Biliary Cirrhosis: An Appraisal

The Croonian Lecture 1975

W. N. MANN, MD, FRCP
Senior Physician, Guy's Hospital, London

The way in which biliary cirrhosis is caused remains undetermined. Whether we are considering secondary biliary cirrhosis that follows upon a demonstrable obstruction of the biliary tract, or the primary form of the disease in which no such obstruction is found, the processes leading to a gross enlargement of the liver with cellular infiltration, massive fibrosis and hepatocellular regeneration are still largely unknown. However, many facts are known and, in particular, recent work suggests that immunological abnormalities might be concerned in the pathogenesis of the primary form of the disease, although, of course, they may be only effects or epiphenomena, rather than causes. Nature has only a limited number of tunes in her repertoire when it comes to responding to changes in the environment; for instance, the pathological changes, sometimes even the clinical features seen in response to the tubercle bacillus, the Treponema pallidum, crystals of beryllium, and whatever is the causal agent of sarcoidosis, are very similar and sometimes indistinguishable. Histological identity is no proof of aetiological identity. The same may equally be true of immunological reactions seen in the laboratory. If a classification depends on one or the other, or on a combination of these and other features of a syndrome, without regard to the whole, there may be fragmentation where there should be unification, while a proliferation of nomenclature leads to confusion of thought. This applies to some current concepts of chronic disease of the liver.

Cirrhosis of the liver has been known for many centuries. The first record in the English literature is that by John Brown (1685), a surgeon to St Thomas's Hospital, who described, with illustrations, the autopsy on a soldier with ascites and a 'liver less than normal'. But the disease was well known before that. Versalius (1543) observed that there was an opinion prevalent among anatomists that the liver was reduced in size by drinking and described the autopsy on a lawyer who appropriately died while at table. He found a belly full of blood from rupture of the portal vein and noted that the whole liver was pale, indurated and studded with nodules. There are many relevant observations in Morgagni (1761, 1819), notably the case of Caspar Lombria, an alcoholic Venetian nobleman with ascites. To Morgagni we owe the first description of secondary biliary cirrhosis: he observed that, in the presence of gall stones, the liver may be hard, green and scirrhous. Laennec (1819) first gave cirrhosis its name; from the Greek κυρρός, tawny coloured.
In 1826, Rayer published from Montpellier his beautiful atlas of diseases of the skin, the plates drawn by James Young, an expatriate Scotsman from Paisley. He first described xanthelasma of the eyes, 'yellow plaques, the colour of chamois leather, slightly raised, neither warm nor red and sometimes disposed in a somewhat symmetrical manner'. It was due to Addison's interest in dermatology that he saw the association between xanthelasma and, in more general form, xanthomatosis, with a special, although at that time unspecified, kind of cirrhosis of the liver, as well as with diabetes mellitus. Addison and Gull (1851) together wrote a most important paper: 'On a certain affection of the skin, vitiligoidea—(a) plane, (b) tuberosa; with remarks.' In this, the authors distinguish vitiligoidea, that is, xanthoma, from vitiligo and keloid. Five cases are described, the first too sketchy to be of any value. Of the four remaining, one had diabetes and three had chronic jaundice. The association was evident to Addison, for he wrote: 'The connection of the affection of the skin with hepatic derangement is obvious. In what way the defective action of the liver operates, can perhaps no further be explained at present, than by the general theory of disordered circulating fluid'.

It is fortunate there is still a memorial to these patients in contemporary wax models in the Gordon Museum at Guy's Hospital, illustrating the lesions Addison and Gull described, as well as an illustration in the paper itself, a paper that excited great interest. During the next twenty years or so, a daunting number of papers appeared in the English, French and German literature dealing with the association of xanthelasma and disease of the liver, and the relationship between obstructive jaundice and cirrhosis.

Murchison (1868) observed that in this sort of 'xanthelasmic jaundice', the jaundice is remarkable for its persistence, and the enlargement of the liver is considerable. He, too, demonstrated that along the portal tracts and between the lobules the liver was 'pervaded by a dense deposit of fibrous tissue and masses of minute corpuscles and nuclei'. Two years earlier, Wyss (1866) had described the appearance of bile thrombi, 'cholestasis', in patients with chronic jaundice. He described them as 'green or brownish bodies of a rounded or lengthened shape, sometimes branched, and usually between 2 and 5 micromillimetres in diameter, but sometimes more'. He pointed out that these thrombi were found only between the liver cells, never within them, and he regarded them as casts of the fine capillary bile ducts. Although Virchow (1857) was probably the first to recognise clearly the relationship between obstructive lesions in the main bile ducts and cirrhosis, it was Moxon (1873) who first recognised that jaundice and xanthomatosis might follow a simple stricture of the hepatic duct, for he showed that xanthomatosis might follow a variety of causes of biliary obstruction and that it was not a peculiar manifestation of some indeterminate hepatic disease. He described a sailor in the Queen's service whose illness had lasted a year and a half when he was admitted to Guy's Hospital. He was deeply and darkly jaundiced and xanthomata affected the palms of the hands, the ears, cheeks and scrotum. At autopsy, the bile ducts had dilated above a simple stricture and the liver was large.
and finely lobulated. In spite of the patient's youth, there was considerable atheroma of the aorta and the cerebral vessels. Biopsy of the skin in another, similar patient demonstrated the presence of 'radiated acicular crystals'. In these observations of Moxon we have the first description of secondary biliary cirrhosis, that is, biliary cirrhosis associated with demonstrable gross obstruction of the extra-hepatic bile duct, and also a note on the association of xanthomatosis with premature atherosclerosis.

