

PROGRESS IN STANDARDIZATION : 5

The morphology of cirrhosis: definition, nomenclature, and classification

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This article provides guidelines on the definition, nomenclature, and classification of cirrhosis, hepatic fibrosis, and chronic hepatitis. Cirrhosis is considered according to its etiology and morphological characteristics, these being complementary rather than alternative.

The aim of this paper is to provide guidelines for the pathologist on the definition, nomenclature, and classification of hepatic cirrhosis and related conditions. Many systems of classification are in current use in different parts of the world (Table 1). This hinders comparisons of published data and the accurate evaluation of relationships between cirrhosis and liver cancer. Different words have been used to describe essentially similar features; thus 'septal', 'regular', 'uniform', 'micronodular', and 'monolobular' all refer to a particular morphological pattern of cirrhosis which is widely recognized. Conversely, a single word may be applied to a variety of forms; for example, 'portal' cirrhosis means one with regular, small nodules to some, but is used by others for any cirrhotic liver without further qualification. Another weakness of some classifications is that they are based on a mixture of pathogenesis,

morphology, and etiology (e.g. 'post-necrotic', 'portal', and 'biliary' cirrhosis). There is, therefore, a need for a logical and readily reproducible system.

The diagnosis of cirrhosis is considered important because it has serious clinical and prognostic implications which are different from those of hepatic fibrosis. Cirrhosis is held by most to be an irreversible state, and instances of regression from established cirrhosis to normal liver architecture are rare and open to doubt. Fibrosis and chronic hepatitis are both discussed separately at the end of the paper.

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 morphological terms but, in spite of many attempts, no single definition exists that does not require further elaboration or qualification. At the Fifth Pan-American Congress of Gastro-enterology,

the essential features were considered to be generalized involvement of the liver by concurrent parenchymal necrosis, regeneration and diffuse fibrosis resulting in disorganization of the lobular architecture. There are many who consider that the altered vascular relationships are an equally or even more important feature. In the publication '*Diseases of*

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the liver and biliary tract'^a, sponsored by the Fogarty International Center and the International Association for the Study of the Liver, no simple definition is attempted, but a lengthy explanation is given of what should be regarded as cirrhosis of the liver. All would agree, however, that cirrhosis is a chronic, progressive condition that results in liver cell failure and portal hypertension.

In this article *cirrhosis is defined as a diffuse process characterized 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, e.g., focal nodular hyperplasia, do not constitute cirrhosis. Nodularity without fibrosis, e.g., the nodular hyperplasia associated with Felty's syndrome or induced by drugs and chemicals, is not cirrhosis, nor is diffuse fibrosis without nodularity, e.g., hepatoportal sclerosis. Cirrhotic nodules do not develop simultaneously in all parts of the liver and the precise time of onset cannot be determined. The borderline between pre-cirrhotic lesions and cirrhosis is not always sharp and is particularly difficult to establish in biopsy material. Finally, there are conditions where both generalized fibrosis and nodularity are present, e.g., 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 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 generalized throughout the liver, but it is variable in extent and distribution, e.g., focal, diffuse, multilobular (see Glossary, pages 530-531). Fibrosis linking portal tracts with centrilobular areas is particularly important because it is associated with the development of portal-systemic vascular shunts within the liver, which play an important part in the pathological effects of the disease.

The *nodules* of a cirrhotic liver lack normal lobular organization and are surrounded by fibrous tissue. They are often referred to as 'regenerative' or 'hyperplastic', terms that imply concepts of patho-

genesis 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 either be 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 following necrosis, dissection of lobules by fibrosis, and remodelling associated with altered vascular relationships are probably all operative. The rate of development of fibrosis and abnormal parenchymal nodules varies in different forms of chronic liver disease. In prolonged biliary obstruction and haemochromatosis, for instance, fibrosis dominates the picture, parenchymal architecture is little altered, and nodules form late; by contrast, normal lobular architecture is usually lost early when cirrhosis follows alcoholic or viral hepatitis.

CLASSIFICATION

In the past, cirrhosis has often been classified on the basis of a mixture of pathogenesis, morphological appearances, etiology, 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 (e.g., post-hepatic) are often difficult to apply because the pathogenesis of a particular cirrhosis may no longer be evident at the time of examination. Morphological and etiological 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 characterization of cirrhosis in an individual case should take into account the morphological features, etiology, stage of evolution, activity, and complications of the disease.

Morphology

Subdivision of cirrhosis into different morphological categories is better described as characterization rather than classification, for the reasons already noted. These categories do not represent different

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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
postnecrotic	postcollapse	postnecrotic	irregular	macronodular	type A	nonalcoholic, toxic, multilobular, atrophic, trabecular, variform, coarsely nodular, healed yellow atrophy
posthepatic	incomplete septal				type B	

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 etiological agents. Morphological patterns may reflect etiology, 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 both at a macroscopic and a microscopic level.

(a) *Micronodular pattern* (Fig. 1, 3, 6, 7). 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* (Fig. 2, 4, 5, 8, 9). Many nodules are more than 3 mm in diameter, but 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 recognized. In one, the macronodules are divided by slender, sometimes incomplete septa that link mainly portal tracts. The fine, reticulate pattern of fibrosis makes nodularity inapparent to naked-eye examination and renders histological diagnosis difficult. This seems to be a common pattern in the tropics and subtropics ('incomplete septal' or 'post-hepatic' 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 was formerly assumed to result from necrosis ('post-collapse' or 'post-necrotic' 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 at 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.

Etiology

The first of the three categories listed below includes established associations between etiological factors and cirrhosis, but the precise nature of the associations, and of the pathogenetic mechanisms involved, is often far from clear. Etiological diagnosis is usually reached by a combination of epidemiological, clinical, biochemical, immunological, and histological investigations. The histological characteristics and markers are discussed under 'Diagnosis' (see pages 524-527). In the second category, the association between an etiological agent and cirrhosis is debatable or controversial. 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 etiologies and should not be regarded as a disease entity.

(a) *Cirrhosis with established etiological associations.* The following factors are recognized:

Viral hepatitis

Alcoholism

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

Biliary disease (intra- and extra-hepatic)

Venous outflow obstruction (veno-occlusive disease, Budd-Chiari syndrome)

Toxins and therapeutic drugs (e.g., certain pyrrolizidine alkaloids with allyl side chains, methotrexate, oxyphenisatine, alpha methyl dopa)

Intestinal by-pass operations for obesity

Other (e.g., sarcoidosis)

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

Autoimmunity

Mycotoxins

Schistosomiasis

Malnutrition

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, owing to

a variety of causes. Chronic active hepatitis, in which these mechanisms are probably important, is discussed separately in a later section. It should be regarded for the present as a pattern of disease rather than as an etiological entity.

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 etiological factors is not proven.

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. The pathogenesis of hepatic fibrosis and cirrhosis after intestinal by-pass operations for obesity is uncertain at present.

(c) *Cirrhosis of unknown etiology.*

(i) *With well-defined pattern*—Indian childhood cirrhosis

(ii) *Without well-defined pattern*—'cryptogenic' cirrhosis

DIAGNOSIS

Recognition of cirrhosis

Recognition is usually easy at *autopsy*, 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 recognize 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 severely 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* before or after processing, with or without fibrous tissue at the margins of the fragments or partially surrounding them. If the fibrous tissue is scanty, it may be recognized only with the help of reticulin or collagen stains.

(d) *Fibrous septa* traversing the specimen, often with abnormal lobular architecture, e.g., 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 autopsy 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. An impression may be gained that cirrhosis is incipient, or at an early stage of development, or fully developed. This can have a bearing on treatment, since incipient cirrhosis might be halted after removal of a causal agent, for example in haemochromatosis, before changes become irreversible. 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 increased difficulty in biopsy diagnosis. Few would accept that a liver with fully developed cirrhosis can ever revert to its normal architecture.

Etiology

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 that may help to determine some important causes (Table 2).

Table 2. Morphological markers and etiology of cirrhosis ^a

Etiology	Common morphological pattern ^b	Fat	Cholestasis	Iron	Copper	Acidophilic bodies	Xanthomatous change	PAS positive globules	PAS negative globules	Mallory's hyalin	Ground-glass hepatocytes
Viral hepatitis	macro or micronodular	-	-	-	-	+	-	-	-	-	+ ^c
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	-	±	-	±	-	-	-	±	+	-

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

^b Progression is generally from micro to macronodular.

