CIRRHOSIS OF THE LIVER

A clinical study of 100 cases in Glasgow, 1946 - 1957.

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C O N T E N T S

INTRODUCTION

This thesis is based on a study of 100 patients in whom a diagnosis of cirrhosis of the liver was made. All but 4 of the patients were admitted to the Professorial Medical Unit in the Royal Infirmary, Glasgow, between 1946 and 1957. The 4 exceptions were examined at the out-patient department of the hospital.

Although much has been written about liver disease in the past 20 years, there have been very few publications devoted to the clinical picture and natural history of cirrhosis in any one part of this country, and, as far as I am aware, a study of this nature has not been reported from the West of Scotland. Such a study is of interest because cirrhosis is not an entity in itself but an end stage of several pathological processes, some of which are recognised while others are still obscure. It is therefore valuable to analyse from time to time, in the light of present knowledge, the nature and importance of the several predisposing causes and to record the changes which have taken place in the aetiology and course of the disease. This I have endeavoured to do, with particular reference to portal cirrhosis, about which so much remains unknown.

The thesis is composed of 9 chapters, the first 7 of which are concerned with portal cirrhosis and the last 2 with biliary cirrhosis and haemochromatosis. In the appendix the case histories of the 89 patients with portal cirrhosis are reported, and 13 of the cases are illustrated with photomicrographs.

The aetiology, clinical picture and course of portal

cirrhosis are described in detail and the problem of diagnosis discussed.

Neither biliary cirrhosis nor haemochromatosis are common, and the small numbers involved made it difficult to draw firm conclusions. Examples of both primary and secondary biliary cirrhosis are cited and the value of operative cholangiography in the diagnosis of the problem case of obstructive jaundice is emphasised. In the final chapter on haemochromatosis I have compared my clinical experience with that reported by the leading authorities on the disease, and I have drawn attention to the frequency of duodenal ulcer as an associated phenomenon. The unusual occurrence of haemochromatosis in a woman is described.

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CHAPTER 1

Aetiology of Portal Cirrhosis

Although there have been many advances in our knowledge of the aetiology of liver diseases in the past twenty years, the problems concerned with the aetiology of portal cirrhosis remain largely unsolved. One of the reasons for the slow advancement of our knowledge in this field may lie in the failure to recognise that many injurious factors may produce the same clinical and pathological pictures, and our efforts to apply an explanation which will fit one group of patients may not fit another. The causal factors would appear to vary from country to country and advances in knowledge from one part of the world may not be applicable to another. Veno-occlusive disease, for example, is a not uncommon cause of cirrhosis in the West Indies and is probably due to a toxin derived from the infusion of certain local plants. The pathogenesis of this disease has only recently been discovered and there is, as far as is known, no counterpart in this country. Cirrhosis is also common in Hong Kong and is almost always attended by massive splenomegaly. In some instances splenomegaly may precede the recognition of the hepatic lesion. The cause of the disease almost certainly differs from the cause in Britain. In some parts of the United States the association between alcoholism and portal cirrhosis is so close that for many writers there the term portal cirrhosis is synonymous with alcoholic cirrhosis. This is not the case in the Glasgow area.

In recent years it has been tempting to apply data gained from animal experiments to clinical problems and to blame dietary deficiency for the disease in all regions of the globe. This, too, has certain pitfalls and some of the discrepancies which cannot be ignored are summarised by Waterlow and Bras (1957). They record, for example, that the incidence of fatty liver disease in Brazil is high but cirrhosis is uncommon and, conversely, cirrhosis is often found in Gambian children but is seldom preceded by fatty liver disease.

The present chapter is based on a study of eighty-nine patients with portal cirrhosis, all of whom were seen by one Medical Unit in Glasgow Royal Infirmary between 1946 and 1957. Seventy-one of the patients were seen and examined personally.

In the search for possible aetiological factors the following five points were carefully assessed:

1. Presence or absence of a history of excessive alcohol consumption either past or present.
2. Presence or absence of a history of jaundice.
3. The dietary habits of the patients with special reference to protein intake.
4. Presence or absence of a history of gall-bladder disease or of biliary colic.
5. Presence or absence of exposure to a hepato-toxic chemical recently or in the past.