If these observations are brought together, it will be seen that cases of jaundice with xanthomatosis showed progressive enlargement of the liver, with the microscopical appearance of proliferating fibrous tissue spreading out from the portal tracts to enclose separate liver lobules, and aggregates of round cells. This condition was clearly a different one from cirrhosis of the liver usually associated with alcoholism—'gin-drinker's liver'.

EARLY EXPERIMENTAL EVIDENCE

The foregoing observations, spread over some fifty years, were clinical and pathological. The next quantum of evidence came from experiment. In 1872, Mayer in Vienna described, after ligation of the common duct, 'some augmentation of the quantity of connective tissue, both intra- and extralobular', as well as round cell infiltration. The next year, Wickham Legg (1873) at St Bartholomew's Hospital made some successful experiments in the cat. In these, Legg found that the proliferation of fibrous tissue, together with infiltration with lymphoid corpuscles, took place in a matter of hours after the ligature had been applied and that it continued so long as the animals lived. It was very great, even in animals that survived only four days after operation. He thus commented on a remarkable phenomenon: the enormous speed with which fibrosis takes place after obstruction, complete or partial, of the main bile ducts, in contrast with other forms of cirrhosis in which fibroblastic activity is indolent and, except in primary biliary cirrhosis, less severe. Legg also saw the 'lymphoid corpuscular infiltration' that Mayer had observed, and that stimulates so much speculation today.

Legg's experiments were repeated, confirmed and extended by Charcot and Gombault (1876) and their very important paper described the alterations in the liver that follow ligature of the bile duct in the guinea-pig. They described how each liver lobule was separated, the one from the other, by newly formed sclerotic fibrous tissue, tending to cause the lobules to disappear, and how this formation was attended by the proliferation of new bile ducts. They observed that these experimental changes in the liver reproduced more or less exactly those encountered in man when the common duct is obstructed by a calculus. They described specifically the finely lobulated olive-coloured liver of a woman with a stone in the ampulla, and pointed out that the lobulation was a fine one and not of the hob-nailed variety.

It was the view of Charcot and Gombault that biliary stasis was the factor responsible for biliary cirrhosis, a view contested by Mangelsdorf (1882) who
believed it was the consequence of an inflammatory process provoked by a seepage of bile through damaged bile capillaries; that is, through the ductules, a conception perhaps nearer the truth.

VICTOR CHARLES HANOT
It is just over a hundred years since Hanot presented his thesis to the University of Paris on ‘Hypertrophic Cirrhosis with Chronic Jaundice’ (1875).

Victor Charles Hanot was fortunate in neither his professional nor his private life. He was born in 1844 in the Faubourg Saint-Antoine, a poor quarter in the east of Paris. He became a pupil of Charcot and occupied the post of chef de clinique. He was appointed physician to the Hôpital Saint-Antoine, but circumstances long denied him a chair. He wrote many papers on pathological conditions, lectured specially on diseases of the liver and, in 1895, addressed the annual meeting of the British Medical Association on ‘Bronzed Diabetes’, which he had described with Chauffard in 1882. The following year, having been elected professor agrégé, he died by his own hand, just before taking the chair, on account of domestic infelicities. He enjoyed music and the arts, but he was subject to periods of despondency. Hanot was a sad, but considerable figure who deserves to be remembered better in the history of cirrhosis (Gilbert, 1896).

Hanot clearly described the disease we now know as primary biliary cirrhosis, separating it from biliary cirrhosis of secondary type that follows upon some demonstrable obstruction in the main biliary tracts—an impacted stone, a stricture, or a growth. He particularly commented upon the great size the liver might attain due to the extensive fibrosis that is so characteristic a feature, and upon the delayed onset of ascites and the other complications of portal obstruction. He nevertheless regarded the essential cause an obstructive one, which he attributed to a catarrhal inflammation in the minute intrahepatic biliary channels. Anatomically, at least, he was not far from the truth. What emerges, both from Hanot’s and other observations, as well as from the experimental work already described, is how quickly and how extensively both cellular infiltration round the bile ducts and fibroblastic proliferation can follow biliary obstruction, whether it be gross or minute, of the large or the small biliary passages. The first chemical observations were recorded by Chambard (1878) whose colleague, Quinquaud (1878), measured the elevation of the blood lipids when xanthomata were found, and observed that the fatty matter in the blood might then be as high as six times the normal figure.

The problem of biliary cirrhosis has been stated. Why does obstruction of the bile ducts produce so rapid and extensive a degree of fibroblastic proliferation, leading to the production of dense fibrous tissue? Why is this process attended (or preceded) by round cell infiltration about the minute bile ducts? Why is there this similarity between the pathological changes in the liver produced by gross obstruction and those changes that take place when there is no gross obstruction? It is not surprising that Hanot postulated a fine catarrhal inflammation of the
minute ramifications of the biliary system producing an intrahepatic, as opposed to an extrahepatic, obstruction.