^c May also be seen in "healthy" carriers.

(a) *Viral hepatitis* (Fig. 10, 11, 12). Demonstration of the hepatitis B surface antigen in liver cells is helpful, although 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 etiology. The antigen can be demonstrated by immunofluorescent and immunoperoxidase methods, by electron microscopy, and by a variety of empirical methods, such as aldehyde-fuchsin or orcein staining. 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. Apart from this, there are no specific markers for cirrhosis due to hepatitis viruses. The cirrhosis is often active at some stage (see under 'Activity' below, page 527). In areas of the world where hepatitis B is common, a macronodular pattern of cirrhosis usually predominates.

(b) *Alcoholism* (Fig. 13, 14, 15). 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. Fatty 'cysts' may remain evident in portal tracts. The most helpful histological feature is the presence of alcoholic hepatitis, characterized by liver cell swelling with or without fatty change, pericellular fibrosis, Mallory's hyalin, and focal infiltration by neutrophils. Hyalin is also found in other conditions (see Table 2). In the pre-cirrhotic liver, changes of alcoholic hepatitis are typically centrilobular, but once cirrhosis has developed the precise location is less clear. Small, PAS-negative globules which represent greatly enlarged mitochondria may be seen at any stage. Siderosis is common.

(c) *Haemochromatosis* (Fig. 30). Primary or familial haemochromatosis can usually be distinguished from cirrhosis of the alcoholic with superimposed siderosis, except in the late stages. Earlier, haemochromatosis is characterized by increasing 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. There may be fatty change. When cirrhosis develops in haemochromatosis it is, at first, micronodular. In haemochromatosis secondary to anaemias, the appearances are broadly similar.

(d) *Wilson's disease* (Fig. 16). 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 in nodules by appropriate staining (e.g., rhodanine or rubeanic acid methods), but copper is also demonstrable in some other conditions (Table 2).

(e) *Alpha-1-antitrypsin deficiency* (Fig. 17). 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 that follows prolonged biliary obstruction. Dense hyalinized fibrous septa surround nodules. Intracytoplasmic globules of faintly eosinophilic material that are positive with the PAS stain after diastase digestion are characteristic. They are sometimes scanty and unevenly distributed, and are most abundant near portal tracts. Similar globules can occasionally be found in other diseases, and the diagnosis of alpha-1-antitrypsin deficiency should be confirmed by estimation of the serum enzyme level and by phenotyping. In heterozygous subjects there may be scanty globules; the association between the heterozygous state and liver disease is less well established.

(f) *Primary biliary cirrhosis* (Fig. 18, 19, 20). The characteristic lesion is seen in wedge biopsies and less often in needle biopsy specimens. 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 organized 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, granulomas diminish in number, and bile ductules proliferate. At this stage there is increasing fibrosis and cholestasis, often inconspicuous earlier, at the periphery of the lobules. Mallory's hyalin is sometimes prominent and, rarely, xanthomatous change may be present. Piecemeal necrosis may lead to confusion with chronic active hepatitis. Paucity of bile ducts, presence of lymphoid aggregates, positive copper staining, hyalin, and peripheral cholestasis favour the diagnosis of primary biliary cirrhosis. Lobular architecture remains intact for long periods. The term 'primary biliary cirrhosis' is to some extent misleading as this is a disease with a long natural history and cirrhosis is a late development.

(g) *Secondary biliary cirrhosis* (Fig. 21). Portal fibrosis and septum formation predominate, and parenchymal alterations are often slight. There may be morphological cholestasis owing to persisting obstruction to bile ducts, but this is not invariable or necessary for diagnosis. The septa are often oedematous, and contain proliferated bile ducts. Lobular architecture survives for long periods, and groups of adjacent nodules form complex parenchymal islands resembling the pieces of a jig-saw puzzle. A somewhat similar pattern may also be seen in inborn errors of metabolism, congenital hepatic fibrosis, and mucoviscidosis.

(h) *Venous outflow obstruction* (Fig. 22). Helpful diagnostic features include a micronodular pattern with predominantly centrilobular fibrosis that gives 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 etiological agents in all cases of cirrhosis.

(j) *Intestinal by-pass 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* (Fig. 23). The cirrhosis is typically micronodular in pattern and there is fibrosis around individual cells or small groups of cells. Ductular proliferation is seen. Mallory's hyalin is prominent, widespread, and not recognizably 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 (e.g., 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 im-

proved 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 follow 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 in histological preparations.

CIRRHOSIS AND CANCER OF THE LIVER

Available evidence indicates that cirrhosis is linked with hepatocellular (or liver cell) carcinoma but not with cholangiocarcinoma (intrahepatic bile duct carcinoma). The increased risk of malignancy may depend on the etiology and the duration of the cirrhotic process, and its onset may be preceded by certain dysplastic cellular changes.

In areas with a low incidence of carcinoma, many cases arise in patients with cirrhosis of several years' duration, but in the high-incidence areas of the tropics and subtropics, carcinoma and cirrhosis are commonly present at the same time. In both low- and high-incidence areas, the morphological pattern of cirrhosis is most often macronodular. In low cancer incidence areas, most cirrhosis is probably alcoholic in origin, and in such cases the development of a macronodular pattern is a matter of time. It has been suggested that this is associated with an increasing risk of malignancy. There is so far no evidence that alcohol itself is carcinogenic. However, necrosis and proliferation of liver cells take place during the cirrhotic process from whatever cause, and it has been shown in animal experiments that an increased rate of cell turnover enhances carcinogenesis by a

variety of agents. In the high cancer incidence areas, most cirrhosis is macronodular in pattern and is non-alcoholic in origin. Other etiological agents such as the widely prevalent mycotoxins and hepatitis B may be responsible for the accelerated development of a greater number of tumours in cirrhotic and, in some cases, normal livers. The presence of more potent carcinogenic factors is also supported by the much younger age of patients with both liver cell carcinoma and cirrhosis.

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. 24, 25, 26). 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.

Finally, the presence of persistently raised blood levels of alpha-fetoprotein in a cirrhotic patient is a strong indication of the development of liver cell carcinoma.

CHRONIC HEPATITIS

DEFINITION

Chronic hepatitis has been defined as inflammation of the liver continuing without improvement for at least 6 months.^a In addition to the inflammatory infiltration, there is a variable degree of liver cell damage. Many examples of chronic hepatitis follow acute hepatitis, but in others, no acute attack can be identified clinically. The borderline between chronic hepatitis and preceding acute hepatitis is often indistinct, and in those forms of chronic hepatitis in which cirrhosis develops, this transition is often also difficult to define.

CLASSIFICATION

Morphology

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

(a) *Chronic persistent hepatitis* (Fig. 27). This is a somewhat non-specific picture characterized by portal tract expansion and inflammatory cell infiltration. There is a variable and often slight degree of liver cell

damage in the lobules, as shown by focal necrosis, and acidophilic bodies. The chief importance of the category lies in its distinction from chronic active hepatitis; in chronic persistent hepatitis, 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 'chronic lobular hepatitis' has been used by some authors.

Chronic persistent hepatitis carries a good prognosis. In a minority of patients the lesion progresses to chronic active hepatitis.

(b) *Chronic active hepatitis* (Fig. 28, 29). 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. Cirrhosis may develop, and the inflammation and necrosis may continue or subside. Not all histologically active cirrhosis is preceded by a demonstrable pre-cirrhotic stage of chronic active hepatitis.

Chronic active hepatitis has a worse overall prognosis than chronic persistent hepatitis, but the milder forms may regress to chronic persistent hepatitis or fibrosis, especially after treatment. The prognosis varies according to morphological pattern, severity, and etiology. Chronic hepatitis and liver cancer rarely co-exist.

^a *Diseases of the liver and biliary tract. Standardization of nomenclature, diagnostic criteria and diagnostic methodology.* Fogarty International Center Proceedings No. 22. Washington, DC, DHEW Publication No. (NIH) 76-725.

Etiology

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 of widely varied etiology. Many instances of chronic persistent hepatitis are thought to follow acute viral hepatitis.