In those patients who were not seen personally some assessment was made where the case notes were adequate. Fortunately the standard records consisted of a series of

printed questions answered at the time of admission, dietary history and alcohol consumption being included in the questionnaire, so that it has been possible to make an assessment in most instances.

A patient was considered to be alcoholic if he admitted either to habitual drinking to excess or to heavy bouts of drinking over a period of years. It is difficult to define exactly what is meant by "excess". Each patient was asked how much money was spent on alcohol a week. Over two pounds a week for a period of years was regarded as the lower limit of excess and in fact all the patients judged to have alcoholic cirrhosis exceeded this figure or spent £1 to £2 weekly for very many years.

Jaundice was often considered by the patient to be synonymous with a bad colour, or a feeling of nausea, and a positive history of hepatitis was not accepted unless the patient had observed a yellow colouration of the skin or had dark urine with pale stools in association with the general symptoms of hepatitis.

The dietary history was taken with reference to the composition of the main meal of the day and to the amount of meat, fish, eggs, milk and cheese taken in an average week. Many patients were extremely vague in replying to questions concerning their dietary habits and it soon became apparent that the very broadest of classifications should be used. The diet has therefore been considered poor when the patient took little meat or first-class protein. Such patients ate meat

about once a week or less often, bought fish infrequently, and did not drink milk. Their main meal of the day consisted of soup (usually vegetable), potatoes, vegetable, tea and bread. Those who ate meat several times a week and who had an average two course meal each day were judged to have an average diet. In some instances, I believe that this diet was inadequate, but it did not differ from the diet taken by many other patients admitted to hospital, and who had not cirrhosis. The dietary classification is therefore on the broadest lines consisting of only two groups of patients, namely, those with an average, and those with a poor diet.

In this thesis the usual social classification has been used:

Class 1. Higher salaried professional and business people.

Class 2. Middle-class professional and business people - e.g. clergy; schoolteachers; shopkeepers.

Class 3. Skilled workers.

Class 4. Semi-skilled worker.

Class 5. Unskilled worker.

In addition to data already mentioned, each case report has been carefully studied to determine whether any hitherto unrecognised factor was responsible in part or in whole for the development of cirrhosis.

The aetiology of portal cirrhosis will be discussed under the three headings of alcoholic cirrhosis, post-hepatitis cirrhosis, and cryptogenic cirrhosis.

a) Alcoholic Cirrhosis

The association of alcoholism with cirrhosis has never

been disputed, although the precise nature of the relationship is still undetermined. There is evidence that alcohol may exert a direct toxic action on the liver, even when the diet is adequate in protein (Ashworth, 1947), but hepatic cirrhosis of comparable severity to that seen in man has never been produced in laboratory animals. Alcohol may cause liver damage indirectly by impairment of nutrition. It has been convincingly demonstrated that deficiency of certain amino-acids will lead to fatty infiltration and ultimately to diffuse hepatic fibrosis, and such is the usual sequence of events in alcoholic cirrhosis (Himsworth, 1950). Lastly, alcohol may potentiate the action of other hepato-toxic substances, such as chloroform (Rosenthal, 1940).

The incidence of alcoholic cirrhosis varies from time to time and from place to place. In the United States it is still the commonest cause of cirrhosis, accounting for 54 per cent (Patek and Post, 1941) to 92 per cent (Olsen, 1950) of all cases of cirrhosis. In France the position is similar to the United States; Chabrol and Girauld (1953) have stated that 94 of 98 patients with cirrhosis admitted to one Paris hospital since 1945 were chronic alcoholics. In this country there has been a gradual decline in the association of the two conditions from approximately 50 per cent before the first world war (Garland and Philips, 1953) to 18 per cent at the present time (Sherlock, 1955). In some areas alcoholic cirrhosis would appear to be even less common than the latter figure would suggest. In Oxfordshire, not one of 35 cases of cirrhosis was attributed to

alcoholism (Kelsall, Stewart and Witts, 1947). Nevertheless in most areas of Great Britain there are still a small number of patients in whom excessive alcohol consumption would appear to be responsible in some part for the development of cirrhosis.

