A New Look at Cirrhosis

T.W. WARNES, MD, FRCP

Consultant Physician, University Department of Gastroenterology and Physician in Charge, Liver Clinic, Manchester Royal Infirmary

Cirrhosis of the liver comprises nodular parenchymal regeneration, diffuse fibrosis and disorganisation of the lobular architecture, with connective tissue bands uniting central lobular zones with the portal tracts. Cellular necrosis is present at some stage of the disease and all parts of the liver are involved, although not every lobule is necessarily affected. The necrosis is followed by bridging fibrosis in which fibrous tissue septa bridge the portal tracts and central veins. New blood-vessels then grow into the fibrous septa so that afferent blood from the portal veins and the hepatic artery is shunted to efferent tributaries of the hepatic veins without coming into adequate contact with the hepatocytes[1]. About one-third of the total blood flow perfusing the cirrhotic liver may by-pass sinusoids, and hence functioning liver tissue, through these channels.

At an ultrastructural level, another fundamental problem becomes evident. The space of Disse or hepatic perisinusoidal space separates the sinusoidal lining cells from the plasma membrane of the hepatocytes. Normally, plasma has free access to this space because of gaps in the sinusoidal lining cells that rest directly on the microvilli of the hepatocytes without an intervening basement membrane. This open circulation facilitates rapid interchange of material between the blood and the hepatocytes. In cirrhosis, however, the sinusoid appears as a typical capillary surrounded by a continuous basement membrane[2]. The cirrhotic cell becomes starved of essential nutrients due partly to the shunting of blood away from the sinusoids and partly to the capillarisation of the hepatic sinusoids, with loss of the normal gaps in the sinusoidal lining cells. The access of blood and its constituents such as bilirubin to the hepatocytes is further limited by the deposition of collagen fibres laid down in the Disse space[2].

These factors contribute to the development of jaundice in some patients with cirrhosis[3], but various types of cirrhosis may produce different functional defects. In alcoholic liver disease centrizonal damage is usually a prominent feature and may be associated with elevated levels of serum glutamate dehydrogenase[4]. In chronic active hepatitis, active hepatocellular necrosis is associated with high serum transaminase levels, while in primary biliary cirrhosis damage to the intrahepatic bile ducts produces cholestasis which is reflected in elevated levels of serum alkaline phosphatase (ALP) of 'liver' type[5]. All forms of cirrhosis are associated with retention of intestinal ALP in serum[6], probably due to damage to glycoprotein receptors on the cell membrane of the hepatocyte, which results in an interruption of the enterohepatic circulation[7] of this isoenzyme. Static tests on serum can therefore provide some diagnostic information in the cirrhotic patient. Also available are dynamic tests which may indicate the nature and degree of the functional deficit in different types of cirrhosis. These include studies of bromsulphthalein (BSP) kinetics[8] and the galactose tolerance test[9]; the latter is largely independent of hepatic blood flow and provides an estimate of functional liver cell mass.

The development of portal hypertension is due in part to the pressure of regenerating nodules on the hepatic venous outflow tract, as can be demonstrated by the vinylite injection-corrosion method[10]; in alcoholic liver disease it is also related to the deposition of collagen in the Disse space[11]. The presence of portal hypertension can be most conveniently demonstrated by measurement of the wedged hepatic vein pressure; while the correlation with bleeding from varices is not absolute, this relatively simple technique, which is free from serious complications, can be used to follow the course of the disease and the effects of treatment. The development of portal hypertension should be seen as a dynamic process that is potentially reversible, either spontaneously or as a result of conventional medical treatment of alcoholic hepatitis and also established cirrhosis[12, 13]. Propranolol has recently been shown to decrease the gradient between the wedged and the free hepatic vein pressures in cirrhosis and this drug may be used in preventing recurrent bleeding due to ruptured varices in patients with portal hypertension[14]. Techniques are also available for sclerosing oesophageal varices, either by the transhepatic [15, 16] or the oesophageal route. Sclerosis using the rigid Negus oesophagoscope[17, 18] requires a general anaesthetic. Recently, an injection needle has been designed for use with the flexible fibre-optic endoscopes but it is not yet clear whether a rigid outer tube should also be employed in order to achieve compression of the varices[19]. If so, this technique also has the disadvantage of requiring a general anaesthetic. Some workers do not use compression and therefore avoid this problem[20]. Promising results have been obtained with both approaches, and it appears that there has been a decline in the number of patients with portal hypertension who require surgery.