Chronic active hepatitis is not a single disease entity, but has many etiological associations. Active chronic hepatitis and chronic active liver disease are sometimes used synonymously with chronic active hepatitis. The term chronic aggressive hepatitis has been used to describe the morphological picture alone, whereas the other terms have also been used to describe a clinical syndrome. Chronic active hepatitis may follow acute viral hepatitis, often identifiable as type B. It may be due to drugs (e.g., oxyphenisatine, alpha methyl dopa, isoniazid), 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 etiological factors, but with high serum levels of abnormal antibodies (e.g., against smooth muscle) and multisystem disease, a primary disturbance of immunity has been postulated ('lupoid hepatitis').

Chronic inflammation is also part of a number of specific disease processes (e.g., alcoholic hepatitis,

sarcoidosis), but the term 'chronic hepatitis' is not normally used in this context.

Primary biliary cirrhosis is histologically distinct from chronic active hepatitis. However, it shares some of its features (e.g., piecemeal necrosis). The distinction between the two conditions has been discussed under 'primary biliary cirrhosis' in an earlier section (page 526).

DIAGNOSIS

This will not be discussed in detail in the present paper. However, 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.

HEPATIC FIBROSIS

DEFINITION (Fig. 30, 31, 32)

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. New fibrous tissue is the result of fibroblast activity, but other cells, notably the fat-storing perisinusoidal cells of Ito, probably participate also.

The differential diagnosis of fibrosis from cirrhosis may be difficult, particularly in needle biopsy specimens. 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.

CLASSIFICATION

Morphology

Fibrosis can be classified according to its location (see glossary also):

focal—e.g., in healing granulomatous diseases such as sarcoidosis.

zonal—this may be centrilobular (e.g., in alcoholic liver disease) or periportal (e.g., in obstructive biliary disease).

multilobular—e.g., following massive necrosis due to viral hepatitis, toxins, or drugs.

diffuse—e.g., in congenital syphilis, alcoholism, hypervitaminosis A.

portal—e.g., in schistosomiasis, hepatoportal sclerosis.

bridging—e.g., in obstructive biliary disease (portal to portal), venous outflow obstruction (centrilobular

to centrilobular), posthepatic scarring (centrilobular to portal).

other—periductal (e.g., in primary sclerosing cholangitis), perivenular (e.g., in alcoholic hepatitis, schistosomiasis).

Etiology

Fibrosis is a component of many forms of liver injury rather than a disease in itself. Etiological 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 recognized:

congenital—e.g., congenital hepatic fibrosis.

metabolic—e.g., mucoviscidosis.

inflammatory—e.g., sarcoidosis, tuberculosis, and other infectious diseases.

parasitic—e.g., schistosomiasis.

toxins and drugs—e.g., vinyl chloride, thorium dioxide suspension, methotrexate.

vascular—e.g., hepatoportal sclerosis, veno-occlusive disease, infarcts.

physical—e.g., radiation.

A prolonged phase of fibrosis without nodule formation commonly precedes many forms of cirrhosis (e.g., biliary cirrhosis, haemochromatosis). During this stage fibrosis may be reversible if the causal factor (e.g., iron overload) can be eliminated.

HEPATIC FIBROSIS AND CANCER OF THE LIVER

Several agents, notably vinyl chloride, arsenic, and thorium dioxide suspension, 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 outline and deeply eosinophilic cytoplasm in which nuclear remnants may be present.

ballooning degeneration, change in which a liver cell is swollen and cytoplasm is clear. 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, new fibre formation leading to excess collagen.

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

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

focal fibrosis, small areas of fibrosis inside lobules or nodules.

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

periportal fibrosis, fibrosis around portal tracts.

portal fibrosis, fibrosis strictly confined to the portal tracts.

multilobular fibrosis, fibrosis replacing several contiguous lobules.

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

periductal fibrosis, concentric fibrosis around intra hepatic bile ducts.

ground glass hepatocyte, liver cell with cytoplasm that 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, necrosis of individual or few liver cells.

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

confluent necrosis, merging of adjacent areas of necrosis.

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

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

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, presence of stainable iron in the liver.

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

TECHNIQUES

FIXATION

The ideal fixative for light microscopy is 10% buffered formalin. Some other fixatives may interfere with special staining techniques, e.g., copper cannot be demonstrated in tissue fixed in Zenker's, Carnoy's, or Bouin's solutions.

SECTIONS

Paraffin-embedded tissues should be sectioned at 4–7 μ m. Step sections may be helpful but serial sections are rarely necessary.

STAINING

Routine stains

In addition to haematoxylin and eosin, silver impregnation for reticulin, a connective tissue stain (e.g., Masson's trichrome), and an iron stain are considered most useful for routine diagnosis of cirrhosis, chronic hepatitis, and hepatic fibrosis.

Special stains

The following stains are helpful, particularly for determining etiology in liver disease:

(a) stains for neutral lipid, e.g., oil red O on frozen sections;

(b) periodic acid–Schiff (PAS) with and without diastase digestion for: glycogen (diastase digestible);

cytoplasmic globules of alpha-1-antitrypsin deficiency; inclusions of type IV glycogenosis (pectinase digestible) and myoclonus epilepsy; lipofuscin (ceroid);

(c) colloidal iron stain for mucopolysaccharides, e.g., in Hurler's and Hunter's syndromes;

(d) stains for copper, e.g., rubeanic acid and *p*-dimethyl-amino-benzylidene rhodanine;

(e) stains for hepatitis B surface antigen: (i) Gormori's aldehyde fuchsin, (ii) Shikata's orcein.

SPECIAL MICROSCOPY

Polarizing microscopy—useful for demonstrating talc, protoporphyrins, malarial material, and schistosomal pigments.

Ultraviolet microscopy—useful for demonstrating porphyrins, vitamin A, and lipofuscin.

Electron microscopy—this can demonstrate the components of the hepatitis B virus and is helpful in a variety of metabolic disorders.

IMMUNOLOGICAL METHODS

Immunofluorescence

Immunoperoxidase

Immuno-electron microscopy—used to identify the components of the hepatitis B virus, alpha-1-antitrypsin, and other antigens.

ACKNOWLEDGEMENTS

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RÉSUMÉ

LA DESCRIPTION MORPHOLOGIQUE DE LA CIRRHOSE: DÉFINITION, NOMENCLATURE, ET CLASSIFICATION

La description morphologique de la cirrhose est depuis longtemps un sujet controversé. Les définitions et la nomenclature appliquées dans ce domaine sont variables et les nombreuses classifications différentes en vigueur dans le monde entier rendent difficile la comparaison des données publiées. C'est pourquoi on a besoin d'un système simple et reproductible qui pourrait servir de référence pour le diagnostic, la recherche et l'épidémiologie.

Le présent article fournit à l'anatomopathologiste un guide pour les définitions, la nomenclature et la classification de la cirrhose et des affections étroitement apparentées que sont l'hépatite chronique et la fibrose hépatique. Pour la préparation de ce document, il a été tenu compte de l'expérience et de l'opinion de nombreux hépatologues et l'on a tenté d'étudier une grande variété de matériels provenant de régions géographiques différentes.

Les caractéristiques étiologiques et morphologiques de la cirrhose sont examinées séparément. La cirrhose a souvent été classée jadis sur la base d'un mélange d'étiologie, de pathogénie, d'aspects morphologiques ainsi que de qualificatifs et de noms propres (par exemple, « alcoolique », « post-nécrotique », « septale », « de Laennec »). Cette sorte de mélange engendre la confusion et il est indésirable; la morphologie doit être clairement séparée des conceptions étiologiques et pathogéniques.

La subdivision de la cirrhose en différentes catégories morphologiques constitue plutôt une caractérisation qu'une classification, car ces catégories ne représentent pas nécessairement des maladies différentes mais peuvent correspondre à divers stades d'un unique processus morbide. Néanmoins, il y a des raisons pour continuer à subdiviser la cirrhose sur une base purement morphologique. Cela permet d'étudier les types sous l'angle épidémiologique, et de les rapporter à des agents étiologiques présumés ou établis; de ces types dépendent l'évolution, le pronostic, et le risque de cancer primitif du foie, de même que la facilité ou la difficulté du diagnostic histologique.

