HEPATOCYTE HYPERPLASIA IN CHRONIC LIVER DISEASE

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ABSTRACT

The occurrence of hepatocyte hyperplasia is often described in chronic liver disease, but it is not absolutely clear in all cases what mechanism induces this development. It is suggested that this may be a response to damage to or loss of hepatocytes, but it is recognised that in several examples of chronic liver disease the features of hepatocyte hyperplasia are present when there is no substantial concurrent evidence of major hepatocyte destruction. Even in cirrhosis, the nodules of hyperplastic hepatocytes are referred to as "regenerative", a term derived from the assumption that much hepatocyte necrosis had occurred at an earlier stage in the disease. Such major necrosis has not been identified in most cases of cirrhosis.

The purpose of this study was to assess the incidence of hepatocyte hyperplasia in liver biopsy specimens and post mortem material from patients with chronic liver disease. It was hoped to identify correlations with other morphological changes and to assess the part it might play in the pathogenesis of portal hypertension.

A point counting method was used to determine the ratio of two cell thick hepatocyte plates (generally taken to represent hyperplastic liver cells) to single cell thick plates (the normal arrangement in the human adult).

It was found that the ratio in normals is remarkably constant and single plates were far more abundant than thick plates. An increased incidence of thick plates was found in patients with cirrhosis, active chronic hepatitis, chronic alcoholism, but not in patients with chronic persistent hepatitis.

The duration of the disease before thick cell plates were substantially increased varied in the different conditions. Portal hypertension seemed to be noted at about the same time as thick cell plates became abundant.

No evidence was found that suggested thick plate formation was a direct consequence of liver cell necrosis.

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ERRATA

Page 24.	Line 12	Shikata, et al. 1974;
Page 110.	Line 3	absolutely
Page 150.	Line 12	interfere
Page 150.	Line 28	haemoconcentration

PART 1

INTRODUCTION

INTRODUCTION

In 1929 Rolleston and McNee referred to cirrhosis as the main form of chronic liver disease. Descriptions of structural change were derived mainly from post mortem tissue, and in such instances the final or end stage of the disease process frequently was a cirrhotic liver. With the development and widespread use of the liver biopsy procedure, structural alterations have been noted during the evolution of certain liver diseases.

Chronic liver diseases which are of interest in this study are chronic alcoholic liver disease, active chronic hepatitis and primary biliary cirrhosis. These diseases have been extensively studied by the use of liver biopsy specimens obtained by means of percutaneous aspiration, open liver biopsy (wedge biopsy) or liver material obtained at peritoneoscopy. Percutaneous aspiration is the most widely used procedure today.

This was first employed by Paul Ehrlich in 1883 in a study of the glycogen content of the diabetic liver and in 1895 by Lucatello in Italy; it became useful in the diagnosis of hepatic abscesses. In temperate climates the method did not achieve early popularity because of the undoubted risks involved. But before and during the last war, however, there were many cases of non fatal hepatitis which stimulated investigators to obtain hepatic material for histological study.

Liver biopsy by the needle technique was reintroduced by Huard, May and Joyeux (1935) in France, Baron (1939) in the United States, Iversen and Roholm (1939) in Denmark, Axenfeld and Brass (1942) in Germany and Dible, McMichael and Sherlock (1943) in Britain. Tripoli and Fader (1941) were the first to use the Vim Silverman needle for hepatic biopsy via the subcostal route.

Although various needles for hepatic biopsy have been used and described, two techniques, aspiration or punch biopsy are basic. In current procedures the Menghini (1958) and the Vim Silverman needles are representative of the two techniques. The Menghini aspiration is the most widely used of the needle

techniques as it usually produces an adequate sample for histological appraisal. It may produce a fragmented biopsy in patients with cirrhosis and in such cases the Vim Silverman needle which has a cutting edge has been preferred.

Recently Rake, Murray-Lyon, Ansell and Williams (1969) described the use of a modified Vim Silverman needle (Vim-Tru-Cut) produced by Travenol Laboratories. They claim that this needle produces consistently good and unfragmented biopsy specimens in patients with cirrhosis. They also found that it was easier to use than the ordinary Vim Silverman needle and that it was less painful to the patient, probably because of its very sharp cutting edge. The introduction of the various safer needles and especially the increase in the number of trained operators has now resulted in needle biopsy being an accepted procedure in most general hospitals.

The small biopsy specimen has been found to be representative of changes in the whole liver (Schiff and Billing, 1969). This is also true of most cirrhosis, although in the coarsely nodular liver (macronodular) it is possible to aspirate a large nodule and find the architecture normal (Braunstein, 1956). Granulomas representing sarcoidosis and tuberculosis, tumour deposits and abscesses may be missed. In a comparison of the results of needle biopsy and operative biopsy there was complete agreement in 76.9%, minor differences in 16.1% and in only 7% did needle biopsy completely miss the lesion (Federlin and Sandritter, 1961). Baggenstoss (1966) reviewed 800 non-neoplastic liver biopsy specimens without reference to any clinical information in order to evaluate the adequacy of histological changes for accurate diagnosis. He was able to give a correct morphological diagnosis in 73% , incorrect diagnosis in 2% and the biopsy was not diagnostic in 25%.

Operative biopsy allows assessment of the macroscopic appearance of the liver and the selection of any abnormal area. It is less liable to sampling error, but the biopsies obtained often contain histological artefacts as a result of the anaesthetic and operative trauma (Rubin, 1963). The livers of more than half the population have some degree of fibrosis around portal tracts immediately

beneath the capsule (Petrelli and Scheuer, 1967), and in one quarter there may be extension of fibrous tissue from portal tracts to central veins such that cirrhosis may be simulated. Also operative biopsies may show artefactual changes such as patchy loss of glycogen, haemorrhages and polymorphonuclear infiltration (Sherlock, 1962). Peritoneoscopy combined with needle biopsy, like operative biopsy allows visualisation of the surface of the liver and biopsy of selected sites (Caroli and Ricordeau, 1961). More than one biopsy may be taken. The specimen is subcapsular and may therefore be fibrotic and again not representative of the interior of the liver.

Microscopical examination of the specimens obtained by biopsy in chronic liver diseases, especially, primary biliary cirrhosis, active chronic hepatitis and in chronic alcoholics, show changes such as overgrowth of connective tissue, distortion of pattern, infiltration with chronic inflammatory cells and changes in hepatocytes. Hepatocyte changes may include various forms of necrosis, fatty changes and evidence of hyperplasia.

The problem of hepatocyte hyperplasia does not appear to have been stressed in chronic liver disease and when remarked has been ascribed to regeneration or a reaction to damage or loss of hepatocytes (Popper and Orr, 1970; Mistilis and Blackburn, 1970). It is recognised however, that in several examples of chronic liver disease, the features of hepatocyte hyperplasia are noted and there is often no evidence of substantial hepatocyte destruction or loss. Even in cirrhosis, the nodules of hyperplastic hepatocytes are referred to as "regenerative", a term derived from the assumption that much hepatocyte necrosis had occurred at an earlier stage in the disease. Such necrosis has not been identified in most cases of cirrhosis. Similar assumptions have been made for other conditions, but it has been pointed out that evidence of severe hepatocyte destruction preceding hyperplasia is often lacking (Weinbren, 1975).

The purpose of this investigation is to evaluate liver biopsies and post mortem material for the purpose of assessing the incidence and the time of appearance of hepatocyte hyperplasia in chronic liver disease.

Chronic active liver disease

Clinically a chronic liver disease could be defined as a disease of the liver which has been present for at least six months (Sherlock, 1974), and showing disturbed liver function tests. Apart from cirrhosis and primary biliary cirrhosis, four categories of chronic active liver disease are distinguished on morphological criteria and one may develop into another (Baggenstoss, Soloway, Summerskill, Elveback and Schoenfield, 1972). The four categories are chronic aggressive or active chronic hepatitis; chronic persistent hepatitis (De Groote, Desmet, Gedigk, Korb, Popper, Poulsen, Scheuer, Schmid, Thaler, Uehlinger and Wepler, 1968); subacute hepatitis with bridging (Boyer and Klatskin, 1970) and subacute hepatitis with multilobular necrosis (Baggenstoss et al, 1972), a more severe lesion than the previous one.

Many other chronic disease processes of the liver are known to end in cirrhosis of the liver. Such diseases include chronic alcoholic liver disease, active chronic hepatitis, primary biliary cirrhosis, inherited metabolic disorders such as haemachromatosis, Wilson's disease, and several disorders of amino acid and carbohydrate metabolism. More recently alpha 1-antitrypsin deficiency (Berg and Eriksson, 1972), has been associated with chronic liver disease. Various drugs and toxins too, after prolonged use may produce a chronic liver disease. Chronic liver disease may therefore include many different types of liver lesions. This study is concerned with chronic persistent hepatitis, active chronic hepatitis, primary biliary cirrhosis and alcoholic liver disease.

Chronic persistent hepatitis

This is a relatively benign condition and carries a good prognosis in most instances (Becker, Scheuer, Baptista and Sherlock, 1970). Its diagnosis is based on liver biopsy specimens and is characterised by portal inflammatory infiltration with few other changes (De Groote et al, 1968). There is no distortion of the architecture and usually there is little damage to the limiting plate. Physical examination may be completely normal or there may be slight hepatomegaly, the liver edge sometimes being tender (Sherlock, 1974). In

particular signs of chronic liver disease such as vascular spiders, splenomegaly or oedema of the ankles are not detected.

The serum bilirubin is normal or slightly increased. The serum alkaline phosphatase is usually normal. The serum transaminase level is most often elevated. The total globulin is usually within normal limits and the serum immunoglobulin G (IgG) is but slightly increased. Tests for Australia antigen (HB-Ag) may be positive.

Active chronic hepatitis

It was first described in 1950 by Waldenström. He drew attention to a form of chronic liver disease occurring predominantly in young women and characterised by moderate jaundice, acne, amenorrhoea,hepatosplenomegaly and hypergammaglobulinaemia. In 1951 Kunkel, Ahrens, Eisenmenger, Bongiovanni and Slater reported a preliminary observation in a similar disorder. Bearn, Kunkel and Slater (1956) discussed the same entity in a paper titled "chronic liver disease in young people". Active chronic hepatitis was initially thought to occur only in young women. However Willocx and Isselbacher in 1961, found that it also affects males and produces clinical features identical with those encountered in females. A rather similar condition in women around the age of the menopause was reported by Cattan, Vesin and Bodin (1957). The association with a lupus erythematosus like syndrome and with L.E. cells in the blood was noted by Joske and King in 1955, and Krook in 1961. Mackay, Taft and Cowling (1956) from Australia, coined the term "lupoid hepatitis". The prominent cellular infiltrate led Good (1956), Page and Good (1960) to use the term "plasma cell hepatitis". Read, Sherlock and Harrison (1963) used the term "active juvenile cirrhosis", although they recalled that the condition was not always a cirrhosis in the earlier stages and did not always affect young people. Passwell, Theodor and Cohen (1971) reported that the disease occurred even in babies. It is therefore evident that the disease affects both sexes in all age groups.

Terminology is confusing because the disease has given rise to many terms,

including, chronic liver disease in young women (Bearn, Kunkel and Slater, 1956), plasma cell hepatitis (Good, 1956; Page and Good, 1960), active juvenile cirrhosis (Read, Sherlock and Harrison, 1963), chronic liver disease in young people (Willocx and Isselbacher, 1961), progressive hepatitis (Blackburn, 1961), lupoid hepatitis (Mackay, Taft and Cowling, 1956), autoimmune hepatitis, and liver disease in young women with hypergammaglobulinaemia (Jones and Castleman, 1962). Most cases so reported are variants of the same disorder. The term active chronic hepatitis (Geenen, Hensley and Winship, 1966; Sherlock, 1966), is now widely accepted, for it embodies two of the essential features of this disorder, namely established chronic progressive liver disease and superimposed episodes of active disease. Although this is a generalised disease affecting many organs other than the liver, the term active chronic hepatitis directs attention to the major organ involved (Mistilis, Skyring and Blackburn, 1968; Mistilis, 1968).

Many circulating antibodies have been described in active chronic hepatitis, but there is a lack of organ specificity of most of these antibodies. Recent investigations have shown the presence of a specific liver membrane auto-antibody in the serum of HB-Ag negative chronic active hepatitis (Hopf, Karl-Hermann Meyer Zum Buschenfelde and Arnold, 1976).

The incidence of antibodies to smooth muscle is about 60% and to non-organ and non-species-specific mitochondria about 25% in most series (Doniach, Roitt, Walker and Sherlock, 1966; Doniach et al, 1970). Antinuclear factor is present in about 70% of patients with active chronic hepatitis and it could be detected in patients with no L.E. cells in the blood (Mistilis, Skyring and Blackburn, 1968; Doniach et al, 1966). The presence of these antibodies is associated with a rise in the serum immunoglobulin levels and in active chronic hepatitis, serum IgG levels are particularly elevated, but high values for serum IgM and IgA may also be found (Feizi, 1968; Sherlock, 1974).

On the basis of serological findings some patients with active chronic hepatitis have been found to have sera positive for the Australia antigen (HB-Ag) and

negative for smooth muscle antibody, antinuclear factor and L.E. factor, while other patients have been found positive for the auto-antibodies and negative for both HB-Ag and the auto-antibodies (Wright, 1970; Bulkley, Heizer, Goldfinger, Isselbacher and Shulman, 1970). These are exceptions (Chaudhuri and McKenzie, 1971; Mathews and Mackay, 1970), but in general the dissociation between high titre smooth muscle antibody and the presence of HB-Ag is supported by several authors (Vischer,1970; Wright, 1970).

Primary biliary cirrhosis

The association of the clinical picture of prolonged obstructive jaundice (cholestasis) without mechanical obstruction to major bile ducts is well known. It was first described in 1851 by Addison and Gull and later by Hanot in 1892. Hanot described it as a form of hypertrophic cirrhosis with chronic icterus and the term Hanot's cirrhosis has been used since that time. The association with high serum cholesterol levels and skin xanthomas led to MacMahon and Thannhauser in 1949 coining the term "xanthomatous biliary cirrhosis".

Ahrens, Payne, Kunkel, Eisenmenger and Blondheim (1950), called the condition primary biliary cirrhosis. Since then this condition has been described under many different names. Baggenstoss, Foulk, Butt and Bahn (1964) termed it "cholangiolitic hepatitis". Sherlock in 1959, said that cirrhosis was only a late manifestation of the disease and so preferred tocall it "chronic intra hepatic" obstructive jaundice.

Rubin, Schaffner and Popper (1965), accurately described the basic lesion as "chronic non suppurative destructive cholangitis". It has the merit of avoiding the term "cirrhosis", for a true cirrhosis with loss of pattern and the presence of nodular hyperplasia occurs late in the disease. But the term primary biliary cirrhosis is now so firmly established that it probably will not be displaced.

It is a chronic liver disease showing obstructive features, both clinically and biochemically. Patients usually present with itching and jaundice appears late in most cases. It is predominantly a disease of adult females, most often seen

between 40 and 55 years (Sherlock, 1959).

Like active chronic hepatitis, this disease too shows a number of serological features. Several circulating antibodies have been described and of these the most frequent is the non organ specific mitochondrial antibody. This antibody occurs so constantly in primary biliary cirrhosis that it is of diagnostic importance in symptomatic and asymptomatic patients (Walker, Doniach and Doniach, 1970; Fox, Scheuer and Sherlock, 1973). The incidence of non organ specific mitochondrial antibodies in this disease varies from 87% to 100% in most series (Klatskin and Kantor, 1972; Doniach et al, 1966; Walker, Doniach, Roitt and Sherlock, 1965; Goudie, MacSween and Goldberg, 1966). Antinuclear antibodies occur in 46% of the patients and smooth muscle antibodies are found in about 50% (Doniach et al, 1966). Paronetto, Schaffner, Mutter, Kniffen and Popper (1964), found antiductular antibodies and MacSween, Gray, Armstrong and Mason (1973), described the presence of bile canalicular antibodies in patients suffering from this disease. But however these were not specific for primary biliary cirrhosis, being detected in other liver diseases too.

The presence of these antibodies is usually associated with a rise in serum immunoglobulins and in this disease IgM levels are particularly elevated, although a rise in IgG and IgA levels may also be found (Feizi, 1968).

The classical lesions in primary biliary cirrhosis, at least in the earlier stages, involve the larger interlobular and septal bile ducts (Rubin, Schaffner and Popper, 1965; Scheuer, 1967), and as these are not always included in a needle biopsy, the diagnosis may be missed (Scheuer, 1970). Multiple sections of a biopsy may have to be examined before bile duct lesions or granulomas are found.

Although active chronic hepatitis and primary biliary cirrhosis are distinguished without much difficulty in most cases, the clinical and morphological features are sometimes confusing. Thus, patients with the clinical features of primary biliary cirrhosis may sometimes show liver biopsy sections suggestive of active chronic hepatitis (Rodes, Bruguera, Bordas and Teres, 1971), and sometimes

the microscopical features may have aspects common to both diseases (Sherlock, 1974).

Alcoholic liver disease

Alcoholic liver disease is a major cause of ill-health and mortality in most countries. In the United States, cirrhosis, most of it alcoholic, is now the fourth commonest cause of death in the fourth to the sixth decades (Popper, Davidson, Leevy and Schaffner, 1969).

That the liver may be damaged by prolonged alcohol ingestion has been realised since the time of Vesalius, and the association is so firmly accepted that the term cirrhosis is often interpreted by the patient as a form of alcoholism (Brunt, 1971). The association of alcoholism with cirrhosis of the liver was recognised by Mathew Baillie in 1793, who said that the process ..... "is commonly produced by a long habit of drinking spirituous liquors".

Christoffersen and Nielsen (1972) define chronic alcoholism as the consumption of more than 50 grams of alcohol per day, for a period of greater duration than one year. In the production of alcoholic liver disease, the amount and duration of intake are important. Many studies from various parts of the world, attest to the high daily intake in cirrhotics. Pequignot (1961) postulated a 'relative danger' intake of 80 to 160 grams daily and a 'high danger' intake of over 160 grams daily. It probably takes 10 years or more of drinking to produce a cirrhosis (Eghoje and Juhl, 1973). The pattern of drinking is probably significant in that continuous drinkers fare somewhat worse than intermittent heavy drinkers (Brunt, 1973). Fatty change, hepatitis and cirrhosis are well recognised hepatic complications of chronic alcoholism.

The association of alcoholism with fatty change in the liver was first noted by Addison in 1836. The accumulated lipid is predominantly triglyceride. There is no convincing evidence that fatty change leads to cirrhosis in man. The steatosis may persist for months or years but disappears quite rapidly on cessation of drinking.

Alcoholic hepatitis is a fairly distinctive clinico-pathological entity. It may occur in an otherwise normal, fatty or cirrhotic liver. It commonly follows a bout of heavy alcohol consumption and it is characterised clinically by abdominal pain, nausea, vomiting, fever, jaundice and occasionally ascites (Green, Mistilis and Schiff, 1963). The liver is usually enlarged and tender. F.B. Mallory first drew attention to this lesion in 1911. Since then clinicians and pathologists have used various terms for this clinico-pathological syndrome, including progressive alcoholic cirrhosis (Hall and Morgan, 1939), acute hepatic insufficiency of the chronic alcoholic (Phillips and Davidson, 1954), florid cirrhosis (Popper, Szanto and Parthasarathy, 1955), acute sclerosing hyalin necrosis (Edmondson, Peters, Reynolds and Kuzma, 1963), and steatonecrosis-Mallory body type (Harinasuta, Chomet, Ishak and Zimmerman, 1967). The most popular term however, seems to be "acute alcoholic hepatitis", first used by Beckett, Livingstone and Hill in 1961.

Microscopically there is focal, usually centrolobular liver cell swelling with necrosis and infiltration by neutrophils. The hyalin, first described by Mallory in 1911 is not pathognomonic, but is characteristic of alcoholic liver injury, when it is associated with the picture of alcoholic hepatitis. Hyalin now appears to be non specific. It has been identified in the liver in many disease processes, including, primary hepatic carcinoma (Keeley, Iseri and Gottlieb, 1972), the lobular periphery in primary biliary cirrhosis (Monroe, French and Zamboni, 1972; MacSween, 1973), chronic aggressive hepatitis, even without cholestasis (Gerber, Orr and Denk, 1973), Wilson's disease and in Indian childhood cirrhosis (Nayak, Sagreiya and Ramalingaswami, 1969).

In 1968, Rubin and Lieber found that alcohol consistently produced an acute injury reaction in volunteers, but why only a small proportion, perhaps 10 to 12% of heavy drinkers develop chronic irreversible disease is unknown.

Most workers seem to think that alcoholic hepatitis is pre-cirrhotic and that the proliferation of hepatocytes is a compensatory phenomenon (regeneration) to the loss of hepatocytes (Gerber and Popper, 1972; Rubin and Lieber, 1974;

Smetana, 1972.)

Cirrhosis

The stony hard liver with dropsy is said to have been known to Erasistratos of Alexandria, nearly 3 centuries B.C. Laënnec coined the term cirrhosis, derived from the Greek "kirrhos", meaning tawney, because the projecting nodules were of fawn or yellowish russet bordering on the greenish. The first anatomical description of a nodular liver corresponding to the usual 'gross' appearance of a cirrhotic liver is credited to Morgani.

Cirrhosis is a term used to describe a progressive chronic liver disease, produced as the end result of a number of different pathological processes. Certain morphological criteria should be satisfied before a liver is classified as cirrhotic. The process is diffuse, i.e. it involves the whole liver, though not necessarily every lobule. There is a disturbance of the normal vascular pattern or architecture and the liver plates are usually hyperplastic. A variable amount of fibrous tissue, is found between the islets or nodules of parenchymal cells, but this may sometimes take the form of fine septa. Clinically, cirrhosis manifests as portal hypertension or as hepatocellular failure or both.

The normal pressure in the portal vein is 6 to 7 mms. of mercury (Sherlock, 1971). In cirrhosis it may rise to 20 or 30 mms. mercury (Reynolds, Hidemura, Michel and Peters, 1969). Portal hypertension could present as haemetemesis and/or melaena due to leakage of blood from oesophageal varices. Some may present with ascites or with ankle oedema. The spleen enlarges progressively, but the size bears no relation to the height of the portal venous pressure (Krook, 1957). An enlarged spleen is the single most important diagnostic sign of portal hypertension (Sherlock, 1971), and if the spleen cannot be felt or is not seen to be enlarged on a plain film of the abdomen, the diagnosis of portal hypertension is questionable (Sherlock, 1971). Oesophageal varices may be demonstrated using a barium swallow. Oesophagoscopy is also a reliable method of demonstrating varices.

Hepatocyte hyperplasia

Liver cell proliferation or hyperplasia, is a frequent accompaniment of disease processes in the human and animal liver. The proliferated cells are often morphologically recognisable and can be found in many conditions, including cirrhosis and various forms of hepatitis. They are seen also during recovery after hepatic trauma and after exposure to hepatotoxins. What is not always clear is whether the proliferation represents a primary reaction to an external stimulus or a response to loss of functioning hepatic tissue. The term 'regeneration' or the more correct 'compensatory hyperplasia' represents a response to damage to or loss of part of the population of liver cells, i.e. a response to loss of functioning liver tissue. Regeneration or compensatory hyperplasia occurs characteristically in the periportal regions (Weinbren, 1959; Bucher, 1963). In some, the lobular pattern is retained (lobular hyperplasia), while in others it is replaced by irregular nodules of proliferated hepatocytes, in which the vascular architecture is much altered (nodular hyperplasia).

It is well established that livers chronically exposed to small doses of certain drugs, poisons and hepatotoxins show hypertrophy and hyperplasia of the hepatocytes, without a prior loss of functioning hepatocytes. Experimentally it has been found that the drug phenobarbital, causes liver enlargement due to parenchymal cell hypertrophy and hyperplasia in rats (Herdson, Garvin and Jennings, 1964). Thorpe and Walker (1973), showed that insecticides such as dieldrin and D.D.T. produce liver cell hyperplasia in mice. More recently it has been shown that hepatocyte hyperplasia may be produced by the oral contraceptives (Mays, Christopherson and Barrows, 1974) and by synthetic anabolic steroids (Sweeney and Evans, 1976). The repeated exposure of experimental animals to small doses of hepatotoxins insufficient to cause the death of hepatocytes, acts as a stimulus to the proliferation of the liver cells. This produces a hepatomegaly and the liver changes in the mouse include an increased rate of DNA synthesis (Wright, Potter, Wooder, Donninger and Greenland, 1972).

Hepatocyte hyperplasia has also been described in patients suffering from rheumatoid arthritis and its variant Felty's syndrome (Blendis, Ansell, Lloyd Jones,

Hamilton and Williams, 1970; Blendis, Parkinson, Shilkin and Williams, 1974; Sweeney, 1975; Harris, Rash and Dymock, 1974). This hyperplasia is thought to be the pathogenetic factor in the production of portal hypertension seen in such patients. Sweeney describes in his case the presence of twin celled plates at the periphery of the hepatic nodules which suggested that the liver underwent generalised hyperplasia before nodule formation occurred. He suggests that a drug used in the treatment of rheumatoid arthritis may have been responsible for the growth of the hepatocytes.

The normal adult liver parenchyma consists of cell walls or plates which are one cell thick (Elias, 1949), and are separated from each other by the lacunae or spaces in which the vascular sinusoids run. The plates may be two cells thick in the livers of children under 5 years old (Morgan and Hartroft, 1961). The work of Lewis (1912), illustrates that the foetal liver is constructed of plates up to three cells thick. From birth to about one month of age the majority of the hepatocyte plates are multilayered. At the age of three years one cell thick plates predominate and by the age of five years all livers examined showed the adult type of architecture (Morgan and Hartroft, 1961). They state that multilayered plates in the liver of a person above five years of age suggests 'regeneration'.

When the hepatocytesundergo hyperplasia, certain microscopical and biochemical changes occur which help in its identification and localisation.

1) Owing to the rapid multiplication of cells the liver would exhibit many cells with mitotic nuclei and there is an increased DNA synthesis. Both these changes are early phenomena and may not be identifiable in livers examined after established hyperplasia.

2) As mentioned above, the most important and easily identifiable feature of hepatocyte hyperplasia in any person above five years of age, is the occurrence of thick plates. These thick plates could be easily identified under the light microscope in ordinary H and E preparations, but is best visualised in Gordon

and Sweet's reticulin preparations under phase contrast. Each thick plate stands out prominantly between two sinusoids.

3) In a few instances, as for example in active chronic hepatitis, the hepatocytes tend to arrange round a central dilated bile canaliculus giving a 'gland' or 'acinar' appearance.

The purpose of this investigation is to assess the incidence of liver cell hyperplasia in chronic liver diseases such as active chronic hepatitis, primary biliary cirrhosis and alcoholic liver disease, and to check if the findings are related to the presence of portal hypertension in such diseases.

The normal liver lobule

As mentioned above, the adult liver parenchyma consists of plates one cell thick, separated from each other by the vascular sinusoids. In the adult liver, in any histological section a few plates appear thick, due to tangential sectioning (Elias, 1949). It is clear from Elias's three dimensional reconstruction that the classical idea of cords of cells radiating like the spokes of a wheel from a central hub is no longer tenable.

A description of the structure of the hepatic lobule is provided by Rappaport (1973). The continuous mass of parenchymal laminae are tunnelled by capillaries and are arranged in such a manner that the smallest structural units are formed by the mass of cells immediately surrounding the terminal branches of the blood and biliary vessels in the portal tracts. A special layer of cells, the limiting plate or lamina, abuts on the vascular bundle. The classical hepatic lobule consists of segments of a number of these portal structural units draining towards one hepatic venous radicle.

PART 2

MATERIAL AND METHODS

MATERIAL

Two sets of material were used.

First Set

This consisted of post mortem and biopsy material obtained from patients diagnosed as suffering from cirrhosis of the liver and who died in the Hammersmith Hospital during a 27 year period ; 1948 to 1974. The clinical details of these patients were obtained from their case notes and post mortem records. This investigation was on patients who had previous liver biopsies performed on them.

Second Set

This consisted of material from living patients. It was a quantitative analysis of liver plates in normal adult livers and in livers of patients suffering from primary biliary cirrhosis, active chronic hepatitis, alcoholic liver disease, chronic persistent hepatitis and cirrhosis. Most of this material was from patients admitted to this hospital, but some material had been referred to this department from other institutions. The relevant clinical details were obtained from the case notes. The material is from patients treated between the years 1953 and 1974. All the patients had been clinically, biochemically and histologically diagnosed as suffering from a chronic liver disease. The histological criteria used to diagnose the different chronic liver diseases will be discussed later.

In the post mortem study, multiple sections taken from different areas of each liver were available. The majority of the biopsies were done by the aspiration technique and in a few patients, serial biopsies at varying intervals during the course of the disease had been performed. The aspiration biopsy was performed with the Vim Silverman or the Menghini needle. In some patients, especially those suspected of suffering from primary biliary cirrhosis, open (wedge) biopsies were taken at laparotomy.

The morphologically normal liver biopsies were from patients who underwent laparotomy for staging of Hodgkin's disease, but had no hepatic or splenic involvement.

The tissue obtained was fixed in formol-saline, dehydrated, cleared and paraffin embedded. Sections were cut, mounted and stained by the undermentioned methods. Most of the staining techniques are done routinely on all liver biopsy specimens referred to this department.

Stains

The routine laboratory haematoxylin and eosin stain was done on all biopsy specimens. The reticulin fibres were impregnated by Gordon and Sweet's silver method. The thickened liver plates in chronic liver disease are well visualized by phase contrast microscopy in such preparations. Iron in hepatocytes, Kupffer cells and in portal tracts is best identified in sections stained by the modified Perl's prussian blue technique. Glycogen was stained by Best's carmine method or the periodic acid-Schiff technique. An orcein stain (Shikata, 1974; Deodhar, Tapp and Scheuer, 1975), was done in patients whose serum was positive for Australia antigen (HB-Ag). Hyalin was demonstrated by the use of the luxol-fast blue stain (Becker and Treurnich, 1959), although it was quite apparent in H.E. sections.

METHODS

First Set

All the patients in this group who came to post mortem, had one or more biopsies performed on them during life. The biopsy and post mortem material were stained using the techniques described above.

The aim of this study was to document various aspects of hepatocyte hyperplasia in chronic liver disease, from its very early stages to the end stage cirrhosis. All biopsy specimens with a retained pattern were examined for confirmation of the diagnosis, for the presence of liver cell hyperplasia, its time of development and its relationship, if any, to the production of portal hypertension.

Second Set

The biopsy sections indexed as chronic persistent hepatitis, primary biliary cirrhosis, active chronic hepatitis, alcoholic liver disease and cirrhosis were examined for confirmation of the diagnosis. Some were rejected as they failed to fulfil the criteria used for their diagnosis. The selected biopsy material fell into the following groups:-

1. Normal controls consisted of biopsy specimens from five adult patients with normal liver histology.

2. Twenty two patients fulfilled the criteria for primary biliary cirrhosis, and a total of 35 biopsies were available.

3. There were 39 biopsy specimens from twenty nine patients proved to have active chronic hepatitis.

4. 39 biopsy specimens were from 37 chronic alcoholics.

5. Five biopsy specimens from five patients proved to have cirrhosis of different causes.

6. Five biopsy specimens from five patients in whom a diagnosis of chronic persistent hepatitis was made.

A quantitative estimation of the single cell thick plates and plates two or more cells thick in each of the liver biopsy specimens was done by a morphometric technique described by Chalkley (1943), Loud (1962) and Weibel (1969). This is a point counting method, using a calibrated grid. The calibrated area is on a circular slab of transparent glass, which is made to fit the eye-piece of a standard light microscope. The calibrated section is a square and it is further subdivided into 100 equal squares by horizontal and vertical lines. The grid was inserted into the 8X ocular of a binocular Reichert light microscope. The liver cell plates were examined at a magnification X320 by scoring points overlying thick (2 or more cells) plates against points overlying single cell thick plates. Each point counted is an intersection of a horizontal and a vertical line. One hundred such points were present in each field and the counts were recorded on a laboratory counter. In this way, a comparison was made of the incidence of

"hits" on thick plates versus "hits" on single plates . This procedure is considered to give an accurate assessment of the areas occupied by the structures under study (Chalkley, 1943).

In each of the five normal liver biopsy specimens 100 fields of 100 points each were counted. The mean ratio for each slide and the mean of all five slides were calculated.

The surface area available in aspiration needle biopsy specimens is small when compared to that of wedge biopsies. Every second field in a needle biopsy section was counted and every field if the biopsy specimen was small or fragmented. As many fields as possible were point counted in each biopsy specimen and this usually involved 15 to 20 fields.

Primary biliary cirrhosis

This investigation comprised 35 biopsy specimens from a total of 22 patients. Nineteen of these were wedge biopsies taken at laparotomy, and the rest were needle biopsies, performed by the aspiration technique. The biopsy specimens range from the very early asymptomatic stage of the disease to the final cirrhotic stage. Sixteen of the patients were investigated and treated in the Hammersmith Hospital. The rest were from other institutions and their biopsy material was referred to this department for diagnostic purposes or for confirmation of their diagnosis. Large bile duct obstruction was eliminated at laparotomy in 17 patients. None of the twenty-two patients in this group had any history of exposure to drugs which may have caused a cholestatic jaundice.

The clinical biochemical and histological features of this disease are well documented by Sherlock (1959), Rubin, Schaffner and Popper (1965) and by Scheuer (1967). Lately many immunological features have been associated with primary biliary cirrhosis and these are well described by Walker, Doniach, Roitt and Sherlock (1965), Doniach, Roitt, Walker and Sherlock (1966), Feizi in 1968, Doniach and Walker in 1969 and by Walker, Doniach and Doniach in 1970.

The majority of patients (80 to 90%) have mitochondrial antibodies in their sera and this finding provides reliable confirmatory evidence of primary biliary cirrhosis when the biopsy findings are consistent (Klatskin and Kantor, 1972). In this study it was done on 8 patients and all 8 gave positive results.

Clinically they had one or more of the following features at some stage in the course of the disease :- pruritus, jaundice often of the obstructive type, bone pain, steatorrhoea, or the signs and symptoms of cirrhosis. A majority of the patients in the present study presented with pruritus. Although symptoms and signs of portal hypertension may be the initial manifestation in some patients (Kew, Varma, Dos Santos, Scheuer and Sherlock, 1971; Zeegen, Stansfeld, Dawson and Hunt, 1969), none in this study presented with it.

Biochemically they have the features of an obstructive jaundice, such as elevated levels of alkaline phosphatase, 5-nucleotidase and high serum cholesterol values.

Most criteria that are helpful for a histological diagnosis, remain confined to the portal tracts. A pathognomonic feature is the damage or destruction of the septal and larger interlobular bile ducts (Fig. 14, 22). Such bile ducts may not always be included in an aspiration biopsy and hence wedge biopsies are preferred, at least in the early stages (Scheuer, 1967). Affected portal tracts show dense aggregates of lymphocytes and plasma cells together with occasional germinal centre formation. Granulomas with both epithelioid and giant cells may be present in close proximity to the damaged bile ducts (Fig. 14, 26). Less often granulomas appear in the parenchyma. Smaller portal tracts are infiltrated with chronic inflammatory cells and a late consistent feature is a reduction in the number of smaller bile ducts and ductules (Fig. 18). This is a most helpful diagnostic feature, especially in smaller aspiration biopsies which often fail to exhibit large portal tracts.

A tabulated questionnaire listing a number of different histological features was completed for each stained section. The histological material was studied without knowing whether evidence of portal hypertension was present.

Each biopsy specimen was examined for the histological features of active chronic hepatitis too, as features of both diseases could co-exist clinically and histologically (Rodes et al, 1971; Sherlock, 1974).

Cirrhosis (biopsy specimens with a distorted architecture), was classified as micronodular, macronodular or mixed, on the criteria described by Sherlock (1968) and Scheuer (1968).

Hyperplasia

All biopsy specimens were examined for evidence of hepatic cell hyperplasia and a morphometric analysis of the single and two or more cell thick plates in each biopsy specimen was done. An attempt was made to correlate plate thickness with 1) the duration of the disease and 2) the occurrence of portal hypertension.

Active chronic hepatitis

This series comprised 39 biopsy specimens from a total of 29 patients. These were all aspiration biopsies performed on patients admitted to the Hammersmith hospital. Features identical to that of active chronic hepatitis are thought to occur in some cases of drug hepatitis. The drugs often incriminated are, oxyphenisatin (Reynolds, Peters and Yamada, 1971) which is used as a laxative, the antihypertensive agent - methyl dopa, isoniazid, phenylbutazone, and oxyphenylbutazone (Sherlock, 1974). The patients selected for this study, gave no history of contact with such drugs.

A combination of clinical, biochemical, immunological and histological criteria were used for the selection of the material. Clinically the disease continued without improvement for over six months and the patients had evidence of a chronic liver disease such as, mild chronic jaundice, persistent spider naevi, persistent hepatosplenomegaly, evidence of portal hypertension and a

hypergammaglobulinaemia. Some patients, in addition to the disease of the liver, had a simultaneous involvement of other organs such as the skin, pleura, joints, colon, kidney and the lungs. The majority of such patients had a positive L.E. cell phenomenon.

The onset was insidious in most, but a few presented with an acute onset resembling acute viral hepatitis. The majority of such patients (those with an acute onset), had a persistent hepatitis-associated antigenaemia (HB-Ag +ve).

The more important histological criteria which help in making a diagnosis are:-

1) A widening of portal tracts together with much plasma cell, lymphocyte and histiocyte infiltration. In most portal tracts, the inflammatory process extends beyond an eroded limiting plate between subadjacent hepatocytes (Fig. 32, 39), some of which appear to be enmeshed in small islands within the mass of inflammatory cells ("piecemeal necrosis").

2) Periportal hepatocytes are often arranged in gland-like formations (rosette), the tiny lumen being represented by a dilated canaliculus surrounded by 5 to 7 swollen parenchymal cells (Fig. 38, 39, 42).

3) The parenchymal cells are diffusely swollen with patchily stained cytoplasm (Fig. 32).

4) Other evidence of hepatocyte damage is present.

5) Varying degrees of Kupffer cell prominence may sometimes be seen.

6) Fibrosis may be found.

The stained sections were examined under the light microscope and a tabulated questionnaire as in the primary biliary cirrhosis investigation, was completed.

Hyperplasia

All the biopsy sections were examined and studied for evidence of hepatocyte hyperplasia and a morphometric analysis of the hepatic plates was performed by

the point counting technique. Areas of hyperplasia were defined and an attempt was made to correlate plate thickness with the duration of the disease and with the occurrence of portal hypertension.

Alcoholic liver disease

The material for this study was from patients with a history of alcohol ingestion for periods ranging from one year to over twenty years. In all cases there was a clear history of excessive alcohol intake, usually greater than 160 grams daily. Many cases were rejected where alcohol intake appeared to be occasional or indefinite or where clinical and histological features strongly suggested another well defined disease pattern.