Epidemiology

Both the incidence and the mortality rate of cirrhosis in England and Wales have been rising over the past decade. In a recent study from Birmingham[21], cirrhosis was found to account for about 0.3 per cent of all admissions to hospital. The annual incidence increased from 5.6/100,000 in 1959 to a peak of 15.3/100,000 in 1974 and then fell slightly. This increase was attributable to alcoholic cirrhosis, the incidence of all other forms remaining fairly stable. Comparable results have been obtained in the North Western Region[22], where the average incidence of alcoholic cirrhosis from 1976 to 1980 was 8.9/100,000. It rose from 6.4/100,000 in 1976 to 10.5/100,000 in 1980. The male:female ratio decreased from 3.1 in 1976 to 2.3 in 1980, due to the increasing incidence of female cirrhotics. In Scotland, in contrast, the incidence of alcoholic cirrhosis appears to be higher, and an overall annual incidence of 14.6 per 100,000 has recently been reported from Tayside[23].

Aetiology

A vast number of disorders can be associated with cirrhosis; the common causes are shown in Table 1.

Table 1. The commoner causes of cirrhosis.

Alcohol	
Virus hepatitis	
Autoimmune	chronic active hepatitis
	primary biliary cirrhosis
Toxins, drugs	
Metabolic	haemachromatosis
	Wilson's disease
	alpha-1 antitrypsin deficiency
Cryptogenic	
Other	

Alcohol is generally thought to be the most common cause of cirrhosis in the USA and the UK, but is a much less important factor in most parts of Africa and Asia. Conversely, cirrhosis due to infection with hepatitis B virus is common in Africa and many parts of Asia but rare in the UK.

A wide variety of other disorders can cause cirrhosis, for example prolonged obstruction of bile flow or hepatic venous return. Indian childhood cirrhosis has been selected for discussion, since a recent histological finding has suggested the possibility of a new form of treatment, as well as childhood cirrhosis due to biliary atresia, to illustrate the theme that cirrhosis may be partly reversible.

Alcoholic Cirrhosis

The total contribution of alcoholic liver disease to the cirrhosis burden in this country is controversial, but it is likely that less than 30 per cent of alcoholics develop cirrhosis[24]; there are a number of possible explanations for this. Immunological mechanisms may be involved in the perpetuation of hepatic damage produced by alcohol[25, 26]. An abnormally high frequency of HLA-B8 was initially reported in alcoholics with cirrhosis[27]. However, a recent study from Norway has shown an association between HLA-BW40 and alcoholic cirrhosis[28], and another study from Chile an increased frequency of HLA-B13[29]. The evidence in relation to tissue-typing is clearly contradictory. In addition to individual variations in susceptibility to alcohol, it is possible that the latter can act synergistically with other noxa, such as infection with hepatitis B virus[30], to produce cirrhosis.

There is no doubt that alcoholic hepatitis is a potentially pre-cirrhotic lesion. In serial biopsies Galambos has shown that 38 per cent of patients with alcoholic hepatitis develop cirrhosis[31], but survival is dramatically improved by the discontinuation or reduction of alcohol consumption[32]. There is some evidence of a beneficial effect of corticosteroid treatment on immediate mortality in encephalopathic patients with severe alcoholic hepatitis[33], but no evidence that steroids, or any other drug, diminish the tendency of alcoholic hepatitis to progress to cirrhosis.

In established alcoholic cirrhosis, abstension from alcohol significantly improves survival[34].

Virus Hepatitis

Both viral hepatitis and chronic active hepatitis (which can be virus-induced) may progress to cirrhosis, but it is not clear how often this sequence of events occurs. Over the past few years, the introduction of new techniques for detection of hepatitis A and B viruses in blood has helped clarify this problem, as has the recent discovery of non-A, non-B hepatitis (a form of virus hepatitis not due to hepatitis A or B, cytomegalovirus or the Epstein-Barr virus). It is now apparent that there is no chronic carrier state for type A hepatitis; the virus is invariably eradicated and is not therefore a cause of chronic hepatitis or cirrhosis.

The incidence of carriers of hepatitis B virus varies enormously from country to country. The carrier rate in the UK is the lowest in the world, estimates varying from 0.03 to 0.1 per cent of the population. In the USA it is between 0.1 and 0.3 per cent, but rises to 10-15 per cent in parts of Asia and Africa[35].

The major route of hepatitis B transmission in most parts of the world is by vertical transmission from mother to baby—contamination with the mother's blood probably occurs during passage through the birth canal. Major racial differences in susceptibility to transmission of the B virus by this route exist[36], and may underlie the differing incidence of hepatitis B carriage in different countries.

Type B hepatitis accounts for about 20 per cent of cases of sporadic hepatitis in this country. Following an attack of acute type B, between 5 and 10 per cent of individuals fail to eradicate the virus and become chronic carriers. Roughly one-third of these will develop chronic active hepatitis, often with cirrhosis.