Dans le présent article, la cirrhose du foie est définie comme un processus diffus caractérisé par la fibrose et un remaniement de l'architecture normale du foie conduisant à des nodules de structure anormale. La simple division en type micronodulaire et type macronodulaire est conseillée. Un foie cirrhotique dans lequel presque tous les nodules ont moins de 3 mm de diamètre est de type micronodulaire, alors que le foie dans lequel de nombreux nodules dépassent cette dimension est dit macronodulaire. Lorsque des micronodules et des macronodules sont présents en proportion à peu près égales, on utilise le terme « mixte ».

Certaines étiologies de la cirrhose peuvent être considérées comme bien établies (par exemple, l'hépatite virale, l'alcoolisme, certains troubles métaboliques), et d'autres sont discutables (par exemple, la malnutrition); enfin il y a les rares cas où existe une entité clinique, morphologique et géographique bien définie mais aucun indice quant à l'étiologie (par exemple, cirrhose de l'enfant en Inde). Les cirrhoses de cause inconnue et de types variables sont quelquefois désignées comme « cryptogénétiques ».

La partie relative au diagnostic de la cirrhose comprend les rubriques: découverte, types morphologiques, étiologies particulières, activité, et complications; chacune d'elles est examinée dans ses détails essentiels et ses caractères importants sont illustrés.

Dans l'état actuel des connaissances, il semble qu'il y ait un lien entre la cirrhose et le carcinome hépatocellulaire mais pas avec le carcinome biliaire (cancer des voies biliaires intrahépatiques). L'importance du risque de malignité dépend de l'étiologie et de la durée du processus cirrhotique. La malignité peut être précédée par un stade de dysplasie hépatocytaire, et elle se développe le plus fréquemment dans la cirrhose macronodulaire.

L'hépatite chronique a été définie comme une inflammation du foie se prolongeant sans amélioration pendant au moins 6 mois. Dans l'hépatite chronique persistante, l'architecture des lobules reste intacte et le pronostic est bon. Cette forme doit être distinguée de l'hépatite chronique active, laquelle évolue fréquemment vers la cirrhose. Les critères diagnostiques de chaque forme sont étudiés et illustrés. L'hépatite chronique comme la cirrhose n'est pas une entité morbide unique et son étiologie comprend l'hépatite virale, les substances médicamenteuses et l'auto-immunité. Le cancer primitif du foie complique rarement l'hépatite chronique.

La fibrose est définie par la présence d'un excès de collagène dû à la formation de nouvelles fibres et elle est classée selon sa localisation, par exemple: focale, portale, « en pont » (bridging). Le terme de fibrose désigne une composante de maintes formes de lésions hépatiques, mais lorsqu'il est utilisé en nosologie il implique l'absence de cirrhose ou d'hépatite chronique. En soi, la fibrose provoque peu de symptômes cliniques ou de troubles de la fonction des hépatocytes, mais à elle seule elle peut entraîner l'hypertension portale (par exemple, sclérose hépatique congénitale, sclérose hépatoportale, schistosomiase). Certains cas de sclérose hépatique, particulièrement ceux qui sont dus à des suspensions d'oxyde de thorium ou de chlorure de vinyle, sont associés à un risque accru d'angiosarcome hépatique.

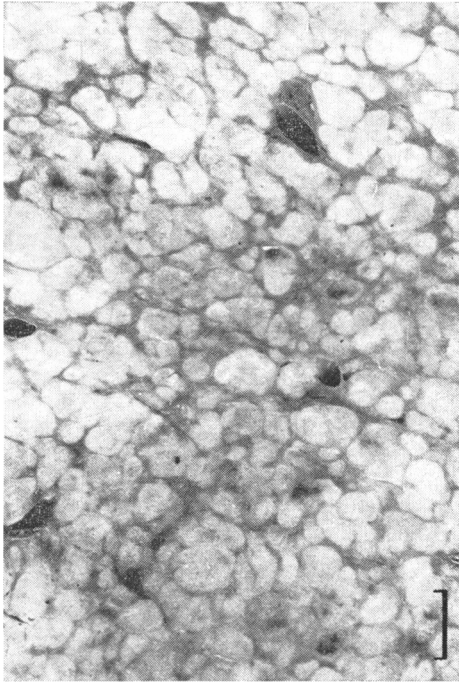


Fig. 1. Cirrhosis with a micronodular pattern in a middle-aged, male, actively drinking alcoholic: *nearly all* the nodules are less than 3 mm in size (indicated by scale).

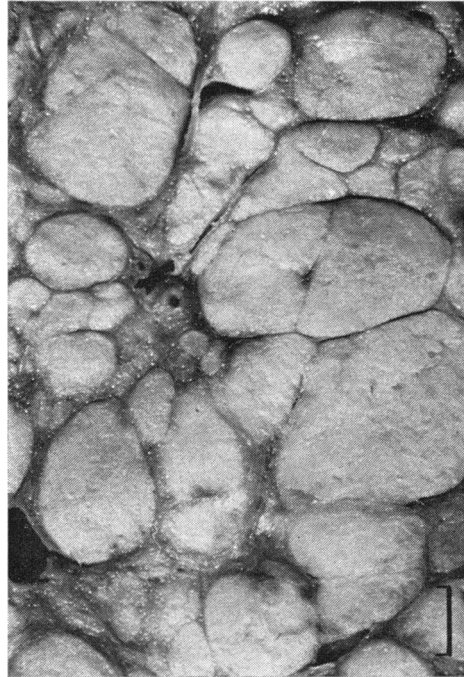


Fig. 2. Cirrhosis with a macronodular pattern in an elderly male with a history of hepatitis many years before, but tests for hepatitis B antigen negative: *many* of the nodules are larger than 3 mm in diameter (indicated by scale).

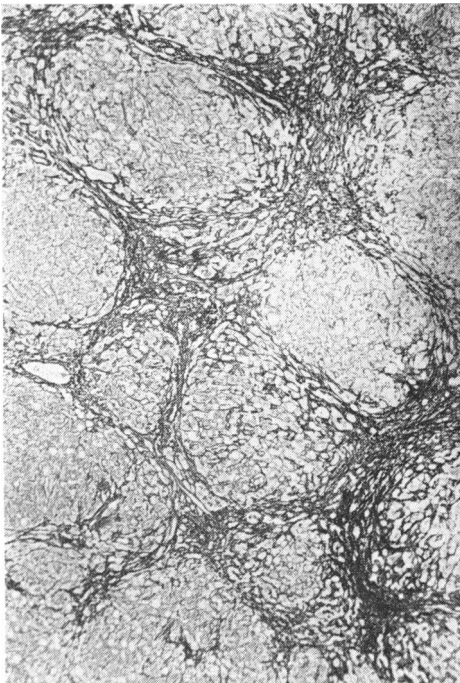


Fig. 3. Cirrhosis with a micronodular pattern in an active alcoholic: the nodules are almost uniform, lack any normal structure, and are roughly lobular or sublobular in size. Reticulin $\times 24$.

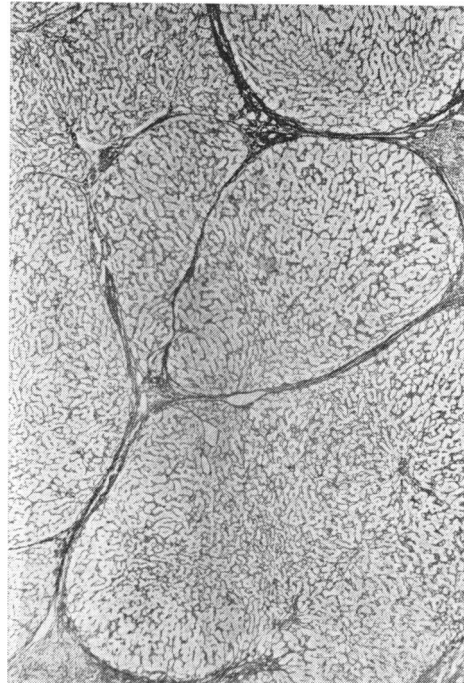


Fig. 4. Cirrhosis with a macronodular pattern, no history of hepatitis but hepatitis B antigen present on testing: the macronodules are divided by slender, sometimes incomplete septa ('incomplete' or 'post-hepatic' pattern). Reticulin $\times 24$.