All biopsy specimens, except for one which was done at laparotomy, were obtained by percutaneous aspiration.

Clinically, the patients either presented with symptoms of acute liver disease such as nausea, vomiting, abdominal pain and jaundice, together with disturbed liver function tests, or with the signs and symptoms of a chronic liver disease.

Histologically the livers of these patients had one or more of the following features:

1) Fatty change (steatosis). Although non specific it is the commonest microscopical feature observed in alcoholic livers. It is not confined to any particular site in a lobule being diffusely scattered in most livers. It differs in extent too. Some have a very extensive infiltration while others may not have any at all. Fatty infiltration may be observed in cirrhotic livers too.

2) Alcoholic hepatitis (Fig. 47). This is a characteristic microscopic feature of alcoholic liver disease. It is usually focal and centrolobular (Edmondson et al, 1968). This area exhibits liver cell swelling and necrosis.

Some cells may contain hyalin and such cells, as well as the obviously necrotic

cells, may be surrounded by neutrophils (satellitosis).

Hyalin is now thought to be non specific, having been described as occurring in a number of disease processes involving the liver. But hyalin, when associated with the picture of alcoholic hepatitis is characteristic of alcoholic liver injury (Popper and Schaffner, 1974). Alcoholic hepatitis may or may not be associated with steatosis in the liver. It may occur even in a cirrhotic liver. The presence of hyalin in the periportal areas in chronic alcoholics is indicative of cirrhosis (Christoffersen and Nielsen, 1972).

3) Megamitochondria. These are often found in alcoholic livers and are distinct from alcoholic hyalin. (Iseri and Gottlieb, 1971). It is a non-specific change occurring in many non alcoholic livers. It may not always be visible under the light microscope, but its presence is readily confirmed by electron microscopy. Under the light microscope, the large mitochondrion appears as a rounded body about the size of a red blood corpuscle in the cytoplasm of the hepatocytes. It is P.A.S. negative.

4) Increased iron storage. Most livers of chronic alcoholics exhibit an increased iron storage and it is best detected by the modified Perl's prussian blue stain.

There were 39 biopsy specimens from a total of 37 patients. All these patients were seen and treated in this hospital. The stained sections were examined under the light microscope and a tabulated questionnaire was completed.

Hyperplasia

Areas of hyperplasia were defined and a morphometric analysis of the hepatic plates was performed by the point counting technique. It is extremely difficult to assess the hyperplasia in cells which are laden with fat but attempts were made to identify sinusoidal walls in order to delineate the plates. An attempt was made to correlate plate thickness with the duration of alcohol consumption and with the occurrence of portal hypertension.

Chronic persistent hepatitis

The diagnosis is based on liver biopsy changes (Becker et al, 1970). A proportion of the patients gave a history strongly suggesting acute viral hepatitis six months to one year before. Vague ill health or fatigue was the commonest symptom and hepatomegaly the only physical sign in most. Biochemical tests are often abnormal, the commonest being a mild to moderate elevation of the serum transaminase (Becker et al, 1970). In a few cases the serum may be positive for the Australia antigen (HB-Ag +ve). Most patients make a complete recovery, but a few, may end up as active chronic hepatitis.

Histologically, the changes are confined mainly to the portal tracts. A chronic inflammatory infiltration consisting chiefly of lymphocytes is observed in the portal areas. The limiting plate is usually undamaged. The lobular architecture is preserved and there is usually little or no fibrosis (De Groote et al, 1968).

Five biopsy specimens fulfilling the above histological criteria were selected. They were aspiration biopsies from five different patients. The stained sections were examined under the light microscope and a questionnaire was completed. The biopsy specimens were further examined for evidence of hepatocyte hyperplasia and an analysis of the hepatic plates was performed by the point counting technique.

Cirrhosis

It is a chronic liver disease morphologically characterised by nodules of liver cells with a disturbed vascular architecture associated with varying degrees of fibrosis. It is the end stage of a number of chronic disease processes affecting the liver. Clinically the patients present with signs and symptoms of a chronic liver disease and /or with evidence of portal hypertension.

This investigation comprised 5 biopsy specimens from 5 patients. In two of them the cirrhosis followed excessive alcohol intake, one followed active chronic hepatitis, another primary biliary cirrhosis and the fifth, primary haemachromatosis.

The stained sections were examined under the light microscope. A morphometric analysis of the liver plates was performed by the point counting technique.

PART 3

RESULTS

RESULTS

SET 1

This study was performed on patients who were diagnosed as suffering from cirrhosis of the liver at post mortem and who had had liver biopsies performed on them during life. These sections were reviewed in order to observe the earlier stages of liver disease in patients who were known to develop cirrhosis and portal hypertension. The point counting investigation on biopsy material referred to as Group II indicated that some patients had a higher incidence of thick plates than others and that thick plates were more frequent in patients with cirrhosis. Apart from duration, no firm evidence was available that some lesions with a predominence of single plates actually progressed to lesions with a predominence of thick plates and ultimately to cirrhosis. It was hoped that the repeated samples taken from the patients with ultimate cirrhosis might indicate the progression envisaged.

It might be considered possible, although highly unlikely, that lesions with predominantly thick plates could represent a different disease entirely from those with predominantly single plates so that a study of early to late specimens from cirrhotic patients seemed relevant.

It was not considered necessary to undertake point counting in this series.

Alcoholic Cirrhosis

Of a total of 50 patients confirmed as having alcoholic cirrhosis only 9 had had a liver biopsy performed during life. They all had clinical evidence of portal hypertension at the time of the initial biopsy and microscopically their biopsy specimens show a loss of the normal vascular architecture and the presence of hyperplastic nodules.

Primary biliary cirrhosis

Of the 11 patients confirmed at post mortem as having primary biliary cirrhosis, 7 had one or more biopsy specimens taken at varying intervals during life. Of the 7 patients, 3 had 2 serial biopsies each performed on them. The rest had one biopsy each. The biopsy specimens of 4 of the patients showed a loss of the

normal vascular architecture and the presence of hyperplastic nodules at the time of the initial biopsy. Clinically they all had evidence of portal hypertension.

The other 3 patients had no clinical evidence of portal hypertension at the time of the initial biopsy. Their liver biopsy specimens showed a retained vascular pattern with few hyperplastic hepatocyte plates. With time they developed clinical evidence of portal hypertension. The biopsy specimen of one patient at this time showed a loss of the normal vascular pattern and the presence of hyperplastic nodules. The liver biopsy specimens of the other two patients showed a diffuse hyperplasia of the liver plates with a retained vascular pattern. Subsequent biopsies showed a loss of the normal vascular pattern and the presence of hyperplastic nodules.

Active chronic hepatitis

Of a total of 13 patients confirmed as suffering from active chronic hepatitis at post mortem, 11 had one or more liver biopsies performed on them before death. Serial liver biopsies were performed on 5 patients.

The initial liver biopsy specimens of 10 patients showed a loss of the normal vascular architecture and the presence of large hyperplastic nodules. Clinically they all had the signs and symptoms of cirrhosis.

The other patient also had clinical evidence of portal hypertension at the time of the initial liver biopsy. Histologically the liver biopsy specimen showed a retained vascular pattern and a diffuse hepatocyte hyperplasia. The patient died two years later and the liver was cirrhotic at post mortem.

POINT COUNTS

SET II

Normal adult liver

Each field contains 100 points. A total of 100 fields in each of the 5 normal liver biopsy specimens was point counted and reproduced below is the mean point count for each biopsy specimen.

S72/2640 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}} = \frac{7684}{262} = \frac{28.9}{1}$

S72/91 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}} = \frac{7925}{260} = \frac{29.4}{1}$

S72/1182 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}} = \frac{7433}{275} = \frac{27.0}{1}$

S73/890 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}} = \frac{7731}{265} = \frac{29.1}{1}$

S72/3392 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}} = \frac{7274}{279} = \frac{26.0}{1}$

Mean of all 5 biopsy specimens $= \frac{27.5}{1}$

Standard deviation $\pm$ 1.3

This would be referred to as the single : thick plate ratio for a normal adult liver.

Cirrhosis

A total of five liver biopsy specimens showing histological evidence of cirrhosis due to different causes were included for morphometric analysis.

Alcoholic cirrhosis

S73/504 $\frac{\text{Points overlying single plates}}{\text{Points overlying thick plates}}$

This is referred to as the single to thick plate ratio.

$\frac{10}{69}$ $\frac{8}{74}$ $\frac{11}{72}$ $\frac{10}{71}$ $\frac{8}{78}$ $\frac{7}{68}$ $\frac{14}{74}$ $\frac{12}{72}$ $\frac{10}{74}$

$\frac{9}{76}$ $\frac{8}{78}$ $\frac{6}{72}$ $\frac{12}{74}$ $\frac{11}{74}$ $\frac{14}{73}$ $\frac{14}{72}$ $\frac{12}{71}$ $\frac{9}{76}$

Mean ratio $\frac{\text{Single}}{\text{Thick}} = \frac{1}{7.1}$

S72/3942 $\frac{8}{84}$ $\frac{10}{84}$ $\frac{11}{79}$ $\frac{9}{80}$ $\frac{11}{78}$ $\frac{9}{82}$ $\frac{9}{84}$ $\frac{10}{80}$

$\frac{11}{79}$ $\frac{11}{74}$ $\frac{12}{72}$ $\frac{11}{79}$ $\frac{10}{81}$ $\frac{9}{75}$ $\frac{14}{76}$

Mean ratio $\frac{\text{Single}}{\text{Thick}} = \frac{1}{7.7}$

Cirrhosis following active chronic hepatitis

S61/242 $\frac{10}{78}$ $\frac{8}{79}$ $\frac{14}{72}$ $\frac{12}{76}$ $\frac{7}{81}$ $\frac{6}{79}$ $\frac{12}{72}$ $\frac{11}{73}$ $\frac{14}{71}$ $\frac{13}{75}$

$\frac{8}{81}$ $\frac{12}{75}$ $\frac{11}{76}$ $\frac{9}{72}$ $\frac{8}{71}$ $\frac{10}{75}$ $\frac{11}{72}$ $\frac{8}{79}$ $\frac{7}{80}$ $\frac{8}{76}$

Mean ratio $\frac{\text{Single}}{\text{Thick}} = \frac{1}{7.6}$

Cirrhosis following primary biliary cirrhosis

S53/1471

$\frac{12}{73}$ $\frac{10}{69}$ $\frac{9}{75}$ $\frac{7}{81}$ $\frac{10}{72}$ $\frac{5}{77}$ $\frac{8}{80}$ $\frac{9}{69}$

$\frac{7}{78}$ $\frac{11}{69}$ $\frac{8}{72}$ $\frac{11}{74}$ $\frac{8}{80}$ $\frac{8}{82}$ $\frac{9}{79}$ $\frac{6}{74}$ $\frac{8}{75}$

$\frac{7}{71}$ $\frac{8}{80}$ $\frac{7}{81}$

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{8.8}$

Cirrhosis due to primary haemachromatosis

S60/1572

$\frac{11}{75}$ $\frac{8}{78}$ $\frac{9}{76}$ $\frac{12}{77}$ $\frac{11}{74}$ $\frac{14}{69}$ $\frac{14}{72}$ $\frac{11}{71}$ $\frac{8}{76}$ $\frac{9}{78}$

$\frac{14}{69}$ $\frac{11}{80}$ $\frac{9}{79}$ $\frac{10}{78}$ $\frac{15}{68}$ $\frac{12}{75}$ $\frac{11}{78}$ $\frac{8}{81}$ $\frac{9}{79}$ $\frac{10}{75}$

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{8.5}$

Mean ratio for all cirrhotics $\frac{\text{single}}{\text{thick}} = \frac{1}{8}$

Standard deviation $+\frac{1}{-0.6}$

Chronic Persistent Hepatitis

Points overlying single plates
Points overlying thick plates

This is referred to as the single : thick plate ratio.

S73/3798

78/4	80/3	79/1	80/2	86/6	69/3	74/3	78/2	80/4	74/3
75/2	80/2	79/5	84/3	79/4	84/3	78/2	81/2	74/2	75/3

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{26.6}{1}$

S70/3022

73/2	74/3	85/2	77/5	64/4	79/4	67/2	66/6	74/2	75/2
78/2	80/2	78/3	75/7	78/4	85/3	74/4	80/4	79/2	75/3

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{25.6}{1}$

S75/87

81/4	78/2	72/4	73/4	84/2	83/2	82/1	74/2	66/3		
75/2	75/5	85/3	80/2	77/3	74/5	83/2	81/2	85/3	79/2	82/2

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{28.6}{1}$

S75/454

75/2	73/3	72/1	70/1	74/2	73/3	65/9	70/2	77/6	84/1	
75/2	73/4	77/5	71/4	76/4	69/2	76/4	72/2	78/1	73/3	75/1

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{25.0}{1}$

Chronic Persistent Hepatitis

S75/1606

80/4	79/3	74/3	74/1	68/3	76/1	81/2	73/4	73/2	79/2
76/4	80/2	78/4	80/2	80/2	80/2	78/5			

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{27.4}{1}$

Mean of all 5 slides $\frac{\text{single plates}}{\text{thick plates}} = \frac{26.7}{1}$

Standard deviation ± 1.5

POINT COUNTS

Primary biliary cirrhosis - Although a total of 35 stained slides were available point counts were performed only on 34. The slide that was omitted contained a fragmented specimen with distorted liver cell plates.

This has been referred to as the single : thick plate ratio.

	ern	ears	ension	rplasia

S73/90

6/78	4/79	8/74	9/73	10/76	11/76	8/76
9/79	4/72	10/71	8/69	10/78	9/74	6/75
8/77	10/74	9/76	6/75	7/77	9/71	

lost 7 Yes Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{9.3}$

S73/2191

70/10	46/30	60/21	66/15	67/12	61/6
43/29	45/30	62/18	65/14	69/11	70/10
71/8	68/11				

retain 2 No Periportal and intra-lobular

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{3.8}{1}$

S68/94

19/52	16/55	14/53	9/68	19/51	15/65
19/56	12/61	15/51	12/56	19/51	12/52
12/58	15/57	10/62	15/58	16/59	11/64

retain 5 Yes Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{3.95}$

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S67/598				
50/38 36/58 39/53 30/60 29/49 39/55				
38/65 60/29 56/34 69/21 30/62 34/59	Retain	3	Yes	Diffuse
41/50 44/49 35/55 36/54 31/58 48/45				
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{1.22}$				
S66/842				
14/70 16/68 13/69 11/71 15/65 14/67				
14/66 10/72 12/69 18/65 9/71 10/72	Retain	3.5	Yes	Diffuse
12/68 14/64 16/66 18/64 14/69 10/72				
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{5.2}$				
S66/2779				
11/71 12/69 24/52 16/63 10/72 9/71				
11/73 30/59 28/61 14/68 13/71 16/69	Retain	3	Yes	Diffuse
24/65 14/68 12/72 14/71 28/61 11/69				
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.1}$				

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

							Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S59/1193										
10/71	16/69	15/75	30/59	18/60	14/75					
9/80	15/75	11/68	10/71	8/70	11/69		Retain	3.5	Yes	Diffuse
13/71	14/68	18/65	12/72	18/69	14/68					
Mean ratio single/thick = 1/4.96										
S59/1308										
15/67	22/55	26/46	44/31	57/17	32/45					
52/30	62/24	36/37	53/28	42/42	69/12		Retain	2	No	Periportal and focal
67/12	58/40	68/13	68/14	44/42	27/53					
Mean ratio single/thick = 1.5/1										
S73/90										
6/78	4/79	8/74	9/73	10/76	11/76	8/76				
9/79	4/72	10/71	8/69	10/78	9/74	6/75	Lost	7	Yes	Diffuse
8/77	10/74	9/76	6/75	7/77	9/71					
Mean ratio single/thick = 1/9.30										

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates								Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S59/1308											
15/67	22/55	26/46	44/31	57/17	32/45	52/30					
62/24	36/37	53/28	42/42	69/12	67/12	58/40		Retain	2	No	Periportal
68/13	68/14	44/42	27/53	68/14	69/17						
Mean ratio single/thick = 1.53/1											
S58/57											
20/60	20/57	26/58	24/60	27/58	18/53						
28/55	25/61	18/53	24/54	22/58	18/67			Retain	2-3	Yes	Diffuse
20/52	19/55	24/54	23/61	20/62	20/52	18/54	25/61				
Mean ratio single/thick = 1/2.60											
S58/227											
18/58	13/68	27/37	13/68	9/61	12/65						
44/33	55/23	15/62	18/61	16/55	16/58			Retain	3-4	Yes	Diffuse
18/56	12/70	12/65	13/55	40/38	58/30	45/39	49/50				
Mean ratio single/thick = 1/2.09											

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

							Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S61/2534 Patient with 4 serial biopsies										
18/70	14/65	12/72	10/69	16/70	10/69	30/50				
53/31	61/26	25/56	25/60	15/70	12/70	58/38	Retain	3	Yes	Diffuse
18/70	10/72	60/30	16/74	15/72	19/74					
Mean ratio single/thick = 1/2.43										
S62/1460										
15/67	17/67	16/64	10/71	8/70	20/55	18/72				
20/61	10/70	21/71	18/67	12/74	10/82	15/81	Retain	4	Yes	Diffuse
22/68	10/78	14/72	14/71	8/78	9/80					
Mean ratio single/thick = 1/4.94										
S65/502										
15/65	14/70	18/68	12/70	11/69	15/72	10/76				
8/78	18/75	11/73	13/73	20/71	14/74	12/69	Retain	7	Yes	Diffuse
11/78	18/71	19/73	10/80	12/69	11/78					
Mean ratio single/thick = 1/5.30										

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

							Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S73/1962										
16/61	15/80	14/74	9/72	12/64	8/69					
14/73	13/76	10/67	9/72	10/74	11/77	9/69	Retain	14	Yes	Diffuse
15/81	12/72	5/82	9/69	14/71	12/74	10/79				

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{6.41}$

S64/3113 Patient with 2 serial biopsies										
33/44	76/8	55/29	80/4	80/2	63/21	42/41				
71/6	63/15	66/8	72/6	38/39	57/23	70/7	Retain	2	No	Periportal
59/18	23/56	70/7	22/63	44/21	70/8					

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{2.70}{1}$

S65/707										
62/18	63/19	58/16	60/18	59/12	67/14	76/17				
77/16	41/40	69/7	40/24	73/8	49/25	40/25	Retain	2.5	No	Periportal
47/23	62/15	70/15	73/19	59/21	60/15					

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{3.30}{1}$

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

								Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S57/1970											
15/62	17/68	17/69	29/50	16/70	44/31	22/73					
16/73	74/9	30/50	19/70	18/68	41/41			Retain	3	Yes	Diffuse
20/74	19/60	30/50	16/73	21/69	35/45	19/71					

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{2.27}$

1955 biopsy Patient with 3 serial biopsies.

16/74	14/72	15/69	20/58	15/80	16/71						
18/79	16/70	19/81	12/72	13/69	16/71	14/70	10/69	Retain	$2\frac{1}{2}$-3	Yes	Diffuse
14/74	18/72	17/71	10/70	19/65	15/70						

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.65}$

1956 biopsy :- S58/1426

10/70	19/70	18/72	8/74	16/76	15/72						
16/71	14/70	8/74	18/70	16/79	14/72	17/71	14/72	Retain	3.5	Yes	Diffuse
14/70	16/79	15/75	18/80	19/76	16/74						

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.87}$

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

								Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
1958 Biopsy - S58/1528											
10/79	18/80	15/76	14/74	8/75	16/73			Retain	5.5	Yes	Diffuse
9/81	15/72	16/70	8/74	16/80	4/72	10/71	19/70	5/79			
4/81	6/80	15/72	14/71	17/74							
Mean ratio single/thick = 1/6.29											
S53/1067 Patient with 2 serial biopsies											
15/70	15/71	45/22	27/53	17/73	21/57						
24/58	12/62	15/67	25/54	15/69	30/54	13/70		Retain	3	Yes	Diffuse
38/44	20/64	14/71	18/72	12/76	31/54	16/68					
Mean ratio single/thick = 1/2.90											
S58/2572											
8/65	10/60	5/67	10/70	4/59							
10/56	9/66	8/60	6/70	8/66	8/59	10/63		Lost	8	Yes	Diffuse
9/62	6/70	9/69	8/71	9/73	8/68	10/71	7/70				
Mean ratio single/thick = 1/8.11											

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S70/2565 - Patient with 3 serial biopsies.				
18/71 20/61 14/72 15/70 10/69 12/68 16/70				
18/69 15/65 16/68 18/71 10/75 18/68 9/72	Retain	4	Yes	Diffuse
10/70 12/80 12/69 9/71 9/77 14/69				
Mean ratio single/thick = 1/5.10				
S73/2390				
10/78 18/69 12/72 11/71 10/68 11/65				
16/73 19/74 12/69	Retain	7	Yes	Diffuse
Mean ratio single/thick = 1/5.36				
S74/2767				
10/72 8/80 9/79 12/79 15/75 8/74 9/81 8/80	Lost	8	Yes	Diffuse
6/73 10/72 11/79 9/75 10/74 9/80 11/68 8/72 7/81 8/75 10/74				
Mean ratio single/thick = 1/8.10				
S53/1471				
12/73 10/69 9/75 7/81 10/72 5/77 8/80				
7/78 11/69 8/72 11/74 8/80 8/82 9/79				

Primary Biliary Cirrhosis

Points overlying single plates / Points overlying thick plates

								Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S53/1471 (Cont'd)											
6/74	8/75	9/69	7/71	8/80	7/81			Lost	5	Yes	Diffuse
Mean ratio single/thick = 1/8.90											
S69/1398											
74/8	78/7	60/12	36/49	65/14	62/14						
15/78	69/15	19/69	15/70	30/50	59/32	69/20		Retain	3	Yes	Focal
8/75	12/72	11/69	69/15	60/25	10/73	20/54					
Mean ratio single/thick = 1/1.3											
S72/1049 - Patient with 2 serial biopsies											
82/4	80/5	72/7	66/21	81/4	25/60						
53/29	71/14	75/6	79/8	62/22	51/31			Retain	2-3	No	Focal
64/18	59/11	30/52	76/12	60/13	20/55	15/60	72/14				
Mean ratio single/thick = 2.67/1											
S72/1336 (1972 biopsy)											
10/73	12/74	14/79	10/80					Lost	7	Yes	Diffuse
9/74	8/79	10/75									
Mean ratio single/thick = 1/7.30											

Primary Biliary Cirrhosis

Points underlying single plates / Points underlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S57/1073 - Patient with 2 serial biopsies				
24/60 79/11 9/71 76/5 77/11 77/9 76/10				
48/37 69/15 72/9 24/65 71/10 74/9 80/8	Retain	2	No	Periportal
74/9 32/50 80/10 39/40 79/8 74/6				
Mean ratio single/thick = 2.72/1				
S60/942				
61/9 70/18 60/19 59/24 75/18 58/20 53/23				
55/28 68/14 60/23 60/25 35/48 37/35	Retain	5	No	Diffuse
65/25 34/49 20/65 31/52 21/53 53/20 54/25				
Mean ratio single/thick = 1.67/1				
S70/2227				
77/8 54/31 61/19 78/10 76/6				
63/15 74/12 80/8 60/25 71/17	Retain	-	No	Periportal
76/6				
Mean ratio single/thick = 4.90/1				

FIG. 1

PRIMARY BILIARY CIRRHOSIS - PLATE / DURATION OF RATIO SYMPTOMS

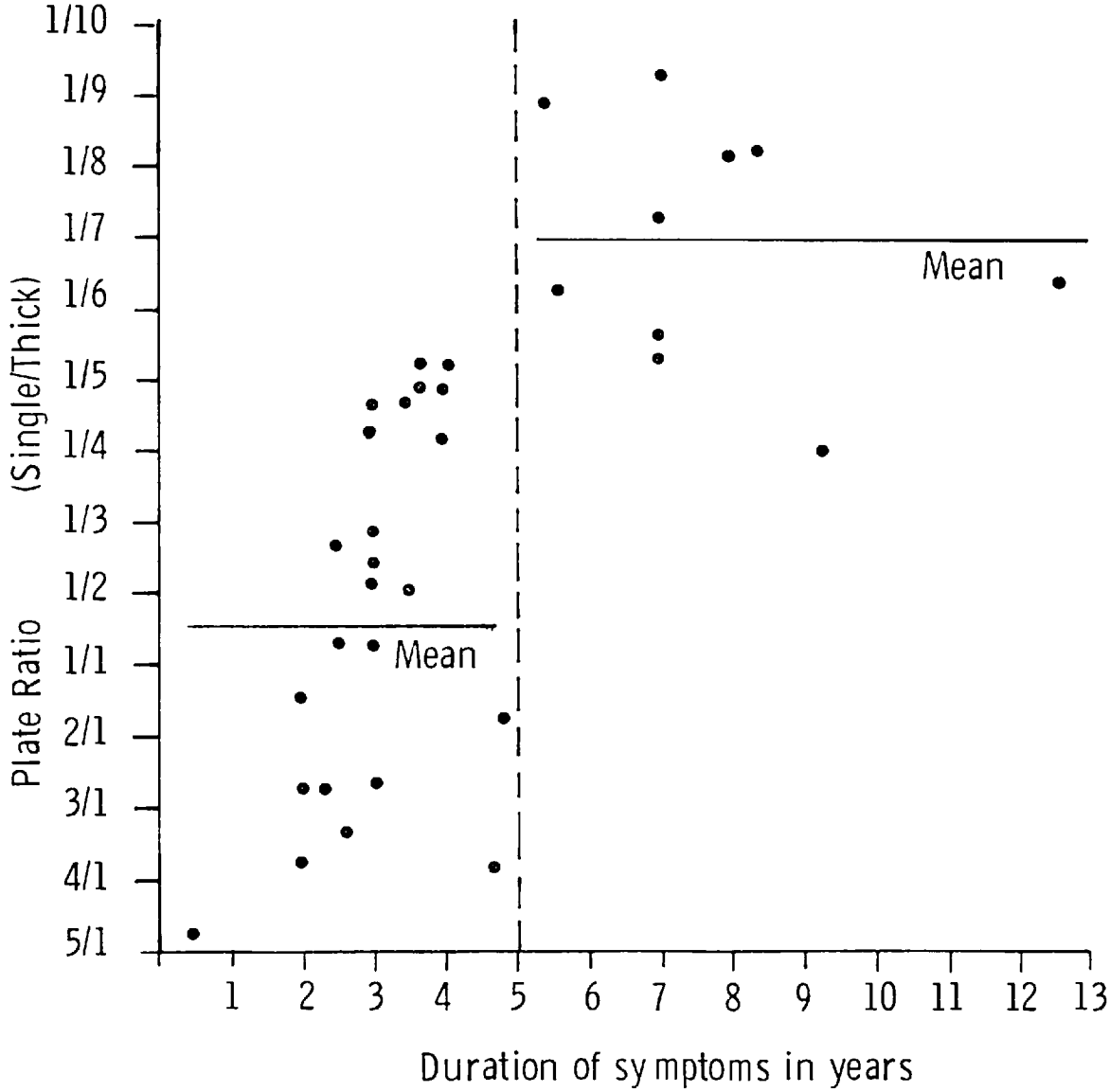


FIG. 2

PRIMARY BILIARY CIRRHOSIS - PLATE / VASCULAR RATIO PATTERN

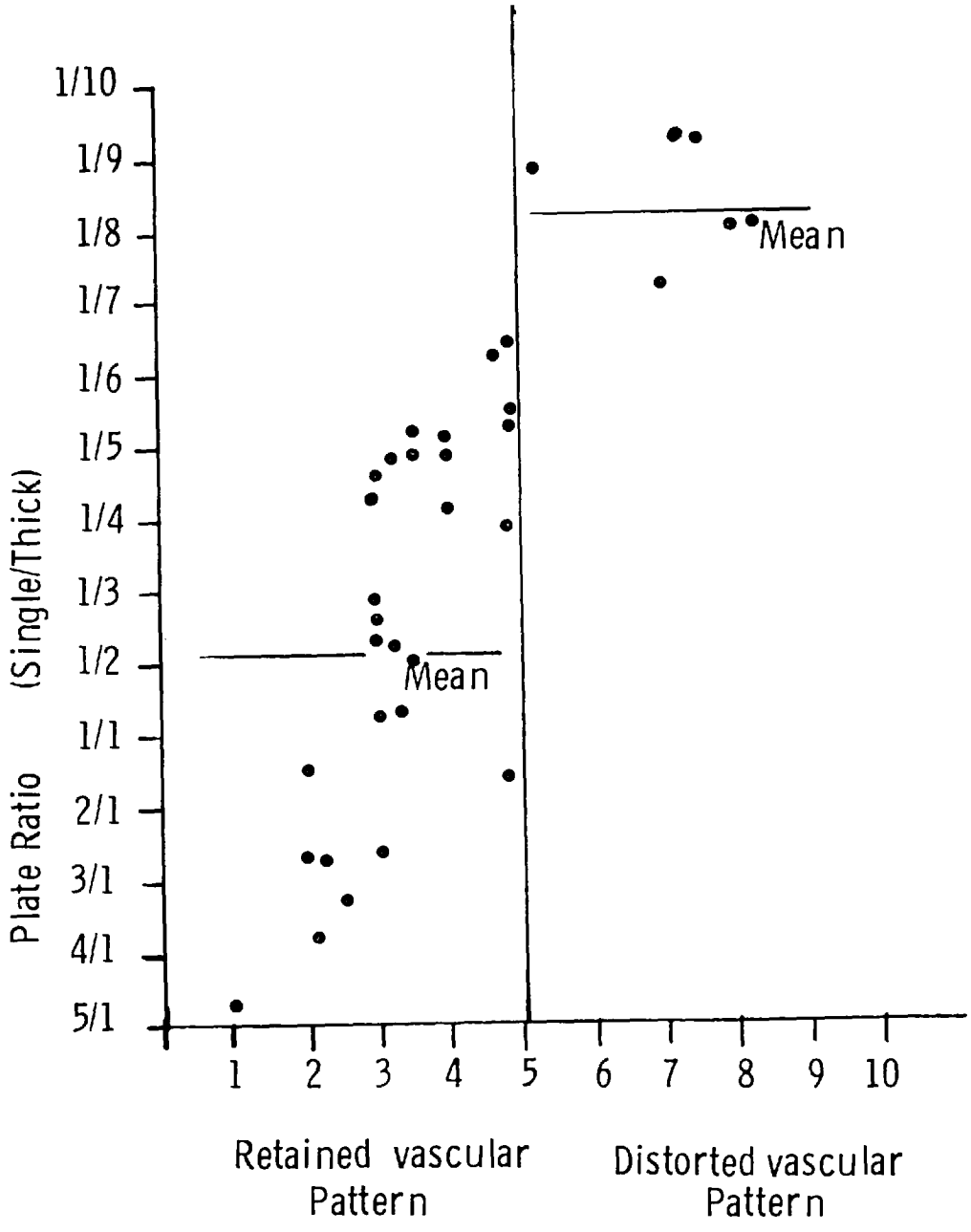


FIG. 3

PRIMARY BILIARY CIRRHOSIS - PLATE / PORTAL RATIO HYPERTENSION

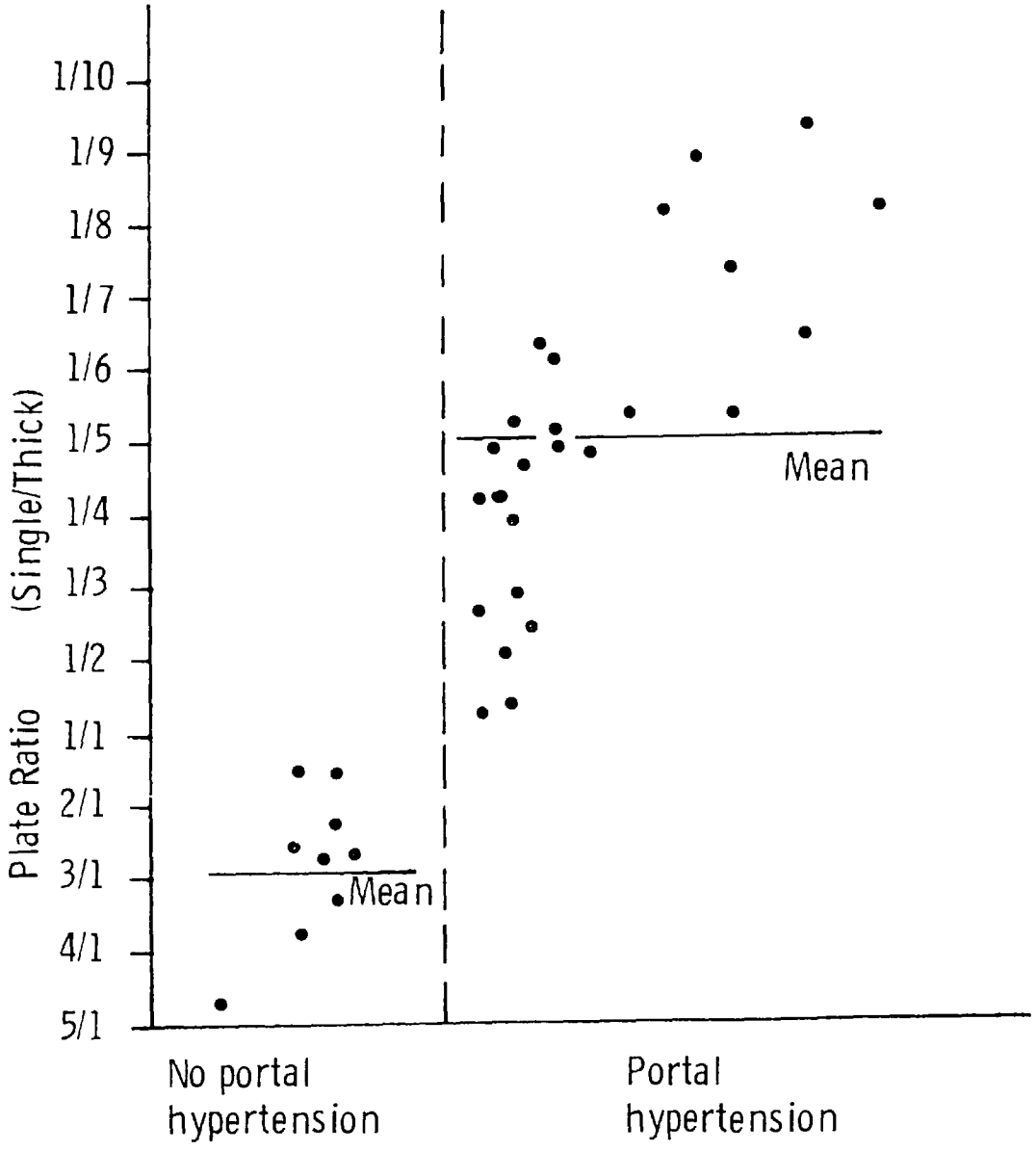
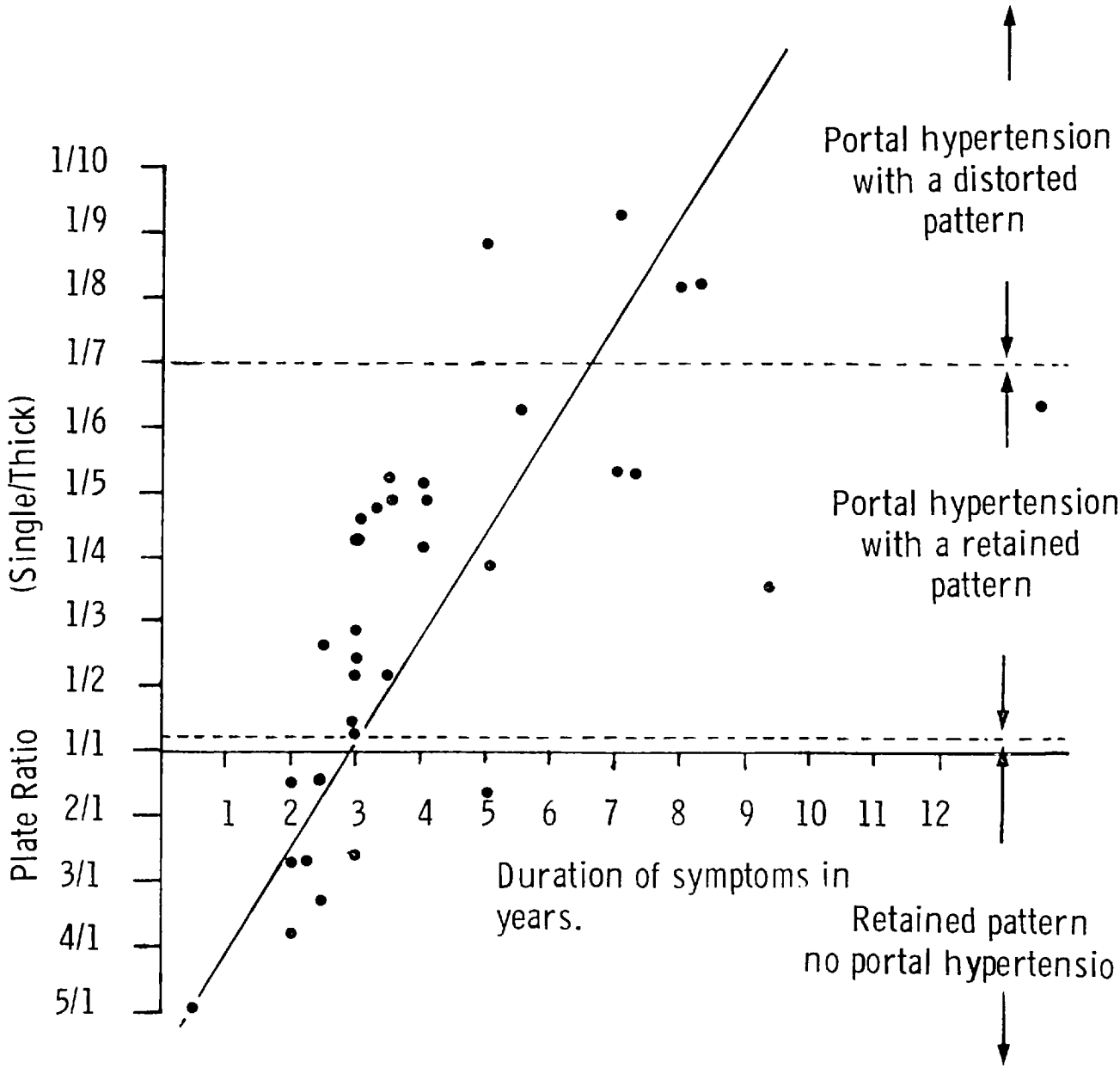


FIG. 4

PRIMARY BILIARY CIRRHOSIS - SUMMARY CHART



Active Chronic Hepatitis

Active chronic hepatitis - Although a total of 39 biopsy specimens were available only 33 were suitable for point counts. The 6 specimens omitted contained distorted liver cell plates due to extensive fibrosis.