THE SKIN
It was the changes in the skin that first drew Addison’s attention to the disease. They deserve more attention, for in one of the dermatological features might lie at least a clue to unlocking the aetiological secrets still hidden from us. A notable feature of biliary cirrhosis, whether primary or secondary, is the presence of pruritus. It may long anticipate jaundice in either form of the disease. I recall a patient who complained of intolerable itching, and of no other symptoms or signs for nearly a year before belated investigation showed that he had a carcinoma of the ampulla of Vater. He was never visibly jaundiced before the operation. Sherlock (1974) reported that in no fewer than 57 of a series of 100 patients with primary biliary cirrhosis pruritus was the presenting symptom. Why is it that this itching, always ascribed to the accumulation of bile salts in the skin, may so long precede the appearance of bile pigments in the skin? We do not know why gross obstructive lesions of the biliary passages, producing many other manifestations of obstruction, do not necessarily cause jaundice—something upon which few authors comment and none attempt to explain.

A comment on this problem has been made recently by van Berge Henegouwen et al. (1974) who remarked that, in the rare disease benign recurrent intrahepatic cholestasis, the serum bile-acid levels might be very high while the serum bilirubin level remains normal. This suggested to them that the dissociation was due to an enzyme deficiency that interfered with the transport of bile acid by the liver cell. They postulated that this might be the cause, and not the result, of cholestasis, a subject considered in more detail later.

The second dermatological feature of biliary cirrhosis is the colour of the skin. The jaundice, normally following the pruritus, is slow to appear at least in the primary form of the disease. Never, in the primary cases, of a bright yellow colour, it quickly assumes a greenish hue from oxidation of the pigments. In the later stages of the disease, the patient may appear like a well-weathered bronze statue, the colour of long-standing jaundice being modified by the increased content of melanin in the skin. The cause of this melanosis is unknown. The rôle of iron is uncertain. One of the main paths of excretion of iron is in the bile, accounting for as much as half the daily excretion. However, Whitlock (1951) examined the skin in four cases of melanosis with cirrhosis and found no free iron in any of them. Williams (1967) and Smith et al. (1967) mentioned the frequency of siderosis in cirrhosis generally, and stated that pigmentation had ‘an increased incidence in cirrhosis, whether or not there is excess iron deposition’. However, although iron absorption appears to be facilitated in cirrhosis, iron levels in the blood are but little raised, certainly in portal cirrhosis.

The third and striking feature of biliary cirrhosis is that of xanthomatosis. Only a minority of patients, in spite of raised serum lipid and cholesterol levels that
may exceed three or even six times the normal levels, demonstrate this feature. Xanthomatosis can be expected when the total serum lipid level exceeds 1,800 mg/100 ml. The phospholipids, cholesterol and neutral fats are all elevated in order of decreasing magnitude. Xanthelasma tends to precede the xanthomata and can be expected at a serum lipid level of 1,300 mg (Ahrens et al., 1949). Similar levels produce similar pictures whether the cirrhosis be primary or secondary in character. The lipid picture was elucidated by Thannhauser and Magendautz (1938), so completing the work of Chambard.

A further dermatological feature, not uncommon but rarely mentioned, is a papular dermatitis with transient lesions not dissimilar from those of acne.

**BILIARY CIRRHOSIS, OTHER FORMS OF CIRRHOSIS, AND VIRAL HEPATITIS**

Immunological reactions, and the detection of antimitochondrial antibodies, allow a diagnosis of primary biliary cirrhosis to be made with fair certainty, even in early cases where clinical and histological changes are hardly specific. The meaning of these reactions aetiologically is open to various interpretations, but it is natural today that, where the aetiology of liver disease is uncertain, the role of the ubiquitous viruses of hepatitis should be implicated. An increasing proportion of liver disease of uncertain origin is ascribed to the effects or the late results of viral infection, sometimes on the grounds of finding antibodies that will necessarily be present in a proportion of sera tested, however selected.

![Fig. 1. The incidence of primary biliary cirrhosis](image)

First, consider the frequency of biliary cirrhosis. It is not a rare disease. Of 92 cases of cirrhosis admitted to the medical wards of Guy’s Hospital, 28 were biliary and 64 portal. The incidence of all forms of cirrhosis was one in 200 admissions to the medical wards. Of the cases of primary biliary cirrhosis, 70 per cent were
women and 30 per cent were men. While the cases in women occurred between the ages of 45 to 60, the cases in men were spread equally (Fig. 1). These figures correspond in general with other series (Ahrens et al., 1950; Sherlock, 1974).

These are the figures for primary biliary cirrhosis. Figures for secondary biliary cirrhosis are difficult to obtain because, in clinical records not kept with a study of cirrhosis in mind, the diagnosis is a secondary one to the primary exciting cause (stone, growth of the pancreas), or may not be indexed at all. However, in a short series of autopsy figures at Guy's Hospital (Adams, 1974), of 21 cases of biliary cirrhosis only 2 were primary and 19 were secondary. Of the causes of obstruction that might lead to secondary biliary obstruction, Cameron and Hou (1962), put carcinoma of the pancreas as the most frequent cause (35 per cent), followed by stones (21 per cent), and other tumours (10 per cent).