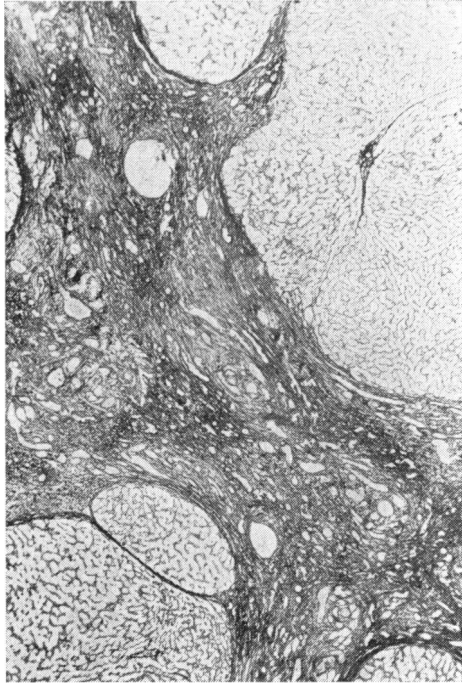


Fig. 5. Cirrhosis with a macronodular pattern, etiology unknown: the macronodules are separated by broad fibrous septa ('post-collapse' or 'post-necrotic' pattern). Reticulin $\times 24$.



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 recognized only with the help of reticulin or collagen stains. Reticulin $\times 60$.

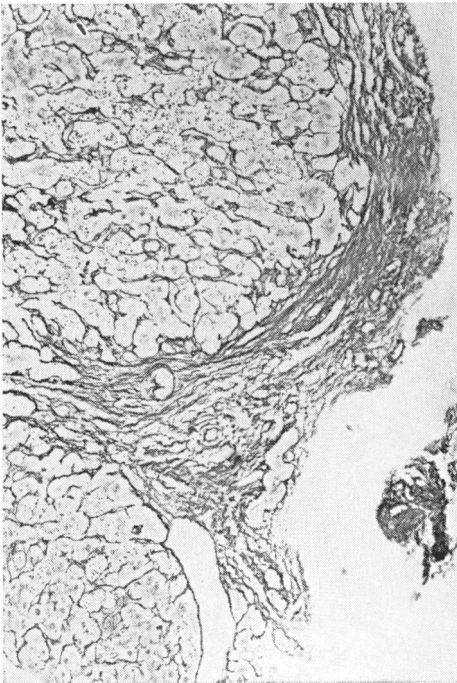


Fig. 7. Part of a cirrhotic nodule from a fragmented needle biopsy showing the fibrous edge that represents a split septum. An abnormally placed vessel is present at the bottom. Reticulin $\times 160$.

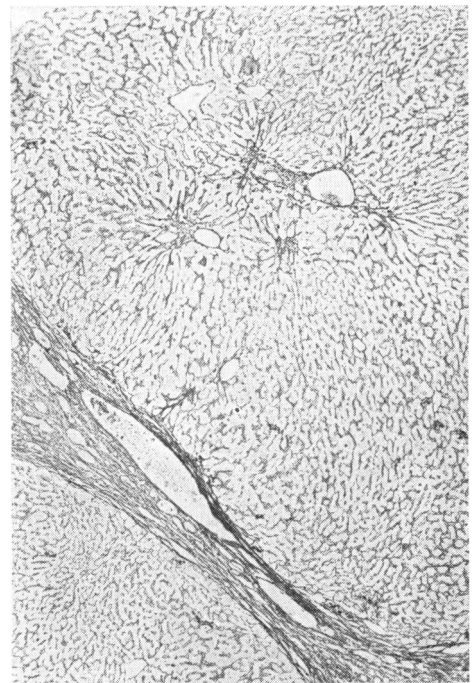


Fig. 8. Two cirrhotic macronodules separated by a fibrous septum. Note the abnormal size and distribution of vessels both within the nodules and the intervening septum. Reticulin $\times 40$.



Fig. 9. Adjacent areas of liver parenchyma in cirrhosis may grow at different rates, and produce nodular remodelling shown in the upper half of the field. Reticulin $\times 96$.

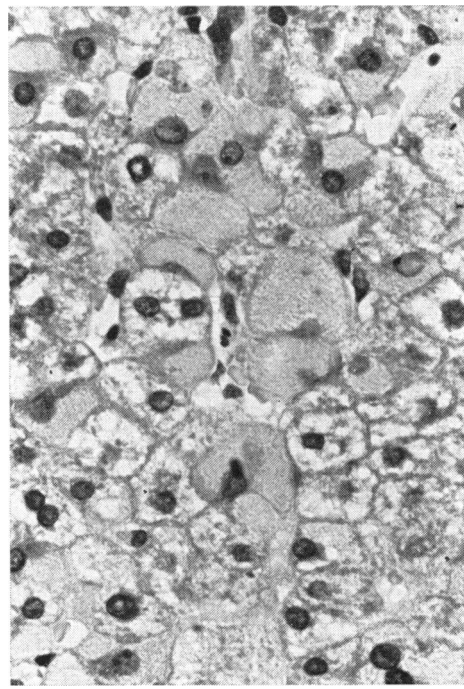


Fig. 10. Swollen, 'ground glass' hepatocytes showing finely granular, eosinophilic cytoplasm due to the presence of hepatitis B surface antigen. Haematoxylin-eosin $\times 384$.

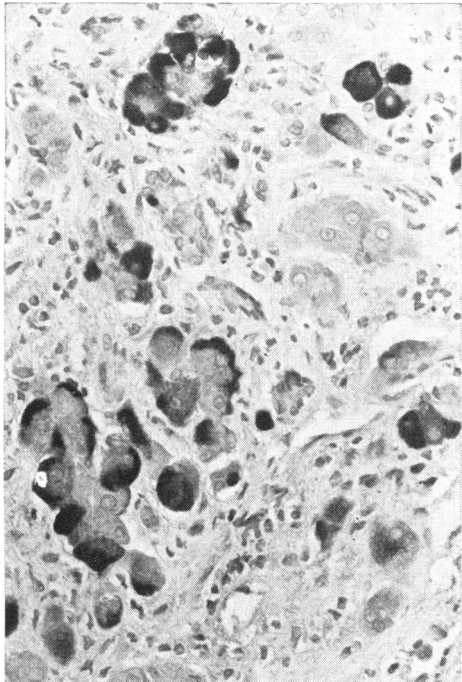


Fig. 11. 'Ground glass' hepatocytes. Shikata's orcein technique $\times 240$.

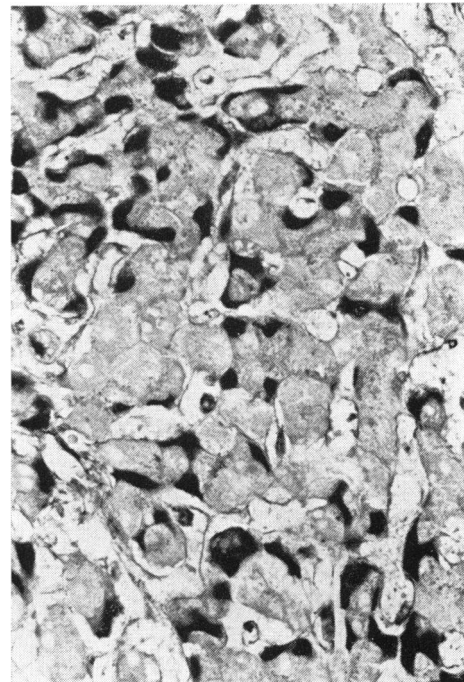


Fig. 12. 'Ground glass' hepatocytes. Gomori's aldehyde fuchsin, an alternative to orcein $\times 400$.

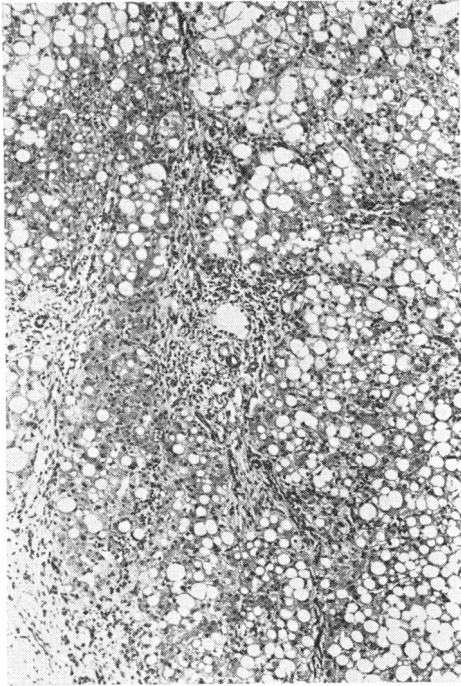


Fig. 13. Alcoholic hepatitis: inflamed fibrous septa dissect the liver into nodules; there is also extensive diffuse fibrosis within the parenchyma; liver cells show fatty change. Haematoxylin–eosin $\times 60$.