$\frac{10}{79}$ $\frac{12}{72}$ $\frac{9}{74}$ $\frac{11}{69}$ $\frac{8}{79}$ $\frac{8}{80}$

$\frac{9}{75}$ $\frac{9}{72}$ $\frac{11}{78}$ $\frac{13}{68}$ $\frac{10}{80}$ Lost 5-6 Yes Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{7.50}$

S72/1083

$\frac{65}{19}$ $\frac{73}{9}$ $\frac{47}{29}$ $\frac{55}{30}$ $\frac{76}{10}$ $\frac{72}{12}$

$\frac{68}{15}$ $\frac{75}{12}$ $\frac{65}{20}$ $\frac{78}{15}$ Retain 1/2 No Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{3.94}{1}$

S72/2286

$\frac{51}{38}$ $\frac{48}{40}$ $\frac{63}{25}$ $\frac{61}{29}$ $\frac{58}{30}$

$\frac{42}{42}$ $\frac{46}{41}$ $\frac{50}{39}$ $\frac{50}{35}$ $\frac{54}{35}$ Retain 2 No Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1.47}{1}$

S72/2641

$\frac{10}{74}$ $\frac{12}{78}$ $\frac{15}{75}$ $\frac{11}{80}$ $\frac{12}{69}$

$\frac{9}{75}$ $\frac{8}{76}$ $\frac{9}{80}$ Lost 3-4 Yes Diffuse

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{7.05}$

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S71/3553				
14/61 13/62 10/72 18/70 10/71				
16/60 14/71 12/70 12/65 14/72	Retain	2	Yes	Diffuse
Mean ratio single/thick = 1/5.0				
S69/1855				
61/30 60/32 54/40 64/28 61/29				
60/31 58/34 55/32 65/27 57/38	Retain	1	No	Diffuse
Mean ratio single/thick = 1.84/1				
S69/3209				
15/57 9/61 18/58 12/65 14/62 17/55 16/59				
18/55 14/60 14/57 13/59 14/61 20/50	Retain	2-3	Yes	Diffuse
Mean ratio single/thick = 1/3.9				
S68/2404				
13/54 16/52 18/49 16/58 16/59 14/50				
14/55 13/56 18/55 14/58 14/48 19/47 18/54	Retain	1	Yes	Diffuse
14/59 12/58 15/52 14/51 15/54 17/49 18/50				
Mean ratio single/thick = 1/3.46				

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S67/464				
18/54 20/49 21/50 28/54 34/48				
21/59 25/54	Retain	9/12	Yes	Diffuse
Mean ratio single/thick = 1/2.20				
S67/2458				
14/65 18/60 18/55 19/58 20/62				
18/64 17/68 15/62 19/54 18/59	Retain	1¼	Yes	Diffuse
15/61 17/60 17/55 18/54				
Mean ratio single/thick = 1/3.44				
S66/2778				
12/68 10/70 8/72 10/71 9/69				
11/75 10/76 12/67 7/72 8/70	Retain	2½	Yes	Diffuse
Mean ratio single/thick = 1/7.3				
S66/241				
39/40 35/49 31/50 32/55 35/48				
30/51 36/49 31/55 34/49 29/51	Retain	1	Yes	Diffuse
Mean ratio single/thick = 1/1.50				

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S61/2394				
$\frac{10}{69}$ $\frac{15}{70}$ $\frac{9}{70}$ $\frac{19}{68}$ $\frac{18}{61}$ $\frac{14}{72}$				
$\frac{19}{74}$ $\frac{14}{65}$ $\frac{19}{69}$ $\frac{18}{70}$ $\frac{19}{70}$	Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.4}$				
S61/196				
$\frac{15}{65}$ $\frac{12}{70}$ $\frac{16}{63}$ $\frac{21}{59}$ $\frac{10}{74}$ $\frac{12}{79}$				
$\frac{13}{69}$ $\frac{16}{68}$ $\frac{12}{71}$ $\frac{14}{70}$	Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.87}$				
S59/1474				
$\frac{14}{68}$ $\frac{16}{64}$ $\frac{15}{61}$ $\frac{18}{69}$ $\frac{19}{68}$ $\frac{18}{64}$				
$\frac{20}{62}$ $\frac{18}{70}$ $\frac{18}{69}$ $\frac{17}{67}$	Retain	1	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{3.8}$				
S58/1438				
$\frac{13}{75}$ $\frac{12}{74}$ $\frac{10}{74}$ $\frac{8}{79}$ $\frac{17}{70}$				
$\frac{18}{70}$ $\frac{10}{75}$ $\frac{11}{74}$ $\frac{7}{78}$ $\frac{8}{77}$	Retain	$2\frac{3}{4}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{6.5}$				

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

							Vascular Pattern	Duration of symptoms	Portal hypertension	Areas of Hyperplasia
S58/2130										
12/30	10/72	9/71	8/79	14/68						
11/74	10/75	8/75	9/78	8/75			Retain	$2\frac{3}{4}$	Yes	Diffuse
Mean ratio single/thick = 1/7.0										
S57/1272										
19/60	17/59	18/61	17/63	19/55			Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio single/thick = 1/3.3										
S70/3406 - Patient had 2 serial liver biopsies										
41/48	34/51	30/55	40/49	29/51	30/52					
24/58	38/48	40/49	28/51				Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio single/thick = 1/1.53										
S72/3300										
19/66	20/61	14/68	14/65	15/69	18/72	18/74				
17/71	18/70	12/68					Retain	3	Yes	Diffuse
Mean ratio single/thick = 1/4.1										

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S69/1730 - Patient had 2 serial biopsies				
$\frac{17}{62}$ $\frac{19}{64}$ $\frac{18}{66}$ $\frac{21}{59}$ $\frac{16}{68}$ $\frac{15}{65}$				
$\frac{18}{70}$ $\frac{17}{69}$ $\frac{16}{60}$ $\frac{17}{62}$	Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{3.70}$				
S72/2125				
$\frac{12}{74}$ $\frac{20}{70}$ $\frac{12}{72}$ $\frac{14}{69}$ $\frac{10}{71}$				
$\frac{19}{70}$ $\frac{18}{74}$ $\frac{12}{74}$ $\frac{21}{61}$ $\frac{20}{72}$	Retain	3	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{4.5}$				
S72/1075 - Patient had 2 serial biopsies				
$\frac{31}{49}$ $\frac{28}{55}$ $\frac{22}{52}$ $\frac{25}{48}$ $\frac{35}{40}$ $\frac{28}{52}$				
$\frac{24}{52}$ $\frac{34}{48}$ $\frac{30}{51}$ $\frac{31}{58}$	Retain	6/12	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{1.75}$				
S73/2926				
$\frac{29}{48}$ $\frac{25}{55}$ $\frac{22}{50}$ $\frac{26}{49}$ $\frac{24}{55}$ $\frac{22}{52}$				
$\frac{21}{51}$ $\frac{23}{52}$ $\frac{20}{56}$ $\frac{21}{59}$	Retain	$1\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{2.30}$				

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

		Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S74/1512 - Patient had 2 serial biopsies					
$\frac{10}{75}$ $\frac{13}{68}$ $\frac{11}{76}$ $\frac{14}{69}$ $\frac{15}{65}$ $\frac{9}{72}$					
$\frac{8}{71}$ $\frac{10}{74}$ $\frac{8}{78}$ $\frac{9}{74}$		Retain	$2\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{6.70}$					
S74/1570					
$\frac{10}{76}$ $\frac{9}{74}$ $\frac{18}{73}$ $\frac{12}{79}$ $\frac{18}{79}$ $\frac{18}{72}$					
$\frac{9}{79}$ $\frac{8}{79}$ $\frac{12}{70}$ $\frac{9}{79}$		Retain	$2\frac{3}{4}$	Yes	
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{6.90}$					
S62/2265 - Patient had 3 serial liver biopsies					
$\frac{59}{29}$ $\frac{60}{30}$ $\frac{64}{24}$ $\frac{58}{32}$ $\frac{61}{35}$ $\frac{62}{28}$		Retain	6/12	No	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{2.0}{1}$					
S64/357					
$\frac{13}{79}$ $\frac{10}{80}$ $\frac{9}{70}$ $\frac{14}{71}$ $\frac{12}{78}$					
$\frac{14}{71}$ $\frac{12}{75}$ $\frac{14}{74}$ $\frac{18}{70}$ $\frac{9}{81}$		Retain	$2\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{6.0}$					

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S69/3135				
$\frac{10}{78}$ $\frac{8}{79}$ $\frac{9}{74}$ $\frac{10}{78}$ $\frac{11}{79}$ $\frac{8}{75}$				
$\frac{12}{74}$ $\frac{9}{76}$ $\frac{7}{79}$	Lost	$7\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{8.20}$				
S59/1882 – Patient had 2 serial biopsies				
$\frac{14}{69}$ $\frac{14}{68}$ $\frac{14}{72}$ $\frac{17}{71}$ $\frac{19}{70}$ $\frac{15}{67}$				
$\frac{14}{71}$ $\frac{14}{76}$ $\frac{10}{72}$ $\frac{11}{70}$	Retain	$2\frac{1}{2}$	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{5.0}$				
S59/2158				
$\frac{13}{71}$ $\frac{12}{72}$ $\frac{16}{68}$ $\frac{14}{74}$ $\frac{14}{69}$ $\frac{10}{75}$				
$\frac{18}{71}$ $\frac{12}{70}$ $\frac{12}{72}$ $\frac{14}{69}$	Retain	$2\frac{3}{4}$		Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{5.3}$				
S58/2669				
$\frac{29}{58}$ $\frac{31}{54}$ $\frac{35}{49}$ $\frac{36}{52}$ $\frac{35}{51}$ $\frac{28}{55}$				
$\frac{27}{58}$ $\frac{30}{54}$ $\frac{34}{49}$ $\frac{25}{59}$	Retain	8/12	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{1.7}$				

Active Chronic Hepatitis

Points overlying single plates / Points overlying thick plates

S58/2571

12/73	10/74	19/70	14/69	11/71	10/72
19/70	15/65	16/69	8/71	11/68	12/71
16/70	18/69	12/71			

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{5.20}$

Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
Retain	1½	Yes	Diffuse

FIG. 5
ACTIVE CHRONIC HEPATITIS – PLATE / DURATION OF RATIO SYMPTOMS

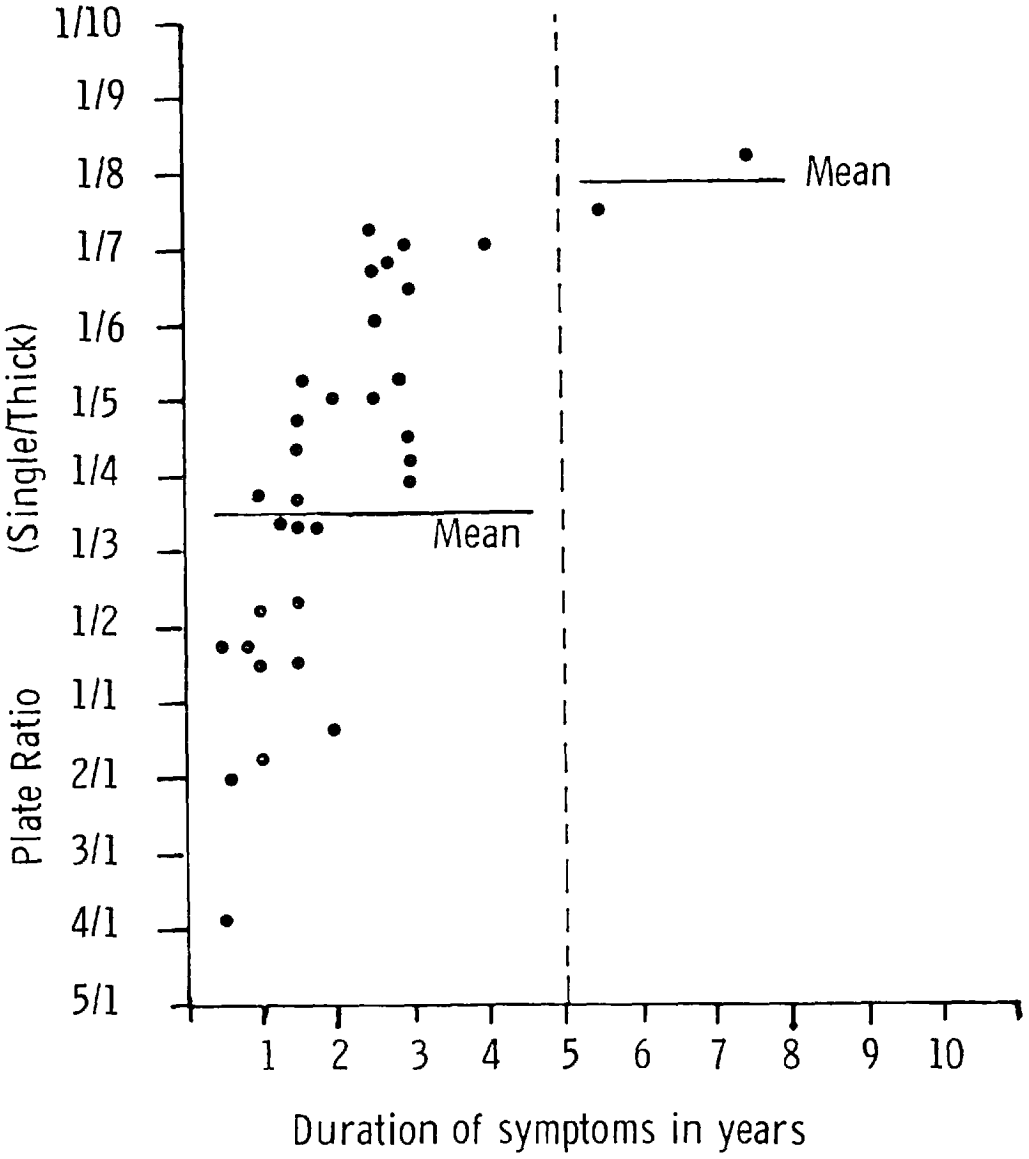


FIG. 6

ACTIVE CHRONIC HEPATITIS - PLATE / VASCULAR RATIO PATTERN

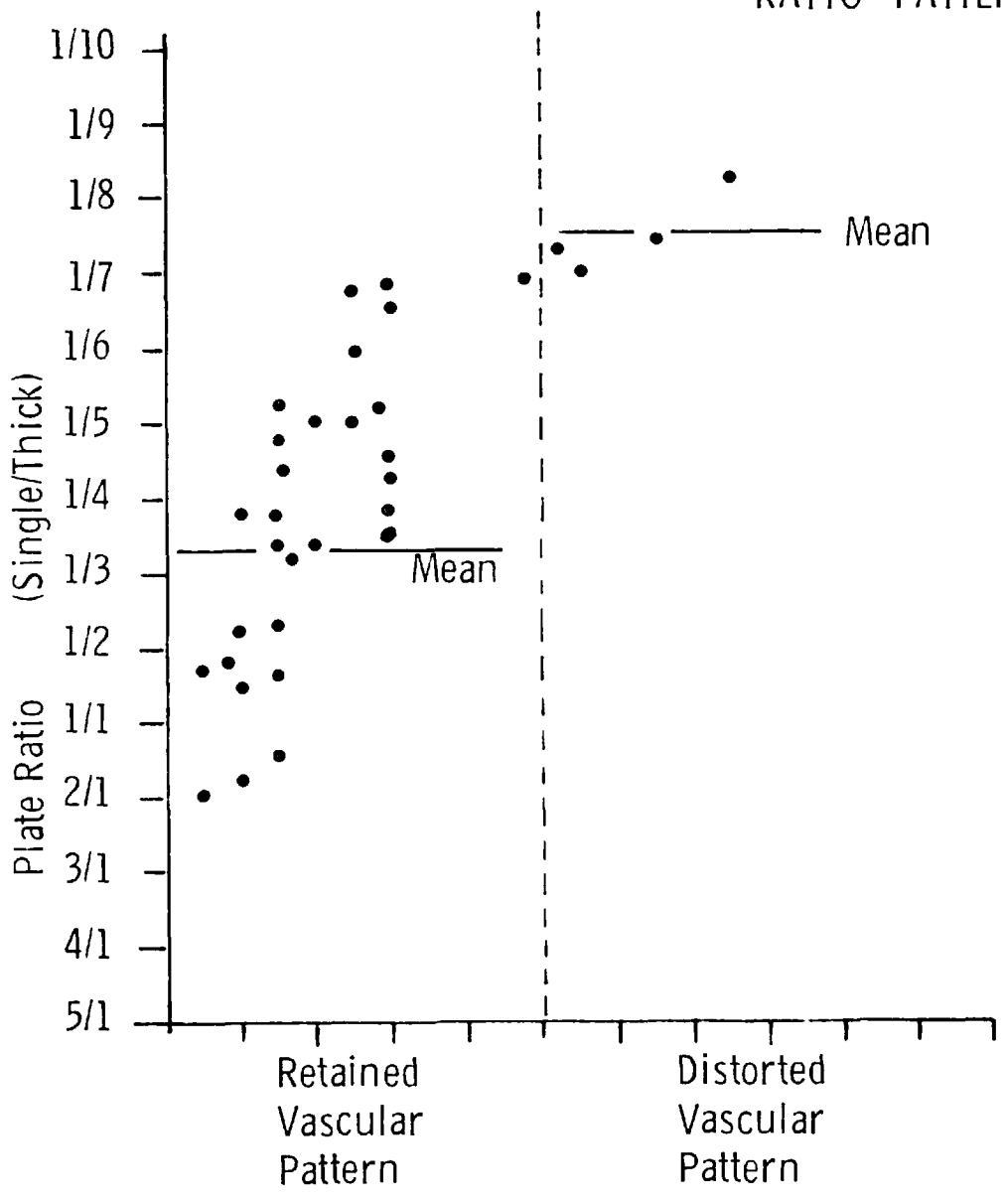


FIG. 7

ACTIVE CHRONIC HEPATITIS - PLATE / PORTAL RATIO HYPERTENSION

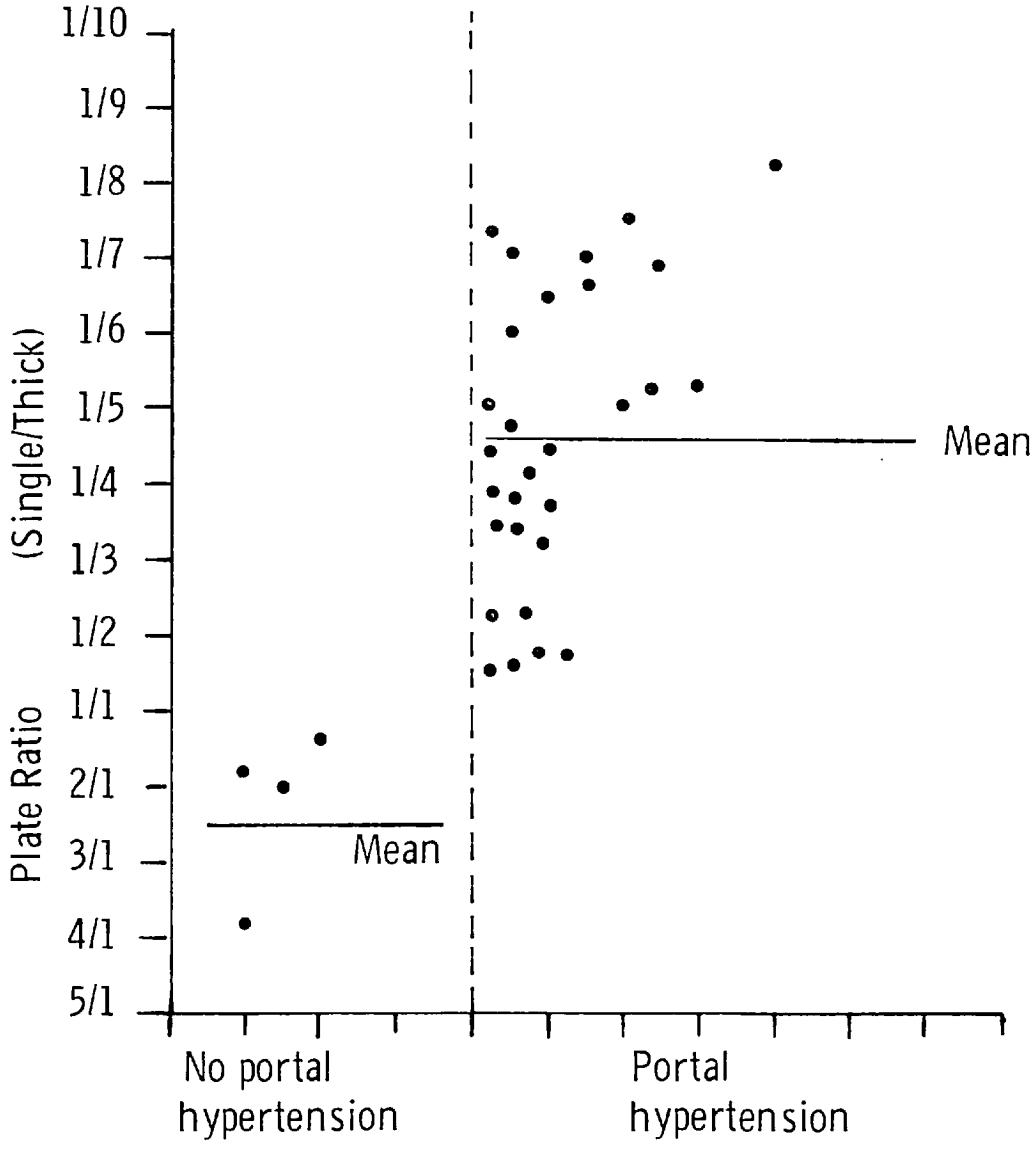
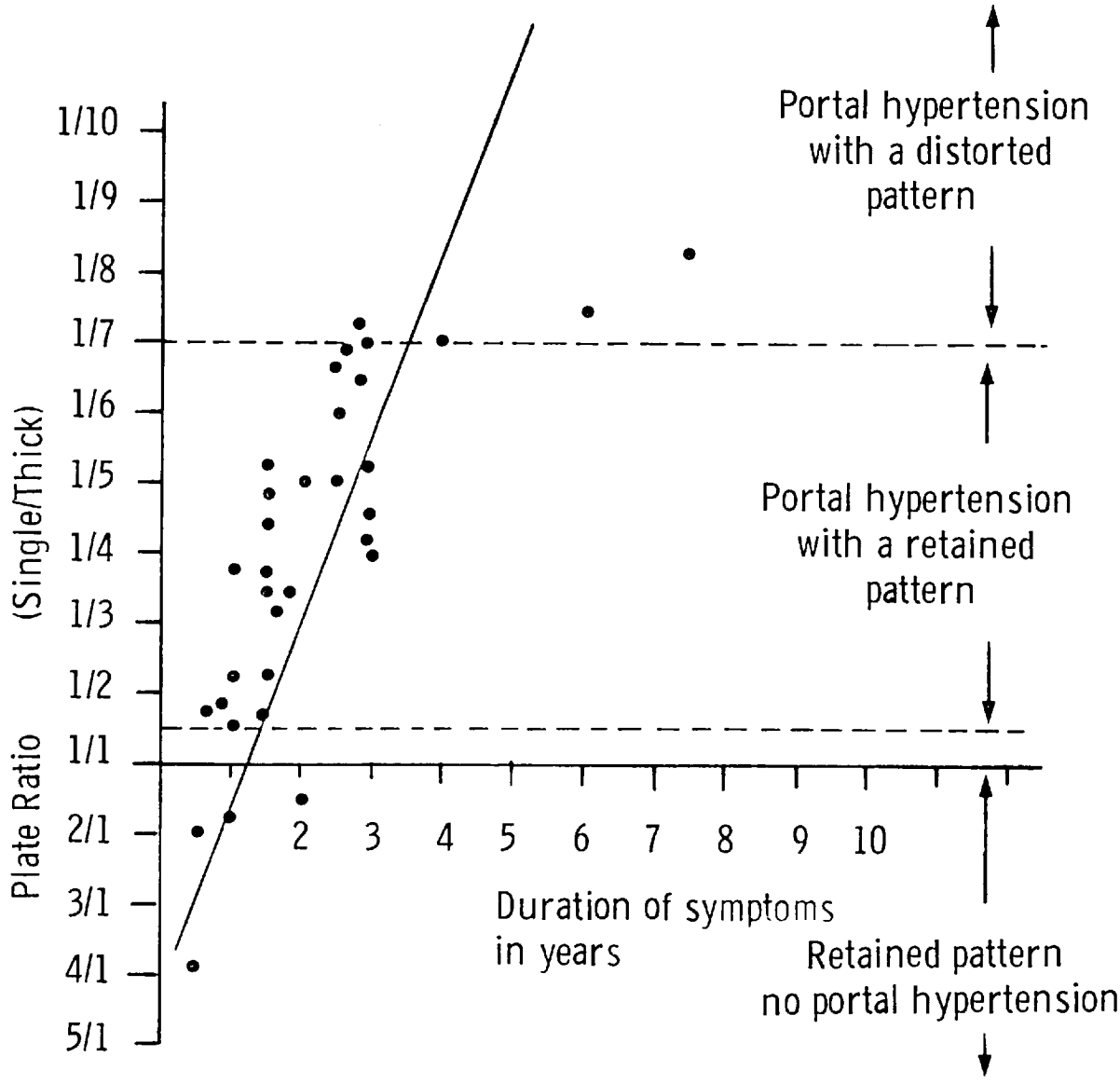


FIG. 8

ACTIVE CHRONIC HEPATITIS - SUMMARY CHART



Alcoholic Liver Disease

Alcoholic liver disease - Although a total of 39 biopsy specimens were available only 36 specimens were suitable for point counts. The 3 specimens omitted contained distorted liver cell plates.

12	45	13	12	15	25	13				
60/21	77/15	80/9	78/19	79/15	75/14		Retain	10	No	Focal
71/18	69/21	68/19	61/22	76/14	73/15	65/18				

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{4.0}{1}$

S74/739

70/19	72/12	81/10	68/21	76/12	81/9	75/15				
78/14	72/19	78/10	72/16	74/12	78/10	76/15		Retain	5	No	Focal
72/14	71/16	74/12	79/8	78/10	71/13					

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{5.60}{1}$

S74/1205

78/11	78/13	68/16	76/10	78/9	62/19						
76/14	78/8	69/17	70/14	74/10	78/8	75/12	75/9	Retain	10	No	Focal
78/12	74/10	76/10	72/14	74/12	76/10						

Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{6.2}{1}$

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

								Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S74/366											
80/12	46/45	78/13	79/12	75/15	68/25	81/13					
60/21	77/15	80/9	78/19	79/15	75/14			Retain	10	No	Focal
71/18	69/21	68/19	61/22	76/14	73/15	65/18					
Mean ratio single/thick = 4.0/1											
S74/739											
70/19	72/12	81/10	68/21	76/12	81/9	75/15					
78/14	72/19	78/10	72/16	74/12	78/10	76/15		Retain	5	No	Focal
72/14	71/16	74/12	79/8	78/10	71/13						
Mean ratio single/thick = 5.60/1											
S74/1205											
78/11	78/13	68/16	76/10	78/9	62/19						
76/14	78/8	69/17	70/14	74/10	78/8	75/12	75/9	Retain	10	No	Focal
78/12	74/10	76/10	72/14	74/12	76/10						
Mean ratio single/thick = 6.2/1											

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S74/1322				
55/36 69/17 74/12 78/10 65/18				
74/14 76/12 76/11 79/9	Retain	4	No	Scattered
Mean ratio single/thick = 4.6/1				
S74/1375				
74/13 68/17 71/15 72/12 71/14 65/18				
72/11 66/19 65/16 68/14 66/15 69/14	Retain	15	No	Diffuse
69/12 68/14 70/10 72/12 71/13 71/12				
Mean ratio single/thick = 5.0/1				
S72/2248				
73/14 67/23 70/15 68/16 63/20 73/14				
75/12 72/11 67/20 70/15 69/12	Retain	10	No	Focal
69/16 71/14 72/12 70/13				
Mean ratio single/thick = 4.62/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

							Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S74/2786										
67/24	64/23	70/15	68/16	73/12	67/14					
71/13	72/12	68/20	67/18	69/15	70/16		Retain	5-8	No	Focal
71/11	70/14	65/18	74/10	69/15	73/11					
Mean ratio single/thick = 4.50/1										
S74/906										
16/57	12/60	9/67	13/65	12/67	10/70	15/65				
12/63	11/69	14/65	14/64	12/68	11/66		Retain	20	Yes	Diffuse
11/70	14/62	11/66	14/64							
Mean ratio single/thick = 1/5.50										
S73/504										
20/62	22/65	18/66	15/68	14/67	17/71	21/64				
20/60	10/70	14/63	18/68	19/66	15/66		Retain	8	Yes	Diffuse
18/64	12/70	14/69	15/68	16/66						
Mean ratio single/thick = 1/4.0										

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

						Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S73/797									
18/58	20/59	15/60	12/70	14/71	18/67				
11/69	19/64	16/66	18/62	15/65	14/66	Retain	10-12	Yes	Diffuse
15/69	14/68	16/66	11/70	12/69	10/71				
Mean ratio single/thick = 1/4.4									
S73/1766									
79/8	80/9	69/15	76/12	77/10	68/9				
71/16	76/13	76/10	71/12	72/14	70/11	Retain	6	No	Focal
68/14	74/10	75/9	76/11	72/14	71/12				
Mean ratio single/thick = 6.0/1									
S73/2669									
76/12	55/29	77/11	72/14	60/30	74/10				
76/11	70/16	76/10	78/9	72/15	71/14	Retain	14	No	Focal
77/11	72/16	74/12	76/14	77/11	79/10				
Mean ratio single/thick = 5.1/1									

Alcoholic Liver Disease

Points overlying single plates
Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S73/2681				
77/12 70/10 67/15 7/12 72/11 69/16 73/10				
71/14 74/11 76/9 77/8 78/10 74/11	Retain	5	No	Minimal
71/12 74/13				
Mean ratio single/thick = 5.90/1				
S73/2957				
80/8 79/10 78/9 81/6 80/7 78/8 77/7				
78/9 76/8 78/10 81/9 80/9 78/10	Retain	6	No	Minimal
Mean ratio single/thick = 9.30/1				
S73/3514				
74/11 76/8 70/12 73/10 69/14				
70/11 71/10 73/9 74/13 71/11	Retain	6	No	Minimal
74/11 75/12 78/8 76/9 74/10				
Mean ratio single/thick = 6.90/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S73/3698				
80/8 72/12 72/10 74/10 75/9 70/13				
74/8 70/10 73/9 69/14 74/12 76/11	Retain	8	No	Minimal
71/14 70/12 78/8 75/10 79/7 80/8				
Mean ratio single/thick = 7.20/1				
S73/3803				
15/65 8/70 17/58 10/66 8/69 14/70 12/71				
11/71 14/68 16/65 10/71 12/69 14/71 12/67	Retain	8	Yes	Diffuse
12/65 14/66 11/72 12/71 16/70 14/72				
Mean ratio single/thick = 1/5.40				
S73/4164				
65/19 71/12 74/10 75/9 68/14 72/10				
74/11 71/12 69/14 74/9 78/8 75/11	Retain	5	No	Minimal
74/10 72/12 74/8 68/14				
Mean ratio single/thick = 6.30/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S75/553				
29/56 31/54 27/54 31/58 28/55				
30/59 34/52 31/55 28/58 32/56	Retain	6	Yes	Diffuse
35/51 36/56 38/54 40/60 35/52				
Mean ratio single/thick = 1/1.70				
S72/21				
73/13 69/18 64/23 77/8 70/17				
71/14 68/20 70/15 71/12 67/18	Retain	10-15	Yes	Minimal
75/15 72/11 78/9 80/10 72/14 73/12 74/12 78/8				
Mean ratio single/thick = 5.22/1				
S72/102				
69/17 70/19 69/15 70/12 72/14				
77/8 71/14 68/16 76/9 72/10	Retain	20	No	Focal
71/15 80/10 79/9 76/12 74/14				
75/12 74/11 78/10 72/8 76/9				
Mean ratio single/thick = 6.0/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

										Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S72/2295													
27/61	21/70	24/69	27/65	20/71									
22/70	28/68	29/61	24/65	25/67						Retain	10	Yes	Diffuse
26/64	24/67	25/68	26/61	18/70	21/67								

Mean ratio single/thick = 1/2.7

S72/3734													
30/60	21/71	20/68	19/69	22/70									
31/60	28/65	29/68	18/72	31/64						Retain	10	Yes	Diffuse
32/61	21/70	22/68	27/64	24/63	26/64	26/65	22/66	30/62	20/69				

Mean ratio single/thick = 1/2.6

S72/3942													
8/84	10/84	11/79	9/80	8/81	11/78								
9/82	9/84	10/80	12/78	14/79	14/76					Lost	20	Yes	Diffuse
10/80	13/75	14/79											

Mean ratio single/thick = 1/7.40

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

						Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S71/2472									
46/39	53/31	55/29	49/34	45/38					
50/35	52/36	56/32	48/39	51/37		Retain	6	Yes	Diffuse
54/36	45/40	55/30	58/31	60/29					
Mean ratio single/thick = 1/1.50									
S70/547									
27/59	21/63	29/56	29/60	31/61	29/58				
28/59	24/61	23/62	30/59	32/58	30/61	Retain	20	Yes	Diffuse
38/57	40/60	39/62	42/55	38/58	43/59				
Mean ratio single/thick = 1/1.9									
S70/813									
72/9	68/18	71/12	72/14	75/10	71/16				
75/11	70/19	73/10	67/18	72/12		Retain	12	No	In some areas
74/10	76/9	70/14	69/16	75/11					
Mean ratio single/thick = 4.30/1									

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S70/1241				
69/21 74/16 68/20 71/17 17/15				
70/18 73/17 65/25 60/28 70/14	Retain	10	No	Diffuse
75/15 72/20 74/12 69/16 71/14				
Mean ratio single/thick = 3.90/1				
S70/2937				
71/18 68/20 69/19 64/25 69/18				
68/21 65/22 73/15 72/14 70/16	Retain	5	No	Diffuse
68/20 69/18 71/14 74/13 74/12				
Mean ratio single/thick = 3.90/1				
S69/2291				
67/18 70/18 74/12 71/15 79/9				
76/10 74/11 69/16 80/9 71/14	Retain	10	No	Diffuse
76/10 70/17 72/15 62/22 70/11				
Mean ratio single/thick = 5.22/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S62/2094 - Patient had 2 serial biopsies				
69/14 70/15 69/14 68/16 73/12 67/18				
70/15 73/11 60/23 61/24 68/18 69/16	Retain	20	No	Diffuse
70/20 67/18 73/15				
Mean ratio single/thick = 4.12/1				
S63/2918				
58/26 51/37 60/24 55/35 56/30				
60/28 63/29 55/32 50/36 54/34	Retain		No	More than previous biopsy
Mean ratio single/thick = 1.80/1				
S62/2988				
69/20 74/15 70/18 72/18 66/24				
69/22 74/19 72/16 74/17 68/21	Retain in 10 places		No	Diffuse
62/25 69/19				
Mean ratio single/thick = 3.60/1				

Alcoholic Liver Disease

Points overlying single plates / Points overlying thick plates

	Vascular pattern	Duration of symptoms	Portal hypertension	Areas of hyperplasia
S59/1947				
43/47 41/50 39/54 44/49 40/52 37/55				
41/49 43/51 43/50 44/52 46/48	Retain	12	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{1.20}$				
S61/301				
35/56 33/58 37/54 36/53 38/54				
34/57 30/59 40/50 39/52 42/51	Retain		Yes	Diffuse
36/55 44/51				
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{1.50}$				
S58/1316				
27/62 30/57 32/55 29/59 23/65				
27/60 29/58 28/59 27/61 22/64	Retain	10-15	Yes	Diffuse
Mean ratio $\frac{\text{single}}{\text{thick}} = \frac{1}{2.20}$				

FIG. 9

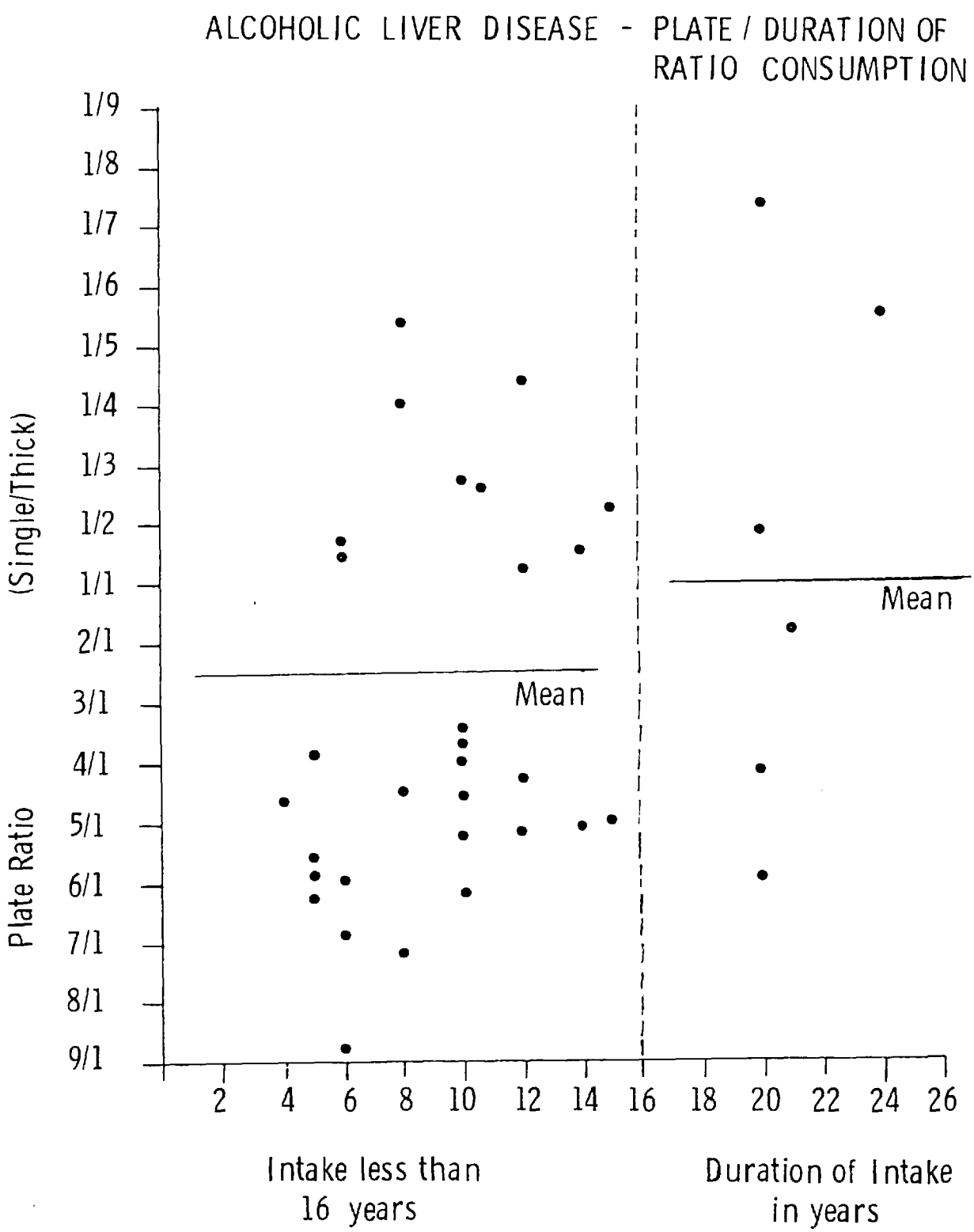

ALCOHOLIC LIVER DISEASE - PLATE / DURATION OF RATIO CONSUMPTION
Plate Ratio (Single/Thick)
1/9
1/8
1/7
1/6
1/5
1/4
1/3
1/2
1/1
2/1
3/1
4/1
5/1
6/1
7/1
8/1
9/1
Mean
Mean
2
4
6
8
10
12
14
16
18
20
22
24
26
Intake less than 16 years
Duration of Intake in years