In this study alcoholic excess was judged to be the causal factor in 10 of the 89 patients (11 per cent). In addition, 2 patients with a past history of jaundice drank excessively and it is uncertain whether alcohol, infective hepatitis, or both of these factors was responsible for the development of cirrhosis. Four patients with cryptogenic cirrhosis had regularly consumed a quantity of alcohol that was above average at some period in their lives, but the quantities professed to be taken were not such as to suggest that these patients were suffering from alcoholic cirrhosis.

All 10 patients with alcoholic cirrhosis were male; 7 were in the age group 30 - 45 while the other 3 were older. Two patients had a skilled trade (social class 3), three were semi-skilled (social class 4) and five were unskilled (social class 5). Alcohol consumption ranged from over £1 a week to about £10 a week, and all but one patient had consumed alcohol to excess for many years, the majority for over 10 years (Table 1). The exception, case 7, had become a heavy drinker after demobilisation from the army, consuming about a bottle of whisky a day between 1946 and 1947. He then became more temperate in his habits, drinking only at weekends. In 1953 he had his first haematemesis and he died in 1954.

Two of the patients were predominantly beer and stout

TABLE 1

Aetiological data on 10 patients with alcoholic cirrhosis

Case No.	Age	Sex	Social Class	Alcohol Consumption per week	Duration	Type	Diet
1	39	M	3	£5-10	16 years	Whisky	Average
2	55	M	4	£5	15 years +	Whisky and beer	Average
3	61	M	5	£1-2	40 years	Whisky and beer	Poor
4	39	M	3	£2-3	15 years +	Beer	Average
5	44	M	5	£2 +	10 years	Beer	Poor
6	32	M	5	£5-10	many years	Whisky and beer	Poor
7	34	M	5	£5	2 years	Whisky	Average
8	38	M	4	£5 +	about 20 years	Whisky Rum	Average
9	42	M	5	£2 +	10 years +	Whisky	Poor
10	69	M	4	£1-2	very many years	Wine	Average

drinkers, one patient drank wine, and the other 7 drank whisky for preference but also drank beer and occasionally other spirits.

Diet was poor in 5 patients and average in the other 5. No patient was emaciated or showed stigmata of vitamin deficiency. One patient (case 6) had previously been in a psychiatric ward with delirium tremens, but no other patient gave a history of alcoholic psychosis and no patient had peripheral neuritis.

Direct questioning failed to elicit a past history of infective hepatitis in any patient, and no-one was thought to have chronic cholecystitis.

Histological material from the liver was obtained at post-mortem in cases A5, A7, and A9. Diffuse hepatic fibrosis was present in cases 5 and 9, but case 7 had a coarse multilobular cirrhosis with considerable round cell infiltration in the bands of fibrous tissue, so that post necrotic scarring of infective origin could not be excluded. The histology of case A9 is shown in figure 1. (See appendix).

This group of patients is remarkable in 4 respects: all the patients were male; all were, or had been, alcoholics; the majority belonged to the lower social classes; and 50 per cent consumed a diet that was definitely substandard. In all 4 respects this group of patients differed from those with post-hepatitis and cryptogenic cirrhosis.

It is difficult to believe that dietary deficiency alone was responsible for the development of cirrhosis, when no

patient was obviously malnourished, and when 50 per cent would not admit to an abnormal dietary regime. Furthermore when 119 patients with pernicious anaemia attending the same medical unit were similarly questioned about their dietary habits, 12 per cent were equally below standard, but none had clinically obvious cirrhosis. It is quite possible, of course, that in certain instances alcohol and dietary deficiency had an additive effect leading to hepatic parenchymal damage, while in others alcohol combined with some unrecognised factor to produce the same clinical and pathological picture. It is well known that the consumption of even a small quantity of alcohol by a patient convalescent from infective hepatitis may lead to a recurrence of jaundice, and this may be but one example of how two hepatotoxic factors may act in concert. Two of the patients with post-hepatitis cirrhosis, presently to be described, had an alcohol consumption which was above average, but both had excellent dietary histories. As both patients had apparently mild infections, it may be that the combined assault of alcohol and virus on the hepatic parenchyma led to areas of massive necrosis with the subsequent development of post-necrotic scarring.