Experiments on human volunteers suggest that the carrier rate after acute non-A, non-B hepatitis is around

30 per cent and is therefore higher than for type B. No currently available measures will decrease the chances of an infection with non-A, non-B hepatitis developing into chronic hepatitis and cirrhosis. Several approaches have been tried with type B. Attempts have been made to prevent a chronic carrier state developing by giving levamisole[37], which acts as a non-specific stimulant of defective macrophage activity and disturbed T cell function. In the treatment of hepatitis BsAg-positive chronic active hepatitis (CAH), two antiviral agents have been investigated. Fibroblast interferon has been disappointing, but some successes have been obtained with human leucocyte interferon[38], including suppression or eradication of Dane particle markers. Adenine arabinoside has also been used with limited success[39], but may be more effective when used with BCG. Steroids are of benefit in some forms of CAH and for the past decade hepatologists have argued about the merits of treating HBsAg-positive CAH with steroids. A recent study from Hong Kong suggests that steroids are contra-indicated[40] but re-analysis of the data has not supported this view[41].

It has recently become possible to prevent vertical transmission of the hepatitis B virus by giving hepatitis B specific immunoglobulin soon after delivery to the baby of a carrier mother[42, 43]. Our newly acquired ability to prevent vertical transmission implies that a screening test for HBsAg should probably be performed on all pregnant women of Chinese or Asian extraction.

Possibly the most exciting therapeutic break-through in hepatology over the past decade has been the recent development of vaccines that will prevent individuals in high-risk situations from becoming infected with hepatitis B virus[44]. There is no doubt that the introduction of this vaccine on a world-wide scale will have an impact similar to that achieved by the polio vaccine, provided it proves as effective in Asia and Africa as it has in the USA.

Chronic Active Hepatitis (CAH)

The autoimmune or lupoid type of CAH was the first to be recognised. It was originally described in a group of young people, predominantly girls around puberty. Shortly after, the same variety of chronic liver disease was recognised in post-menopausal women and among individuals with a positive LE cell test. High serum transaminases and gammaglobulins are usually present, there is an association with other autoimmune disorders, and the response to corticosteroids is good. An increased incidence of HLA-B8 and DRW3 has been found in this type of CAH[45] and a characteristic finding is the presence in serum of a smooth-muscle antibody demonstrated by immunofluorescence of rat kidney; this has anti-actin specificity. Of 44 cases of CAH seen between 1976 and 1981, 43 per cent were of this lupoid variety (Table 2).

With the advent of the hepatitis BsAg test, a second type of chronic active hepatitis was recognised[46]. This is characteristically found in an older age group, is commoner in males, and multi-system involvement is rare. Corticosteroids are of doubtful benefit. Over the past few years the incidence of lupoid hepatitis in the UK has probably been falling, and the proportion of cases of

Table 2. Classification of 44 cases of chronic active hepatitis seen in the University Department of Gastroenterology, Manchester Royal Infirmary, 1976-1981.

	No.	Per cent
Lupoid	19	43.2
Hepatitis BsAg-positive	8	18.2
Cryptogenic	8	18.2
Wilson's	3	6.8
'PBC overlap'	3	6.8
Colitis	2	4.5
Alcohol	1	2.3

CAH due to hepatitis B virus has risen; in our present series it constituted 18 per cent.

It is well recognised that drugs such as methyldopa, salicylates, nitrofurantoin, isoniazid and the laxative oxyphenisatin can cause CAH; oxyphenisatin is no longer available from pharmacies in this country but is still present in some laxatives purchased from health food shops[47]. Wilson's disease may present as CAH and there is a clearly established association with ulcerative colitis. Alcoholics occasionally present the characteristic histological features of CAH; there was one example only of this rare association. In three of our patients the histological appearances were those of CAH but the antimitochondrial antibody titres were high and smooth muscle antibody titres low or absent. Most series include patients on this borderline between the two major autoimmune liver disorders; confusion over pathogenesis has been accommodated by including a 'PBC overlap' group. In 'typical' cases of primary biliary cirrhosis a PBC-specific antimitochondrial antibody (designated M2) is directed against an antigen of the inner mitochondrial membrane, while in cases of CAH that overlap there is, in addition, a second antibody (M4) directed against an antigen on the outer mitochondrial membrane[48]. In 18 per cent of our patients with CAH no aetiological factors could be identified. Some of these cases of cryptogenic CAH are probably due to non-A, non-B hepatitis; clarification of this problem awaits the introduction of a suitable marker[49] for this group of viruses.