FIG. 10

ALCOHOLIC LIVER DISEASE - PLATE / PORTAL RATIO HYPERTENSION

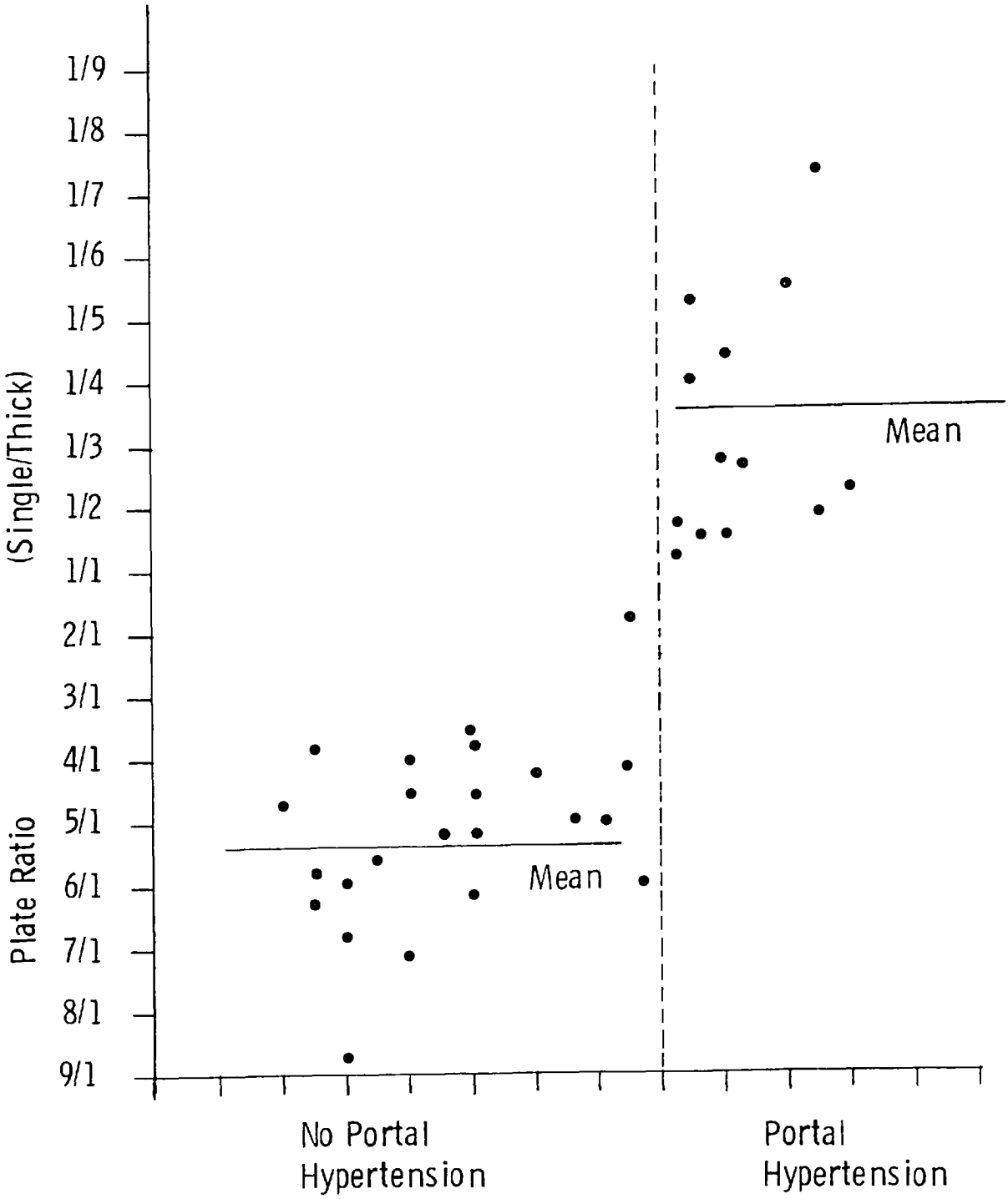
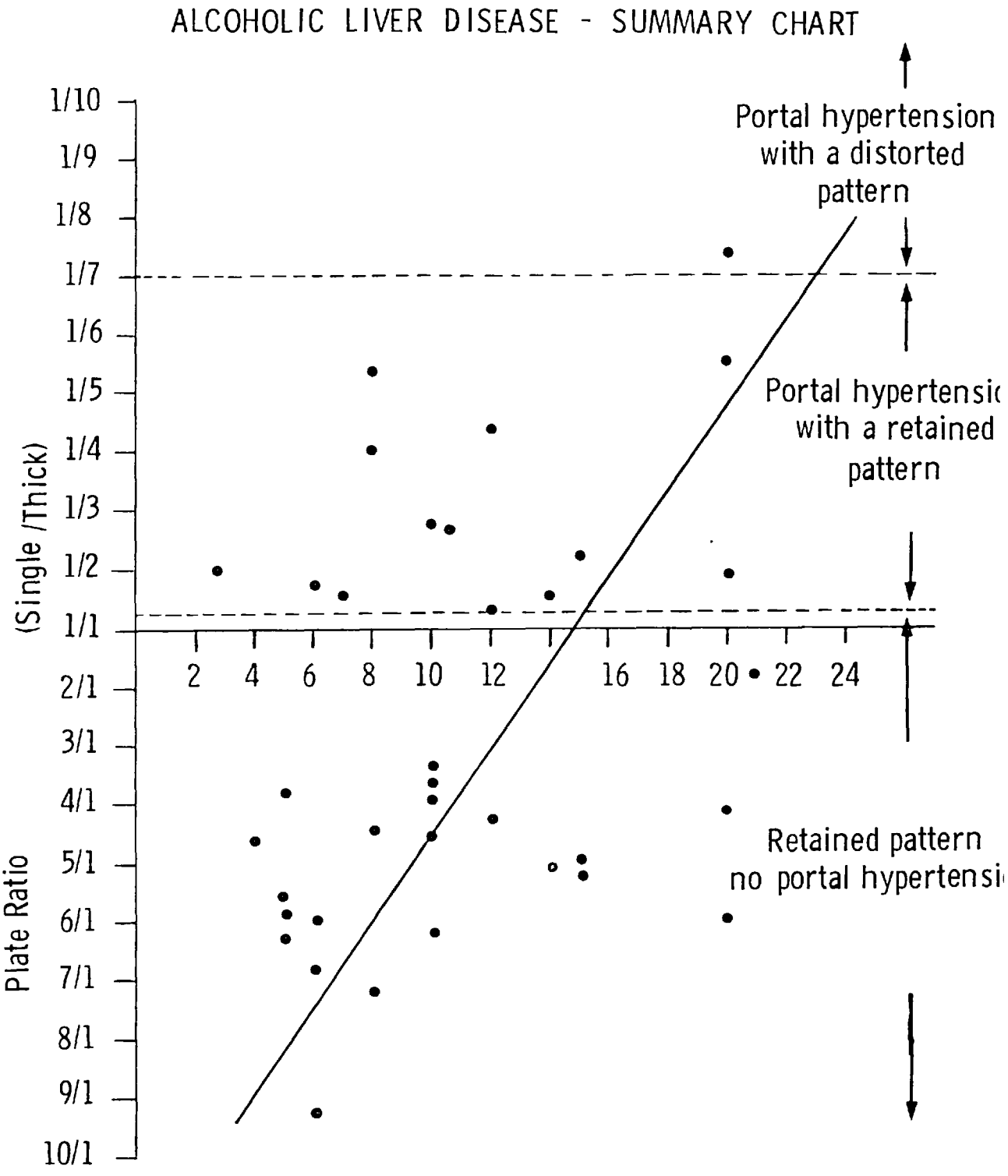


FIG. 11


ALCOHOLIC LIVER DISEASE - SUMMARY CHART
Plate Ratio (Single /Thick)
1/10
1/9
1/8
1/7
1/6
1/5
1/4
1/3
1/2
1/1
2/1
3/1
4/1
5/1
6/1
7/1
8/1
9/1
10/1
2
4
6
8
10
12
16
18
20
22
24
Portal hypertension with a distorted pattern
Portal hypertensi with a retained pattern
Retained pattern no portal hypertensi

PART 4

DISCUSSION AND SUMMARY

DISCUSSION

An investigation into hepatocyte hyperplasia in the chronic liver diseases - primary biliary cirrhosis, active chronic hepatitis, chronic persistent hepatitis, alcoholic liver disease and cirrhosis has been made. These were compared with those of control adult livers.

The investigation was done on two separate sets of material. The first set comprised sections from patients confirmed as having cirrhosis of the liver at post mortem examination and who had had liver biopsies performed during life. Several patients had serial biopsies. The purpose of this study was to observe the time of appearance of hepatocyte hyperplasia and to follow it during the progression of the disease. The material in the very early stages of the disease however was deficient as most patients had few or no complaints at such a stage. By the time symptoms and signs had appeared, the disease was well advanced and most patients had already shown the features of cirrhosis if they were likely to die soon after as a study of post mortem and biopsy material might imply.

The second group of patients provided much more useful material towards this investigation. This material was from patients clinically suspected of suffering from a chronic liver disease and who were subjected to biopsy for confirmation or diagnosis. Most patients had a single biopsy performed, while a few had serial liver biopsies done during the follow-up period. In some instances, liver material was available during the early stages of the disease. These were from asymptomatic patients subjected to biopsy after abnormal liver function tests were noted during routine examination for an unrelated complaint.

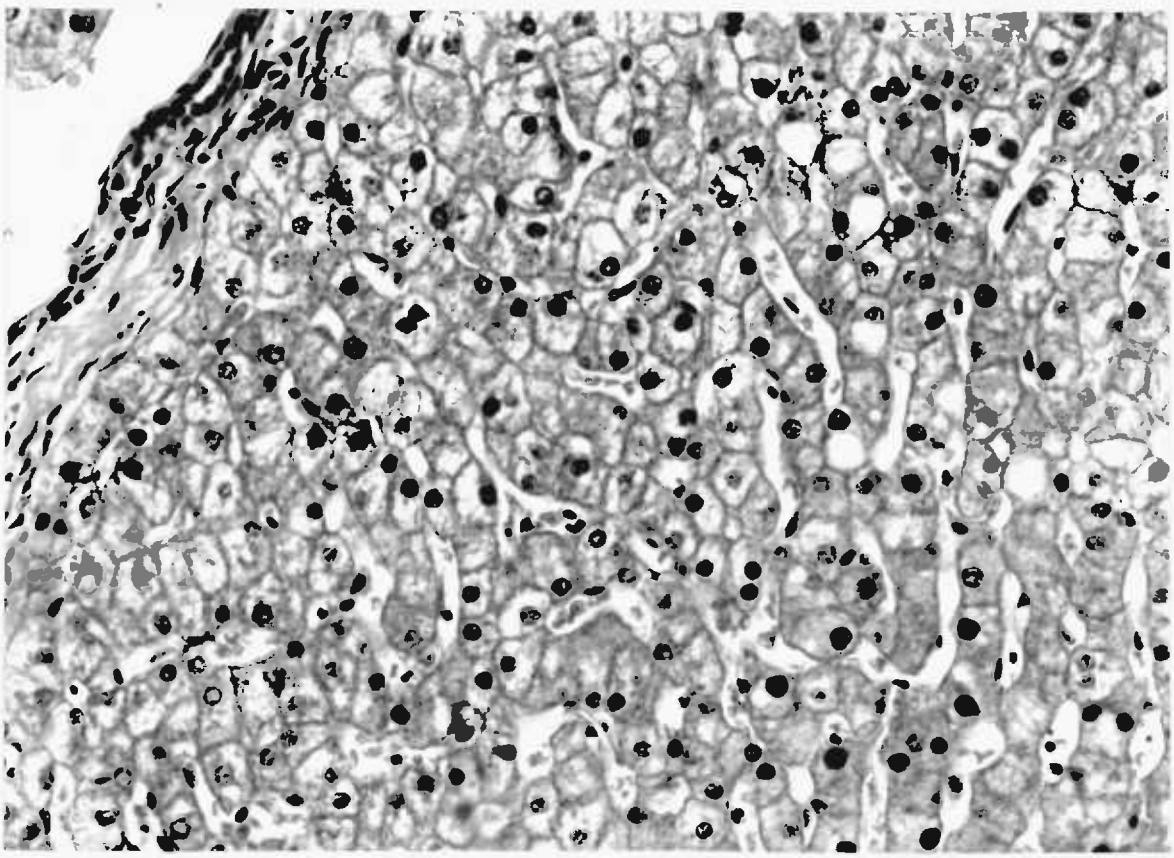
The results may be summarised as follows:

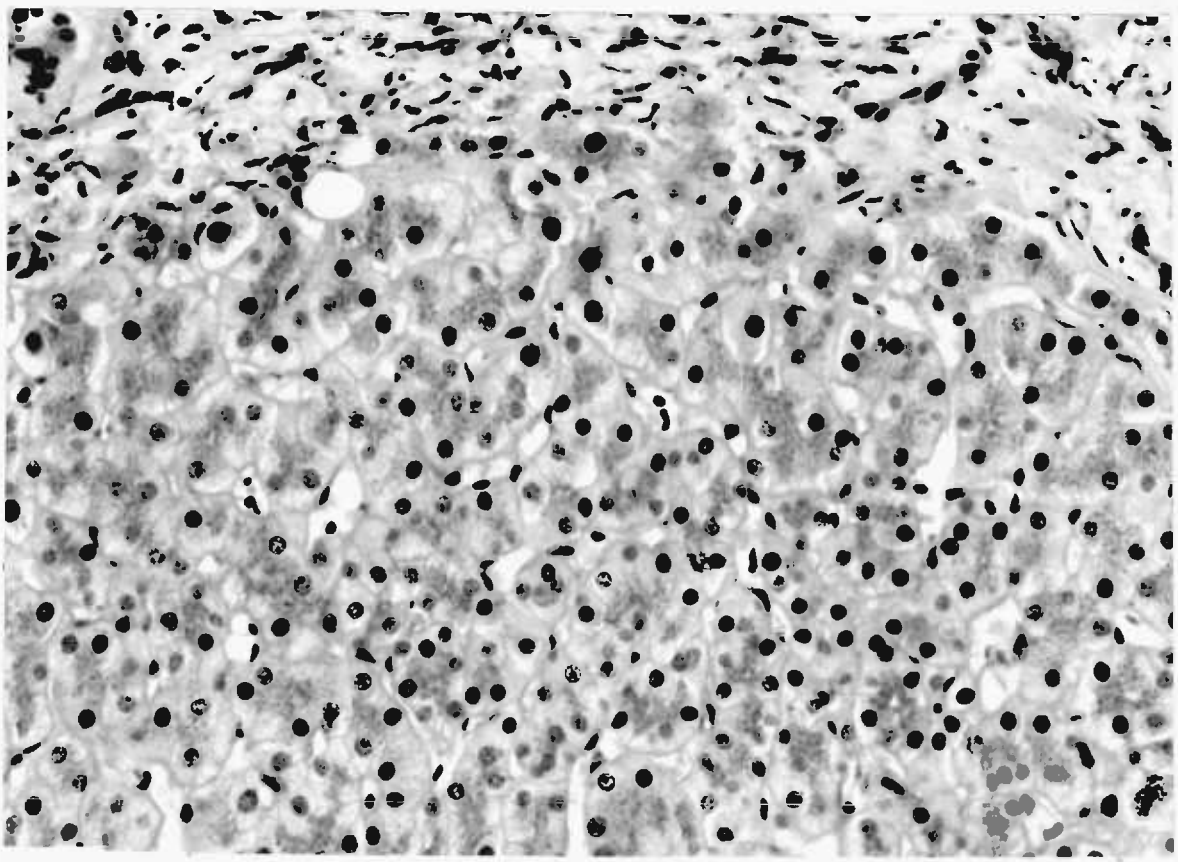
A normal adult liver (Figure 12)

As mentioned previously, the normal adult liver is said to consist mainly of single plates (Elias, 1949) and that of infants of predominantly multi-layered plates (Morgan and Hartroft, 1961).

Figure 12. A section of a normal adult liver showing a predominance of one cell thick plates. Ratio of single : thick cell plates = 27 : 1. (H and E x 400)

Figure 13. A section of a cirrhotic liver showing a predominance of thick cell plates. The patient had clinical evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 8. (H and E x 400).





The present investigation on normal adult liver material confirms these observations. Microscopically, some fields were observed to contain a few thick cell plates. These are one cell thick plates presumed to appear multi-layered, due to their tangential sectioning (Elias, 1949; Scheuer, 1968). On morphometric analysis it was observed that of 100 points in a field, 8 might fall over thick cell plates.

On morphometric analysis, the incidence of points overlying single plates is 27 times as high as the incidence of points overlying thick cell plates. This has been referred to as single : thick ratio of 27 : 1.

Cirrhosis (Figure 13)

In many instances the cause of the cirrhosis remained obscure, even at post mortem examination. Such cases are referred to as 'cryptogenic' cirrhosis. The majority of cirrhotics in most published reviews, fall into this category (Losowsky and Tunbridge, 1963; Stone, 1973). Sherlock (1971) and MacSween and Scott (1973) found that more than 50% of patients with cirrhosis in Great Britain fell into the cryptogenic group. The present post mortem study indicates that 44% of the cirrhotics at the Hammersmith hospital who came to post mortem between the years 1948 and 1974 were labelled 'cryptogenic'.

The investigation of the hepatic plates in cirrhosis (5 cases), revealed a predominance of two or more cell thick plates. All cirrhotics in this investigation (post mortem and biopsy groups), had either clinical or radiological evidence of portal hypertension, which was confirmed in those that came to post mortem. The thick cell plates were diffusely spread and in most biopsy specimens they were gathered into nodules of varying size - hyperplastic nodules.

On point counting, the ratio of points overlying single and double plates respectively appeared remarkably constant, irrespective of the cause of the cirrhosis. All cirrhotics showed a ratio of 1 : 8 (points overlying single : thick cell plates). In most instances these figures could be assessed even from

small fragmented specimens.

Chronic persistent hepatitis

In most biopsy specimens the limiting plate of hepatocytes remained intact, but in a few it appeared mildly eroded. None of the patients had clinical or radiological evidence of portal hypertension.

The liver cell plates were investigated in 5 cases and the plates were predominantly one cell thick. Morphometric analysis showed a ratio similar to that of a normal adult liver.

Active chronic hepatitis biopsy sections as will be seen later, often contain diffusely hyperplastic plates, even when taken relatively early in the disease. Some cases of chronic persistent hepatitis may at times have a dense portal tract inflammation with erosion of the limiting plate and thus simulate active chronic hepatitis. But the types of plates are usually different in the two conditions.

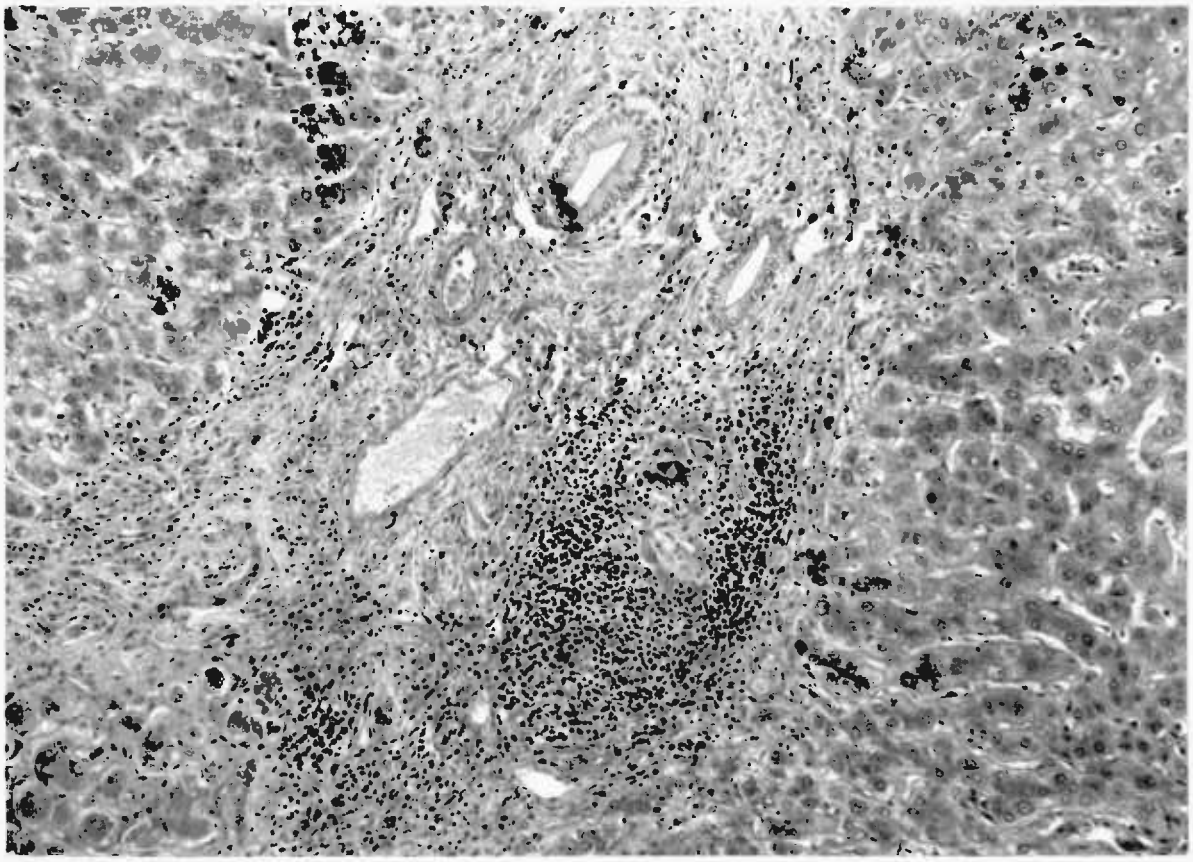
Primary biliary cirrhosis (Figures 14-31)

The histological features are similar to those observed by Rubin, Schaffner and Popper (1965) and Scheuer (1967). Although they described four histological stages in the course of the disease, it was difficult to stage most biopsy sections in such a manner. There is an overlapping of the histological features in a majority of the biopsy specimens. Typical bile duct lesions which were described as being specific for stage 1, were also found together with ductular proliferation (stage 2), fibrosis (stage 3) and with hyperplastic nodules (stage 4). Thus it seemed more convenient in this series to make a histological diagnosis of primary biliary cirrhosis with or without cirrhosis, instead of placing them in any particular stage.

Included in this study was one case of asymptomatic primary biliary cirrhosis. It was essentially similar to that described by Fox, Scheuer and Sherlock in 1973. The patient included in the present investigation was examined for a complaint totally unrelated to the liver when a high anti-mitochondrial

Figure 14. Primary biliary cirrhosis - the section shows an expanded portal tract with a giant cell granuloma around a damaged bile duct. Many thick cell plates are visible peri-portally. There was no clinical evidence of portal hypertension. Ratio of single : thick cell plates = 3.8 : 1.
(H and E x 150)

Figure 15. Primary biliary cirrhosis - a liver biopsy section from a patient who had clinical evidence of portal hypertension. The specimen was obtained 4 years after initial symptoms and it shows a diffuse hepatocyte hyperplasia, with pseudo-duct formation. Ratio of single : thick cell plates = 1 : 5.1.
(H and E x150)



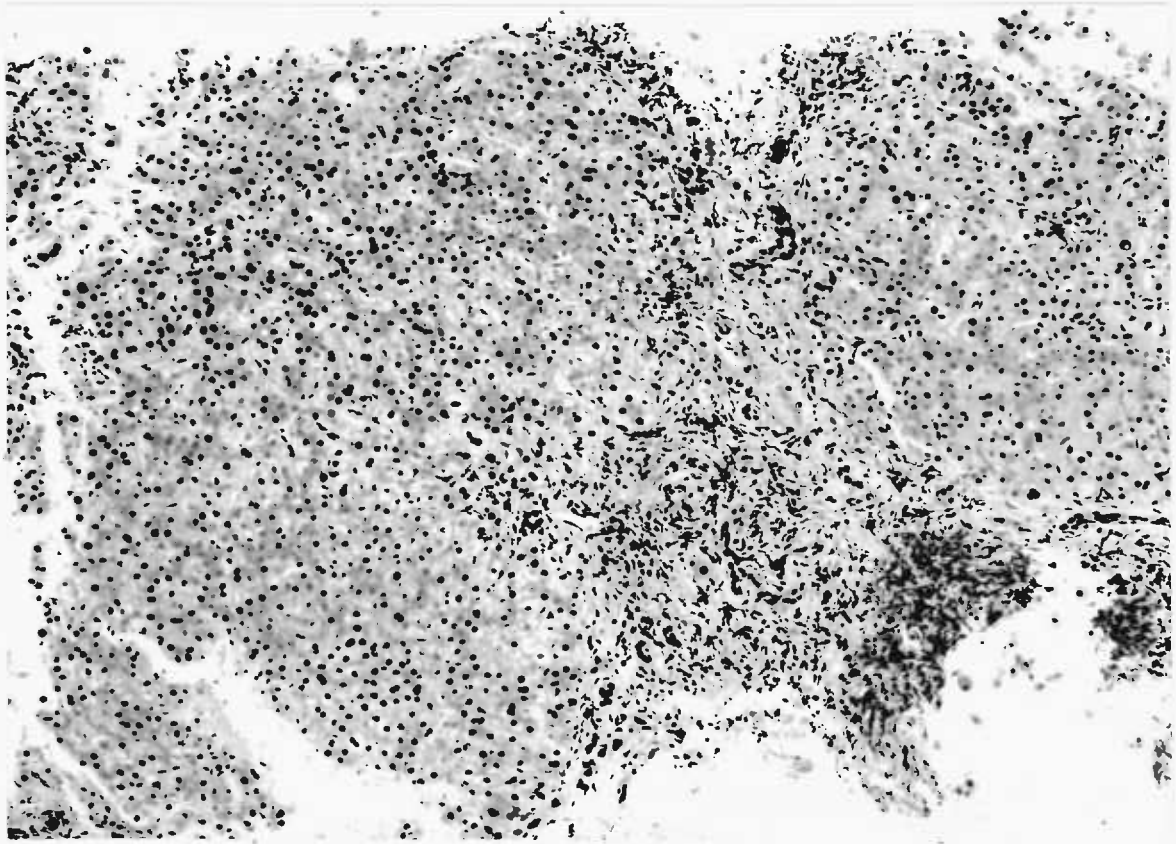
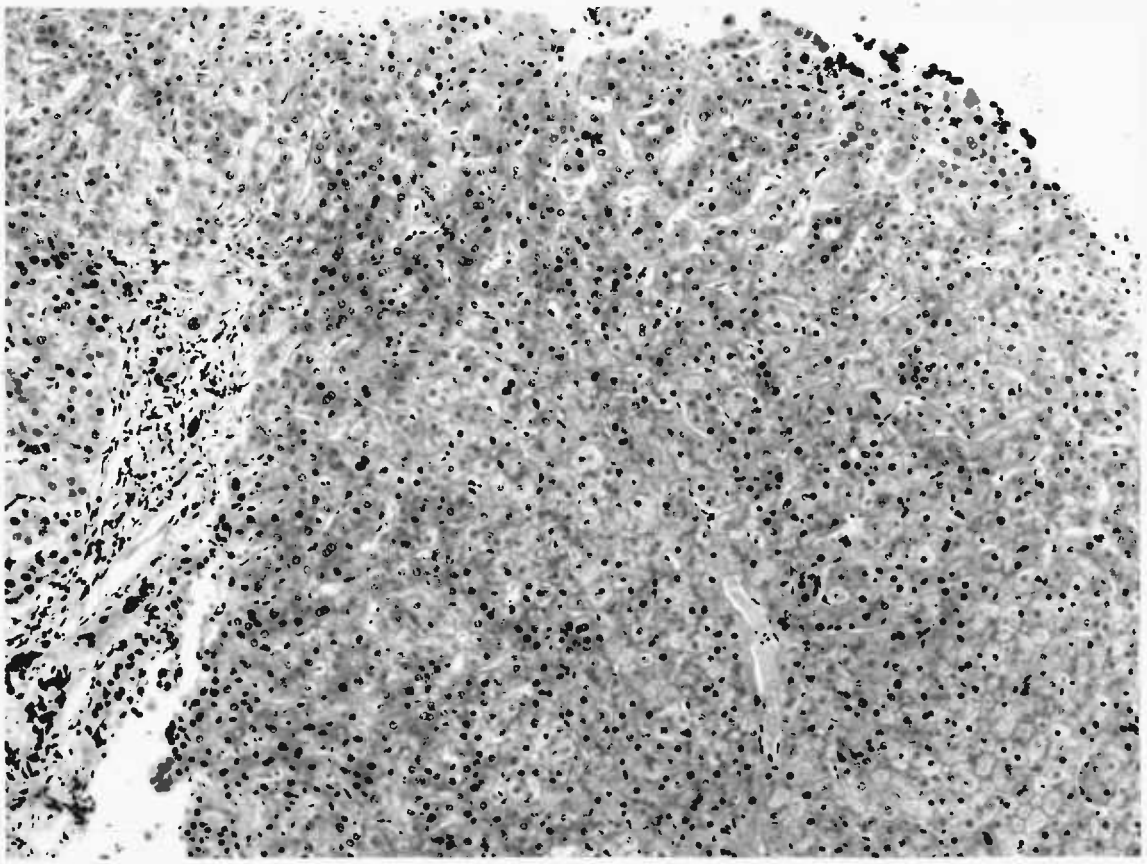


Figure 16. Primary biliary cirrhosis - same patient biopsied 2 years later. The vascular pattern is still retained. There is a diffuse hepatocyte hyperplasia in both periportal and perihepatic venous regions. Ratio of single : thick cell plates = 1 : 5.4.
(H and E x 150)

Figure 17. Primary biliary cirrhosis - same patient biopsied 8 years after initial symptoms. The section shows a loss of the normal vascular pattern (cirrhosis). The hepatic plates are predominantly hyperplastic. Ratio of single : thick cell plates = 1 : 8.1.
(H and E x 150)



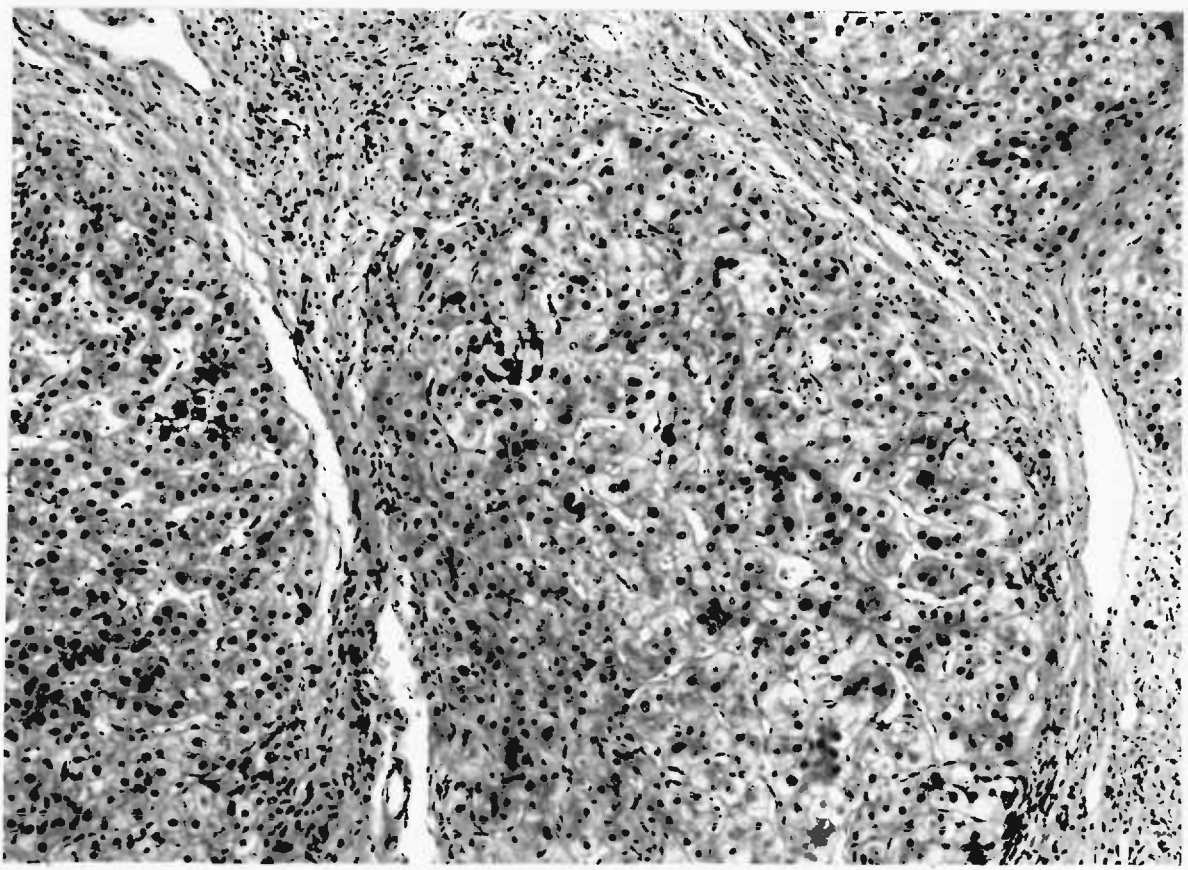
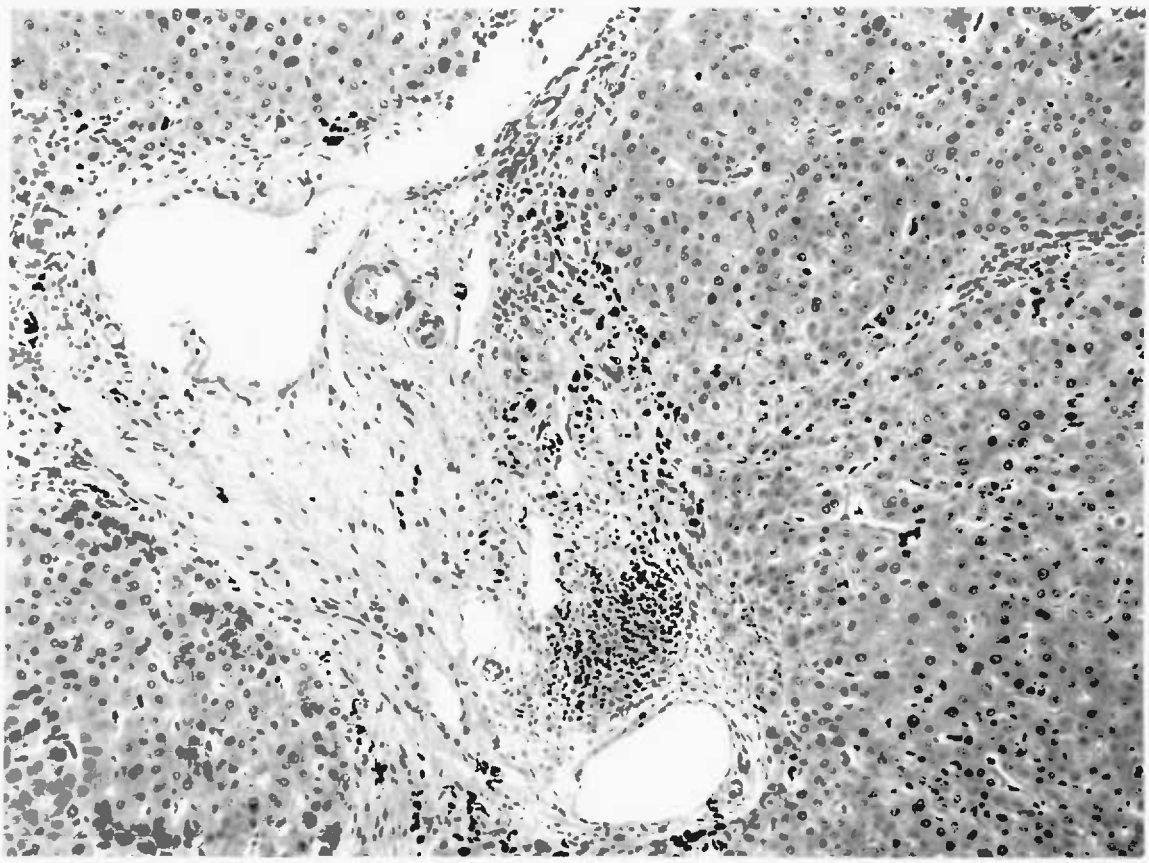


Figure 18. Primary biliary cirrhosis - a portal tract with no bile ducts. There is a dense lymphocyte aggregate. The limiting plate is intact and there are many periportal thick cell plates. No evidence of portal hypertension. Ratio of single : thick cell plates = 1.5 : 1.
(H and E x150)

Figure 19. Primary biliary cirrhosis - another area of the same biopsy specimen showing a hyperplastic focus. The hepatic plates are widened and there is compression of the surrounding liver plates.
(Gordon and Sweet reticulin x 60)