The social classification of patients with alcoholic cirrhosis was low. Presumably the better dietary habits of the well-to-do affords a measure of protection from alcoholic cirrhosis. The same may be true of those communities, such as the Armed Forces, among whom alcohol consumption is high but where food is provided and the diet scientifically balanced.

When it is remembered that the cause of cirrhosis is

undetermined in over 50 per cent of patients, it might be argued that the association of cirrhosis and alcoholism in 11 per cent of cases was fortuitous. However, the association has long been recognised, both in this country and abroad, so that it is likely that alcohol is still a factor in the development of cirrhosis in a certain proportion of cases.

b) Post-hepatitis cirrhosis

It is now well recognised that cirrhosis may occur as a sequel to hepatitis although the reasons for this uncommon complication are not so well understood (Bloomfield, 1938; Rennie, 1945; Sherlock, 1948; Reynell, 1954). In this study 30 patients (34 per cent) gave a past history of jaundice. In 28 patients jaundice was believed to have been caused by the virus of infective hepatitis, while 2 patients had homologous serum jaundice. The clinical data relating to all 30 cases is given in Table 2.

The sexes were almost equally affected with a slight female predominance: 16 females to 14 males. The age distribution ranged from the second to the eighth decade, but the majority of patients were in middle life. Fifteen patients were in the upper 3 social classes, 8 were in classes 4 and 5, and 7 female patients were unclassified through lack of knowledge of their social circumstances.

Two patients gave a history of above average alcohol consumption, and in both the dietary history was satisfactory.

Three patients gave unsatisfactory dietary histories out of 25 in whom adequate information was available. One further

TABLE 2

Aetiological data on 30 patients with post-hepatitis cirrhosis.

Age in Decades	No. of patients	Sex	Social Grade	No. of patients
0-10	0			
11-20	1	Male 14	Grade 1 -	2
21-30	3		Grade 11 -	3
31-40	8	Female 16	Grade 111 -	10
41-50	7		Grade 1V -	4
51-60	8		Grade V -	4
61-70	2		Housewives (Unclassified) -	7
71-80	1			

Alcohol Consumption Above average	Dietary Deficiency	Cholecystitis and Cholelithiasis
7% (2 patients) Both in social grade 1. Cases J1 and J24.	10 per cent (3 patients) Cases J3, J17, J18. Diet unknown in 5 patients.	13 per cent (4 patients: Cases J1, J4, J9 and J30).

patient had idiopathic steatorrhoea and was greatly wasted. The malabsorption of certain products of digestion may have contributed to his liver disease (case J19).

A history of gall bladder dyspepsia was given by 4 patients and 3 of the 4 had gall stones (cases J1, J4, J9 and J30). The diagnosis of cirrhosis was confirmed at operation in all 4 patients, and only in case J30 was there doubt about the type of cirrhosis. This patient had had infective hepatitis in 1924, but had remained well until 1956, when she lost energy and complained of flatulent dyspepsia and upper abdominal discomfort. A small haematemesis led to admission to hospital. Clinically the liver was enlarged and firm, while the histology of a portion obtained by surgical biopsy showed areas suggestive of early biliary cirrhosis, while other areas appeared typical of portal cirrhosis. As no firm conclusion on the cause of the hepatic lesion was reached, the patient has been included in this section because of the past history of jaundice. One further patient must be mentioned (case J20) because of an opacity to the right of the third lumbar vertebra which may have been either a gall stone or a calcified gland. Radiology was not helpful in elucidating this problem and laparotomy was thought to be inadvisable. The clinical history of this case was much more suggestive of infective hepatitis than of gall bladder disease.

A definite interval between the attack of jaundice and the recognition of cirrhosis was observed in 15 patients

(Table 3) and no such interval in 15 patients (Table 4). In the latter group jaundice was continuous over a period ranging from a few months to 5 years, and the prognosis was poor. In the former group the latent interval varied from a few months to 33 years, but was usually 1 to 6 years.

The histology of cases J4, J5, J7, J23 and J26 is shown in figures 2 - 6. (See appendix).