It has been clearly shown that corticosteroids can produce clinical, biochemical and histological remission in severe CAH[50-52], but the role of steroid therapy in milder forms is controversial. Azathioprine alone is ineffective[51] and, although the Mayo clinic trial is frequently interpreted as indicating a beneficial role for azathioprine in combination with prednisone in the maintenance of remission, the value of this drug has not been adequately established.

The reported frequency of cirrhosis after chronic active hepatitis has varied a great deal in different series. Steroids appear to be of benefit in CAH with established cirrhosis, and there are some grounds for believing that they may actually produce histological regression of the cirrhosis[51].

Primary Biliary Cirrhosis (PBC)

In the earlier stages, nodular regeneration in the liver is inconspicuous and the condition is not a true cirrhosis.

Classically, the disorder affects middle-aged women, who present with pruritis and then become jaundiced, many developing xanthelasmata or skin xanthomas. Once jaundice supervenes the prognosis is poor, with an average survival of around five years. However, presymptomatic cases are recognised with increasing frequency[53] and it is now realised that jaundice may be a late feature.

Aetiology

An intriguing recent finding is an association between PBC and water supply[54]. In this Sheffield study there was a suggestion of clustering in certain areas, but this has not been confirmed in epidemiological surveys from other parts of the country.

The association of PBC with autoimmune diseases, the almost invariable presence of circulating antimitochondrial antibodies and the high levels of serum immunoglobulin M, indicate that PBC may have an autoimmune pathogenesis. In contrast to CAH, the frequency of the histocompatibility antigens HLA-A1 and HLA-B8 is not increased in PBC[55], but a recent report from Spain suggests an increased incidence of DRW3[56], an association not confirmed in patients from the UK[57]. PBC exhibits some similarities to chronic graft-versus-host disease and it has been postulated that the disease results from an immune response to the histocompatibility complex antigens present on ductular epithelial cells of the biliary tree[58]. Many patients have raised circulating levels of immune complexes with activation of the classic and alternative complement pathways[59, 60], and complement deposition can be demonstrated around damaged bile ducts[61]. Antigens derived from the biliary tract have been isolated from circulating immune complexes[62].

There is a high incidence of lesions in organs other than the liver. PBC associated with scleroderma[63] may be asymptomatic[64]; polyarthritis, renal tubular acidosis and thyroid disease are also recognised associations. The commonest of these systemic manifestations is, however, the sicca syndrome[65] and the majority of patients suffer from failure of salivary and tear flow. Cross-reacting antigens between bile duct epithelium and salivary gland and between a bile canalicular antigen and an antigen in pancreatic duct epithelium have been demonstrated[66]. It is therefore of interest that abnormalities of pancreatic secretion have recently been demonstrated in PBC, in particular a reduced bicarbonate output following secretin administration[67].

In our series of 31 cases, the commonest physical sign at presentation was hepatomegaly, present in 71 per cent (Table 3). Only 38 per cent were jaundiced at presentation, while xanthelasmata and xanthomata were unusual features.

Laboratory Investigations (Table 4)

An invariable finding was the presence of a raised serum ALP. Only 55 per cent had a raised serum bilirubin. Smooth muscle and antinuclear antibody were found in a minority. It is of interest that the type of smooth muscle antibody present in PBC differs from that found in CAH[68]. A titre of AMA (demonstrated by fluorescence of rat kidney tubules) of more than 1 in 16 was invariably present and in 70 per cent this was greater than 1 in 80.

Table 3. Signs at presentation in 31 cases of primary biliary cirrhosis seen between 1976 and 1981.

Sign	Per cent
Hepatomegaly	71
Pigmentation	55
Splenomegaly	45
Liver palms	41
Jaundice	38
Spider naevi	28
Xanthelasmata	17
Xanthomata	7

Table 4. Laboratory investigations at presentation in 31 cases of primary biliary cirrhosis.

	%
Bilirubin (>17 mmol/litre)	55
Alkaline phosphatase (>100 I.U.)	100
Antimitochondrial antibody ⩾1/16	100
⩾1/80	70
Smooth muscle antibody	15
Antinuclear antibody	37

The diagnosis of PBC should always be confirmed by liver biopsy. The disease is essentially one of injury to, and finally disappearance of, septal and interlobular bile ducts. Four stages are recognised[69]; only in stage 4 is a true cirrhosis present. In stage 1 the 'florid duct lesion' is pathognomonic. However, in stages 2, 3 and 4 the appearances are not diagnostic and should be reported as 'compatible with' PBC.

Treatment of PBC

There is no doubt that the quality of life can be improved. Pruritus frequently responds to the anion exchange resin Questran (cholestyramine) which binds bile acids in the gut and so depletes the body pool. Regular administration of vitamins A and K may be required and steatorrhoea can be partially corrected by means of a low fat diet and supplements of medium chain triglycerides.