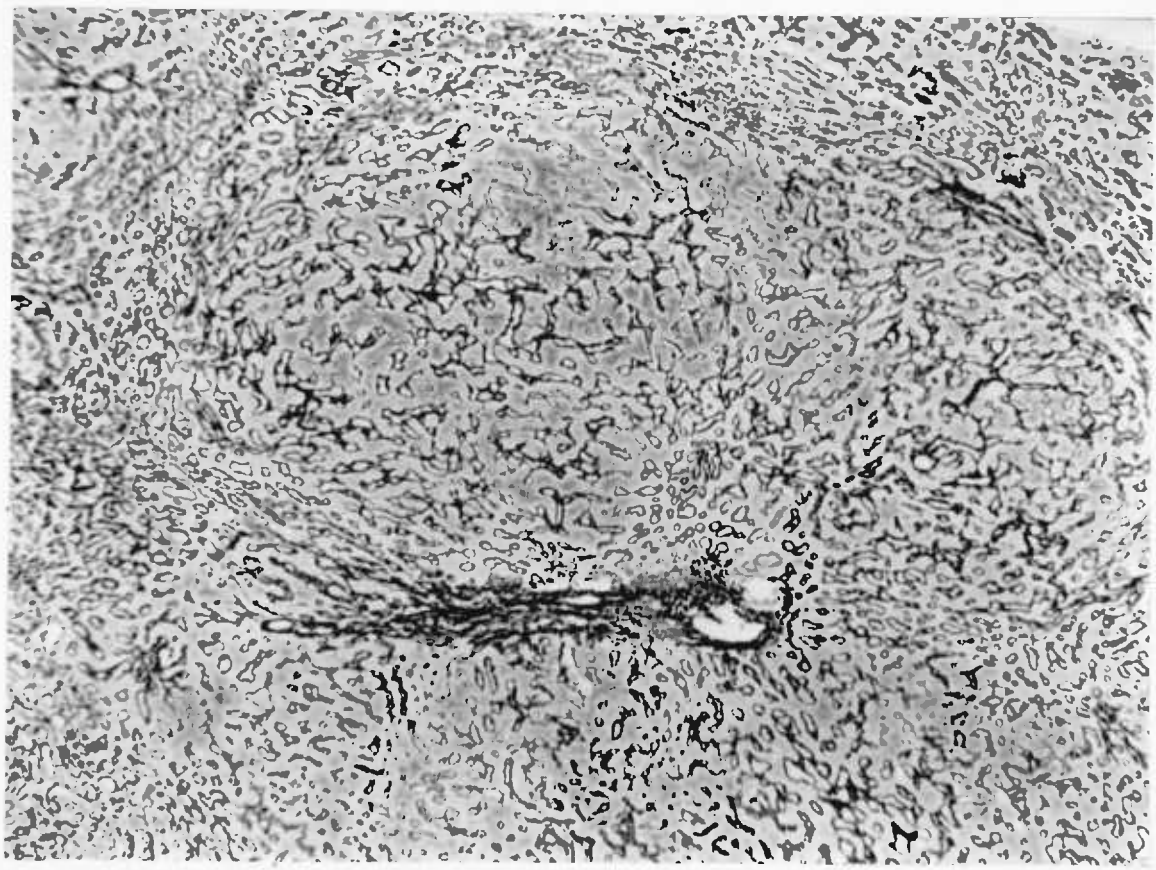
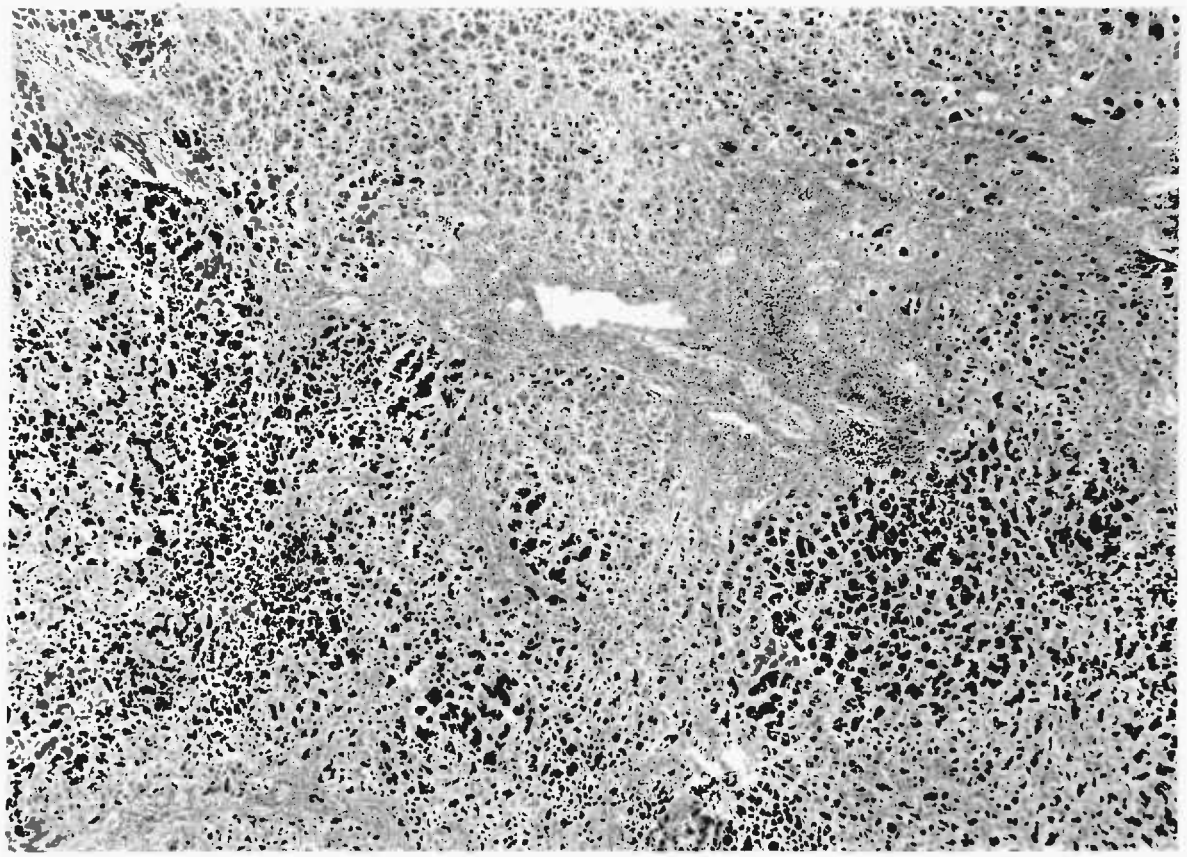


Figure 20. Primary biliary cirrhosis - the same patient at post mortem 4 years later. Section of the liver showing a loss of the normal vascular pattern. The patient had clinical evidence of portal hypertension which was confirmed at post mortem by the presence of an enlarged and overweight spleen and oesophageal varices.
(H and E x 60)

Figure 21. Primary biliary cirrhosis - section showing an enlarged portal tract and a giant cell granuloma surrounding a damaged bile duct. A few hyperplastic hepatocytes are seen in the periportal region. There was no evidence of portal hypertension. Ratio of single : thick cell plates = 3.8 : 1.
(H and E x 150)



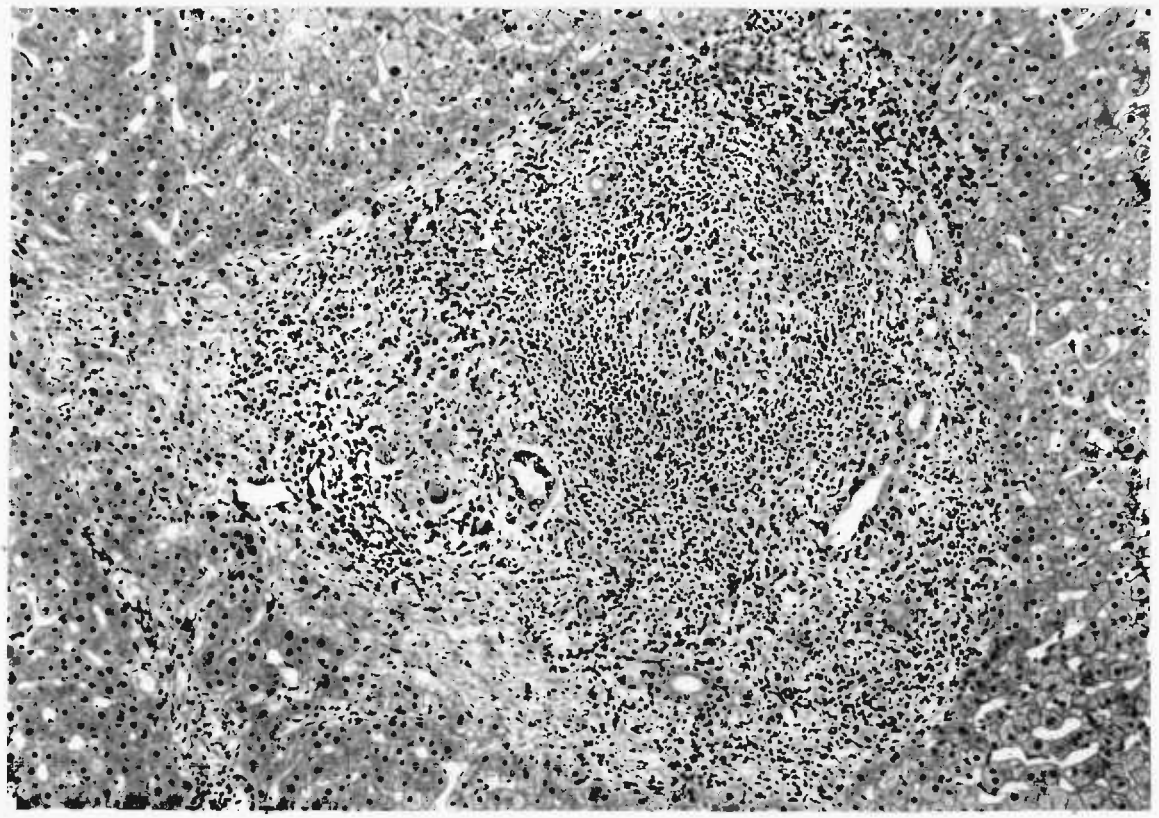
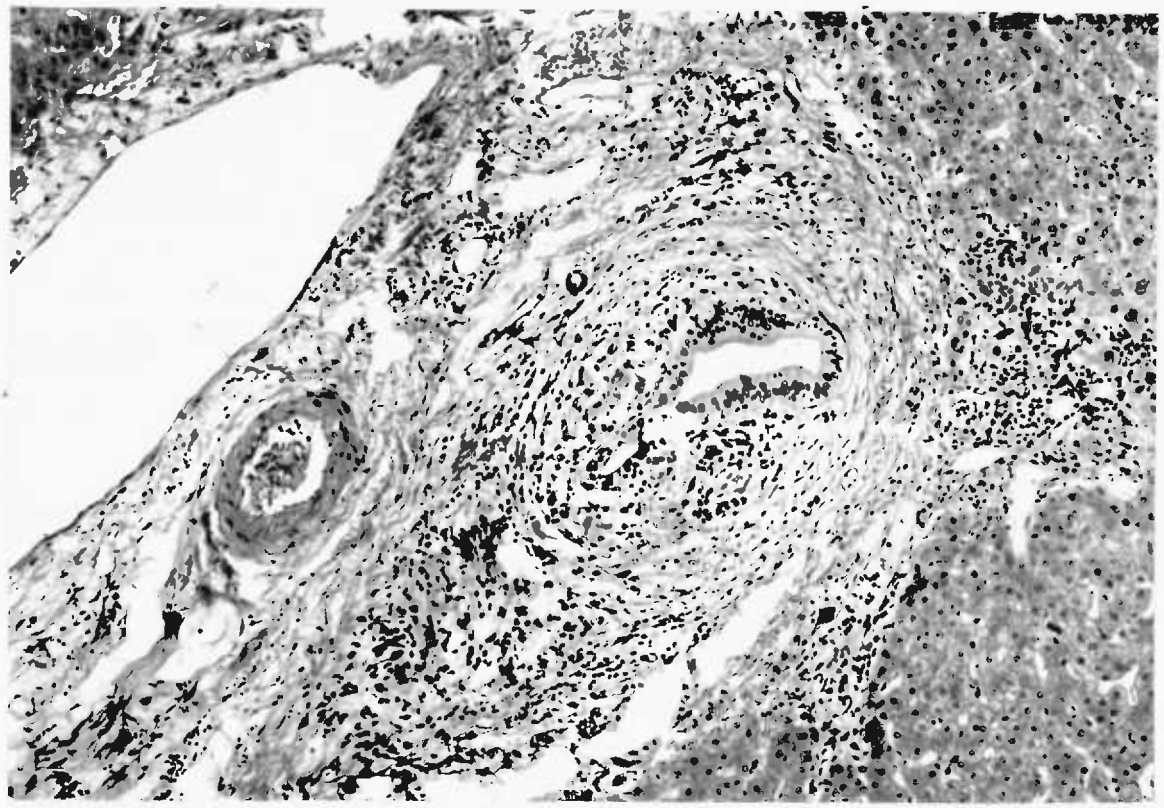


Figure 22. Primary biliary cirrhosis - section showing an oedematous portal tract with partial necrosis of a bile duct epithelium. There are a few surrounding hyperplastic hepatic plates. The specimen was taken 2 years after symptoms. There was no portal hypertension. Ratio of single : thick cell plates = 3.3 : 1.
(H and E x 150)

Figure 23. Primary biliary cirrhosis - section shows a retained vascular pattern. The specimen was taken 3.5 years after the initial symptom. Short fibrous septa radiate from margins of the portal tract into the parenchyma. There is a diffuse increase in the number of thick cell plates. The patient had evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 2.3.
(H and E x80)



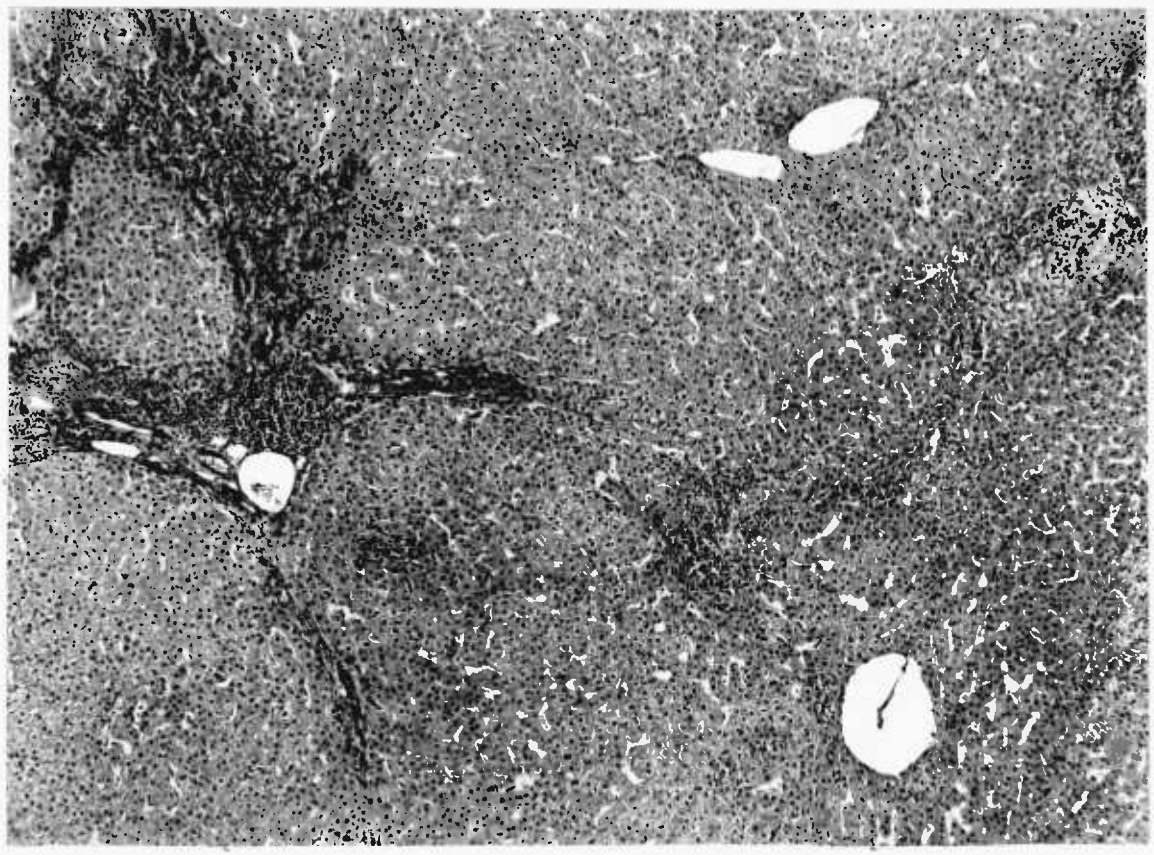
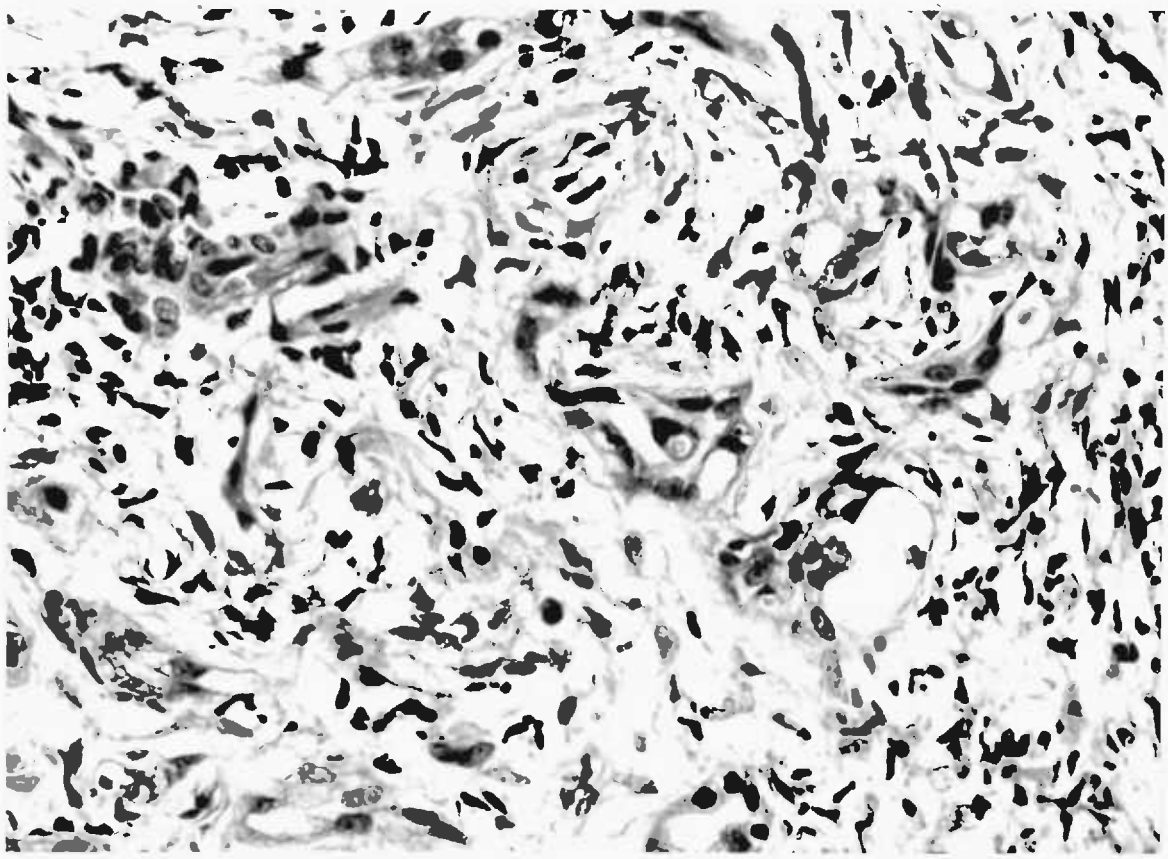


Figure 24. Primary biliary cirrhosis - a portal tract from same specimen as above, showing pseudo-bile duct formation.
(H and E x 550)

Figure 25. Primary biliary cirrhosis - same patient came to post mortem 6 years later. A section of the liver showing a loss of the normal vascular pattern and hyperplastic nodules.
(H and E x 80)



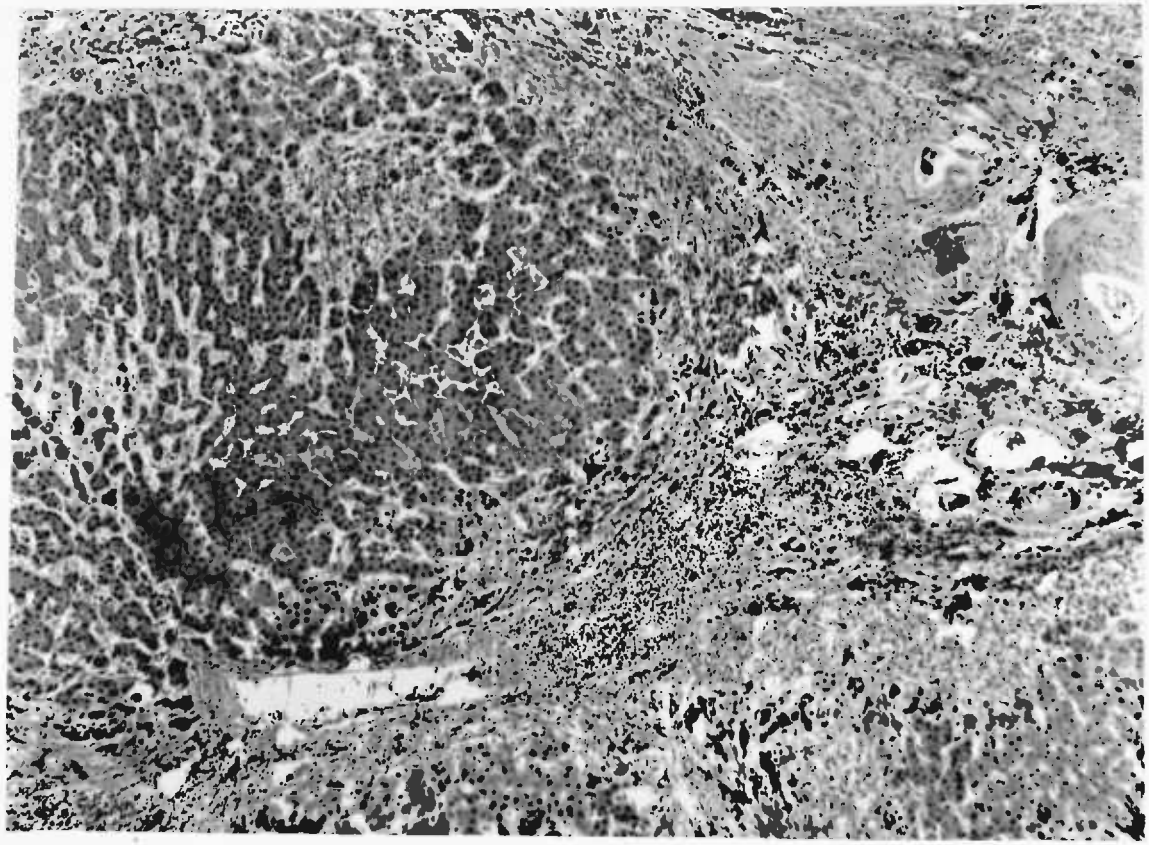
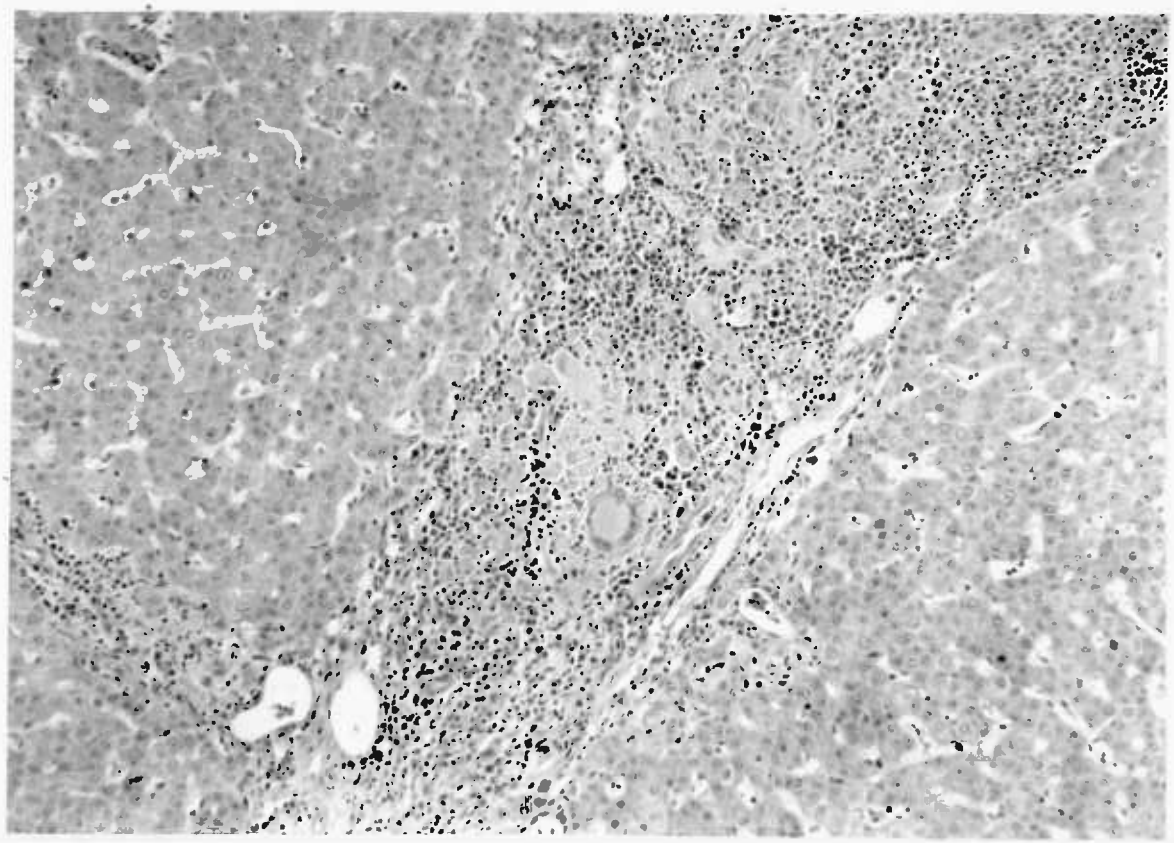


Figure 26. Primary biliary cirrhosis - section shows an inflamed portal tract containing lymphocytes, epithelioid cells and giant cells. There are a few surrounding hyperplastic hepatic plates. The specimen was taken 3 years after symptoms. The patient had no clinical evidence of portal hypertension. Ratio of single : thick cell plates = 2.7 : 1.
(H and E x 150)

Figure 27. Primary biliary cirrhosis - the same patient as above biopsied 3 years later. Section shows a retained vascular pattern with a diffuse increase in the number of thick cell plates. The patient had clinical evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 6.3
(H and E x 150)



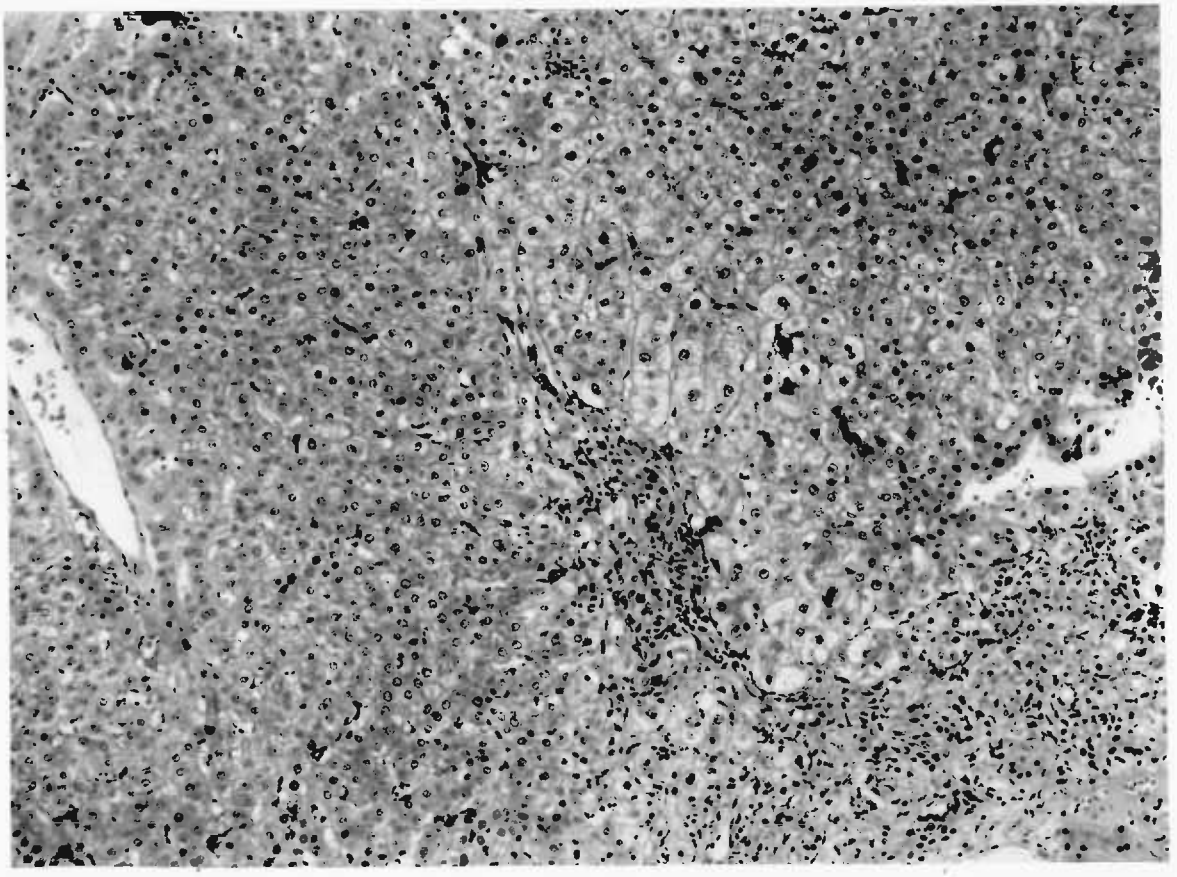
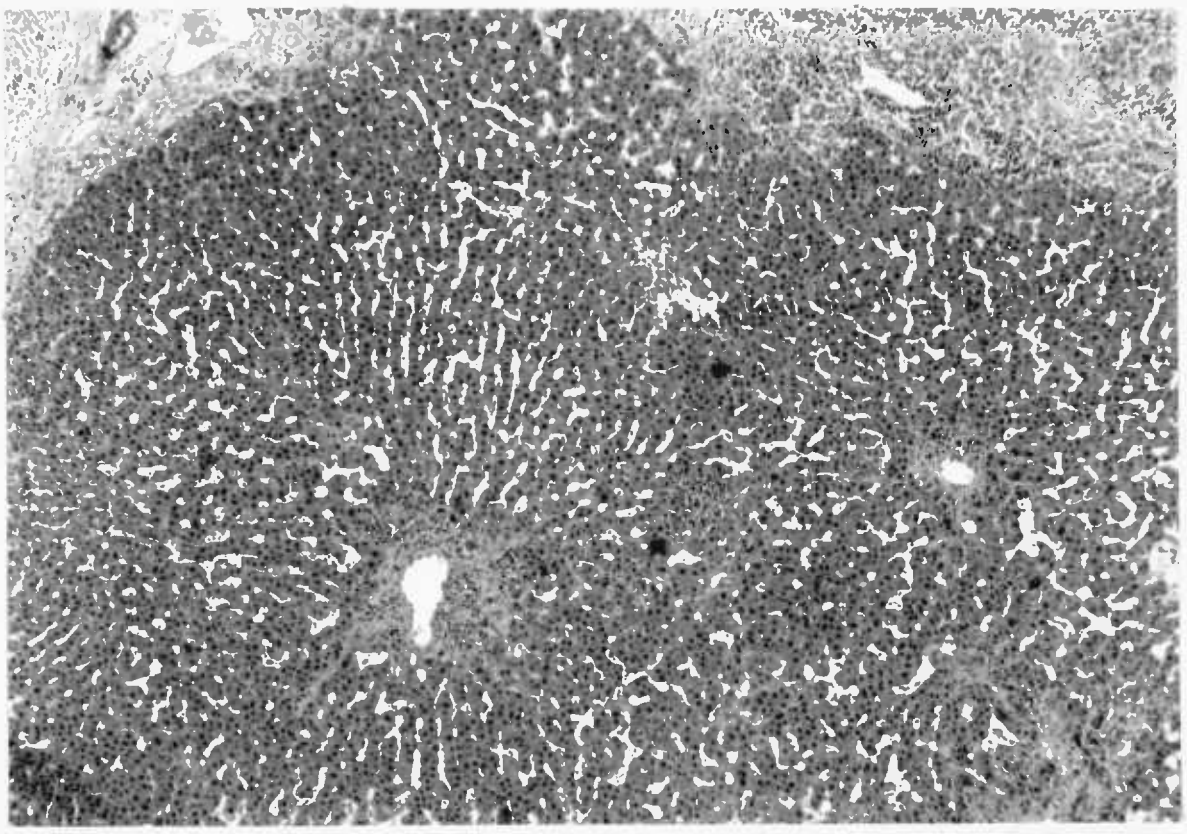


Figure 28. Primary biliary cirrhosis - the section shows a retained vascular pattern and a diffuse increase in the number of thick cell plates. The specimen was taken 3.5 years after the initial symptoms. The patient had clinical evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 4.1.
(H and E x 75).

Figure 29. Primary biliary cirrhosis - a section showing an enlarged portal tract containing an epithelioid cell granuloma. The limiting plate is intact and there is an increased number of periportal thick cell plates. The specimen was taken 2 years after symptoms.
(H and E x 200) Ratio of single : thick cell plates = 1.53 : 1.



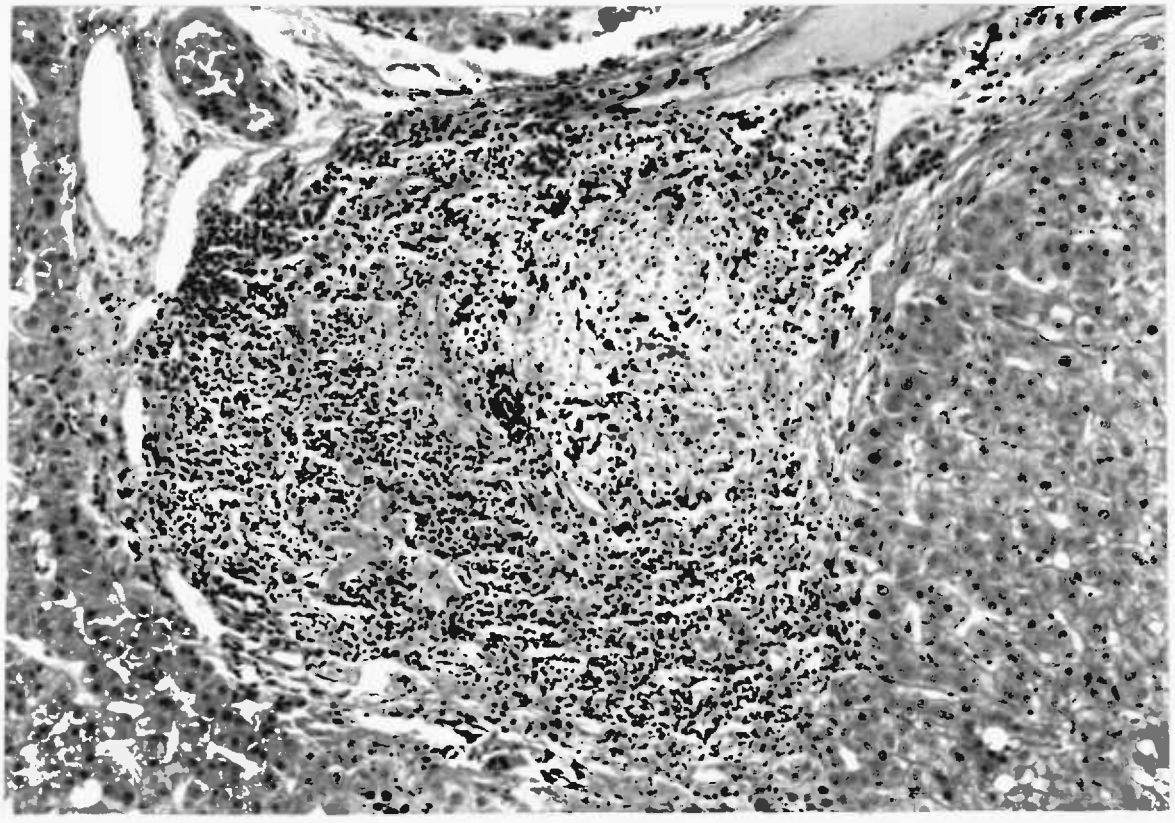
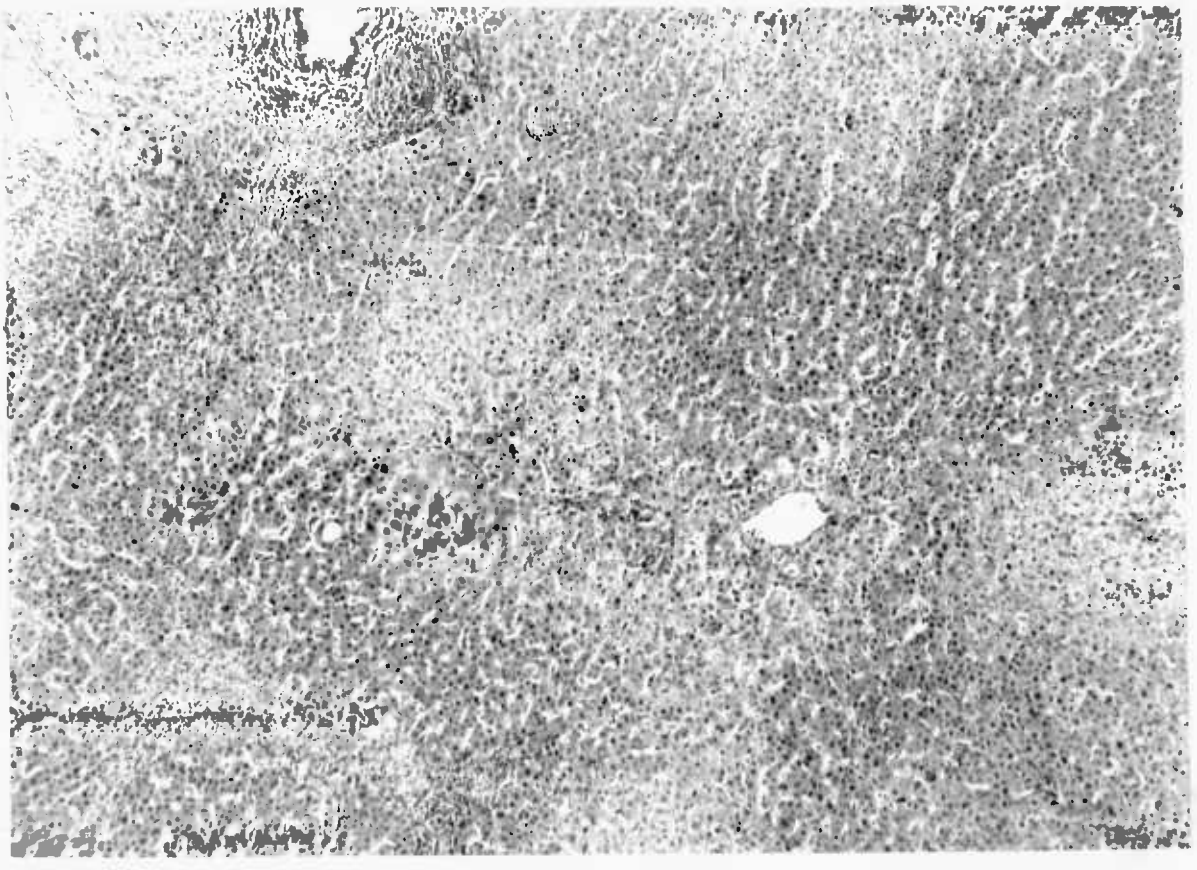
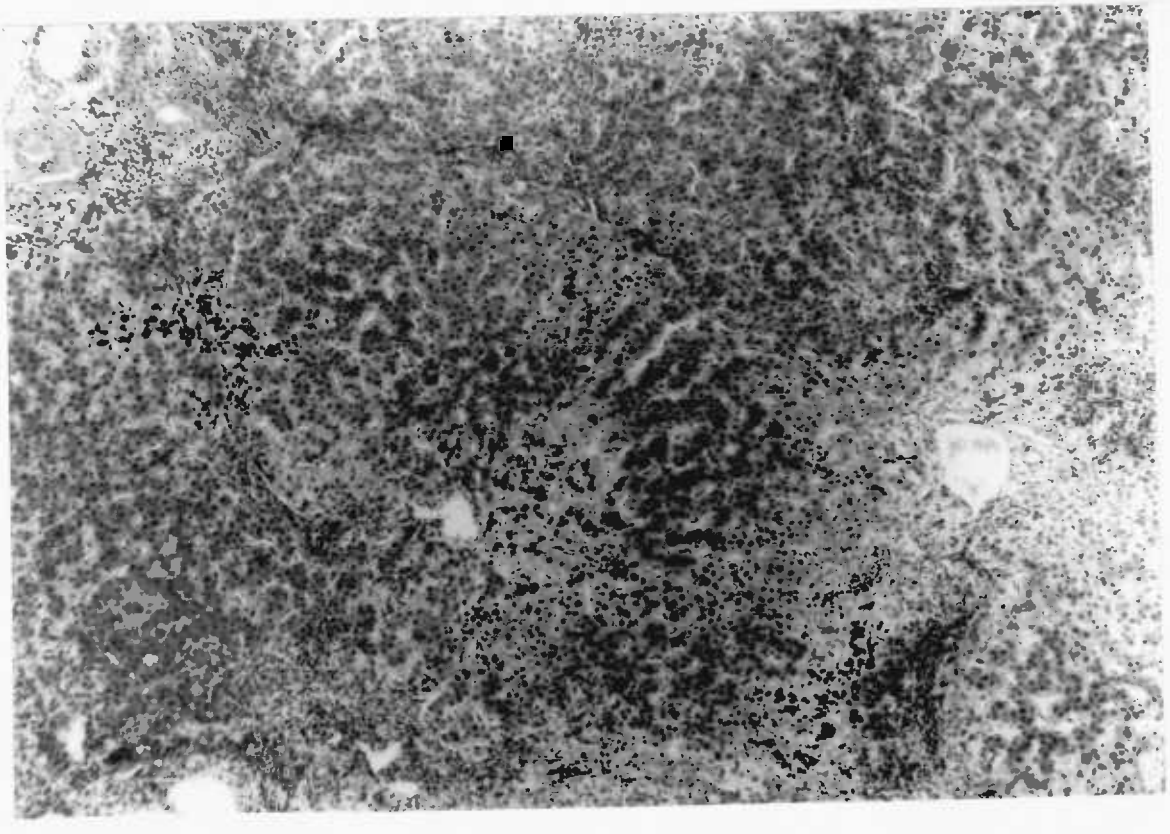


Figure 30. Primary biliary cirrhosis - a section of the same specimen described above showing a retained vascular pattern. The patient had no evidence of portal hypertension. Ratio of single : thick cell plates = 1.5 : 1.
(H and E x 75).