The relation of infection with the viruses of hepatitis to cirrhosis and to various forms of chronic hepatitis has been widely considered, but it is generally conceded that it is unlikely to play any part in the aetiology of primary biliary cirrhosis. Thus, Vischer (1970) found no evidence of Australia antibodies in 13 patients with biliary cirrhosis, 12 of whom had antimitochondrial antibodies. Sherlock (1972) obtained similar negative findings. However, infection with the hepatitis virus has certainly been invoked as a possible trigger for other chronic hepatic conditions thought to be related to, or even to lead to, primary biliary cirrhosis.

There are some aspects of the natural history of infective hepatitis to which little attention has been given. Infective hepatitis, although not very uncommon in endemic form, is only seen in its fullest flowering in the epidemics that almost always accompany wars. There was an epidemic in the Middle East of just such proportions during the Second World War. Between 1st January and 31st March 1944, I saw 131 cases of infective hepatitis, a minority of whom may have received blood transfusions or other infusions. Of these, 129 made a complete recovery; only two continued with liver disease. Between 1st March 1941 and 31st December 1942, a period of nearly two years, among 2,187 'medical casualties' evacuated from the Middle East, there were only five cases of liver disease; four were suffering from infective hepatitis and one from acholuric jaundice. This was while viral hepatitis was epidemic. Again, of about 500 cases of virus hepatitis, only two died of acute yellow atrophy (or acute hepatic necrosis) and that within a week of onset. Paton (1969) gave the death rate from fulminant disease as 0.2 per cent. These figures were, not surprisingly, confirmed by Cullinan (1958) who studied the later history of 1,293 soldiers who had contracted infective hepatitis in 1942, constituting a 1 in 5 sample. Of them, 91.6 per cent were traced many years after. The mortality overall was 0.28 per cent and no case of cirrhosis was encountered (Table 1). It may be assumed that the great majority were examples of natural infection and thus the virus concerned would be hepatitis virus A. These epidemiological studies suggest that Virus A hepatitis was not a cause of cirrhosis, nor of any continuing form of hepatitis, at that time. Of course, the virus of hepatitis may have changed its nature since then, a feature seen in many
Table 1. The prognosis in viral hepatitis.

|                           | Mann (1941-42)       | Mann (1944)       | Mann (1940-45)                        | Cullinan, King and Rivers (1958) |
|---------------------------|----------------------|------------------|--------------------------------------|----------------------------------|
|                           | 2,187 medical casualties | 131 cases of infective hepatitis | 500 (estimated) cases of infective hepatitis | 1,293 cases of infective hepatitis |
| Evacuated from M.E.       | 5 cases of liver disease | 129: complete recovery | 2 deaths from acute yellow atrophy (ac. hep. necr.) | Followed up: 91.6 per cent |
|                           | 4: infective hepatitis | 2: continued jaundice |                                      | Mortality: 0.28 per cent         |
|                           | 1: acholuric jaundice |                                |                                      | Cirrhosis: Nil                   |

examples of viral diseases. I have no evidence, one way or the other, of any chronic changes in the liver that might be caused by virus B.

Lastly, a few comments on portal cirrhosis. The idea has been put about in recent years, and is generally believed, that alcohol is only sometimes a cause of this kind of cirrhosis, at least in the United Kingdom. This is contrary to the experience of all earlier writers from Morgagni onwards. Perhaps this may be because figures are often drawn from hospital records that may, or may not, include accurate social data. Of 30 consecutive examples of cirrhosis of the liver seen in private practice and where the social history was certain, 26 were associated with alcoholism, 2 were biliary and 2 of uncertain aetiology. Nine of the cases were men—all alcoholics.

**CHOLESTASIS**

The term 'cholestasis' means no more than a failure of the bile to flow through the biliary channels. This may occur in a multitude of conditions, quite apart from the obvious cause of gross obstruction to the main ducts. It may occur in poisoning from drugs; it is seen in primary biliary cirrhosis; it can be produced by steroids. It thus may occur in conditions where there is no apparent obstruction to the ducts at all, or where the degree of obstruction is minimal. Contrariwise, in a histological study of patients with gross obstructive jaundice, Gall and Dobrogorski (1961) found thrombi in 14 only of their 44 patients. So there is no point in using the term 'cholestatic jaundice' for conditions that are clearly obstructive, e.g. obstruction from a stone in the ampulla or carcinoma of the head of the pancreas, because bile thrombi do not necessarily form under these conditions. The term 'cholestatic', when used for a variety of conditions that primarily arise in the liver, and in which jaundice is associated with some of the biochemical abnormalities associated with extrahepatic obstruction, such as a
raised serum alkaline phosphatase and a predominance of conjugated bilirubin, has little nosological value. In these so-called examples of 'cholestasis', one of the particular elements is the finding, on microscopical examination of the liver, of bile thrombi or irregular deposits of deeply coloured material, apparently bile pigment, in the canaliculi and between the liver cells. The early discovery of these bile thrombi by Wyss has already been mentioned. Wyss went on to make a further, most important and, I think, previously overlooked observation:

'I have seen one case of jaundice of the liver where these interlobular ducts were not only widened, but filled with bile which was completely viscid and although I made very fine sections of the liver, the contents of these bile ducts did not spill out . . . I can therefore deduce that the extensive obstruction of inter- as well as extra-lobular bile ducts precipitates the mucus in the larger bile ducts.'