Osteomalacia has long been recognised as a complication of PBC and it has been suggested that it may still occur despite the regular intramuscular administration of vitamin D_2. Since the osteomalacia did respond to $1,25(OH)_2$ vitamin D_3, Long *et al.* proposed that there may be a failure of vitamin D_1 hydroxylation in PBC or that hepatic osteomalacia is resistant to vitamin D_2 metabolites[70]. More recently, however, radio-labelled tracer techniques and metabolic balance studies have shown that while osteomalacia is a significant problem in PBC, it is mainly due to malabsorption of vitamin D and is both preventable and treatable by oral or intramuscular administration of the commonly available forms of this vitamin[71].

Regarding specific treatment, corticosteroids given early in the course of the disease can produce dramatic clinical and biochemical improvements[72]. Given in the late stages of the disease, no effect is achieved and, in view of the severe adverse effects seen, particularly severe osteoporosis with crush fractures and also infections, it appears that there is little if any role for steroids in the treatment of PBC.

Azathioprine has been used in a controlled trial[73] but no improvement in survival was obtained and this drug has now been abandoned. With the severe cholestasis of PBC, biliary excretion of copper is decreased and hepatic copper concentrations increase into the range found in Wilson's disease. Copper extravasation from disrupted ductules has been postulated as an important aetiological factor leading to the development of cirrhosis, and penicillamine was introduced primarily for its copper chelating action, by analogy with Wilson's disease[74]. Penicillamine decreases hepatic copper concentrations and also lowers circulating immune complex levels. Liver function tests may improve but no consistent histological changes have been reported and the drug does not appear to prevent the deposition of fibrous tissue or progression to cirrhosis. Improved survival has been reported in some, but not all, studies[75, 76].

Idiopathic Haemachromatosis (IH)

The classical features of this rare disease are well known. Nevertheless, symptoms and signs may be remarkably non-specific. Abdominal pain is a frequent complaint but the mechanism is not understood. Pigmentation is usually not gross, and is often too subtle to trigger recognition of the condition. On the other hand, hepatomegaly is almost invariable and it is vital to check the serum iron and iron-binding capacity in every patient with unexplained hepatomegaly.

Increased intestinal iron absorption appears to be the basic defect. The argument as to whether IH is an inborn error of metabolism[77] or an acquired disorder associated with increased alcohol intake[78] has been resolved by the recent demonstration of a strong association with the histocompatibility antigen HLA-A3[79, 80]; less strong associations are found with B14 and B7[79]. It is likely that individuals who suffer from the disease have to possess a double dose of the IH gene and to be HLA-A3 and either B7 or B14. In alcoholic liver disease the incidences of HLA-A3 and B14 are not increased[81]. A clear difference therefore exists between the two conditions associated with iron overload.

Although most manifestations of the disease improve with venesection treatment, this does not apply to testicular atrophy or the characteristic chondrocalcinosis. There is good evidence that treatment is associated with improved survival[82]. In addition, fibrosis and even established cirrhosis may regress[83, 84].

Once the disease has been diagnosed, it is important to screen all close relatives so that venesection therapy can be started prior to the onset of tissue damage. Abnormal iron metabolism can be demonstrated in one quarter of first degree relatives[85]. Serum iron-binding capacity and serum ferritin should be determined, together with tissue-typing if this facility is available. If any of these biochemical tests suggest increased iron stores, liver biopsy with determination of liver iron concentration should provide a definitive answer. Relatives who are HLA-A3 should be followed with special care.

Wilson's Disease

Onset is usually in adolescence, though occasionally a patient may remain in apparently good health until the sixth decade. The possible hepatic manifestations include jaundice, oedema, ascites, splenomegaly and variceal haemorrhage and tend to appear at an earlier age than do the neurological manifestations, although mixed forms are common. In neurological Wilson's disease there may be no physical signs of liver disease and perfectly normal liver function tests but cirrhosis is almost invariable. Wilson's disease may masquerade as chronic active hepatitis or alcoholic or cryptogenic cirrhosis.