It is essential to have an understanding of the pathology of liver necrosis in order to discuss the problem of why some patients with infective hepatitis should later develop cirrhosis, and the following account is based on the description given by Himsworth (1950). There are two forms of hepatic necrosis, zonal necrosis and massive necrosis. These terms refer only to the extent of the damage within a liver lobule and not to the extent of the damage within the liver as a whole. Zonal necrosis is an acute process affecting every lobule throughout the liver, but the prognosis is good and most patients make a complete functional and anatomical recovery. Should recovery not occur, the patient succumbs to the acute phase of the disease, for zonal necrosis does not exist in a subacute or chronic form. Recurrent attacks of zonal necrosis may lead to the development of cirrhosis.

Massive necrosis, on the other hand, may be either acute or subacute, only part of the liver is affected, and the remaining lobules may be histologically normal or be the site of a zonal lesion. Massive necrosis is never followed by anatomical recovery. Instead, surviving cells proliferate

TABLE 3

Latent interval between attack of jaundice and clinical recognition of cirrhosis in 15 patients. The prognosis for these cases until death or until 1957 is given.

Case No.	Duration and/or intensity of jaundice	Latent Interval	Prognosis after diagnosis of cirrhosis.
1	Mild : a few weeks	3 years	Died 1 year later
2	6 weeks	6 years	Died 4 years later
4	1 week : ill 3 months	25 years	Post-operative death
7	6 weeks : recurrence some months later.	5 years	Died 1st admission
9	18 months	12 years	Untraced after 1 year
10	3 months	3 months	Untraced after 6 months
11	2 weeks : mild	6 years	Alive 1 year later
15	6 months	2 years	Post-operative death
17	2 weeks : mild	6 years	Alive, first seen, 1957.
19	6 months : clinically mild	3 years	Died 2 years later

TABLE 3 (Cont'd.)

Latent interval between attack of jaundice and clinical recognition of cirrhosis in 15 patients. The prognosis for these cases until death or until 1957 is given.

Case No.	Duration and/or intensity of jaundice	Latent Interval	Prognosis after diagnosis of cirrhosis.
20	3 weeks : mild	2 years	Alive 7 years later
24	A few weeks : mild	1 year	Died 18 months later
25	Jaundice 1 month Ill 5 months	6 months	Alive 2 years later
29	Unknown	1 year	Died 1 year later
30	3 weeks	33 years	Alive, first seen, 1957.

TABLE 4

Duration of jaundice until death or until March, 1957 in 15 patients in whom jaundice was continuous or recurrent with only short or doubtful intervals of freedom from icterus.

Case No.	Duration of Jaundice	Alive or Dead
3	1 year	Dead
5	2 years	Dead
6	3 years	Dead
8	2 years	Dead
12	3 years	Dead
13	1 year	Dead
14	4 years	Dead
16	2 years	Alive
18	18 months	Alive
21	5 months	Dead
22	1 year	Dead
23	3 months	Dead
26	3 years	Dead
27	4 years	Dead
28	5 years	Dead

to form nodules without a lobular pattern, and the necrotic areas are replaced by fibrous tissue. The outcome is therefore either death in the acute phase (acute yellow atrophy) or recovery with cirrhosis.

The commonest cause of zonal necrosis is viral hepatitis in which the illness is acute and complete recovery usual. Sometimes, however, when the infection is very virulent or the resistance of the patient lowered, viral hepatitis may progress from a zonal to a massive lesion. The illness is then of longer duration and of greater severity. Complete recovery can no longer take place, and the sequel is post-necrotic scarring which is another term for cirrhosis. This is the generally accepted explanation for the development of post-hepatitis cirrhosis, and study of the clinical histories of the 30 patients under review generally supports this explanation. Fifteen patients had persistent jaundice from the onset of an illness believed to be infective hepatitis to death from cirrhosis. Four patients had jaundice for 3 months or more, acceptable evidence that massive necrosis had taken place during the acute phase of hepatitis (cases J9, J10, J15, and J19). A history of recurrent attacks of jaundice, sometimes of mild degree, was given by a further 7 patients (cases J1, J2, J7, J18, J20, J22, J24). It was believed that viral infection was responsible for jaundice in each case, although it is impossible to be dogmatic on this point. Calculus was excluded as far as possible, and in the 3 patients who came to post-mortem no gall stones were found. The possibility that jaundice was due to

cirrhosis and not to a persistently active viral infection was considered, but rejected. Jaundice is not an early or a prominent feature of portal cirrhosis, occurring usually as a terminal event with parenchymal failure (Rolleston and McNee, 1929), and all of these patients survived for at least a year after the onset of jaundice. It is therefore believed that the illness from which they suffered was a prolonged hepatitis, but it is not known whether cirrhosis was the result of recurrent attacks of zonal necrosis or the initial occurrence of a limited massive necrosis.