Thus, Wyss not only discovered the bile thrombus, but also noted that the dilated ductules contained an unusually viscid mucin. Of course, this increased quantity of mucin could be the consequence of obstruction to the outflow of mucin, secreted in normal quantity. In a search of the literature on biliary cirrhosis, I could find no reference to any analysis of these bile thrombi. In fact, there has been little work or speculation upon their nature and why they form. It is a curious feature that, in haemolytic conditions, where a considerable excess of bile pigment is being excreted, bile thrombi do not generally form, while pigment stones in the gall-bladder are commonplace. The formation of bile thrombi must therefore be dependent on something more than a high concentration of bile pigment in the bile and perhaps on something more than stasis alone.

If the bile thrombi seen in biliary cirrhosis are looked at under the microscope, it will be observed that they contain both neutral and acid substances staining respectively by periodic acid-Schiff and by Hale's colloidal iron method. Most of the acid muco-substance lies in a laminated shell surrounding the bile thrombus: Scott's critical electrolyte test shows that chondroitin sulphates are the main constituents of these muco-substances. The nature of the stainable mucins in the thrombi do not differ from those in normal bile, but they stain more strongly as though they were more concentrated or inspissated (Adams, 1974).

The question naturally arises whether or not some interference with the secretion or excretion of bile salts, by altering the constitution of bile, might promote the formation of bile thrombi in the canaliculi and ductules, and the precipitation of bile pigment within the liver cells themselves. In this respect, it is perhaps worth recalling the very early onset of itching in the presentation of primary biliary cirrhosis and the curiously late onset of jaundice relative to pruritus that is sometimes found even in cases of gross biliary obstruction.

How far might the disordered transport of bile acids be a primary factor in the formation of bile thrombi? How important are disordered secretion and excretion
of the bile acids in the pathogenesis of biliary cirrhosis? In the primary form of the disease, the formation of bile thrombi is not very marked (though always present) early in the disease; it is prominent and progressive in the later stages. By contrast, in secondary biliary cirrhosis, bile thrombi are evidently present at the earliest stage, but it is noteworthy that the other early histological changes in the liver, fibroblastic activity and cuffing of the bile ducts with an infiltration of round cells but not polymorphs (Shorter and Baggenstoss, 1959), give a picture not dissimilar from that of primary biliary cirrhosis.

Clearly there are many questions to answer. To describe the jaundice of biliary cirrhosis as 'cholestatic' seems hardly worthwhile, but that does not mean we must not continue to look for a reason why cholestasis and the formation of bile thrombi occur in this disease. It is suggested that, in primary biliary cirrhosis, there is damage to the endothelium lining the minute bile ducts and that in some way this interferes with the flow of bile and eventually damages those borders of the liver cells that define the canaliculi. What damages the bile ducts in the first instance? Hanot thought it was a catarrhal inflammation. There is evidence, now, of immunological disorders, but how far are these the cause, and how far the consequences, of whatever the primary injury might be? Indeed, there may be two combinations to the lock—a pathological injury and a tissue already constitutionally vulnerable.

The problem of cholestasis could not be better stated than by Popper and Schaffner (1970) who wrote, 'Cholestasis . . . is a disturbance of a secretion of micelles of bile salts. . . . This . . . results in alteration of bile canalicular microvilli, canalicular dilatation. . . . Cholestasis is perpetuated by the effects of retained bile on the hepatocyte'.

And, concerning the function of bile salts: 'The bile salts are the most important elements in the regulation of bile secretion'. 'The later injurious effects of cholestasis are thought to be caused, at least in part, by the accumulation of bile salts, which by their detergent action, decrease the function of the hypertrophic smooth endoplasmic reticulum' of the hepatocytes (Schaffner et al., 1971).

MODERN TIMES

Since the papers by Ahrens and others, the clinical and gross pathological aspects of primary biliary cirrhosis have been fully established and it would be an impertinence to attempt to add to them. The patient, more often than not a woman in middle life, begins first with itching, then with jaundice that shows most of the clinical and biochemical features of an obstructive type. Often, this is variable at first, but gradually becomes progressive until a deep bronzed green colour is attained. Clubbing of the fingers is sometimes seen (Gilbert and Lereboullet, 1902). The liver enlarges to a very considerable size and the spleen is sometimes palpable. As the lipid content of the serum rises, xanthomata appear, while the skin deepens in colour from an increased deposition of melanin. The patient remains in remarkably good health during the greater part of the illness,
because the liver cells themselves are but little damaged and the effects of portal hypertension and failure of hepatic function are seen only in the late stages of the disease when, after many years, the illness passes to its fatal conclusion. Treatment is generally believed to be of little avail, and, in a disease with a course so variable, it is difficult to assess the effects of steroid therapy. Since I first used corticosteroids in 1960, my impression is that their administration can have a favourable effect on the course of the disease, but the general opinion is that they are of limited or little value.