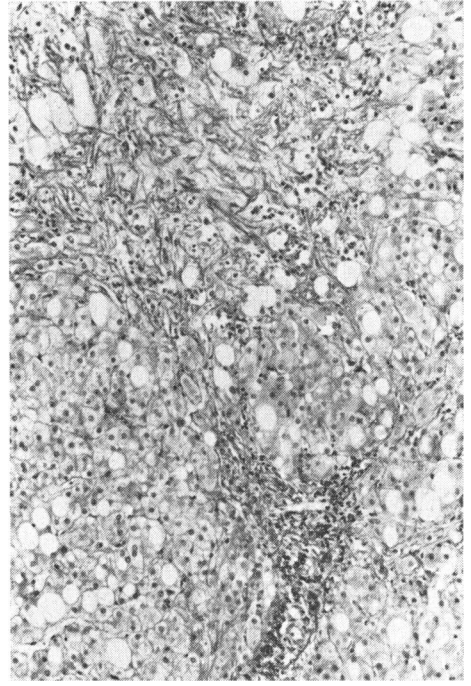


Fig. 14. Alcoholic hepatitis: note fibrosis extending from a portal tract (bottom right), to an area once occupied by a central vein which is now obliterated (top left). This change has been referred to as “centrilobular hyaline sclerosis”, as fibrosis is often rather hypocellular and may be quite dense. Masson’s trichrome $\times 96$.

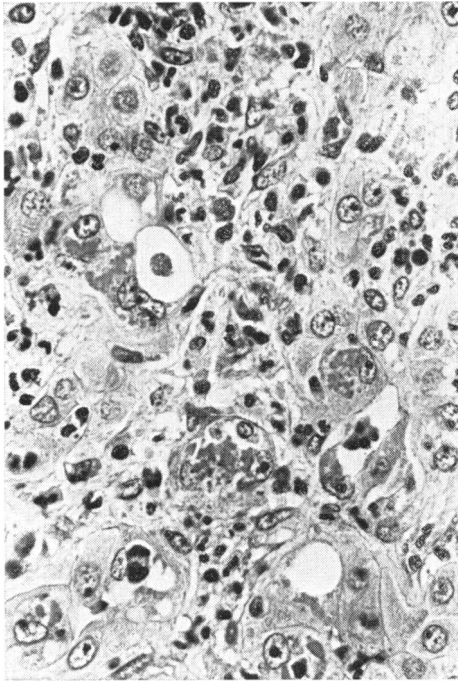


Fig. 15. Alcoholic hepatitis: several hepatocytes contain clumps of Mallory’s hyalin in their cytoplasm. Note the presence of neutrophil polymorphs a characteristic feature. Haematoxylin–eosin $\times 384$.

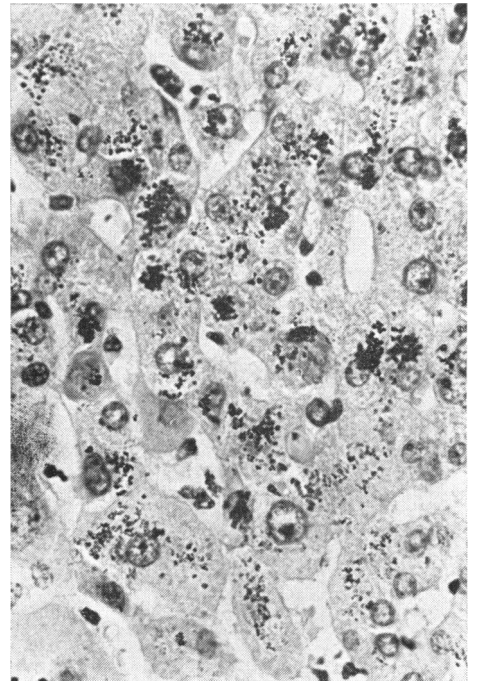


Fig. 16. Wilson’s disease: increased amounts of copper (dark granules) demonstrated by rhodanine. $\times 384$.

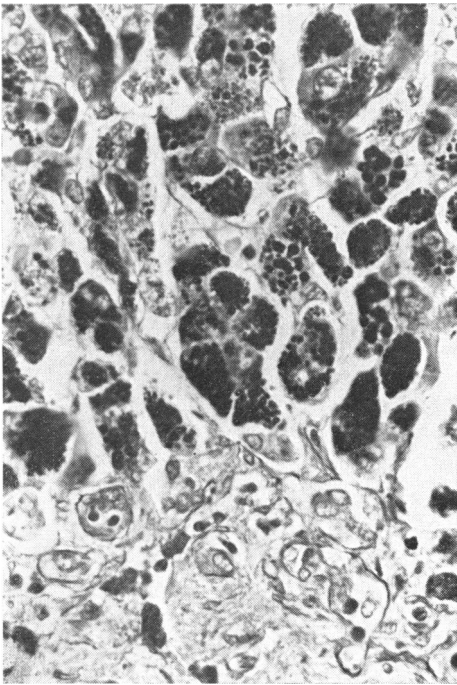


Fig. 17. Alpha-1-antitrypsin deficiency: heavy, intracytoplasmic, PAS positive deposits in hepatocytes. PAS after diastase digestion. $\times 384$.

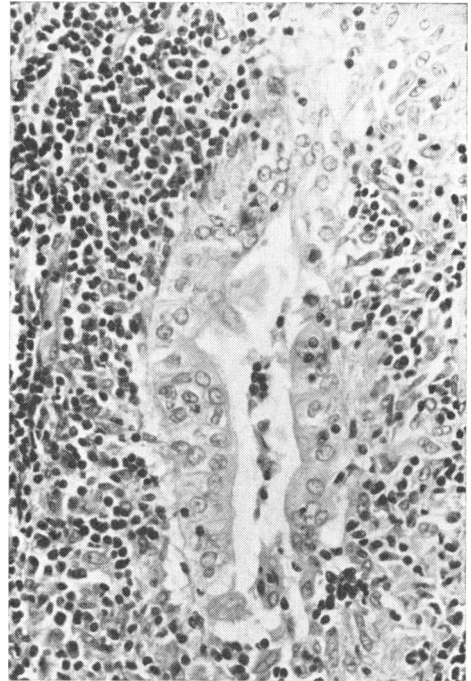


Fig. 18. Primary biliary cirrhosis: the early duct lesion is shown with hyperplasia of the epithelial lining, necrosis, and rupture; a marked chronic inflammatory reaction is present. Haematoxylin–eosin $\times 240$.

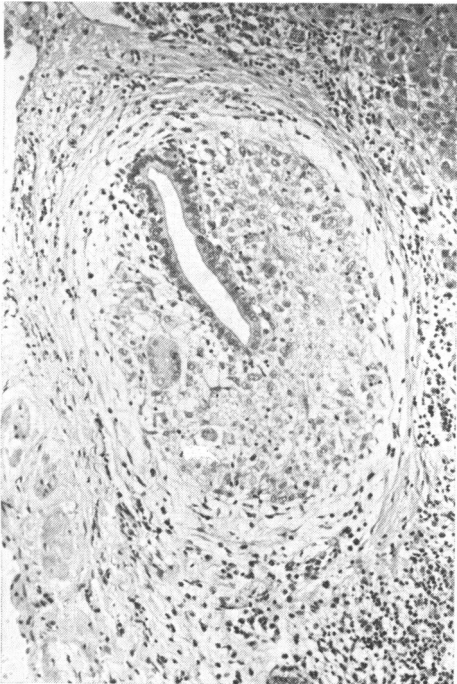


Fig. 19. Primary biliary cirrhosis: a small bile duct surrounded by an epithelioid and giant cell granuloma. Haematoxylin–eosin $\times 96$.