The characteristic biochemical findings include a low serum ceruloplasmin and total copper but an increased free (non-ceruloplasmin-bound) copper. The 24-hour urinary copper excretion is invariably increased. The liver biopsy appearances may be rather non-specific, although glycogen vacuolation of the nuclei, fatty change and Mallory's hyaline, if present, are suggestive. Two points may cause diagnostic difficulty. First, Kayser-Fleischer rings are frequently absent in the hepatic, as opposed to the neurological form of Wilson's disease, even on slit lamp examination[86]. Second, it is often impossible to demonstrate histochemically the increased hepatic copper stores. Thus, the rubeanic acid and rhodanine stains for copper and the orcein stain for copper-binding protein may be negative, despite a markedly elevated hepatic copper concentration. This discrepancy may be related to variations in the chemical form and organelle distribution of copper within the hepatocyte at various stages of the disease. Consequently, it is vital to measure the liver copper concentration chemically; it is invariably elevated. The basic defect in copper homeostasis in Wilson's disease is controversial. Experiments with radio-labelled copper suggest that defective excretion of copper from hepatic lysosomes into bile underlies the accumulation of excess copper in Wilson's disease[87]. An alternative hypothesis is that there is an abnormal form of hepatic metallothionein[88] with an increased avidity for copper, which is consequently not released into lysosomes and thence into bile, or to be manufactured into ceruloplasmin. Failure of synthesis of ceruloplasmin and production of a structurally abnormal ceruloplasmin have also been postulated and, more recently, it has been suggested that Wilson's disease is due to a mutation in a controller gene which results in perpetuation of the fetal type of copper metabolism into childhood[89].

It is important for the clinician to differentiate between chronic active hepatitis due to Wilson's disease and that due to any other cause. In adults, at least, this distinction is usually straightforward and based on serum ceruloplasmin determination. Ceruloplasmin is an acute phase reactant and serum levels in chronic active hepatitis are

either normal or raised[90]. In hepatic Wilson's disease, in contrast, the serum ceruloplasmin is markedly reduced (Fig. 1). Occasionally, however, real diagnostic difficulties remain. Thus, reduced levels of serum ceruloplasmin

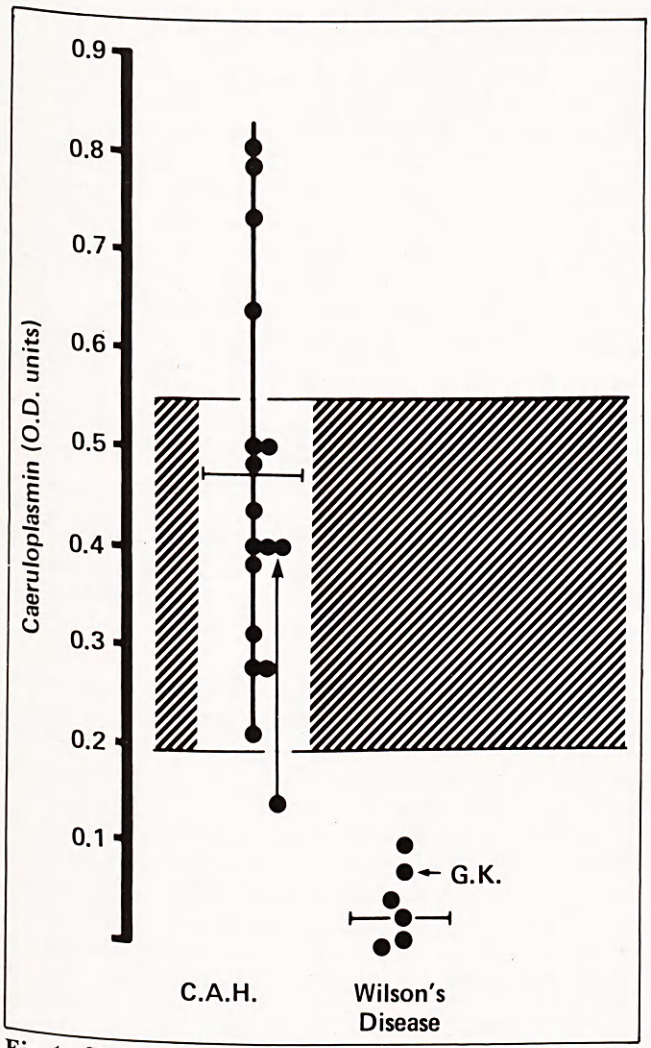

Fig. 1. *Serum ceruloplasmin levels in 16 cases of chronic active hepatitis and 6 cases of hepatic Wilson's disease seen in the Liver Clinic, Manchester Royal Infirmary, between 1976 and 1981. Normal range shown as cross-hatched area. (For patient G. K. see text.)*

have been reported in chronic active hepatitis due to failure of synthesis[91] and a few patients with Wilson's disease have been described with normal ceruloplasmin levels. The correct diagnosis in these circumstances can best be made by means of radio-labelled copper studies; in patients with Wilson's disease there is little or no incorporation of radio-copper into newly synthesised ceruloplasmin[92].