There is very little to say about secondary biliary cirrhosis as such, except that it is remarkable that it happens at all in the form in which we see it. It is commonplace to encounter acute ascending septic cholangitis from obstruction of the common duct (usually by a stone) and the production of intermittent biliary fever which causes, from time to time, even now, a fatal outcome. In acute cases, there may be no jaundice and the liver may be sown with minute abscesses the size of millet seeds, sometimes with the production of profound bacteraemic shock. But in some cases the course is more indolent, and the march of events is very like that seen in primary biliary cirrhosis. Even histologically the diagnosis may be difficult, though bile thrombi appear more marked in the earlier phases in the secondary form. A strange feature is that the pericholangitic cellular exudate is predominantly lymphocytic, while polymorphonuclear cells are few (Gall and Dobrogorski, 1961).

It is curious that, so far as I know, there have been no special studies of the bacteriological aspects of chronic biliary obstruction with consequent hepatic fibrosis. In the active forms, E. coli, Streptococcus faecalis and Klebsiella are the organisms most often found. Perhaps the cause of the chronic hepatic fibrosis in long-standing biliary obstruction lies in the obstruction rather than cholangitic infection. It may lie in the damming back of bile, the consequent interference with the normal flow of bile salts and the formation of bile thrombi. Associated with this is damage to the minute bile ducts, infiltration with round cells and intense fibroblastic activity. It is seen, then, that the two conditions, primary and secondary biliary cirrhosis, are not quite such separate entities as has been supposed.

Histology
Although we know that the minute anatomy of the liver is more like a lump of coral or the labyrinth of the Minotaur, rather than a honeycomb, the representation of the liver as made up of hepatic lobules—regarded only as diagrammatic—still has its value. In Fig. 2, the hepatic lobule, A, is represented as a hexagon with a minute radical of one of the hepatic veins at the centre (Kiernan, 1833). At the periphery, at the junctions of the hexagons, lie the portal tracts consisting of the ramifications of the bile ducts, the portal vein and the hepatic arteries. The conception of the hepatic lobule as a functional unit was questioned as long ago as 1888 by Brissaud and Sabourin, who demonstrated that the liver
parenchyma is centred round the portal vessels, not the hepatic venule, and first used the term ‘portal lobule’. The idea was developed by Mall (1906) and extended by Rappaport and Hiraki (1957). The portal lobule, B, consists of those parts of the hepatic lobules or acini (Rappaport, 1963) that radiate from a portal tract, the hepatic venules lying at the periphery. This makes a functional unit. The intrahepatic bile passages drain into the bile duct in the portal tract, where this is accompanied by a portal venule, hepatic arteriole, and lymphatics. The portal tract is encased in connective tissue, structurally a prolongation of Glisson’s capsule, and this condenses to form a fascial tube separating the liver parenchyma proper from the portal tracts. The bile passages penetrate this fascial lining together with minute arterioles and the finest portal venules. Separating the plate of hepatocytes from the sinusoids, lined with Kupffer cells, lies the space of Disse.

The names of the biliary passages have been the subject of some confusion, and different authors have given different names to the same structures, or they ascribed accepted names to differing portions of these passages. If we concentrate only upon the biliary passages, the structures can be represented as shown in Fig. 3. From this it will be seen that the intrahepatic bile canaliculus (bile capillary), whose walls are formed by the mural microvillus-bearing surfaces of the hepatocytes themselves, become interspersed with squamous, then cubical cells. There is no transition between hepatocytes and ductular cells. This structurally hybrid passage constitutes the canal of Hering. When the hepatocytes no longer take part in the wall of the tube, it becomes the cholangiole. The cholangiole emerges from the liver lobule to join a fine radical of the bile duct in the portal tract. The canal of Hering, together with the cholangiole, is termed the bile ductule. Heretofore, the term ‘canal of Hering’ was given to the whole of the bile passage we now call the ductule, that is, to the structure connecting the bile canaliculus with the bile duct (Williams, 1974).

All this is of importance in understanding the lesion in biliary cirrhosis. The primary injury is in the smallest bile ducts and the cellular, even granulomatous reaction, takes place in the portal tract, within the connective tissue where there are lymphatic vessels. It could only be so, because there is no lymphoid tissue beyond the portal tract. The bile thrombi form in the intralobular biliary passages; that is, in the cholangioles and canaliculi. Following this injury to the bile ducts, the surfaces of the parenchymatous cells of the liver, the hepatocytes, abutting on the canaliculi begin to show degenerative and even necrotic changes (Rubin et al., 1963). Similar changes are seen in secondary biliary cirrhosis which, therefore, cannot easily be distinguished from the primary variety on a single biopsy (Christoffersen and Poulsem, 1970).

Hadzyannis et al. (1970) studied the histological changes in relation to the immunological changes. Following Scheuer’s histological classification (1967), they confirmed the march of events as given above. The primary lesion of primary biliary cirrhosis is in the bile ducts themselves, as Hanot said, and the subsequent
Fig. 2. The structure of the liver (after Mall).
A = the hepatic lobule
B = the portal lobule

Fig. 3. The biliary collecting system in the liver.
damage to the ductules and the canaliculi, and eventually the liver cells themselves, are consequential events. What promotes this inflammation of the ducts in the first place? In secondary biliary cirrhosis, where there is damming back of bile, and stasis is always provocative of infection, the cause is ready to hand. What is the cause of the lesion in primary biliary cirrhosis?