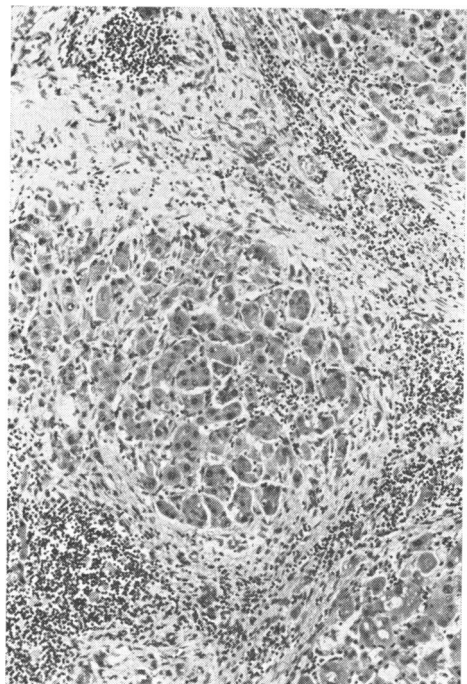


Fig. 20. Primary biliary cirrhosis: established cirrhosis with lamellar fibrosis surrounding a parenchymal nodule. Note absence of bile ducts and the presence of lymphoid aggregates. Haematoxylin–eosin $\times 96$.

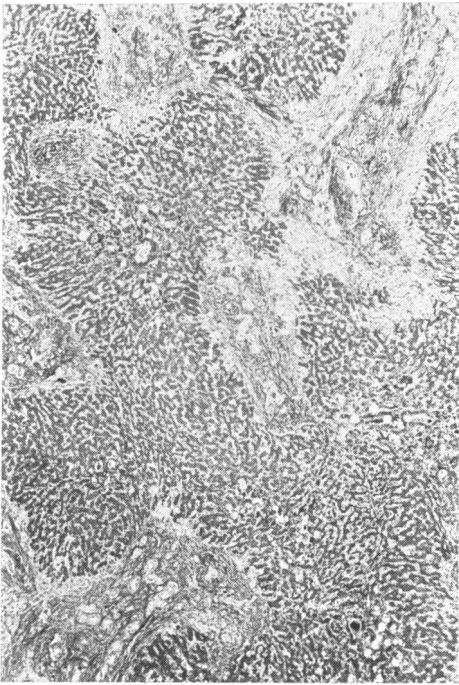


Fig. 21. The characteristic 'jig-saw' pattern of biliary cirrhosis, primary or secondary, in which the out-lines of parenchymal nodules appear to fit together as pieces in a puzzle. Masson's trichrome $\times 24$.

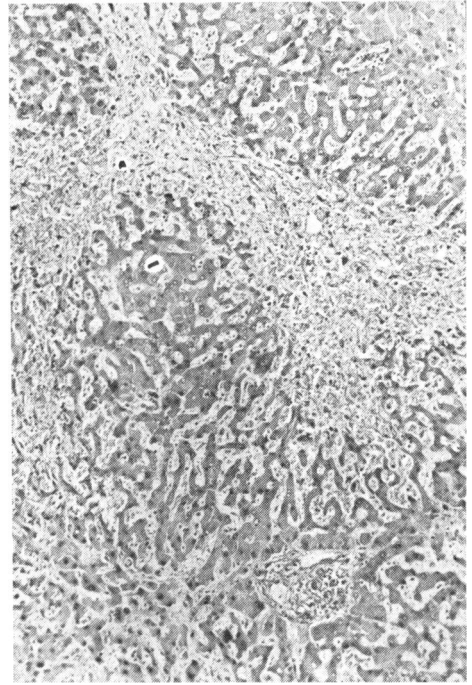


Fig. 22. Venous outflow obstruction: atrophy, collapse, and fibrosis link centrilobular areas giving rise to 'reverse lobulation'. Nodules of liver parenchyma contain portal tracts (bottom right). Haematoxylin-eosin $\times 60$.

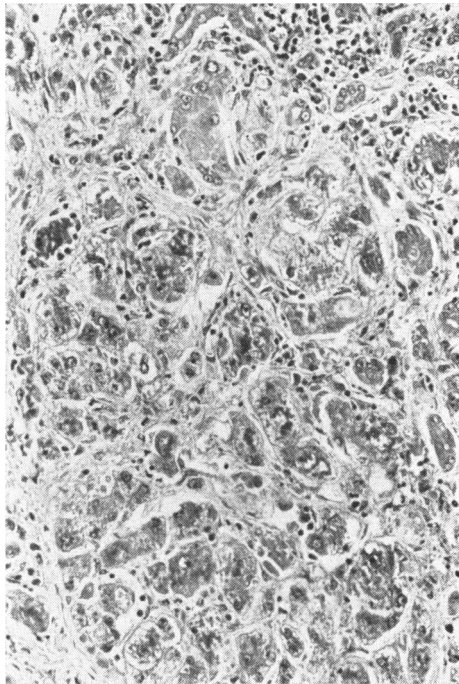


Fig. 23. Indian childhood cirrhosis: the pattern is usually micronodular, pericellular fibrosis is prominent, and large amounts of Mallory's hyalin may be present. Fatty change is minimal or absent. Haematoxylin-eosin $\times 156$.

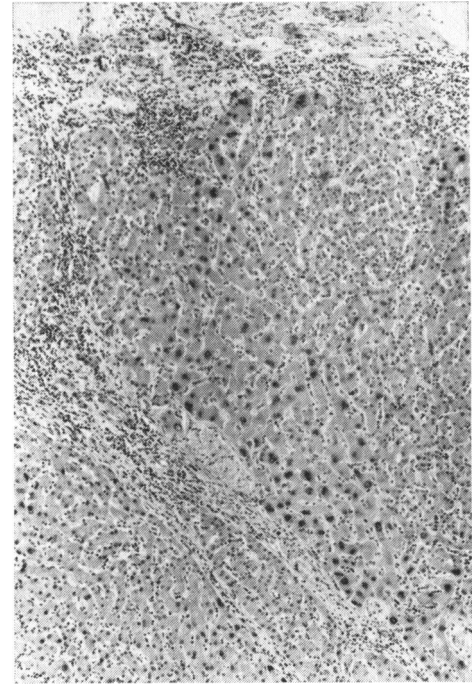


Fig. 24. Liver cell dysplasia: a group of abnormal liver cells with large, hyperchromatic nuclei stand out in a field of cirrhotic macronodules. Haematoxylin-eosin $\times 156$.

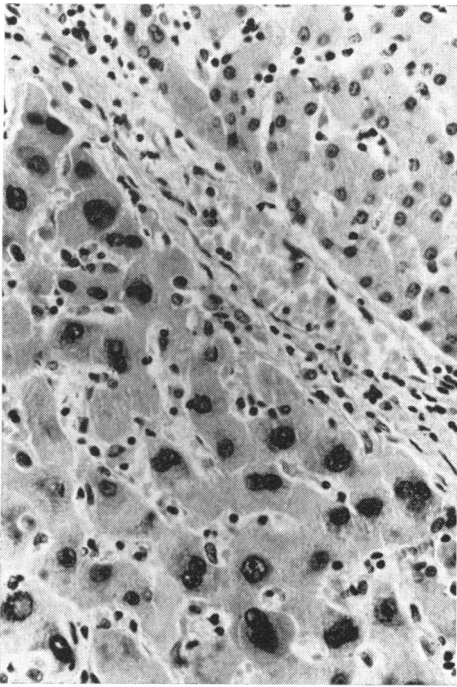


Fig. 25. Liver cell dysplasia: abnormal, dysplastic cells (bottom), are contrasted with liver cells in a cirrhotic nodule (top). Haematoxylin–eosin $\times 240$.