The treatment of Wilson's disease with penicillamine[93] is usually straightforward; the initial daily dose is around 1 or 2g D-penicillamine which is reduced as body copper stores are depleted. In established chronic active hepatitis due to Wilson's disease, response to treatment is sometimes surprisingly poor[86], but there is good evidence that penicillamine can prevent the development of cirrhosis if given sufficiently early. In patient G. K. (Fig. 1) established cirrhosis was diagnosed histologically at six years of age and her parents had been given a hopeless prognosis; she is now in her early twenties and symptom-free on penicillamine, with normal liver function tests.

Indian Childhood Cirrhosis (ICC)

Traditionally, this intriguing condition has been considered to have unique clinical and histological features and to be limited to the Indian sub-continent, Sri Lanka, Burma and Malaysia; it is probably the fourth most common cause of death in large paediatric centres in India. Recently, however, two sibs with ICC have been reported from the UK[94]. The older boy was born in Bangladesh; the younger brother represents the first example of this disease in a patient born in this country. It is therefore important that the diagnosis of ICC is considered in any child of Asian background who presents with chronic liver disease.

Typically, there is an insidious onset, in infancy or early childhood, of abdominal pain and diarrhoea prior to the development of jaundice, hepatosplenomegaly and ascites; the overall progress is steadily downhill and death is from liver failure. The liver histology shows generalised hepato-cellular damage, creeping peri-cellular fibrosis, poor regeneration and florid deposits of Mallory's hyaline[95].

A variety of viral and immunological insults have been postulated and metabolic defects described[94]; the latter include raised urinary levels of tryptophan metabolites[96] and a high concentration of arsenic in the liver[97]. Liver copper levels are also high[98, 99] but it is not certain whether this could be related to cholestasis, the extent of which seems to be variable in different series[100], or whether it represents a unique feature of the disease. Coarse orcein-positive granules have been demonstrated in the cytoplasm of hepatocytes, and since these also stain with copper-specific stains, it has been postulated that ICC may represent a copper storage disorder[101]. Apart from its diagnostic value, this finding implies that therapy with a copper-chelating agent such as penicillamine may offer some hope for this hitherto incurable form of cirrhosis.

Cryptogenic Cirrhosis

This represents a diagnosis by exclusion of the known causes of cirrhosis. Some cases are really alcoholics who have escaped detection. Others have been erroneously placed in the cryptogenic group because of an inability to obtain a liver biopsy (usually due to coagulation problems) or failure to arrange for the appropriate tests (autoantibodies, hepatitis B markers, copper and iron studies) to be performed.

Alpha-1-antitrypsin (A1AT) deficiency

The association between chronic hepatitis and cirrhosis with the homozygous PiZZ form of A1AT deficiency,

though well recognised, is rare. Recently, however, a marked increase of heterozygous MZ A1AT deficiency has been found in cryptogenic cirrhosis[102]. These patients were characterised by an older age, the absence of associated autoimmune disease, negative auto-antibody tests and a poor response to steroids. The serum level of A1AT was normal in half the cases and identification of this important subgroup requires meticulous examination of liver biopsy material for the typical hepatocyte inclusions demonstrated by the immunoperoxidase technique. This study suggests that 20 per cent of cases of cryptogenic cirrhosis may be due to, or associated with, heterozygous A1AT deficiency.

Established Cirrhosis

Early diagnosis of pre-cirrhotic conditions is vital, since treatment can prevent the development of irreversible changes. But what about established cirrhosis? Prednisone increases the survival of female patients with compensated non-alcoholic cirrhosis; in other types of cirrhotic, especially those with ascites, prednisone is ineffective or possibly harmful[103]. When treatment is available for a specific type of cirrhosis, the prognosis is quite favourable. In a recent Birmingham study[21], the five-year survival for chronic active hepatitis was 60 per cent and for alcoholic cirrhosis 35 per cent, but this markedly improved in patients who stopped drinking to 90 per cent for initially well-compensated cirrhotics and 60 per cent for decompensated patients. In a large Australian series, the prognosis for haemachromatosis (a 68 per cent 5 year survival) was better than that for any other kind of cirrhosis[104]. Nevertheless, if no specific treatment is available, the prognosis for a cirrhotic is worse than for many kinds of cancer; in a recent study only 14 per cent of the cryptogenic and post-hepatitic group survived five years[21].

Nevertheless, there are grounds for believing that the prognosis for patients with cirrhosis has improved[24]. This is, presumably, partly the result of earlier diagnosis in the compensated state, partly due to the introduction of specific treatments such as steroids, venesection and penicillamine, and partly the result of more effective management of the complications that contribute to both morbidity and mortality in cirrhosis—portal hypertension, ascites, spontaneous bacterial peritonitis and encephalopathy.

