excess collagen due to new fibre formation.

It may be:

pericellular, fibrosis around individual cells or small groups of liver cells.

diffuse, pericellular fibrosis distributed over most or whole of the lobule.

focal, small areas of fibrosis inside lobules or nodules.

zonal, fibrosis consistently localised to a particular anatomical zone of the lobule.

periportal, fibrosis around portal tracts.

portal, fibrosis strictly confined to the portal tracts.

multilobular, fibrosis replacing several contiguous lobules.

bridging, fibrosis linking central to central, central to portal, or portal to portal areas.

periductal, concentric fibrosis around intrahepatic bile ducts.

'ground glass' hepatocyte, liver cell with cytoplasm which is wholly or partly translucent, lightly eosinophilic, and finely granular; a halo may be present just inside the cell membrane.

Mallory's hyalin, clumped, intertwined, deeply eosinophilic or amphophilic material in the cytoplasm of intact or necrotic liver cells, often surrounded by neutrophil leucocytes.

necrosis

focal, necrosis of individual or few liver cells.

zonal, necrosis consistently localised to a particular anatomical zone of the lobule.

confluent, merging of adjacent areas of necrosis.

piecemeal, focal necrosis at the junction of portal tracts or fibrous septa with parenchyma.

bridging, necrosis linking central to central or central to portal or portal to portal area.

reverse lobulation, appearance of well-defined areas of liver parenchyma with portal tracts at their centres.

rosette, a group of liver cells often surrounded by fine fibrous tissue and arranged around a bile canaliculus.

septum, a wall of fibrous tissue, usually seen as a band separating parenchymal nodules.

siderosis, stainable iron in the liver.

xanthomatous or pseudoxanthomatous change, swollen liver cell or Kupffer cell, showing small pyknotic nucleus and finely vacuolated and reticulated cytoplasm. Bile pigment may be present.

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A list of references is given below as a source of further reading. This is necessarily an arbitrary selection from the wealth of literature published on chronic liver disease. The authors apologise for the inevitable errors of omission and commission.

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- Requests for reprints to Dr L. H. Sobin, Cancer Unit WHO, 1211 Geneva, 27 Switzerland. Colour transparencies, prints, and microfiche are available from: Dr James R. McArthur, Associate Professor of Medicine, Assistant Director, Health Sciences Learning Resources Center, T-252 Health Sciences, University of Washington, Seattle, Wa 98105, USA.