**Immunology**

As neither infection, nor mechanical assault, can be invoked as causing injury to the biliary passages, the question naturally arises whether or not the condition of primary biliary cirrhosis is the result of some immunological disorder. In 1965, Walker *et al.* demonstrated that non-specific antibodies might be demonstrated by immunofluorescence and that the reaction was most marked in cells well endowed with mitochondria. These ‘antimitochondrial antibodies’ are present in the great majority of patients with primary biliary cirrhosis, but they are absent in secondary biliary cirrhosis. Quite apart from the great theoretical interest of the observation, this gave the clinical pathologist a most helpful way of distinguishing the two forms of cirrhosis that are so often difficult to differentiate. Anti-mitochondrial antibodies are sometimes found in other diseases—from 1 to 8 per cent in a variety of so-called ‘auto-immune’ and ‘collagen disorders’ (Walker, 1974; Doniach *et al.*, 1970), while figures as high as 16 per cent may occur in ‘drug jaundice’ (Walker and Doniach, 1971). It is not surprising that, in a disease such as biliary cirrhosis with a chronic parenchymatous destructive lesion, other immunoglobulin titres (especially IgM) may be raised, but in a minority of cases and without, it seems, particular significance, diagnostic or otherwise. In biliary cirrhosis, no specific antibody against material derived from the liver has been found, although Edelston *et al.* (1973) demonstrated cell-mediated immune responses to a protein fraction from human bile both in cases of primary biliary cirrhosis and in ‘chronic active hepatitis’.

On such evidence rests the case for regarding primary biliary cirrhosis as an immunologically determined disease. I say immunologically determined, rather than ‘auto-allergic’, for true auto-immunisation is rare. Immunological reactions are commonplace. Even in the healing of a simple wound they occur. So many conditions labelled auto-immune are essentially hetero-immune. In many diseases where antibodies can be demonstrated they are antibodies to altered auto-proteins—denatured globulins and the like. I showed, in 1938, that it was a simple matter to insert a quinone radical into the molecule of serum albumin and so produce a specific antibody to this new antigen, not only in animals of a different species, but in animals of the same species. If so simple a procedure can produce specific antigens (and presumably something like that accounts for allergic reactions to simple chemical substances like nickel and aspirin), then minute modification of a protein as a consequence of any kind of assault might lead to a train of reactions in which the immunological features were so assertive as to dwarf whatever injury was the primary exciting cause.
There is no need to assume that because a pathological process gives rise to the appearance of lymphocytes in the tissues, the condition is an ‘auto-immune disease’. The current view is that the T-lymphocyte is a cell committed to auto-allergic activities, that is, self-destructive processes. But surely, in the great majority of instances in which it appears, it is carrying out its ordinary function, which is that of protecting the ‘self’ from an invading agent.

It seems to me that there are no qualitative differences in immunological reactions, only quantitative differences. In biliary cirrhosis, it does appear that the earliest detectable abnormality is injury to the epithelium of the biliary ducts. We still do not know the cause of this injury.

To conclude, Hippocrates wrote, ‘Medicine has for long possessed the qualities necessary to make a science. These are original observations and a known method according to which many valuable discoveries have been made over a long period of time. By such a method, too, the rest of the science will be discovered if anyone who is clever enough is versed in the observations of the past, and makes these a starting point of his researches’.

ACKNOWLEDGEMENTS
I am grateful to my colleagues at Guy’s Hospital Medical School, Professor C. W. M. Adams and Professor P. L. Williams, for their kind and generous advice.