A fundamental question is whether fibrous tissue, once laid down, can be removed. This certainly appears to be the case in infancy when cirrhosis may regress following successful operative treatment of biliary atresia[105, 106]. In addition, there is evidence that, in the adult, the cirrhosis associated with chronic active hepatitis[51] and with haemachromatosis[84] may regress with appropriate treatment.

Fibrosis, of course, implies new collagen formation. In collagen biosynthesis (Fig. 2) three polypeptide chains each containing around 1,200 amino acids are assembled. Next, hydroxylation of proline and lysine residues occurs by the enzymes prolyl and lysyl hydroxylase on the rough endoplasmic reticulum; this is followed by glycosylation,

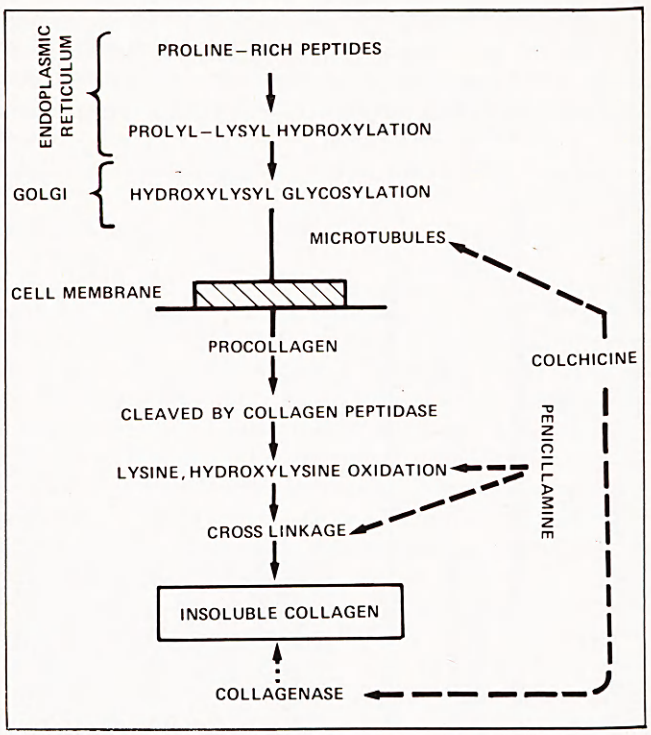

Fig. 2. *The mechanism of action of penicillamine and colchicine on collagen metabolism in cirrhosis.*

with the addition of the sugars galactose and glucose to hydroxylysine residues. The pro-α chains then form into a triple helix. Once the procollagen molecules have been assembled they are secreted across the cell membrane into the extracellular space. At this point the terminal peptides are split off by specific peptidases to produce extracellular tropocollagen. The final step is the formation of cross-links between the molecules making up the collagen fibre, which occurs by oxidative deamination of specific lysine and hydroxylysine residues with subsequent spontaneous cross-linking of the resulting lysine-aldehydes. The insoluble collagen so formed can be broken down by hepatic collagenase. Two different approaches have been employed to attempt to decrease hepatic collagen formation. Penicillamine disrupts collagen cross-linkage and has been employed mainly in primary biliary cirrhosis. Colchicine, on the other hand, inhibits the microtubular transport of procollagen and also activates collagenase.

In a double-blind controlled study colchicine was given in a dose of 1 mg a day five times a week for four years to a group of patients suffering from alcoholic, post-hepatitic or cryptogenic cirrhosis[107]. There were significant improvements in serum biochemistry and clinical features, including ascites, oedema and encephalopathy, and, on liver biopsy, substantial regression of fibrosis was seen in 25 per cent of patients on colchicine.

Conclusion

There have been modest advances in our understanding of the pathogenesis of certain types of cirrhosis, but the present system of classification is not entirely satisfactory. How, for instance, do we classify the type of cirrhosis

found in an individual who drinks 80 g of alcohol a day, is hepatitis BsAg-positive and is noted to be an MZ heterozygote for alpha-1-antitrypsin deficiency? Many cases of cirrhosis may have multifactorial origins; alcohol and the hepatitis B virus may act synergistically in this respect. Some types of cirrhosis, for instance that due to hepatitis B virus, are now potentially preventable, while others may be partially reversible. In inherited disorders such as Wilson's disease and haemachromatosis, for which specific treatments exist, it is vital to screen other family members. In established cirrhosis associated with disorders such as non-A, non-B hepatitis, primary biliary cirrhosis and Indian childhood cirrhosis, the antifibrogenic drugs penicillamine and colchicine hold promise, although it is questionable whether either drug should, as yet, be used outside the confines of a controlled trial. Finally, in some forms of end-stage cirrhosis, liver transplantation should be considered[108].

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