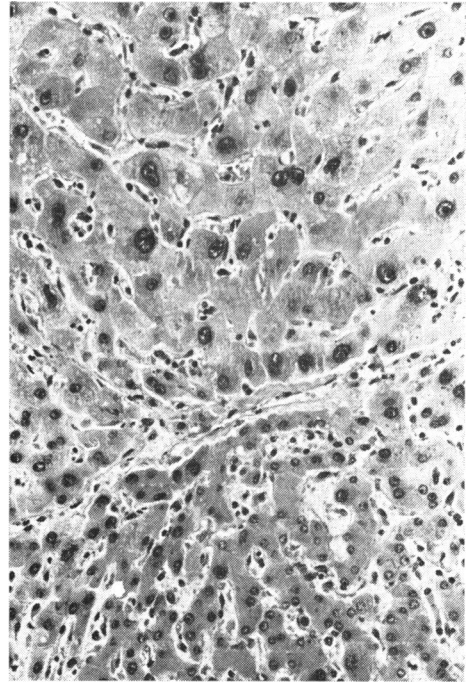


Fig. 26. Liver cell dysplasia: large, hyperchromatic dysplastic cells mingle with normal liver cells within a cirrhotic nodule. Haematoxylin–eosin $\times 240$.

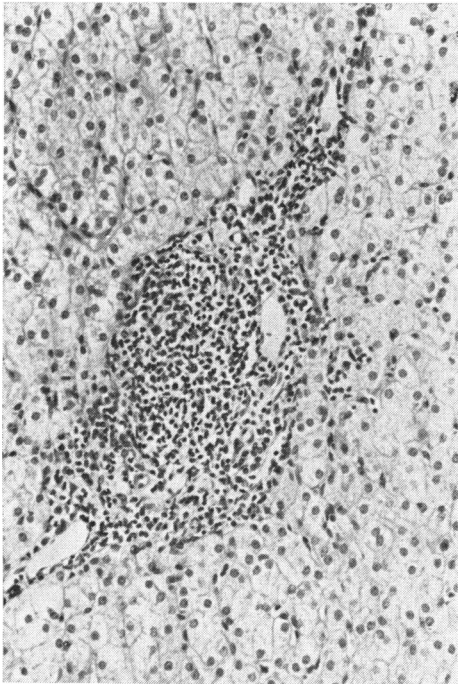


Fig. 27. Chronic persistent hepatitis: expanded portal tract infiltrated by mononuclear inflammatory cells.

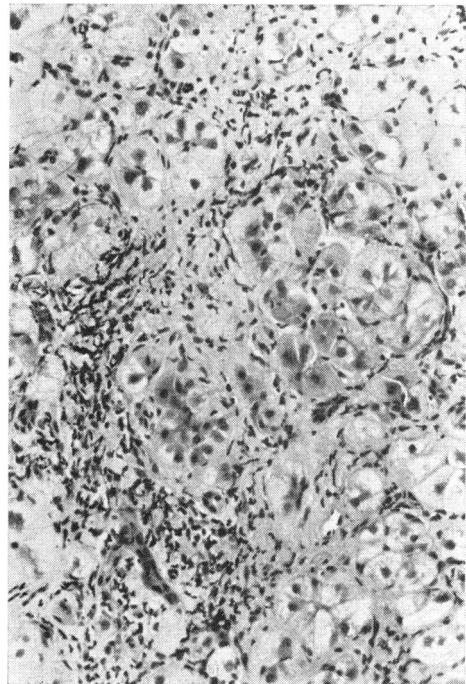


Fig. 28. Chronic active hepatitis: the liver parenchyma is being destroyed by chronic inflammation and fibrosis that spread out from the portal tracts (bottom left); liver cells are swollen, and some are arranged in gland-like structures or rosettes. Haematoxylin–eosin $\times 156$.

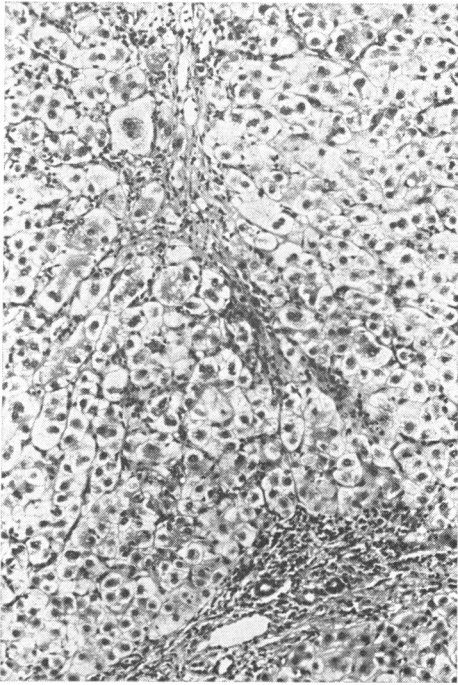


Fig. 29. Bridging necrosis linking portal tract (bottom), with central vein (top), in a case of viral hepatitis B evolving into cirrhosis. Haematoxylin–eosin $\times 96$.

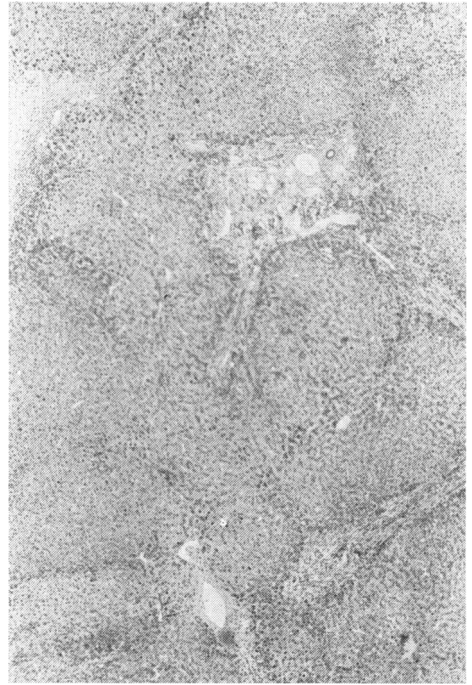


Fig. 30. Hepatic fibrosis, mainly of portal distribution, in a case of haemochromatosis. Haematoxylin–eosin $\times 24$.

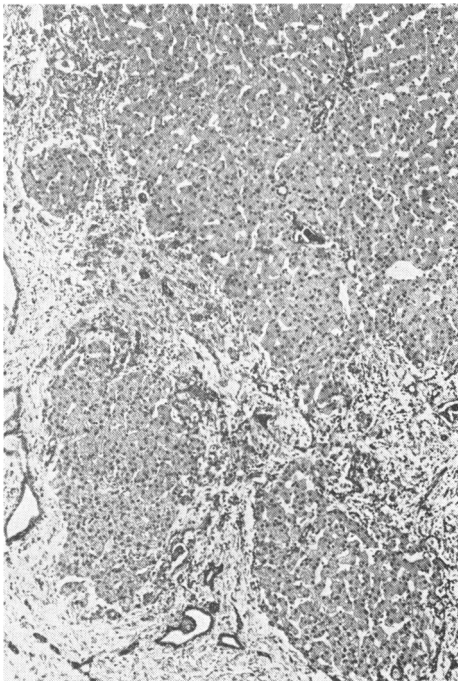


Fig. 31. Congenital hepatic fibrosis: tortuous fibrous septa, containing many dilated bile ducts, separate nodules of liver parenchyma that have largely retained their normal lobular organization. Haematoxylin–eosin $\times 60$.

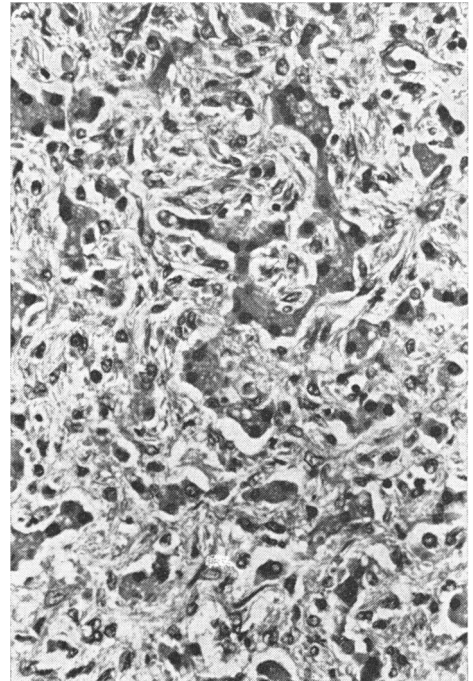


Fig. 32. Congenital syphilis: an example of severe, diffuse, pericellular fibrosis. Masson's trichrome $\times 240$.