In 3 patients jaundice appeared to have been brief and the reason for the subsequent development of cirrhosis is obscure (cases J4, J11 and J25). In one patient (J29) the information regarding the duration and severity of jaundice is inadequate.

The basic reason for the progression of infective hepatitis to cirrhosis is usually ascribed to a particularly virulent infection. Occasionally, however, there is evidence of increased susceptibility of the soil as, for example, in the 3 patients with dietary deficiency, the two patients with above average alcohol consumption, and the patient with steatorrhoea. It is perhaps noteworthy that 3 of these 6 patients had recurring attacks of jaundice, suggesting that the virus may have remained active within the liver instead of succumbing to the defences of the body.

Eight patients gave a history of ill health which preceded the recognition of jaundice by weeks, months, or even by a year or more (cases J2, J5, J15, J16, J21, J23, J25 and J28). Certain

other patients gave a history that was not typical of infective hepatitis in that jaundice was of slight degree or symptoms mild in character. The significance of such an illness in terms of hepatic pathology is uncertain, but it is possible that it represented subacute necrosis. The relationship between these patients and certain other patients with cryptogenic cirrhosis who had similar symptoms but who never became jaundiced is also uncertain, but there may be a connection between the two. Further reference to this will be made in the section on cryptogenic cirrhosis.

In summary, this group of 30 patients with post-hepatitis cirrhosis differed from those with alcoholic cirrhosis in age, sex, and social classification. The reason for the progressive course of the hepatitis can mainly be attributed to the excessive severity of the infection, but in a small proportion of patients (20 per cent) dietary deficiency, alcohol consumption and intestinal malabsorption may have been responsible for the progression of a reversible hepatitis to irreversible cirrhosis. About one quarter of the cases were atypical in that prodromal symptoms preceding jaundice were of unusually long duration. It is suggested that there may be a linkage between this group of patients and certain patients with cryptogenic cirrhosis who had similar symptoms but who never became jaundiced.

c) Cryptogenic cirrhosis

Many patients with undoubted portal cirrhosis give no history of antecedent jaundice or of excessive alcoholism, and the cause of their disease usually defies elucidation. The

assumption, which is often made, that all such cases are the result of infection by the virus of infective hepatitis, the initial infection having passed unnoticed, is, to my mind, unwarranted. In this country there has been a growing awareness of the frequency of cryptogenic cirrhosis, commencing with the report of Kelsall, Stewart and Witts (1947) who gave the incidence as 37 per cent, to the more recent report of Sherlock (1955) who observed an incidence of 49 per cent. My experience has been similar to that of Sherlock in that 54 per cent of 89 patients had no generally accepted cause for their disease. In this section I wish to consider in what manner such cases differed from those with alcoholic and post-hepatitis cirrhosis. I shall also suggest possible aetiological factors.

Alcoholic cirrhosis is a disease of males; post-hepatitis cirrhosis has an equal sex distribution; cryptogenic cirrhosis was commoner among females in the ratio 5 females to 3 males. A difference in the age incidence was also observed. Both alcoholic and post-hepatitis cirrhosis were commoner under the age of 50 years; cryptogenic cirrhosis was more frequent over the age of 50. The social classification resembled the alcoholic group in that 53 per cent of the 30 patients who could be accurately classified belonged to social grades 4 and 5. The relevant clinical data pertaining to all 49 patients is summarised in Table 5.