Figure 31. Primary biliary cirrhosis - section showing a retained vascular pattern and thin fibrous septa radiating from portal tracts into the lobular parenchyma. There is a diffuse hepatocyte hyperplasia. The biopsy specimen was taken 4 years after the initial symptoms. The patient had evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 5.2.
(H and E x 75)





antibody titre was detected. Subsequently it was found that she had disturbed liver function tests and the liver biopsy specimen was compatible with a diagnosis of primary biliary cirrhosis.

The patients in the present study consisted of 17 females and 5 males and this striking female preponderance is similar to the findings of Rubin and his colleagues (1965), Sherlock (1959) and Hoffbauer (1960). Pruritus appeared to be the dominant clinical feature and it was usually followed by jaundice of the obstructive type.

Some authors (Scheuer, 1967; Sherlock, 1972) , suggest that wedge resections are preferable for making a histological diagnosis, as a needle biopsy may not contain sufficient larger portal tracts with the classical lesions. In the present investigation, many needle biopsy specimens were of value for investigation of the plates. All needle biopsies, including the specimen from the asymptomatic patient, showed a definite reduction or a complete absence of bile ductules together with increased cellular infiltration in the small portal tracts.

The overlap in cases of primary biliary cirrhosis and active chronic hepatitis as described by Rodes, Bruguera, Bordas and Teres (1971) and by Sherlock (1974), was observed in two patients in the present study.

Both patients presented with clinical and biochemical features suggestive of primary biliary cirrhosis, but their biopsy specimens had features common to both disease processes. The disease in both patients was well advanced in duration and the hepatic plates appeared diffusely hyperplastic. Both primary biliary cirrhosis and active chronic hepatitis exhibit diffuse hepatocyte hyperplasia in advanced cases. Thus it is difficult to differentiate the two processes on plate thickness, although active chronic hepatitis shows a diffuse hyperplasia even in early biopsies, while primary biliary cirrhosis usually does not (see results later).

The familial incidence of primary biliary cirrhosis as described by Walker, Bates, Doniach, Ball and Sherlock (1972) was observed in the present investigation too, with the positive diagnosis of the disease in two sisters. The rest of the family was not investigated.

Hepatocyte Hyperplasia in Primary Biliary Cirrhosis

Correlation of plate thickness to duration of symptoms (Fig. 1)

It was not possible to be absolutley certain how long the disease had been present before the appearance of symptoms. Liver biopsy examination has shown the presence of destructive bile duct lesions even in asymptomatic patients (Fox, Scheuer and Sherlock, 1973). Duration in this investigation refers to time after the appearance of symptoms.

Of the 35 biopsy specimens investigated in this study, 22 were taken between two and four years from the onset of the initial symptoms. Most of the others were serial biopsies taken later at different intervals.

There appears to be a relationship between the duration of symptoms and the presence of thick cell plates (Fig. 1). The incidence of thick cell plates increases with the duration of the symptoms. Thick cell plates in excess of single plates, i.e. a ratio of single : thick cell plates of less than 1, occurs at about four years after the onset of the first symptom (fig. 1). The incidence of thick cell plates gradually increases from then onwards, until the cirrhotic ratio is reached, on the average 6.5 years from the onset of symptoms.

Correlation of plate thickness and fibrosis

Most sections showed some degree of fibrosis in the portal tracts and 28 of the 35 biopsy specimens contained a marked increase of portal fibrous tissue. In contrast to this, intra-lobular fibrosis was uncommon or was late in appearance. In 9 biopsy specimens short fibrous septa extended from the portal tract margins into the lobules (Fig. 23 , 27 , 31). Linkage between portal tracts or between portal tracts and hepatic venous radicles occurred in 8 specimens. Mild portal tract fibrosis was an early feature and was not associated with diffuse increase in numbers of thick cell plates. Intra-lobular fibrosis and linkage were late features (the earliest case occurring 3.5 years following the initial symptoms) and it occurred when there was an increase in numbers of thick cell plates. But increase in the number of thick cell plates

was also observed in sections devoid of intra-lobular fibrosis and linkage (Fig. 16, 27). Thus it appears that in some instances hepatocyte hyperplasia in primary biliary cirrhosis occurs before intra-lobular fibrosis and distortion of the architecture.

Correlation of plate thickness to erosion of the limiting plate

Damage to the limiting plate or 'piecemeal necrosis' was not a constant feature in this series of patients with primary biliary cirrhosis. Destruction of the limiting plate was observed in 13 biopsy specimens. In most of these it was mild and appeared late in the course of the disease. An appreciable degree of necrosis was observed about 4 years after the onset of symptoms. It was associated at this stage with significant numbers of thick cell plates. Increased numbers of thick cell plates were identified also in many biopsy specimens with intact limiting plates (Fig. 18, 29).

The appearance of thick cell plates in primary biliary cirrhosis is thought by many workers to be regenerative (Scheuer, 1967; Popper and Orr, 1970; Baggenstoss, Foulk, Butt and Bahn, 1964). According to their view, the destruction of hepatocytes induced a compensatory response in the remaining healthy liver cells. The present findings do not entirely confirm this suggestion. Much intra-lobular necrosis and necrosis of the limiting plate (piecemeal necrosis) were not constant features in the biopsy specimens studied. Thick cell plates were noted in many specimens with no such necrosis and although one cannot exclude previous destruction of parenchyma, so far there is no strong evidence for this supposition. It may be then that the occurrence of thick cell plates in primary biliary cirrhosis involves some mechanism other than compensatory hyperplasia.

In most early biopsy specimens, thick cell plates were noted initially in periportal areas. In other specimens thick cell plates were observed in small 'hyperplastic' foci (Fig. 19). In most chronic cases, the hyperplastic plates were more diffusely arranged in both periportal and perihepatic venous regions (Fig. 16, 27, 31). Although the hyperplasia, as seen by the increase in the

numbers of thick cell plates become diffuse with the increased duration of the disease, there was no corresponding increase in hepatocyte necrosis either periportally or elsewhere in the acini.

Active Chronic Hepatitis (Figs. 32-43)

A total of 39 biopsy specimens from 28 patients considered to be suffering from active chronic hepatitis was included in this series. As described by Mistilis, Skyring and Blackburn (1968), the present series too showed a female preponderance, 21 of the patients being females with a mean age of 39.4 years. Other systemic manifestations as described by Mistilis et al (1968), Mistilis (1968), were observed in 7 patients in the present investigation. These patients had many circulating antibodies in their sera. The smooth muscle antibody was present in the sera of all 7 patients and this is in agreement with the findings of Doniach, Roitt, Walker and Sherlock (1966) and with that of Wright (1970), as being the predominant antibody detectable in such patients.

The hepatitis associated antigen (HB-Ag) was detected in 4 patients and none of them had any detectable antibodies in their sera. No differences in liver biopsy appearances was observed in the antigen negative and antigen positive groups. This finding of the presence of HB-Ag and the absence of smooth muscle antibody is in agreement with that of Vischer (1970).

Hepatocyte Hyperplasia in Active Chronic Hepatitis

Correlation of plate thickness to duration of symptoms (Fig. 5)

Of the 39 biopsy specimens, 21 were taken between one and two years from the onset of symptoms. The onset was insidious in 18 patients and in the remaining 10 it was acute resembling viral hepatitis. Jaundice was the prominent initial manifestation. In contrast to primary biliary cirrhosis, pruritus did not appear to be a common presenting feature. In this series patients with primary biliary cirrhosis had an insidious onset and they presented

initially after a longer duration of symptoms than did those with active chronic hepatitis.

In active chronic hepatitis there seems to be a relationship between the duration of symptoms and an increased thick to thin plate ratio (Fig. 5). At the time of the initial biopsy (in a majority of cases about one year from the onset of symptoms), over 90% of the patients showed an increased ratio of thick : thin cell plates. Thereafter, this became more marked until a cirrhotic ratio of 1:8 (points overlying single : thick cell plates) was reached on the average about 4.5 years from the onset of the symptoms (Fig. 5). This change in ratio occurred more rapidly than in primary biliary cirrhosis. Thus in active chronic hepatitis, even in biopsy specimens taken shortly after the clinical onset of the disease, many liver plates appear to be wider than one cell thickness and the hepatocytes therefore seem to be hyperplastic relatively early in the disease, but a long pre-symptomatic period cannot be excluded.

Correlation of the incidence of thick cell plates and erosion of the lamina limitans

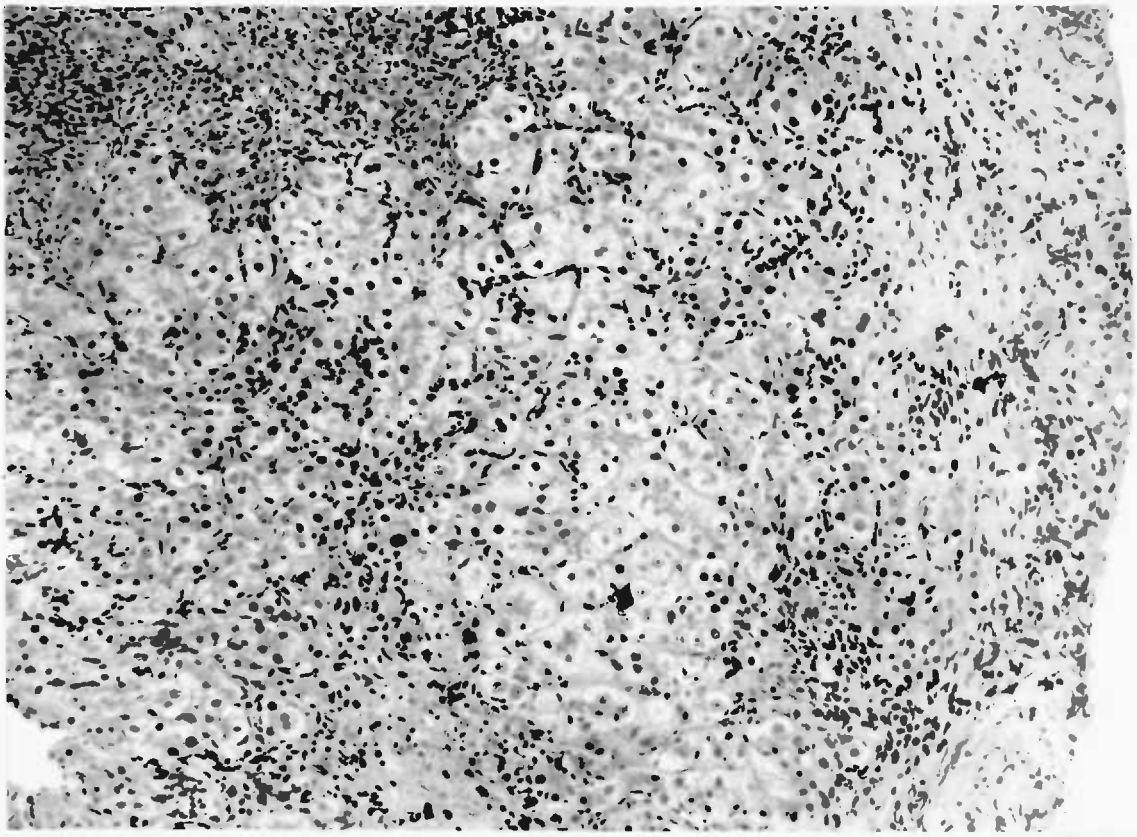
A varying degree of damage to the limiting plate was detected in all the biopsy specimens examined. The periportal hepatocytes were often arranged in gland-like formations (rosettes)(Fig. 38, 42). The number of hyperplastic plates was high and the degree of hyperplasia could not be correlated to the damage to the lamina limitans. A similar appearance of diffuse hyperplasia was observed in specimens with minimal damage to the limiting plate, as much as in those with a greater degree of damage.

Correlatian of incidence of thick cell plates and fibrosis

Varying amounts of fibrous tissue was detectable in all biopsy specimens. Fibrous tissue joining periportal and perivenous regions (Fig. 40) occurred in 26 of the biopsy specimens and in the remaining 13 specimens fibrous septa of varying length and extent radiated from the margins of the portal tracts between the hepatic parenchymal cells. The degree of hyperplasia seemed unrelated to the extent of the fibrosis, an increased ratio of thick to thin cell plates being observed in specimens showing both little and extensive fibrosis. Most biopsy

Figure 32. Active chronic hepatitis - the section shows a heavy chronic inflammatory cell infiltrate in the portal tract with damage to the limiting plate. There is swelling of the parenchymal cells with stippling of the cytoplasm. The specimen was taken 1.5 years after the onset of clinical symptoms. The patient had clinical evidence of portal hypertension. (H and E x 200) Ratio of single : thick cell plates = 1 : 3.7.

Figure 33. Active chronic hepatitis - the same biopsy specimen described above showing the widened plates of hepatocyte hyperplasia. (Gordon and Sweet reticulin impregnation x 200)



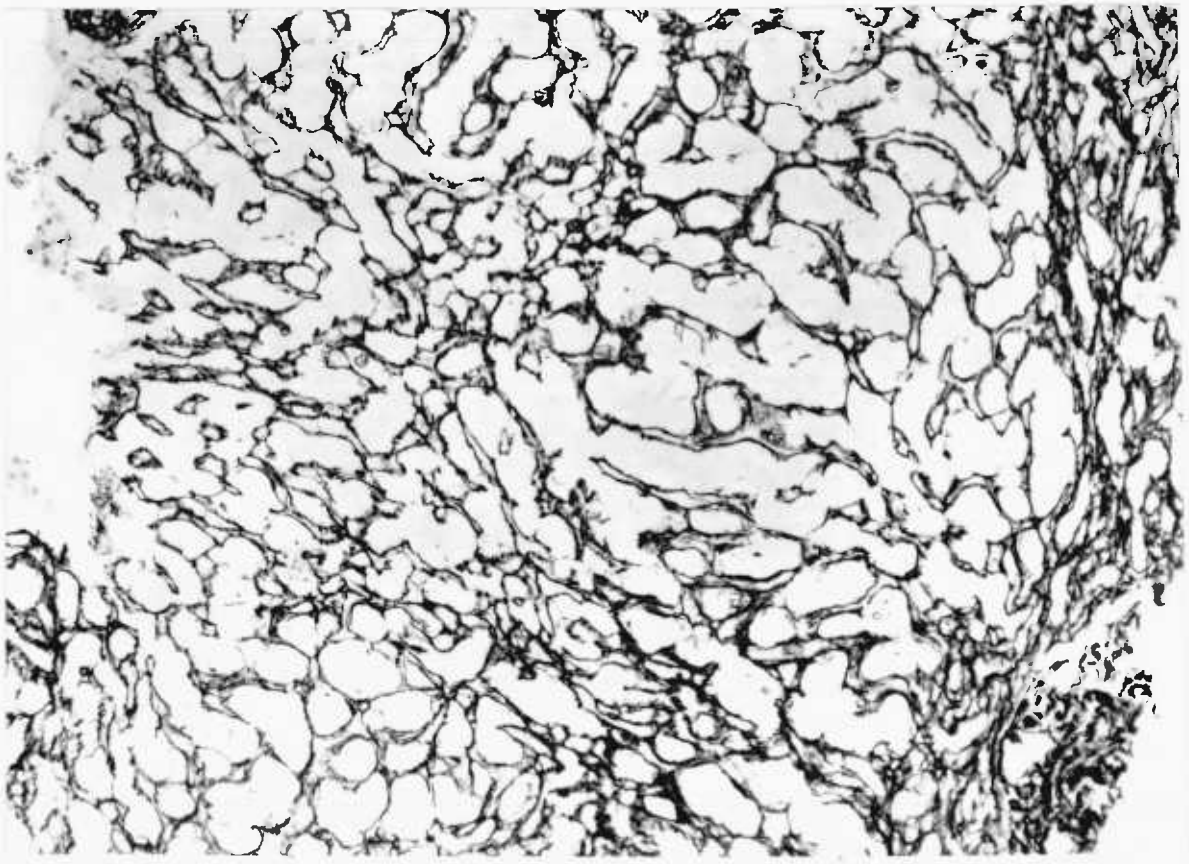
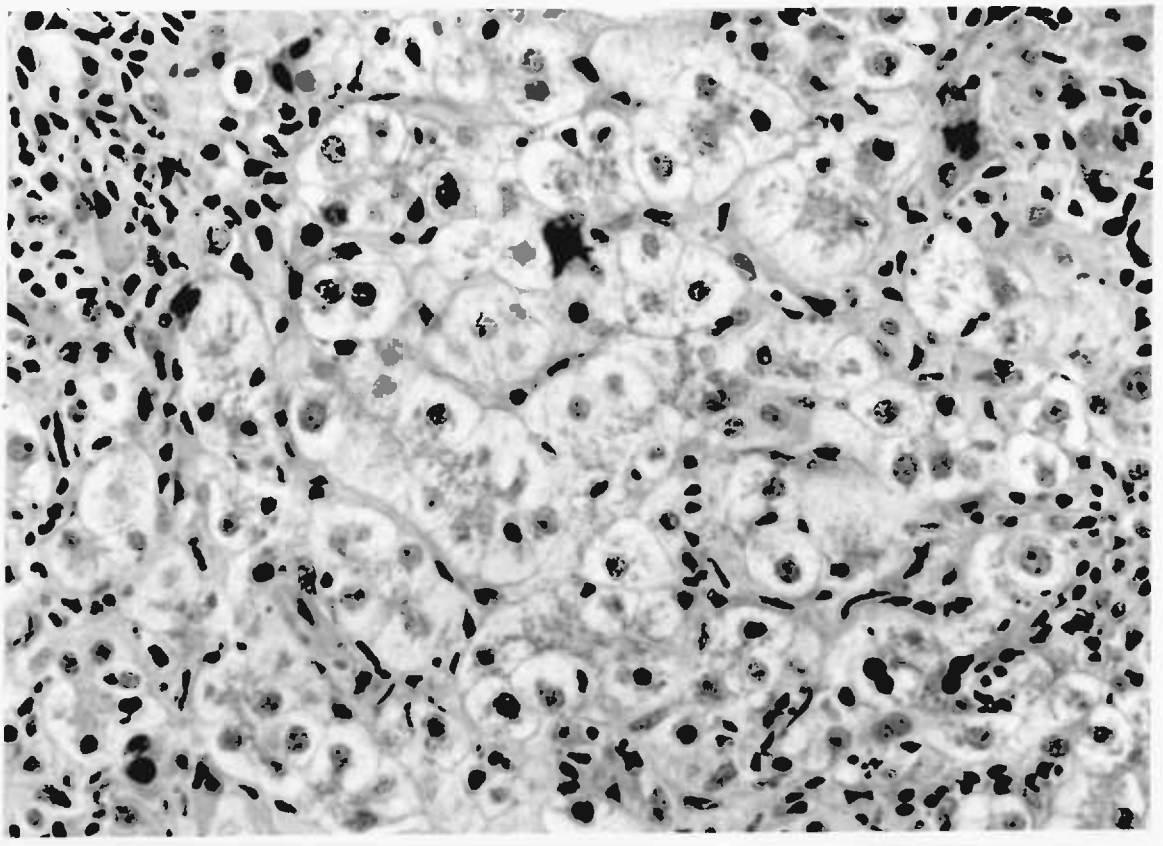


Figure 34. Active chronic hepatitis. - a higher magnification of the specimen described previously showing the thick plates of hepatocyte hyperplasia. Ratio of single : thick cell plates = 1 : 3.7.
(H and E x 525)

Figure 35. Active chronic hepatitis - Gordon and Sweet reticulin impregnation under dark ground illumination showing the hyperplastic liver plates. The patient had evidence of portal hypertension.
(Gordon and Sweet reticulin x 525)



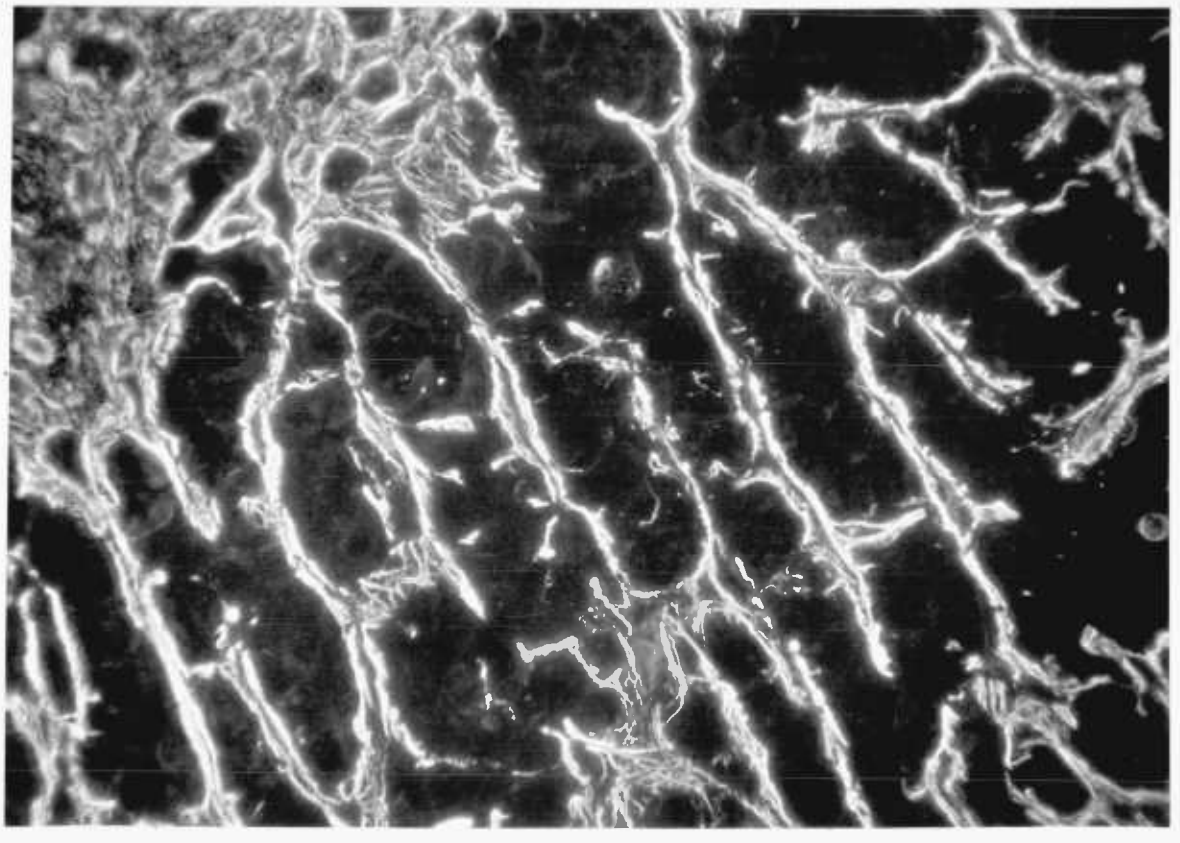
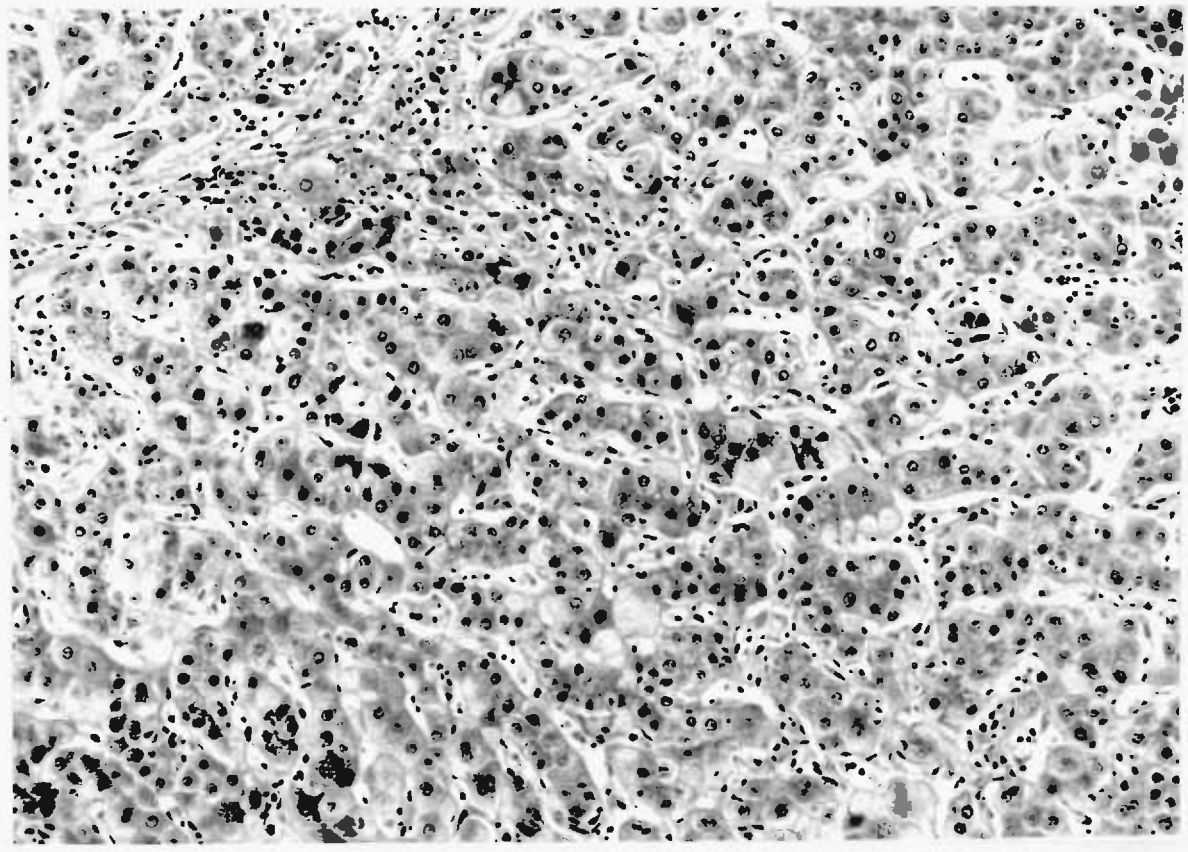


Figure 36. Active chronic hepatitis - section showing the widened liver plates of hepatocyte hyperplasia and a cellular infiltrate in the sinusoids. Specimen taken 2 years after symptoms. Patient had no clinical evidence of portal hypertension. The vascular pattern was retained in many areas. (H and E x 200) Ratio of single : thick cell plates = 1.47 : 1.

Figure 37. Active chronic hepatitis - the same case as above at post mortem 8 years later showing a loss of the normal vascular pattern (cirrhosis). The patient had clinical evidence of portal hypertension which was confirmed at post mortem by the presence of an enlarged and overweight spleen and oesophageal varices.
(H and E x 80)



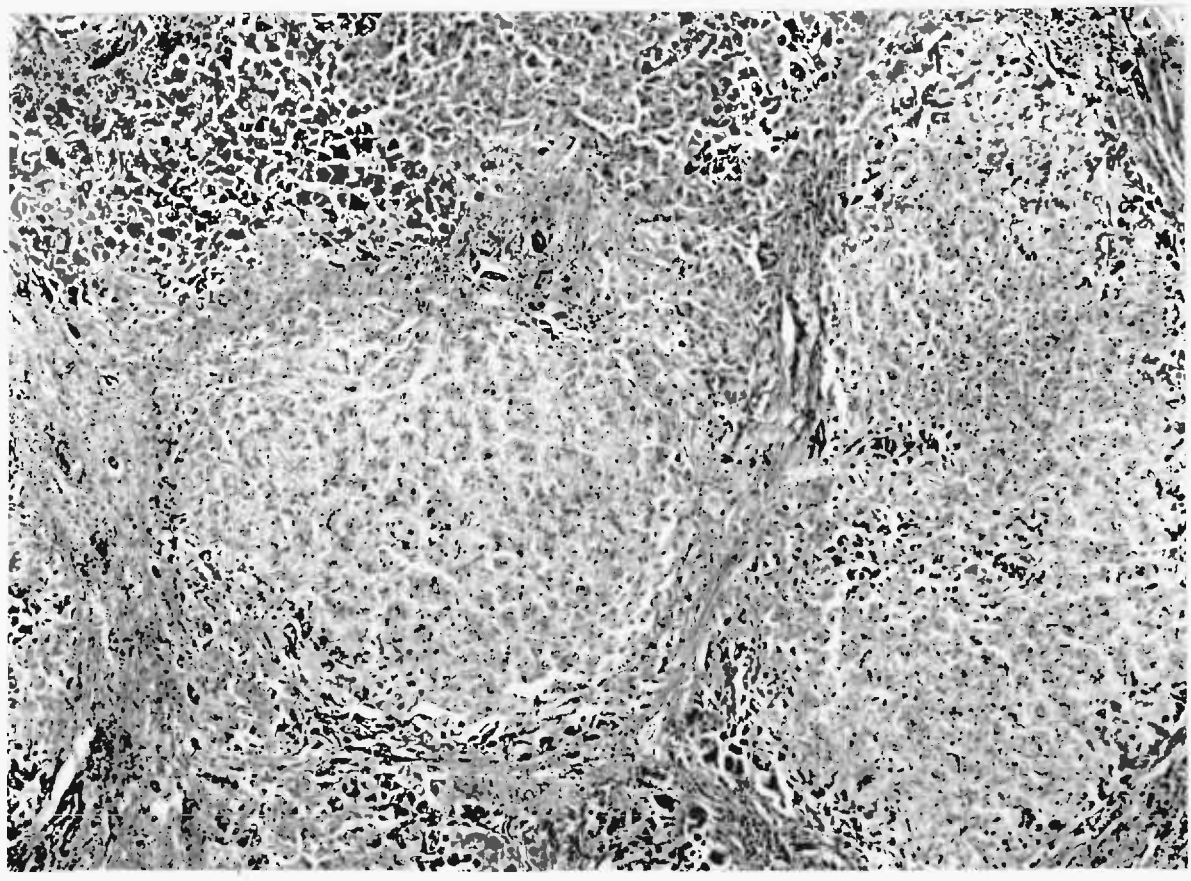
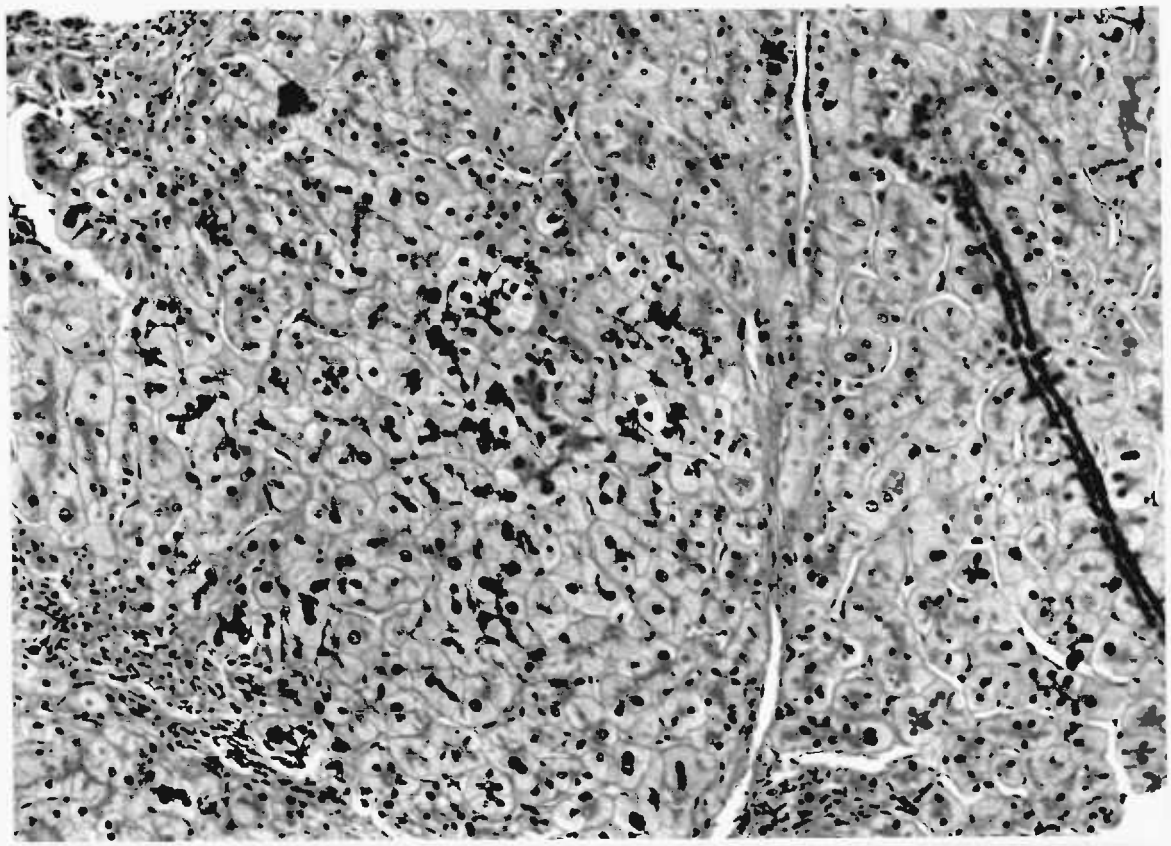


Figure 38. Active chronic hepatitis - section showing a diffuse hepatocyte hyperplasia. The patient had clinical evidence of portal hypertension. A few hepatocytes are arranged in gland-like (rosette) formation. The biopsy was taken 4 years after symptoms. Ratio of single : thick cell plates = 1: 6.9.
(H and E x 200)

Figure 39. Active chronic hepatitis - the section shows a heavy inflammatory cell infiltrate in a portal tract with erosion of the limiting plate. There is a diffuse hepatocyte hyperplasia and 'rosette' formation. The biopsy was taken 3 years after symptoms. The patient had clinical evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 4.1.
(H and E x 200)