References
Adams, C. W. M. (1974) Personal communication.
Addison, T. and Gull, W. (1851) Guy’s Hospital Reports, 7, 265.
Ahrens, E. H., Jr. and Kunkel, H. G. (1949) Journal of Clinical Investigation, 28, 1571.
Ahrens, E. H., Payne, M. A., Kunkel, H. G., Eisenmenger, W. H. and Blondheim, S. H. (1950) Medicine, 29, 299.
Brissaud, E. and Sabourin, C. (1888) Comptes rendus de la Société de Biologie, 8, série, 5, 757.
Brown, J. (1685) Philosophical Transactions of the Royal Society, 15, 1266, and Table 3, Fig. 1, facing 1251.
Cameron, R. and Hou, P. C. (1962) Biliary Cirrhosis, p. 82. Edinburgh and London: Oliver and Boyd.
Chambard, E. (1878) Bulletin de la Société Clinique de Paris, 2, 251.
Charcot, J. M. and Gombault, A. (1876) Archives de Physiologie Normal et Pathologique, 11e serie, tom. 3, 8e année, 272.
Christoffersen, P. and Poulsen, H. (1970) Acta Pathologica et Microbiologica Scandinavica, Section A-B, Supplement 212, 150.
Cullinan, E. R., King, R. C. and Rivers, J. S. S. (1958) British Medical Journal, 1, 1315.
Doniach, D., Walker, J. G., Roitt, I. M. and Berg, P. (1970) New England Journal of Medicine, 282, 86.
Edelston, A. L. W. F., McFarlane, I. G., Mitchell, C. G., Reed, W. D. and Williams, R. (1973) British Medical Journal, 4, 274.
Gall, E. A. and Dobrogorski, O. (1961) American Journal of Clinical Pathology, 11, 2, 126.
Gilbert, M. A. (1896) Bulletin et Memoires de la Société Médicale des Hôpitaux de Paris, 35, 13, 735.
Gilbert, A. and Lereboullet, P. (1902) Gazette Hebdomadaire de Médecine et de Chirurgie, 49, 1.
Hadziyannis, S., Scheuer, P. J., Feizi, T., Naccarato, R., Doniach, D. and Sherlock, S. (1970) Journal of Clinical Pathology, 22, 95.
Hanot, V. C. (1875) Etude sur une Forme de Cirrhose Hypertrophique de Foie, Thèse de Paris, 465: 155, Paris.
Hanot, V. C. (1892) La Cirrhose Hypertrophique avec Ictère Chronique, Paris.
Hippocrates (5th cent., B.C.), Tradition in Medicine, 2, in The Medical Works of Hippocrates, trans. J. Chadwick and W. N. Mann. (1950) p. 12. Oxford.
Kiernan, F. (1833) Philosophical Transactions of the Royal Society, 123. 711.
Laennec, R. T. H. (1819) De L'Auscultation Médiante, § 387. Obs. XXV.
Legg, J. W. (1873) St Bartholomew's Hospital Reports, 9, 161.
Mall, F. P. (1906) American Journal of Anatomy, 5, 227.
Mangelsdorf, J. (1882) Deutsches Archiv für Klinische Medicin, 31, 522.
Mayer, H. (1872) Medizinischer Jahrbücher (Wien), p. 133.
Morgagni, J. B. (1761) De sedibus et causis morborum, Lib V, Epist. Anat. Medica, Art. XXX, 101. Venice.
Morgagni, J. B. (1819) Seats and Causes of Diseases, trans. B. Alexander, letter 38, §30, 302, 306. London.
Moxon, W. (1873) Transactions of the Pathological Society of London, 24, 242.
Murchison, C. (1868) Diseases of the Liver, p. 293. London.
Paton, A. (1969) Liver Disease, p. 42. London: Heinemann.
Popper, H. and Schaffner, F. (1970) Human Pathology, 1, 1.
Quinquaud, M. (1878) Bulletin de la Société Clinique de Paris, 2, 259.
Rappaport, A. M. (1963) In The Liver (Ed C. Rouiller). New York and London: Academic Press.
Rappaport, A. M. and Hiraki, G. Y. (1957) Acta Anatomica, 32, 126.
Rayer, P. (1826) Traité des Maladies de la Peau, plate xxii, item 15. Paris.
Rubin, E., Schaffner, F. and Popper, H. (1963) Journal of the American Medical Association, 183, 334.
Schaffner, F., Bacchin, P. G., Hutterer, F., Scharnbeck, H. H., Sarkorzi, L. L., Denk, H. and Popper, H. (1971) Gastroenterology, 60, 5, 888.
Scheuer, D. J. (1967) Liver Biopsy Interpretation, p. 22. London: Baillière Tindall.
Sherlock, S. (1972) In Recent Advances in Gastroenterology (Ed J. Badenoch and B. N. Brooks), p. 309. Edinburgh and London: Churchill Livingstone.
Sherlock, S. (1974) In The Liver and its Diseases (Ed. E. Schaffner, S. Sherlock and C. M. Leevy), p. 227. New York: Intercontinental Medicine.
Shorter, R. G. and Baggenstoss, A. H. (1959) American Journal of Clinical Pathology, 32, 5.
Smith, P. M., Studley, F. and Williams, R. (1967) Lancet, 1, 133.
Thannhauser, S. J. and Magendautz, H. (1938) Annals of Internal Medicine, 11, 1662.
Van Berge Henegouwen, G. P., Brandt, K. H. and de Pagter, A. G. F. (1974) Lancet, 1, 1249.
Versalius, A. (1543) De humani corporis fabrica, V, 507. Basel.
Versalius, A. (1725) Opera omnia anatomica et chirurgica, cura Boerhave, H. et Albini, B.S., II, 674. Leyden.
Virchow, R. (1857) Verhandlungen der Physikalisch-Medicinischen Gesellschaft in Würzburg, 7, 21.
Vischer, T. L. (1970) British Medical Journal, 1, 695.
Walker, J. G. (1974) Proceedings of the Royal Society of Medicine, 67, 566.
Walker, J. G. and Doniach, D. (1971) In Immunology of the Liver (Ed. M. Smith and R. Williams), p. 55. London: Heinemann.
Walker, J. G., Doniach, D., Roitt, I. M. and Sherlock, S. (1965) Lancet, 1, 827.
Whitlock, F. A. (1951) American Medical Association Archives of Dermatology and Syphilology, 64, 23.
Williams, P. L. (1974) Personal communication.
Williams, R. (1967) Proceedings of the Royal Society of Medicine, 60, 1254.
Wyss, O. (1866) Virchow's Archiv für Pathologische Anatomie und Physiologie und für klinische Medicin, 35, 553.