With the exception of Wilson's disease, a family history of cirrhosis is unusual, and the majority of reports have been concerned with children (Rolleston and McNee, 1929; Ratnoff and

TABLE 5

Aetiological data of 49 patients with cryptogenic cirrhosis

Age in Decades	No. of patients	Sex	Social Class	No. of Patients	Alcohol consumption more than average at some period in past.
11-20	1	Male 18	Grade 1	2	
21-30	2		Grade 11	5	5 per cent
31-40	5	Female 31	Grade 111	7	Cases C5,
41-50	13		Grade 1V	4	C7, C17,
51-60	14		Grade V	12	C18.
61-70	9		Unknown	19	
71-80	5		(Mostly housewives in Grades 1V and V)		

Diet below average
23 per cent
Cases C1, C7, C9,
C19, C22, C26, C29,
C30, C35 and C46.
(Dietary history not known in 6 patients).

Patek, 1942). In the present study 3 patients gave a family history of cirrhosis: cases C8 and C34 were first cousins; case C19 stated that his brother was known to have had a large spleen and to have died from a massive haematemesis.

A history of inadequate diet was given by 10 of the 42 patients (25 per cent) in whom adequate data was available. This figure is appreciably higher than that for post-hepatitis cirrhosis (10 per cent) but lower than that observed for the alcoholic patients (50 per cent). One patient, case C7, had been a prisoner of war with the Japanese. For 3 years diet had been extremely poor, and he had suffered from beri-beri and from recurrent malaria. After the war he returned to the East, and for two years alcohol consumption was above average. In 1948 he had the first of several haematemeses and he died in 1949. This is the only patient with cirrhosis that I have encountered who had been in a Japanese prison camp, yet many thousands of men lived for years in conditions of near starvation without there being, as far as I am aware, an increased incidence of liver disease as a sequel.

Alcohol consumption had been above average at some time in 4 patients (8 per cent), but the amount was less than that generally associated with cirrhosis, and it was not thought to be the predominant cause of the disease.

In approximately 25 per cent of patients there co-existed a disorder which possibly had a bearing on the aetiology of their cirrhosis. These cases merit further discussion because the association is not generally accepted as aetiological.

They will be considered under the heading of the extra hepatic disorder:

a) Steatorrhoea

Two patients, cases C36 and C42 were thought to have steatorrhoea; the diagnosis was proved by fat balance in the former case but not in the latter. The clinical features of case C42 were strongly suggestive of intestinal malabsorption, namely, a very frankly megaloblastic anaemia unresponsive to Vitamin B12 but fully responsive to folic acid. Free hydrochloric acid was present in the gastric juice. The diagnosis of cirrhosis was proved at post-mortem. It will be recalled that one patient with post-hepatitis cirrhosis was also shown to have steatorrhoea in the absence of jaundice. The association between liver disease and steatorrhoea due to pancreatic insufficiency has been described by Sherlock (1955) and by Norris (1957) but there is only a single report of the occurrence of cirrhosis with idiopathic steatorrhoea (Arends, Niewag and Engelhardt, 1954). The association is likely to be more than fortuitous as steatorrhoea is not a common disease in this country. Intestinal malabsorption may be directly responsible for hepatic damage, or alternatively it may render the liver unduly susceptible to damage by some other agent.

b) Pregnancy

The association of pregnancy with cirrhosis is unusual but has been described (Slater 1954). The liver may be damaged in several ways during the course of pregnancy. The dangers of infective hepatitis are increased, as the foetus

has first call on the essential products of digestion, thus causing a relative or absolute deficiency, depending on the dietary intake of protein. Secondly, in the early months of pregnancy 'toxic' vomiting may occasionally be responsible for centrilobular necrosis. Thirdly, the liver may be damaged in eclampsia, periportal haemorrhage occurring in the early stages and lobular necrosis in the more fulminating form (Browne, 1947). It is still unknown whether this lesion is in fact caused by a toxin, or whether it is an allergic vascular reaction similar to that which occurs in the kidney in acute nephritis.

Three of the 31 female patients dated the onset of their illness to pregnancy. None of these patients was known to have had toxaemia of pregnancy.

Case C9: Transient ascites developed after pregnancy in 1939. Admitted to another hospital where a diagnosis of splenic anaemia was made. Ascites subsided and did not recur until 1946, when both liver and spleen were noted to be enlarged. This patient survived until 1953 despite numerous haematemeses and frequent paracenteses during the last year of her life.