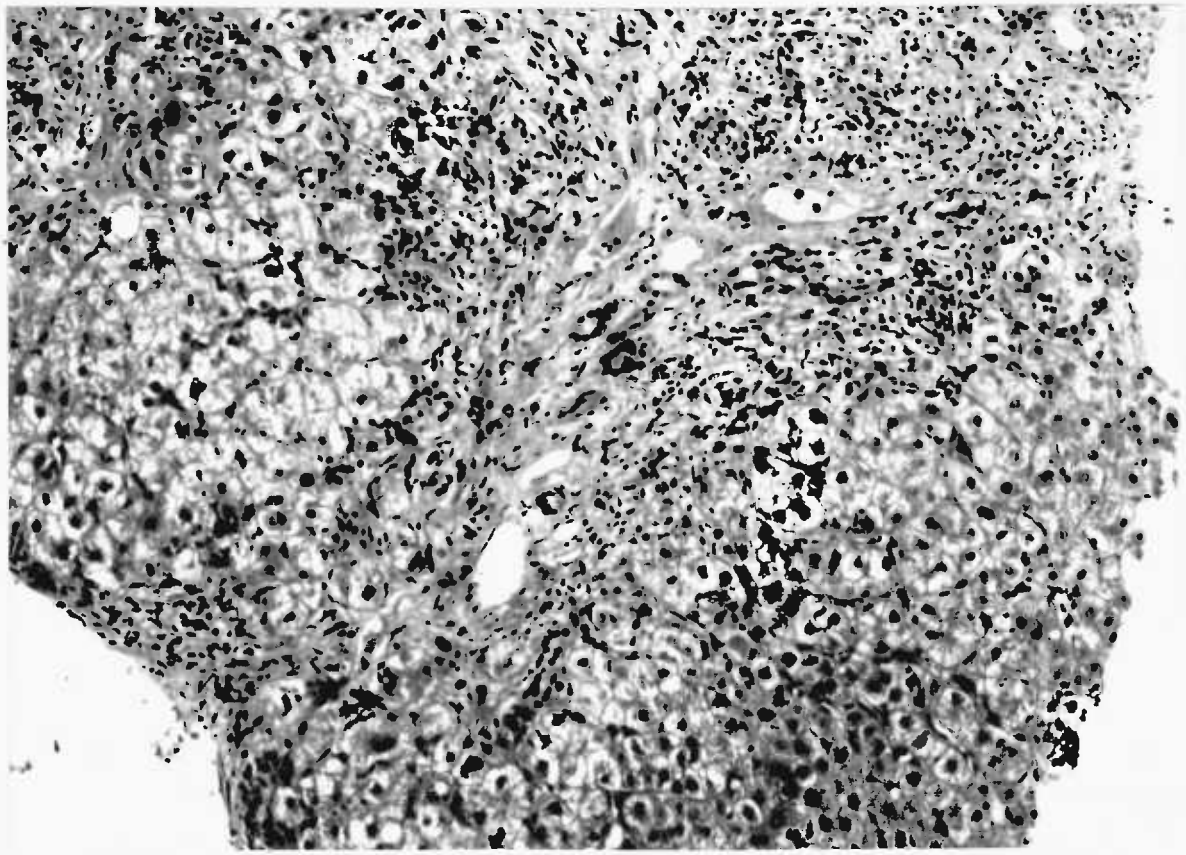
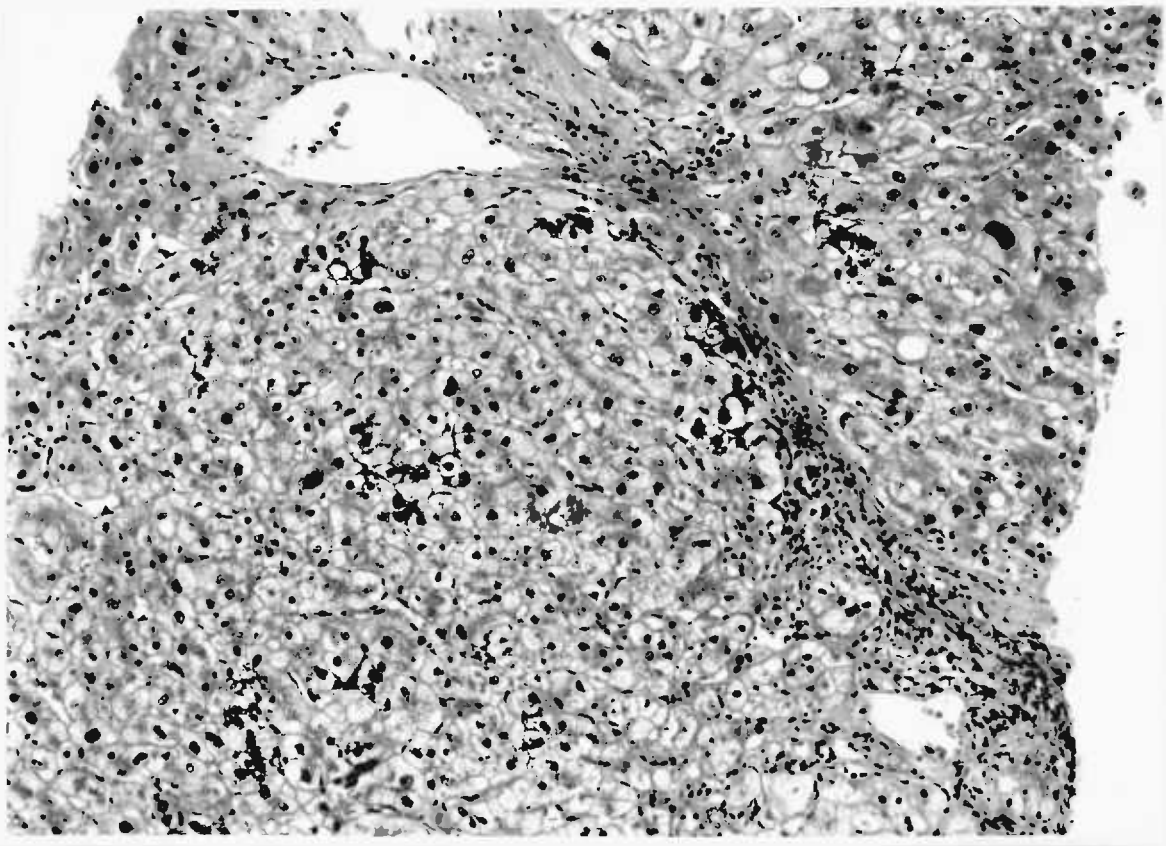


Figure 40. Active chronic hepatitis - section showing fibrous linkage and a diffuse hepatocyte hyperplasia. The section was taken 3.9 years after symptoms. The patient had clinical evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 5.
(H and E x 150)

Figure 41. Active chronic hepatitis - the section shows an enlarged and inflamed portal tract with erosion of the limiting plate. There is a diffuse hepatocyte hyperplasia. The vascular pattern is retained. The section was taken 2 years after symptoms. The patient had evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 5.6.
(H and E x 150)



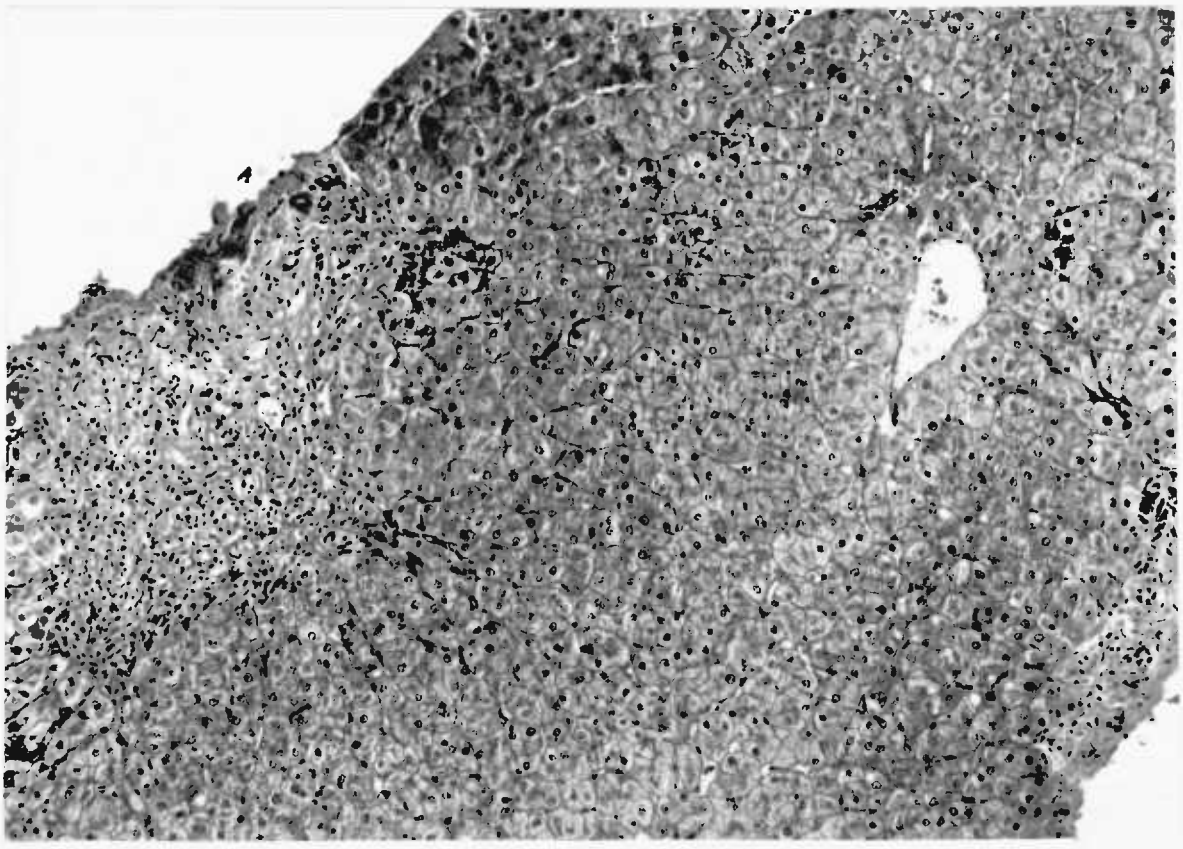
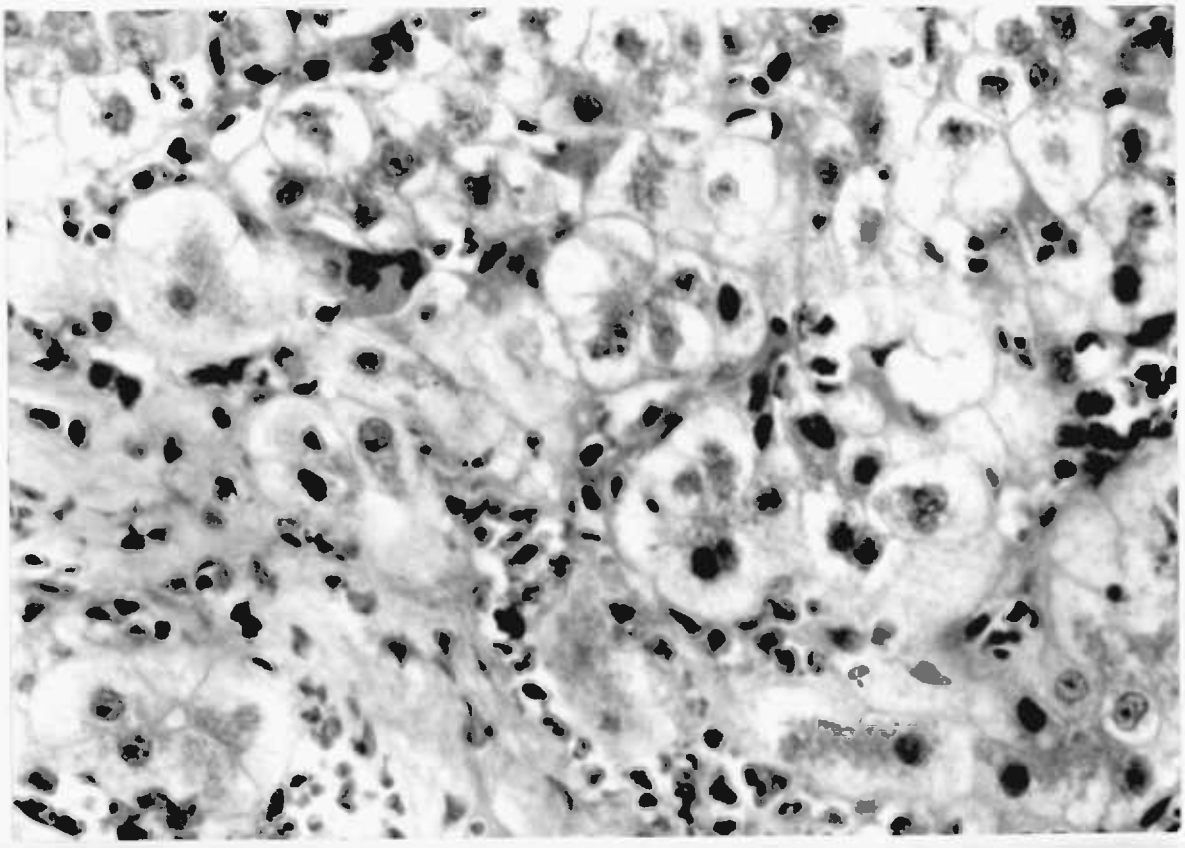
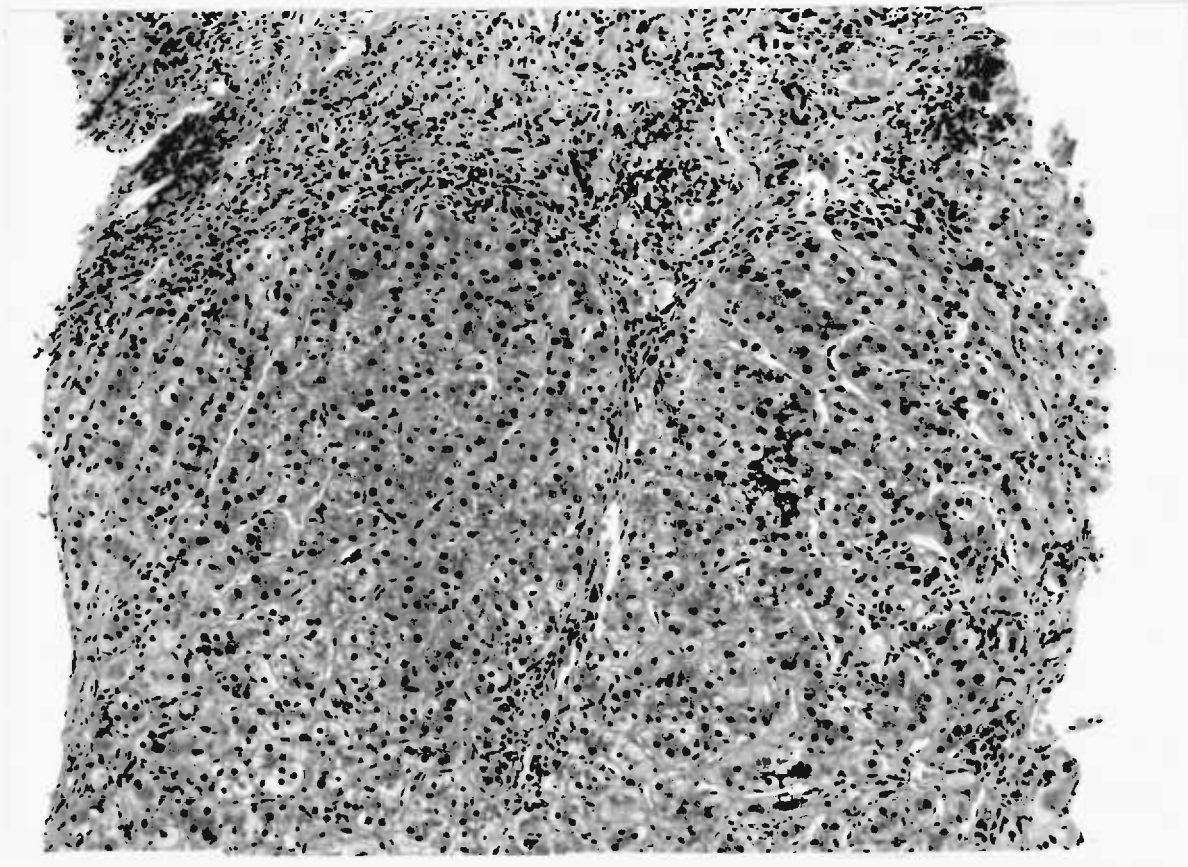


Figure 42. Active chronic hepatitis - section showing swollen and hyperplastic hepatocytes with pseudo-gland (rosette) formation. This biopsy specimen was taken 2.5 years after symptoms. The patient had evidence of portal hypertension. Ratio of single : thick cell plates = 1 : 6.0. (H and E x 600)

Figure 43. Active chronic hepatitis - section showing an inflamed and enlarged portal tract with erosion of the limiting plate and fibrous linkage. There is a diffuse hepatocyte hyperplasia and this patient had evidence of portal hypertension. The specimen was taken 2.5 years after symptoms. Ratio of single : thick plates = 1 : 6.7. (H ane E x 150)





specimens examined had a uniform arrangement of thick cell plates in both the periportal and perihepatic venous regions (Fig. 41).

Several authors (Popper and Orr, 1970; Mistilis and Blackburn, 1970; Sherlock, 1974) consider the presence of thickened hepatic plates in this disease to be a regenerative phenomenon. The presumption has been made that this represents a compensatory response stimulated by destruction of periportal liver cells. Mistilis and Blackburn (1970), attribute the presence of binucleate hepatocytes in plates of double cell thickness as being a regenerative process, while others (Mistilis, 1968; Popper and Orr, 1970; Mackay, Taft and Cowling, 1956), mention that parenchymal regeneration is represented by rosettes of cells and small nodule (micronodule) and large nodule (macronodule) formation. It is true that some necrosis of hepatocytes is seen in all specimens, but the extent of the liver cell hyperplasia appears to be excessive for a regenerative response to this small degree of necrosis. It is known experimentally that a substantial proliferative response requires at least 30% of liver to be resected or damaged (Bucher, 1963). Perhaps it may be that the hepatocyte hyperplasia is an early proliferative reaction in this disease and not necessarily secondary to the loss of functioning liver cells.

Alcoholic Liver Disease

This series comprised 39 biopsies from 37 patients who consumed over 160 grams of alcohol per day for periods ranging from one to over twenty years. Unlike the situation in primary biliary cirrhosis and in active chronic hepatitis, most alcoholics had very few symptoms specifically referable to the liver at the time of the initial presentation. Many presented with non-specific symptoms such as anorexia, nausea, vomiting, weight loss and abdominal pain. A few patients were noted to have hepatomegaly during an examination for some unrelated condition. The various forms of alcoholic liver disease - steatosis, hepatitis and cirrhosis, were diagnosed on the liver biopsy specimen.

A varying degree of fatty change was observed in 37 biopsy specimens. Histological

evidence of alcoholic hepatitis was found in 13 biopsy sections and Mallory's hyalin was detected in 12 of these.

Hepatocyte Hyperplasia in Alcoholic Liver Disease

Correlation of plate thickness and the duration of alcohol consumption

As indicated in figure 9, the incidence of thick cell plates appears to increase with the duration of alcohol consumption, but the change does not occur to the same extent or at the same rate in all patients. The earliest case with an increased number of thick cell plates had consumed alcohol for about four years. After a ten year intake of alcohol only 6 patients in this investigation had an apparent excess of thick cell plates. After 19 years of continuous alcohol consumption, 14 of the 37 patients appeared to show excessive numbers of thick cell plates. All cases with a cirrhotic ratio had a history of over 10 years alcohol consumption.

Correlation of incidence of thick cell plates and fatty change

Steatosis was a very common observation and it was present in all but two of the biopsy specimens. It could not be localised to any particular area of the acinus and in most cases there was a diffuse involvement of the acini. No direct correlation could be found between plate thickness and the presence of fatty change, as thick cell plates were identified in the absence of steatosis and in areas away from fatty change (Fig. 44, 49). Excess steatosis tends to mask the foci of hyperplasia and particular attention was paid to this point (Fig. 49).

Correlation of the incidence of thick cell plates and fibrosis

Portal tract fibrosis was identified in 14 biopsy specimens. Fibrous septa of varying length and thickness radiated from the margins of such portal tracts between the hepatic parenchymal cells and in 6 biopsy specimens linkage was

visible either between portal tracts and hepatic veins or apparently between two adjacent portal tracts (Fig. 44, 48). Thick cell plates were observed in biopsy specimens with no fibrosis and in specimens with minimal fibrosis (Fig. 49, 50). Fibrous linkage was a fairly late feature in alcoholic liver disease and was associated with increase in numbers of thick cell plates, which also were found more frequently in chronic consumers.

In chronic alcoholic liver disease, the hepatocyte hyperplasia appears to be unrelated to the fibrosis and it seems to precede the fibrosis, as relatively increased numbers of thick plates were identified before fibrosis was detected. Appreciable fibrosis was not found in the absence of hepatocyte hyperplasia.

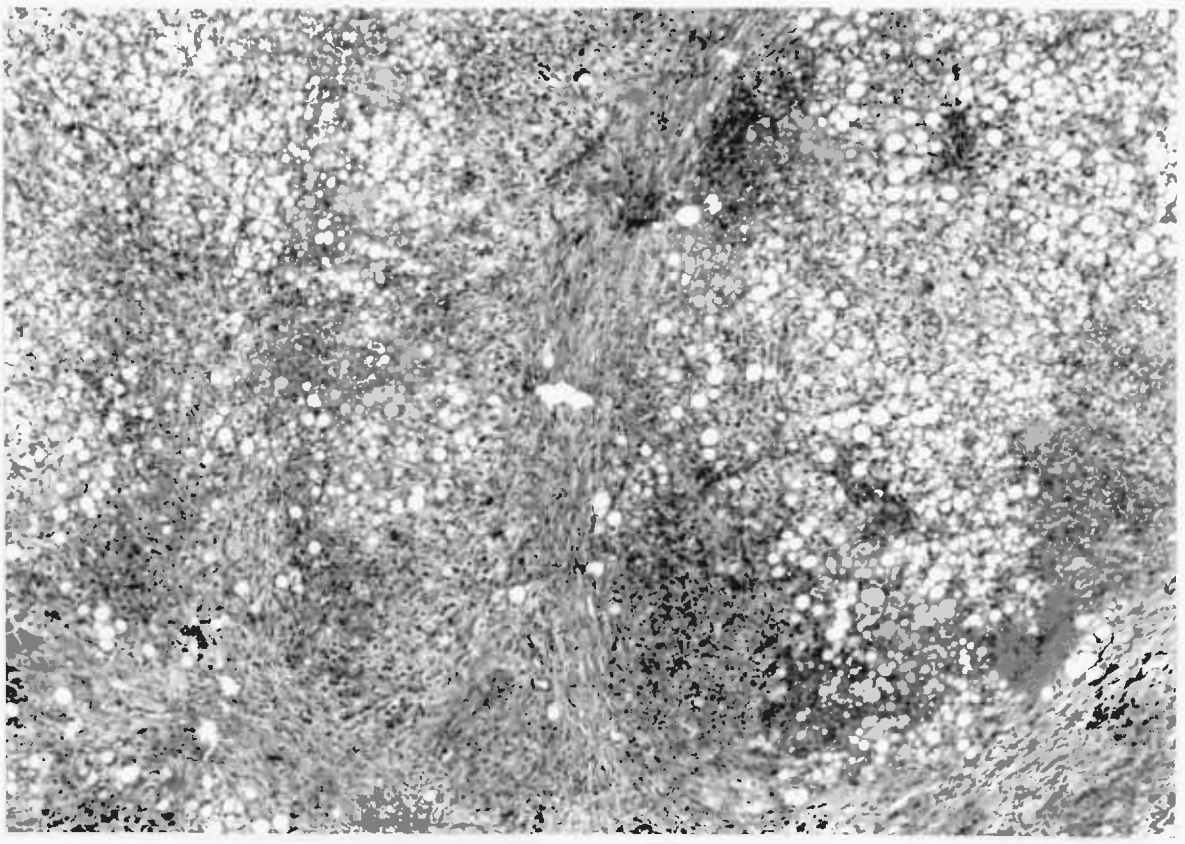
Correlation of incidence of thick cell plates and alcoholic hepatitis

Histological evidence of alcoholic hepatitis was observed in 13 biopsy specimens. These patients had consumed alcohol for periods ranging from 5 to 40 years. Mallory's hyalin was identified in 12 of the biopsy specimens showing histological evidence of hepatitis (Fig. 47). In 4 biopsy sections it was centrilobular (central hyalin necrosis) and in two of these specimens there was additional sclerosis of this region (central hyalin sclerosis). In two specimens the hyalin was observed in the periportal regions and both had evidence of cirrhosis. This is in agreement with the findings of Christoffersen and Nielsen (1972), who suggested that the occurrence of periportal hyalin in chronic alcoholics, often indicates an underlying cirrhosis.

Relatively increased numbers of thick cell plates were detected in 8 of the biopsy specimens with evidence of hepatitis. There was no difference in plate thickness ratios in the biopsy sections with evidence of hepatitis and in those without. Central hyalin sclerosis was observed infrequently in this series and only in biopsy sections showing appreciable liver cell hyperplasia , but liver cell hyperplasia was noted in many specimens with no such necrosis or sclerosis.

Figure 44. Alcoholic liver disease - the section shows extensive fatty infiltration, hepatocyte hyperplasia in areas devoid of fat and fibrous linkage. This patient had clinical evidence of portal hypertension. (H and E x 80) Ratio of single : thick cell plates = 1 : 4.4.

Figure 45. Alcoholic liver disease - reticulin impregnation of the liver biopsy specimen showing numerous hyperplastic nodules with condensation of the surrounding reticulin fibres. There is a fair degree of fatty change. The patient had consumed heavy quantities of alcohol for 15 years and had clinical evidence of portal hypertension at the time of the biopsy. (Gordon and Sweet reticulin x 80)



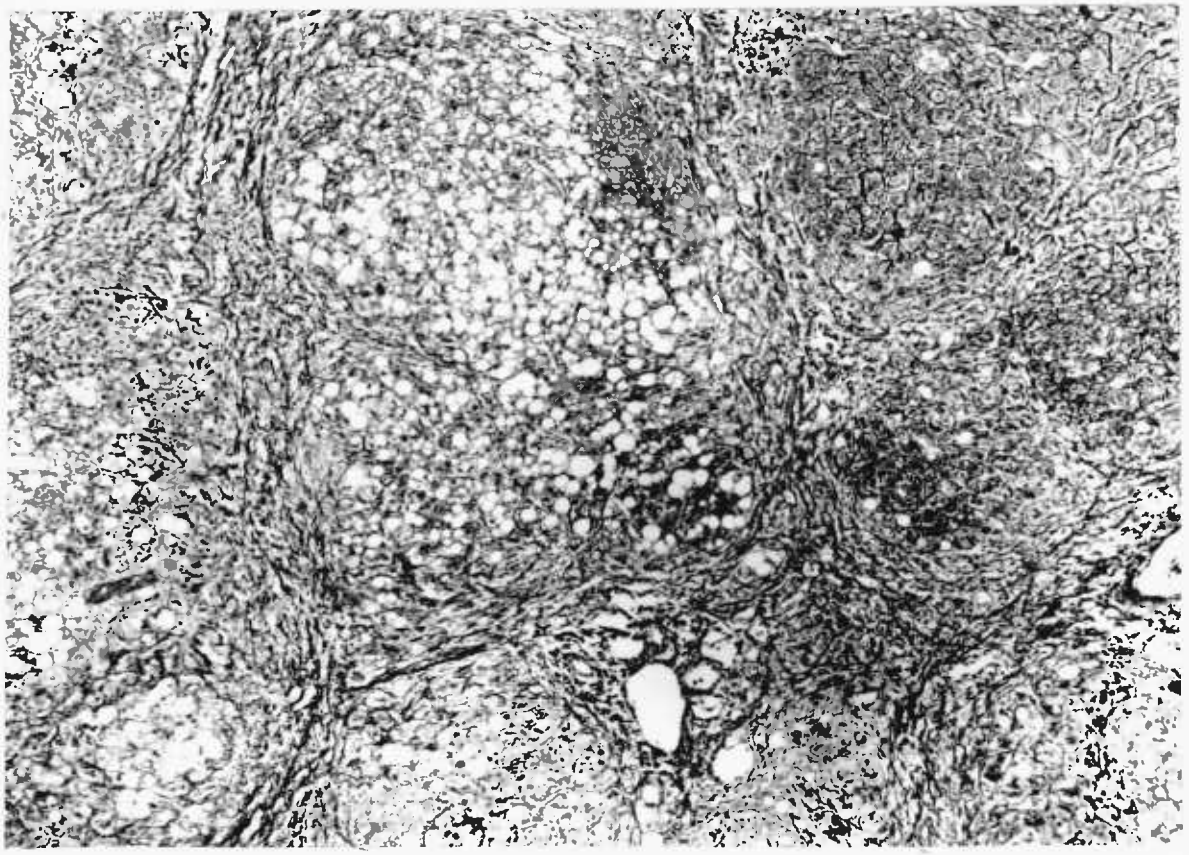
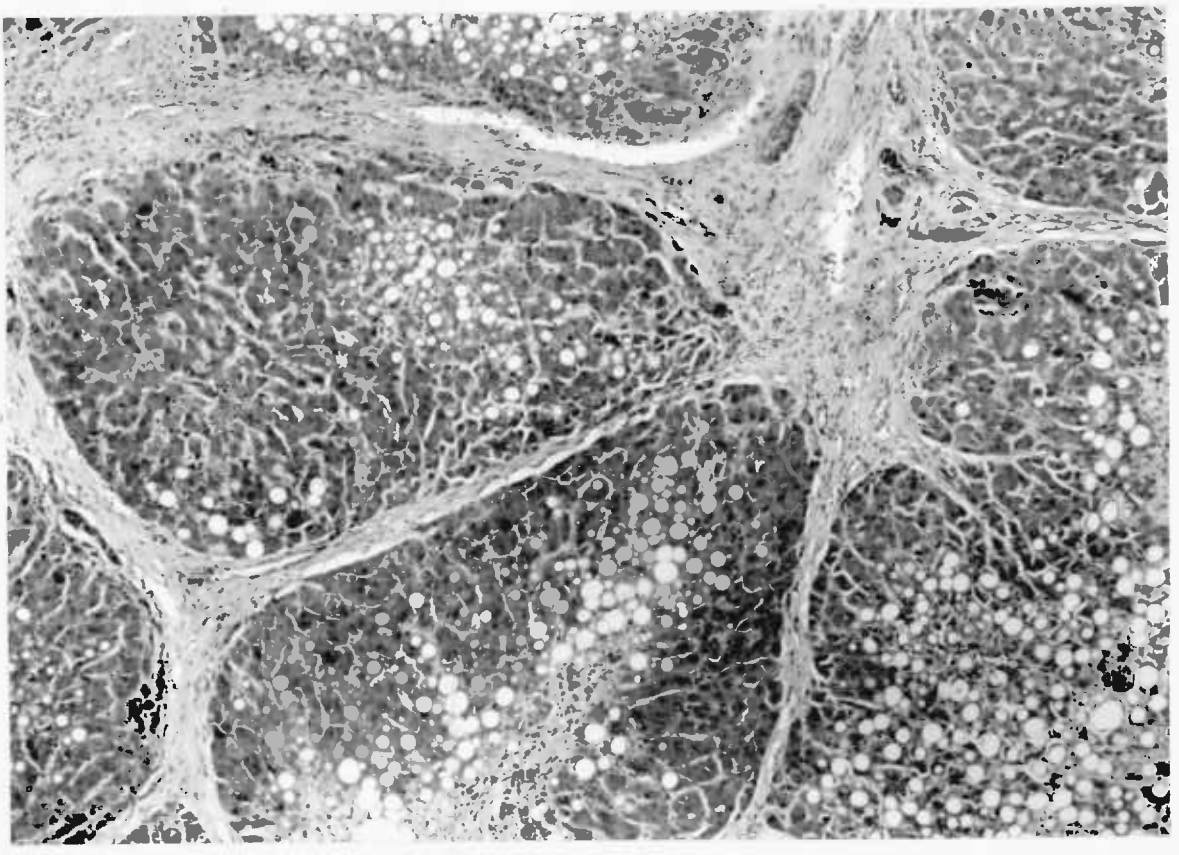


Figure 46. Alcoholic liver disease - same case as described in Figure 45, at post mortem 5 years later. The post mortem section of the liver shows a typical alcoholic micronodular cirrhosis. The presence of portal hypertension was confirmed at post mortem by the demonstration of oesophageal varices and the presence of an enlarged and overweight spleen.
(H and E x 80)

Figure 47. Alcoholic liver disease - the section shows an area of alcoholic hepatitis. There is liver cell necrosis and an inflammatory reaction containing many polymorphs. A few hepatocytes contain alcoholic hyalin (arrow) with 'satellitosis'.
(H and E x 600)



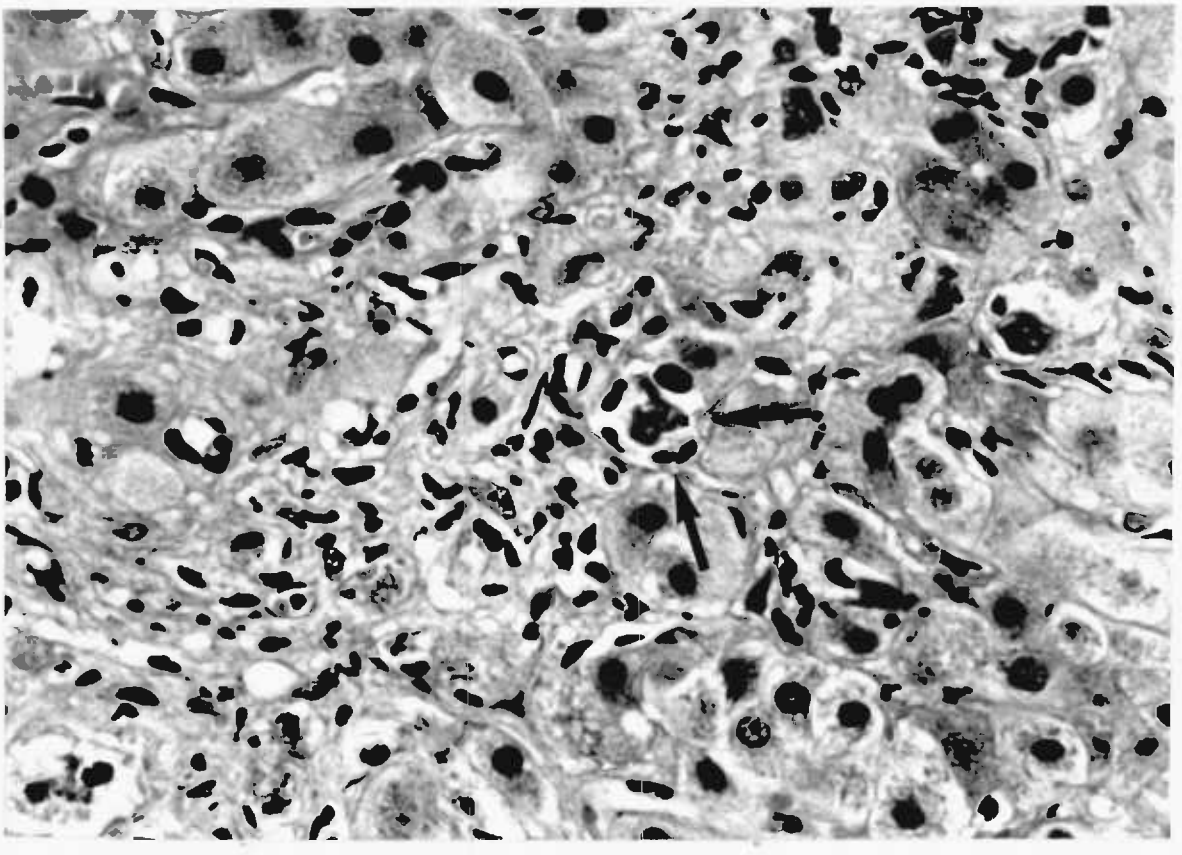
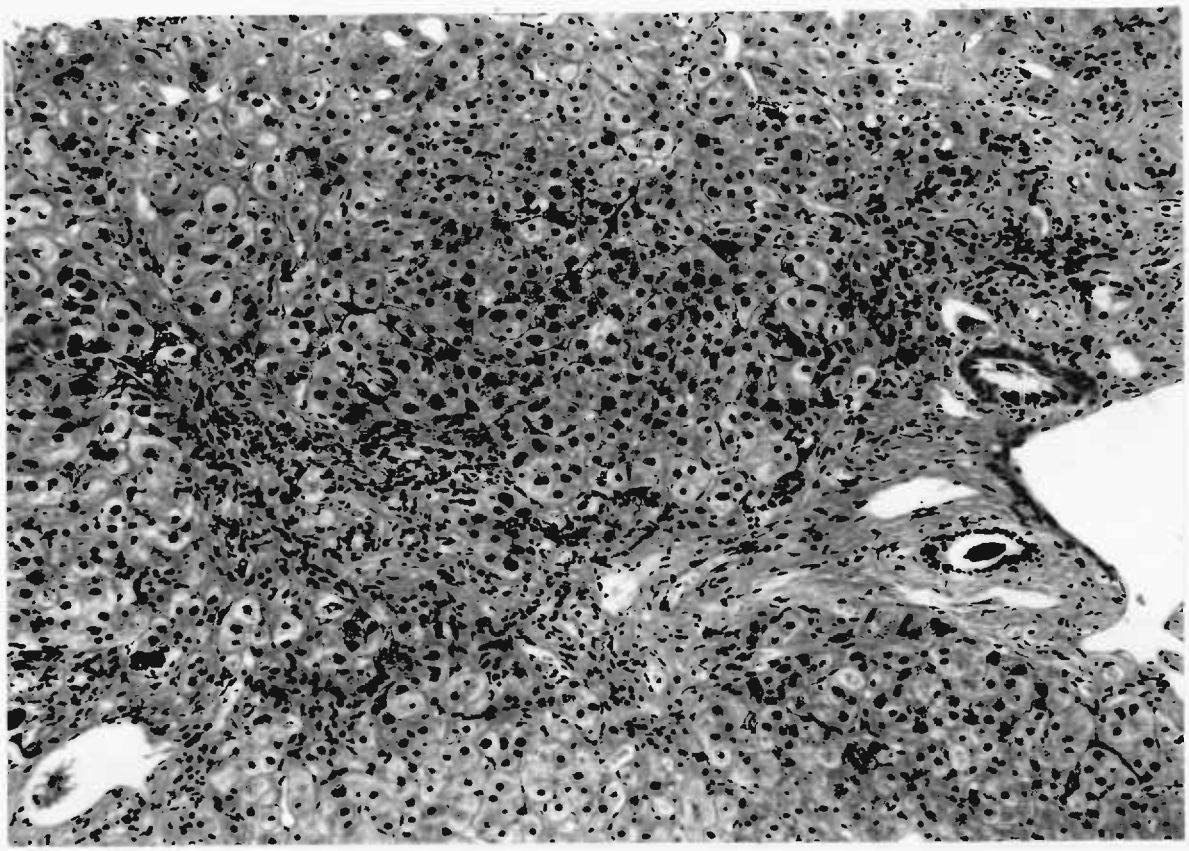


Figure 48. Alcoholic liver disease - the section shows an area of alcoholic hepatitis and fibrous linkage. The normal vascular architecture was preserved in many areas and the hepatocytes exhibit a diffuse hyperplasia. The patient had clinical evidence of portal hypertension. The ratio of single : thick cell plates = 1 : 5.5. The patient gave a history of over 20 years continuous heavy alcohol consumption.
(H and E x 150)

Figure 49. Alcoholic liver disease - an area devoid of fatty infiltration showing many hyperplastic liver cell plates (arrows). There was no clinical evidence of portal hypertension and the patient gave a history of 5 years heavy alcohol consumption. Ratio of single : thick cell plates = 5.6 : 1.
(H and E x 400)



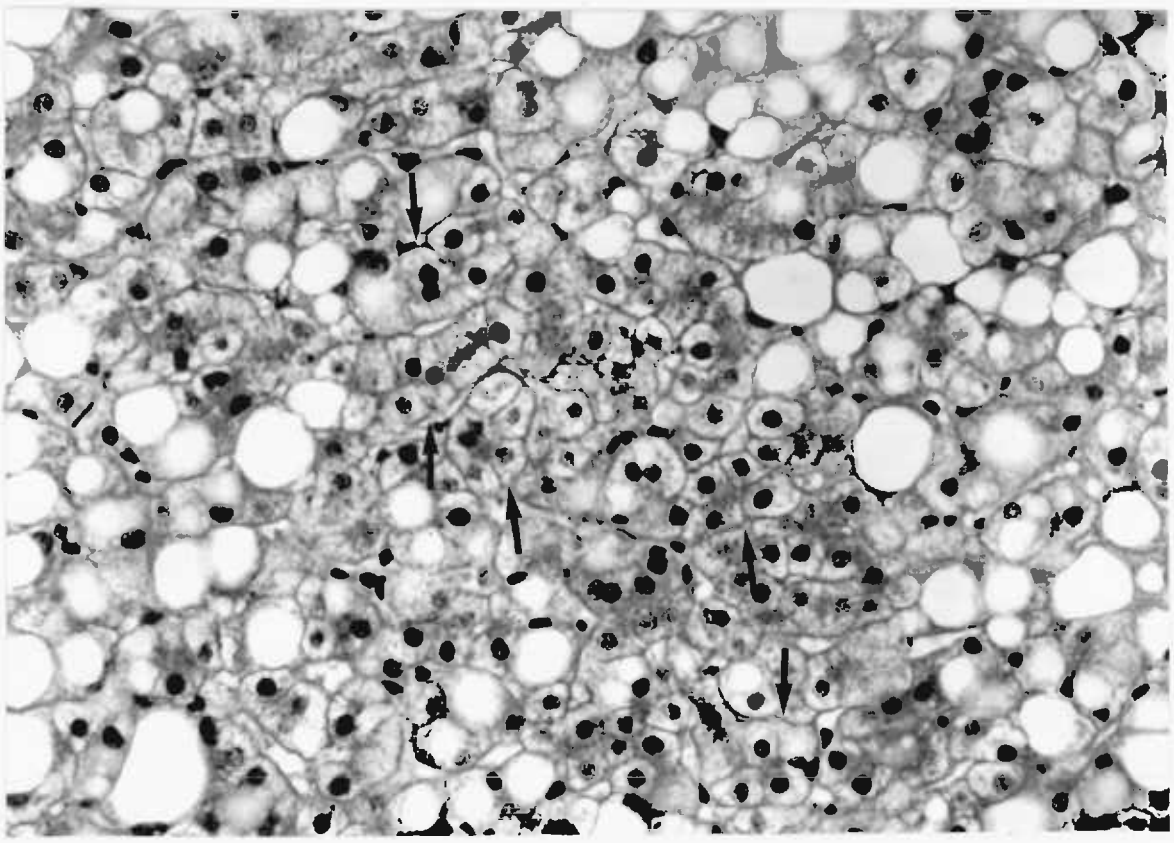
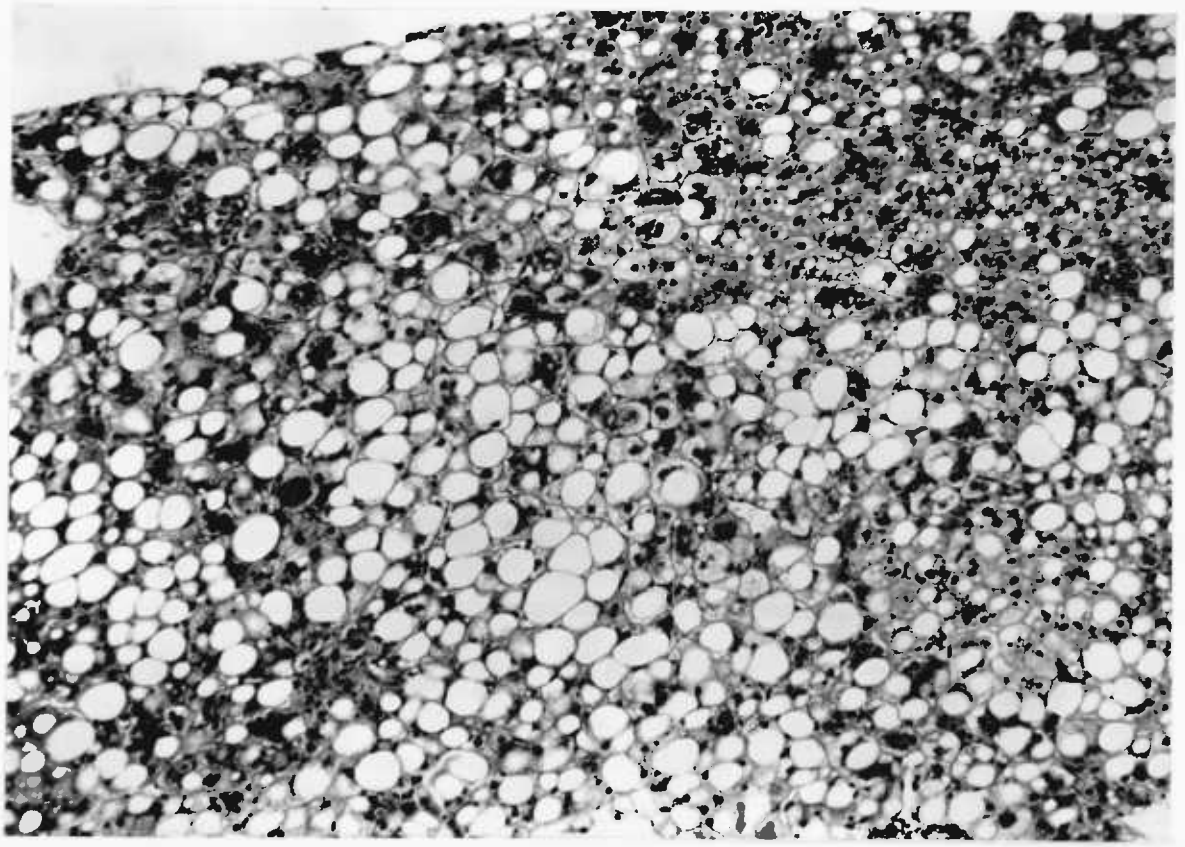
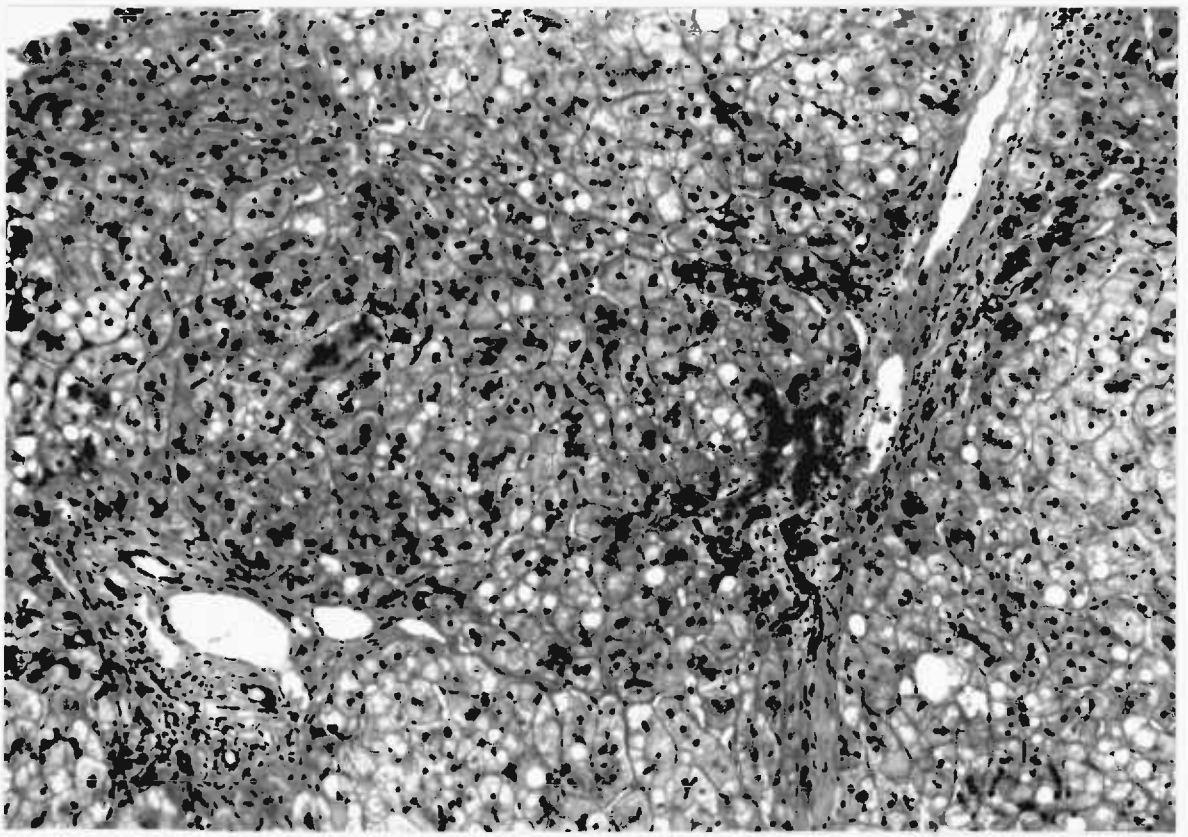


Figure 50. Alcoholic liver disease - some foci containing much fat and other foci with increased numbers of thick cell plates. This is a section of a liver which had a retained vascular pattern. There was no clinical evidence of portal hypertension. History of 10 years heavy alcohol consumption. Ratio of single : thick cell plates = 4.0 : 1
(H and E x 150)

Figure 51. Alcoholic liver disease - the section shows a diffuse hepatocyte hyperplasia and scattered fat infiltration. The patient had clinical evidence of portal hypertension. History of 20 years heavy alcohol consumption. Ratio of single : thick cell plates = 1 : 6.8
(H and E x 150)





The pathogenesis of cirrhosis in chronic alcoholics does not appear to be clear at this stage. Earlier studies, consisting of investigations in rodents, suggested that massive steatosis of the liver itself, suffices to produce cirrhosis (Chaikoff, Connor and Biskind, 1938; Connor, 1938; Hartroft and Ridout, 1951). In the last 20 years however, it became evident that excessive fat accumulation in the liver of man, even after persisting for many years, fails to proceed to cirrhosis, although it may be associated with fibrosis. For instance Kwashiorkor, even with excessive fat in the liver, is not necessarily followed by cirrhosis (Cook and Hutt, 1967).

At present, alcoholic hepatitis is considered by several workers to be a major pathway in the development of cirrhosis in chronic alcoholics (Popper and Orr, 1970); Gerber and Popper, 1972; Schaffner and Popper, 1970; Brunt, 1971; Popper and Schaffner, 1974). They suggest that the cirrhosis is characterised by 'abnormal regeneration'. The sequence postulated is that the loss or damage to the liver cells following the hepatitis may induce a compensatory response in the surviving liver cells and the healthy liver cells are thought to multiply in order to replace the necrosed cells. According to the view of Popper and Orr (1970), this regenerative phenomenon is thought to occur initially on the lobular periphery, but that it soon becomes irregular and its focal accentuation is said to form a nodule - the so-called 'regenerative nodule', which is characteristic of cirrhosis. Gerber and Popper (1972) suggest that the central hyalin necrosis and the sclerosis are pre-cirrhotic lesions, that the central fibrosis following the necrosis, gradually extends towards the inflamed portal tracts and to finally connect the hepatic veins and the portal tracts in a 'bridge' like manner. While this is a reasonable suggestion and stages can be detected which support this view, hepatocyte hyperplasia may be found in some instances in the absence of hepatitis and before the appearance of fibrosis and may not be dependent on fibrosis and distortion.

It seems clear that alcohol is hepatotoxic in man (Rubin and Lieber, 1968). It is well established also that livers chronically exposed to small doses of certain

drugs, poisons and hepatotoxins show a hypertrophy and a hyperplasia of the hepatocytes without a prior loss of functioning cells. The experimental work of Herdson, Garvin and Jennings in 1964, showed that the drug phenobarbital caused liver enlargement in the rat as a result of parenchymal cell hyperplasia. Thorpe and Walker in 1973, found that insecticides such as D.D.T. and dieldrin produce liver cell hyperplasia in mice. Recently Mays, Christopherson and Barrows (1974), found that some oral contraceptives were associated with hepatocyte hyperplasia. Sweeney and Evans (1976) describe the occurrence of hepatocyte hyperplasia following treatment with synthetic anabolic steroids.

Therefore the question which might be posed is whether it is possible that alcohol, a known hepatotoxin, could be responsible for the hepatocyte hyperplasia occurring in chronic alcoholics. The proliferation of hepatocytes in chronic alcoholics could represent a primary reaction and not a response to the loss of functioning hepatic tissue . The present findings indicate that substantial hepatocyte hyperplasia appears after about 8 years of heavy alcohol consumption (Fig. 9), and it may be that hepatomegaly may be related to hyperplasia in some instances even without steatosis.

Plate Thickness and Portal Hypertension in Chronic Liver Disease

In the present investigation, portal hypertension was diagnosed on the radiological demonstration of oesophageal varices together with the clinical evidence of splenic enlargement. The occurrence of these two features together, is strong presumptive evidence of portal hypertension (Kew, Varma, Dos Santos, Scheuer and Sherlock, 1971).

Correlation of increased relative incidence of thick cell plates and portal hypertension in primary biliary cirrhosis

Of the 22 patients in this series, 16 had evidence of portal hypertension at the time of the initial biopsy. The earliest case of portal hypertension was detected 2.7 years from the onset of the first symptom and on an average, it was observed at about 4 years from the appearance of symptoms.

All patients with evidence of portal hypertension had increased numbers of thick cell plates in their livers, the least plate ratio being 1:1.25 (single : thick cell plates), as illustrated in figures 3 and 4.

Portal hypertension with a retained vascular pattern in the biopsy specimen in patients with primary biliary cirrhosis

A retention of the normal vascular pattern was found in 12 of the 16 patients with evidence of portal hypertension. In these 12, portal hypertension appeared before distortion of the normal vascular architecture was identified (Fig. 2 and 4).

The liver biopsy specimens of all 12 patients had a relatively increased incidence of thick cell plates (Fig. 16, 23, 27, 31) and as indicated in figure 4, the ratio of single to thick cell plates lay between 1:1.25 and 1:7. In none of these sections were large hyperplastic nodules found.

Correlation of increased relative incidence of thick cell plates and portal hypertension in active chronic hepatitis

Evidence of portal hypertension was noted in 22 of the 28 patients in this series,

at the time of the initial biopsy. The earliest case recorded was 8 months after the onset of symptoms and portal hypertension was detected on average, about 3 years after the first symptom. Thus portal hypertension seems to occur earlier in active chronic hepatitis than it does in primary biliary cirrhosis if the starting point of each condition is marked by the complaining of symptoms. All patients with portal hypertension had relatively increased numbers of thick cell plates in their liver biopsy specimens and the single to thick cell plate ratio in the specimen taken nearest the time portal hypertension was detected was 1:1.5 (Fig. 7,8).

Portal hypertension with a retained vascular pattern

A retention of the normal vascular pattern sometimes incomplete, but nevertheless identifiable, was found somewhere in the specimens of 21 of the 22 patients with evidence of portal hypertension in this series (Fig. 38, 41). The biopsy specimens of all such patients had a diffuse relative increase in the numbers of thick cell plates and their single to thick cell plate ratio lay between 1:1.5 and 1:7 (Fig. 8). There were no obvious hyperplastic nodules in such biopsy specimens but these were only needle aspirations and may not have been fully representative.

Correlation of increased relative incidence of thick cell plates and portal hypertension in chronic alcoholics

Portal hypertension was thought to be present at the time of the initial biopsy in 13 of the 39 patients suffering from chronic alcoholic liver disease. The earliest case with clinical evidence of portal hypertension followed 6 years of continuous heavy alcohol intake and the majority of patients seemed to develop portal hypertension after 10 to 15 years of heavy alcohol consumption (Fig. 11). All the patients with evidence of portal hypertension had relatively increased numbers of thick cell plates in their biopsy specimens and the single to thick cell plate ratio at the time when portal hypertension was detected clinically was greater than 1:1.2 (Fig. 10,11).

Portal hypertension with a retained vascular pattern in chronic alcoholics

A retained vascular pattern could be identified in the liver biopsy specimens of 11 patients with clinical evidence of portal hypertension (Fig. 48, 51). The livers of all these patients showed a diffuse relative increase in the number of thick cell plates and their single to thick plate ratios lay between 1:1.25 and 1:7 (Fig. 11).

There was histological evidence of centrilobular hyalin sclerosis in 2 of the biopsy specimens from patients with evidence of portal hypertension. In addition, their biopsy specimens had a diffuse relative increase in the numbers of thick cell plates.

Portal Hypertension

Many hypotheses seeking to elucidate the mechanisms underlying the development of this complication have been presented. Kelty, Baggenstoss and Butt (1950) and Baggenstoss (1955) postulated that the repeated injury to the liver cells stimulated the surviving cells to regenerate which led to nodule formation - the so-called "regeneration nodules" and that these nodules were responsible for the distortion of the lobular architecture and the vascular relationships and consequently for the development of portal hypertension. Popper and Orr (1970), stated that the "regeneration nodules" in cirrhosis, interfere with drainage by the tributaries of the hepatic veins and that this produced a post-sinusoidal portal hypertension. They also found the septa to contain anastomotic channels between the vascular systems, namely the branches of the afferent portal vein and hepatic artery and the tributaries of the efferent hepatic veins. These anastomosis contributed to the impairment of the hepatic blood flow but the pressure exerted by the "regeneration nodule" is thought to be the most important factor in the production of portal hypertension in cirrhosis of the liver (Rubin and Popper, 1967; Ziegan and Massman, 1968).

These are possible mechanisms for the production of portal hypertension in a case of established cirrhosis, with distortion of the normal vascular pattern. In the present series it was observed that in many cases of chronic liver disease (primary biliary cirrhosis, active chronic hepatitis and chronic alcoholic liver disease) signs and symptoms of portal hypertension appeared when the liver biopsy specimen still contained some evidence of a retained vascular pattern. The suggested mechanisms discussed above, such as pressure on veins by nodules and excess fibrous tissue with newly formed vessels, were not identified in such biopsy specimens. There might therefore be some other factor or factors responsible for the production of portal hypertension in chronic liver disease.

Portal hypertension in primary biliary cirrhosis

Bleeding from oesophageal varices was thought to be a late and infrequent complication in primary biliary cirrhosis (Sherlock, 1959; Rubin, Schaffner and Popper, 1965). However, reports by Zeegan, Stansfeld, Dawson and Hunt (1969) and by Kew, Varma, Dos Santos, Scheuer and Sherlock (1971),

indicate that portal hypertension could be an early manifestation of primary biliary cirrhosis and indeed sometimes the initial manifestation of the disease. The liver biopsy specimens in such cases, do not always show the nodules that may be involved in the pathogenesis of portal hypertension, and in their absence the basis for the hypertension is not defined.

The present series has confirmed that portal hypertension is neither an infrequent nor always a very late manifestation of the disease. In this investigation, 16 patients in the biopsy group, had evidence of portal hypertension at the time of the initial biopsy. The majority of patients developed portal hypertension about 4 years after the appearance of symptoms (Fig. 4). Some retention of vascular pattern was observed in 12 of the 16 patients with evidence of portal hypertension.

Hoffbauerin 1960, postulated that the small vessels in the portal tracts may be obliterated in the same manner as happens to the bile ducts and that this may be the pathogenesis of portal hypertension in primary biliary cirrhosis. No difference in the number of vessels- venous and arterioles in the portal tracts of patients with and without portal hypertension has been found (Kew et al, 1971) and although counts were not made, no differences were noted in this respect in the present series.

Zeegen and co-workers (1969) suggested that the portal hypertension in primary biliary cirrhosis, in the absence of nodular regeneration, could be pre-sinusoidal due to the resistence produced by the portal tract lesions. However in neither the present series nor in published reports of biopsy and post mortem cases has a gross difference been found in the amount of portal fibrosis or other factors such as cellular infiltration, or lymphoid aggregates in the portal tracts in patients with and without portal hypertension. There was also no Kupffer cell hypertrophy or hyperplasia or significant mononuclear cell infiltration which may have caused an obstruction at a sinusoidal level.

The findings in the present series indicates, that there is a significant relative increase in the numbers of thick cell plates in the livers of patients with evidence

of portal hypertension, as compared with those patients without portal hypertension. A morphometric analysis of the biopsies, reveals that all specimens with a plate ratio of less than 1:1.25 (single : double), are associated with portal hypertension (Fig. 4).

Portal hypertension in active chronic hepatitis

Portal hypertension in patients suffering from active chronic hepatitis is described as a late manifestation and it has been suggested that this occurs as a result of the distortion of the architecture and due to the pressure exerted by the nodules. (Sherlock, 1974; Mistilis et al, 1968). However, the present findings indicate that in active chronic hepatitis portal hypertension might be found early before the usual structural changes of cirrhosis are found.

In the present series evidence of portal hypertension was found in 22 patients. In the biopsy specimens of 21 of these patients a normal vascular pattern was noted in at least part of the specimen.

As was observed in primary biliary cirrhosis, there appeared no difference in the number of vessels in the portal tracts of patients with and without portal hypertension, although no counts were made. No difference was observed in the amount of fibrosis or cellular infiltration in the portal tracts of patients with and without portal hypertension. There was no regular Kupffer cell hyperplasia or an excess cellular infiltration which may have caused an obstruction at a sinusoidal level.

The biopsy specimens of all patients with evidence of portal hypertension showed a diffuse relative increase in the number of thick cell plates. Portal hypertension was reported in patients whose liver biopsy specimens showed a plate ratio of less than 1:1.5 (single : thick). Hepatocyte hyperplasia can therefore be correlated with portal hypertension, although the exact mechanism is not clear.

Portal hypertension in chronic alcoholic liver disease

It was thought that portal hypertension in alcoholics was always a late manifestation

and appeared at the stage of cirrhosis, associated with the destruction of the normal vascular architecture and due to the pressure exerted by the nodules (Baggenstoss, 1955). He found portal hypertension to be much commoner in alcoholic cirrhosis, when compared to other types of cirrhosis. According to his view, the nodules in alcoholic cirrhosis are smaller, more numerous and better developed and consequently, the vascular pattern is much more disturbed.

In 1969, Reynolds, Hidemura, Michel and Peters, reported that portal hypertension could at times be an early manifestation of alcoholic liver disease. Microscopically they found pronounced collagen deposition predominantly in centrolobular regions and no "regenerative nodules" were identified. They termed this entity "centrilobular hyalin sclerosis". The sclerosis was thought to follow the initial "centrilobular hyalin necrosis". According to their view the collagen was deposited in the area of injury filling the central sinusoids and thus obliterating the central veins. This was thought to be the mechanism by which portal hypertension is produced in early cases of alcoholic liver disease.

Centrilobular hyalin sclerosis did not appear to be a common feature in the present series. Centrilobular hyalin necrosis was detected in 4 biopsy specimens and centrilobular sclerosis was observed in 2 specimens, both of which had evidence of portal hypertension. Brunt, Kew, Scheuer and Sherlock (1974) too, in their study on alcoholic liver disease, did not find portal hypertension to be more common in those with central hyaline necrosis or sclerosis.

In the present investigation, 13 patients had evidence of portal hypertension, while 24 did not. Some retention of the normal vascular pattern was found in the biopsy specimens of 11 patients with evidence of portal hypertension. Centrilobular hyaline sclerosis was seen in two.

As observed in cases of primary biliary cirrhosis and active chronic hepatitis, there appeared to be no difference in the number of vessels or in the amount of fibrosis or cellular infiltration in the portal tracts in the livers of patients with and without portal hypertension. Kuppfer cell hyperplasia was not a significant

feature. An excess cellular infiltration was not apparent in the sinusoids.

It was however found that all patients (chronic alcoholics) with clinical evidence of portal hypertension, including the two with centrilobular sclerosis, had a diffuse increase in the numbers of thick cell plates. On morphometric analysis portal hypertension seemed to be present when the plate ratio was 1:1.2 (single : thick cell plates) or less. Thus in chronic alcoholic liver disease in the absence of "regenerative nodules" and centrilobular hyalin sclerosis, the occurrence of portal hypertension seemed to correlate best with relatively increased numbers of thick cell plates.

It is therefore evident that portal hypertension sometimes occurs in patients with chronic liver disease even when a normal vascular pattern can be detected. The biopsy specimens of such patients exhibit diffuse relative increase in the numbers of thick cell plates and morphometry indicates a plate ratio of 1:1.2 (single : thick cell plates) or less.

If it can be taken that the changed ratio represents hyperplasia, the progression of non-hyperplastic to hyperplastic tissue during the course of these conditions may be associated in some way with portal hypertension. Also hyperplasia appears to be associated with chronicity.

An alternative postulate might be that in fact there are two main types of chronic liver disease in each category, one without hyperplasia and with no portal hypertension and the other showing hyperplastic changes. The evidence against this view is found in the group of cirrhotic patients, in whom previous biopsy specimens were available. The transition in this group from normal to hyperplastic plates confirms the impression of progression derived from the time studies and other correlations.

SUMMARY

The patterns of hepatic parenchymal cell plate arrangements have been investigated in normal adult livers and in the chronic liver diseases - chronic persistent hepatitis, primary biliary cirrhosis, active chronic hepatitis, alcoholic liver disease and cirrhosis. The material consisted of biopsy and post mortem specimens received by the Department of Histopathology, Royal Postgraduate Medical School, London.

A point counting method was used and the numbers of hits over thickened plates were compared with the numbers of hits over single cell thick plates. The findings confirm that a normal adult liver is composed of predominantly one cell thick hepatocyte plates and morphometric analysis reveals a mean plate ratio of 27 : 1 (single cell plates : thick cell plates) S.D. $\pm$ 1.3.

The ratio was altered in favour of thickened plates in cirrhosis (1 : 8 single cell plates : thick cell plates).

The biopsy specimens of patients diagnosed as suffering from chronic persistent hepatitis did not show a change in ratio from normal.

Primary biliary cirrhosis

A relative increase in the numbers of thick cell plates is observed in a majority of the biopsy specimens about 3 years from the onset of the initial symptoms. This trend progresses until a ratio close to that found in cirrhosis is reached at about 6.5 years from the onset of the initial symptoms.

No direct association of relative increase in thick plates was found with parenchymal fibrosis, thick cell plates occurring in specimens showing major and minor fibrosis. Intra- lobular fibrosis was almost always associated with relatively increased numbers of thick cell plates. It seems that the liver cell plates thicken before the fibrosis develops as increased numbers of thick cell

plates were identified in the biopsy specimen of the asymptomatic patient in which no fibrosis was found. The findings indicate that hepatocyte hyperplasia becomes apparent before distortion of the vascular architecture is recognised.

Active chronic hepatitis

Hepatocyte hyperplasia appears to be an early and a constant feature in this disease. The liver plates are wider than are cell thick even in biopsies taken shortly after the development of the clinical symptoms. A generalised relative increase in numbers of thick cell plates is observed after about one year. A ratio similar to that found in cirrhosis is reached in most patients about 4.5 years from the appearance of the initial symptoms.

No association could be found with intra-lobular fibrosis. Varying amounts of fibrous tissue was present in all biopsy specimens examined, together with the hepatocyte hyperplasia and thus it was impossible to observe if the liver cell hyperplasia preceded the fibrosis.

Similarly, varying degrees of damage to the limiting plate was detected in all the biopsy specimens studied.

It appears from the observations made in this investigation, that the hepatocyte hyperplasia occurs before the distortion of the vascular pattern.

Alcoholic liver disease

Hepatocyte hyperplasia seems to be a late feature in chronic alcoholics. The incidence of thick cell plates is seen to increase with the duration of alcohol consumption, though not to the same extent in all patients. A generalised relative increase in numbers of thick cell plates is observed following about 8 years of continuous heavy alcohol consumption and a ratio approaching that found in cirrhosis is reached in some patients after 10 to 15 years of continuous heavy alcohol intake.

There was no direct correlation between the incidence of thick cell plates and steatosis, hyperplastic plates being found in biopsy specimens devoid of fat. Hyperplastic plates were detected in the absence of intra-lobular fibrosis. No relationship was found with alcoholic hepatitis, as evidence of hyperplasia was found in its absence, but fibrous linkage was always associated with a considerable amount of hyperplasia.

Popper and Orr (1970) and Mistilis and Blackburn (1970) suggest that in chronic liver disease, the inflammatory process in the portal tracts and/or in the parenchyma, destroy the liver cells nearby and that this loss of cells induces a compensatory response in the remaining healthy liver cells. Therefore the appearance of thick cell plates in chronic liver disease is thought to be a regenerative phenomenon.

In alcoholic liver disease, the necrosis of liver cells, as a result of the alcoholic hepatitis, is considered by many (Popper and Orr, 1970; Gerber and Popper, 1972; Scheuer, 1973; Brunt, 1971) to be the main stimulus responsible for the hepatocyte proliferation - again a regenerative process.

Although it is difficult to quantitate exactly, in the present series hepatic parenchymal cell hyperplasia as seen by the appearance of increased numbers of thick cell plates does not seem to be related to the degree of cellular destruction, but this of course cannot take into account previous unsuspected episodes of substantial cell loss.

The evidence suggests that the hepatocyte hyperplasia may possibly be a primary proliferative response and not necessarily secondary to the loss of functioning liver cells.

Thus it would be more appropriate to refer to the nodules of thickened liver cell plates found frequently in chronic liver disease as hyperplastic nodules and not regenerative nodules and this is now sometimes incorporated into reports and papers (Liver Cancer - W.H.O. report, International Agency for research on Cancer, 1971).

Hepatocyte hyperplasia and portal hypertension

None of the patients with chronic persistent hepatitis showed clinical or radiological evidence of portal hypertension at any stage in the course of the disease.

A majority of the patients with histological evidence of cirrhosis (lost vascular pattern), irrespective of its cause, had evidence of portal hypertension, which was confirmed in those that came to post mortem.

The occurrence of portal hypertension in chronic liver disease is attributed to the distortion of the normal vascular architecture due to the presence of excess fibrous tissue and hyperplastic nodules (Kelty, Baggenstoss and Butt, 1950; Baggenstoss, 1955; Popper and Orr, 1970). The hyperplastic nodules are thought to exert pressure and to inferfere with the drainage by the tributaries of the hepatic veins thus producing a post-sinusoidal block and a subsequent rise of pressure in the portal veins. But it is apparent from the present findings that portal hypertension could be found in patients with chronic liver disease such as primary biliary cirrhosis, active chronic hepatitis and chronic alcoholic liver disease in whose liver biopsy specimens a retained vascular pattern could still be identified. Many of these biopsy specimens do not contain excess fibrous tissue or distorted parenchymal nodules. Thus there may be another mechanism by which portal hypertension is produced in chronic liver disease. The liver biopsy specimens of all patients diagnosed as suffering from a chronic liver disease with evidence of portal hypertension had one common feature - diffuse parenchymal cell hyperplasia.

It is possible therefore that hepatocyte hyperplasia may in some way be a factor in the development of portal hypertension. The precise mechanism is difficult to define and at this stage it is not clear if a mechanical effect (occlusion of sinusoids) is operative or much more complex sequences relating perhaps to the rate of perfusion or intra-lobular haemocentration or to other unknown phenomena (Rappaport, 1973).

APPENDIX

SET 1

27 years of patients dead with cirrhosis (1948 - 1974).

Total deaths during this period 10,650.

Number of patients with cirrhosis 168.

Definite diagnosis at post mortem

Alcoholic cirrhosis	50
Active chronic hepatitis	13
Cryptogenic cirrhosis	69
Primary biliary cirrhosis	11
Viral hepatitis	20
Haemachromatosis	2
Secondary biliary	2
Neonatal hepatitis	1

42 of the cirrhotics had liver biopsies performed during life.

Cirrhotics with previous biopsies

Active chronic hepatitis	11
Alcoholics	9
Cryptogenic cirrhosis	13
Primary biliary cirrhosis	7
Haemachromatosis	1
Secondary biliary	1

SET 2

Primary biliary cirrhosis

Number of patients			22
Number of females	17	Aged 31 to 72.	Mean age 49.7 years
Number of males	5	Aged 49 to 58.	Mean age 55.4 years
Number of biopsy specimens			35
Wedge resections			19
Aspirations			16
Patients with more than one biopsy specimen			8
Patients coming to post mortem			5
Patients in whom extra-hepatic obstruction was excluded at laparotomy or atpost mortem			19
Patients with features of both active chronic hepatitis and primary biliary cirrhosis			2
Patients treated at Hammersmith hospital			16
Patients in other institutions			6
Specimens in which a retained vascular pattern could be detected			28
Specimens with totally lost vascular pattern			6
Patients with portal hypertension			16
Patients with portal hypertension and some evidence of a retained pattern			12

Microscopy

Portal tracts	Number of biopsy specimens
Oedema	32
Granulomata	
With epithelioid cells only	16
With giant cells also	4
Lymphoid follicles	17
Germinal centres	1
Pseudo-duct formation	7

Portal fibrosis	28
Erosion of limiting plate (minimal in most)	13
Portal veins were patent in all the biopsy specimens	
Thickening of arteriolar walls	none

Parenchyma	Number of biopsy specimens
Granulomata	6
Bile pigment precipitate (cholestasis)	2
Kupffer cell hyperplasia	5
Fibrous linkage	8
Short fibrous septa	9
Sinusoids were patent, except in areas with thickened hepatocyte plates, where it appeared narrow.	
Patients tested for mitochondrial antibodies	6
Patients positive for mitochondrial antibodies	6
Lymphocytes were the dominant cell type in the portal tracts.	

Clinical data

Patients presenting with pruritus	16
Patients presenting with jaundice	4
Patients presenting with signs and symptoms of cirrhosis	1
Asymptomatic patients	1
Patients with a family history of primary biliary cirrhosis	1
Longest survival is 12 years from date of diagnosis.	
No differences were noted in the number of vessels - venous and arterioles in the portal tracts of patients with and without portal hypertension.	

Active chronic hepatitis

Number of patients	28
21 females, aged 16 to 67 years. Mean age	39.4 years
7 males, aged 8 to 54 years. Mean age	31.1 years
Number of biopsy specimens	39
Aspirations	39
Wedge resections	none
Patients with serial biopsy specimens	9
Patients coming to post mortem	none
Patients with portal hypertension	22
Patients with portal hypertension and some evidence of a retained vascular pattern in the biopsy specimen	21

Clinical data

Patients with an acute onset	12
Patients with an insidious onset	16
Jaundice was the commonest presenting feature	
Patients with multisystem involvement	7

Biochemical data

Patients with hepatitis associated antigen in their sera (HB-Ag +ve)	4
Patients in whom antibody tests were done	7
Patients positive for smooth muscle antibody	7
Patients positive for mitochondrial antibody	1
Patients with positive antinuclear factor	5
Patients with L.E. cells	6
None of the above antibodies were detected in patients with positive Australia antigenaemia	

Microscopy

Portal tracts	Number of biopsy specimens
Oedema	39

Fibrosis	20
Inflammation	
Heavy	31
Moderate	8
Bild duct proliferation	9
Lymphoid follicles and germinal centres	none
Granulomas	none
Erosion of the limiting plate	39
Thickening of arteriolar walls	none

Portal veins appeared patent in all the biopsy specimens.

Parenchyma

Cholestasis	none
Kupffer cell hyperplasia	5
Fibrous linkage	26
Short fibrous septa	13
Acidophil bodies	6
Fatty change	none
Focal parenchymal necrosis (spotty necrosis)	16
Ground glass cells	none
Swelling or 'balooning' of cells	25
Pseudoglands or 'rosettes'	10

The predominant cell in the inflammatory reaction is the plasma cell.

There was no visible obliteration of hepatic venous radicles in biopsy specimens with a retained pattern, Kupffer cell hyperplasia was not a prominent feature. No significant difference was observed in the amount of fibrosis or cellular infiltration in the portal tracts of patients with and without portal hypertension. There appeared no difference in the number of vessels - venous and arterioles in the portal tracts of patients with and without portal hypertension.

Alcoholic liver disease

Number of patients				37
Sex	Males	26	aged 28 to 65 years. Mean age	46.4 years
	Females	11	aged 34 to 72 years. Mean age	56.3 years
Number of biopsy specimens				39
Aspirations				38
Wedge resections				1
Patients with serial biopsy specimens				2
Patients coming to post mortem				none
Biopsy specimens in which a retained pattern could be identified				26
Biopsy specimens with a total loss of pattern				13
Patients with portal hypertension and evidence of some retention of pattern in the biopsy specimen				11

Microscopy

Portal tracts	Biopsy specimens
Fibrosis	14
Inflammation	
Mild	20
Heavy	19
Mixed infiltrate consisting chiefly of mononuclear cells, neutrophils and histiocytes.	
Bile duct proliferation	8
Erosion of limiting plate	6
Thickening of arteriolar walls	none
Portal veins appeared patent in all the biopsy specimens	

Parenchyma

Cholestasis	none
Kupffer cell hyperplasia	4
Fatty change. Nil	2
Mild	18

Alcoholic hepatitis	13
Mallory's hyalin	
Centrilobular and scattered	10
Periportal	2
Lipogranulomata	1
Fibrous linkage	6
Megamitochondria	2
Haemasiderosis	22
Grade 1	14
Grade 2	6
Grade 3	2
Centrilobular hyalin necrosis	4
Centrilobular hyalin sclerosis	2
Centrilobular sclerosis and portal hypertension	2

Clinical data

Duration of alcohol consumption	Number of patients
Over 20 years	5
Between 10 to 20 years	9
Between 5 to 10 years	20
Between 1 to 5 years	3

Most patients were found to have an enlarged liver or a disturbance of the liver function tests during routine medical examination, or during investigation for some other unrelated complaint. A few presented with jaundice, while others sought medical attention for abdominal pain.

There was no visible obliteration of the hepatic venous radicles in the biopsy specimens with a retained vascular pattern. Kupffer cell hyperplasia was not a prominent feature. No significant difference was observed in the amount of fibrosis or cellular infiltration in the portal tracts of patients with and without portal hypertension. There appeared no difference in the number of vessels in the portal tracts of patients with and without portal hypertension.

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