Case C38: Malaise, anorexia, lassitude followed the birth of a 6th child although there were no clinical features such as anaemia to account for her symptoms. Admitted to hospital 11 months after child-birth with ascites and hepatomegaly. Ascites subsided spontaneously. Splenomegaly has recently been observed, eighteen months after the onset

of symptoms.

Case C43: General malaise persisted after a 4-month miscarriage in June 1952. In September 1953 the patient became aware of left upper abdominal fullness and right upper abdominal discomfort. For several months prior to this she thought her abdomen had been swollen occasionally. She was admitted to hospital in October 1953 with jaundice and found to have, in addition, gross ascites, hepatic enlargement and splenomegaly. Polycythaemia was an incidental finding. Flocculation tests were strongly positive. Polycythaemia was successfully treated by a single dose of radio-active phosphorus (P^{32}) and has not recurred (1953 - 1957). Jaundice and ascites disappeared spontaneously over a period of 6 months. The liver and spleen remain greatly enlarged and liver function tests strongly positive.

While recording these cases I wish to mention two further patients who also dated their symptomatology to pregnancy. One patient, case J4 of the post-hepatitis series, had an illness in 1928 characterised by jaundice for 1 week but ill health for 3 months. In 1941, following delivery of a child, she developed ascites which required paracentesis on one occasion, 12 pints being removed. Ascites did not recur thereafter for a further 12 years. At death in 1953 the liver was the site of nodular hyperplasia.

The other patient is not included in this series. She became aware of discomfort in the left upper abdomen when 6

months' pregnant, and the spleen was found to be enlarged. There was no biochemical evidence of hepatic dysfunction. Two years later she still had splenomegaly, but was otherwise in good health. This patient might have a well compensated cirrhosis, but the diagnosis was not regarded as sufficiently certain to warrant her inclusion in this study.

In all of these cases cirrhosis may have been present before the occurrence of pregnancy, and was almost certainly so in the patient with post-hepatitis cirrhosis. Nevertheless, I have recorded the histories because of the possibility that pregnancy affected the liver in a more direct fashion, either by deprivation of an essential metabolite, or by the addition of an antigen or toxin which was responsible for the initiation of liver disease. It is of interest that in 4 of the 5 patients transient ascites occurred, and that in each case the prognosis thereafter was reasonably good.

c) Polycythaemia vera

Hepatic cirrhosis occurred in association with polycythaemia in 3 patients. This association has previously been described by Lawrence (1955), but it is a rare event. The usual cause of hepatomegaly in this disease is distension of the vascular bed within the liver. The 3 cases will be described and the possible reasons for the development of cirrhosis discussed.

Case C43: This patient has already been described in the previous section relating to pregnancy and cirrhosis.

Case C44: Female, aged 54. Polycythaemia vera was diagnosed in 1951 and she was treated by deep X-ray therapy.

In 1954 there occurred undue bleeding after tooth extraction, and this was followed by loss of energy, slight jaundice and alternating diarrhoea and constipation. On admission to hospital the clinical findings were slight icterus, hepatic enlargement of 3 inches, and splenic enlargement of 4 inches. Liver function tests were impaired: serum albumin 2.8 g. per cent, serum globulin 2.9 g. per cent, serum bilirubin 4.3 mg. per cent, colloidal gold 3, alkaline phosphatase 10.6 Bodansky units. Haemoglobin had fallen from 100 per cent 6 months previously to 50 per cent. Jaundice slowly cleared over a period of 9 months, but the patient remained anaemic. The spleen was removed in 1956 and following this procedure the white cell count has risen to levels over 100,000 per cu.mm., and the haematological picture is indistinguishable from myeloid leukaemia. Liver biopsy performed in 1956 confirmed the development of hepatic fibrosis, and also showed foci of erythropoiesis within the liver.

Case C45: Female, aged 61. Polycythaemia vera was diagnosed in 1946, and she was treated by venesection and by X-ray therapy. In 1951 she received radio-active phosphorus (P^{32}) because of relapse. She was readmitted to hospital in 1955 complaining of general malaise and of redness and swelling of the legs. Clinical examination revealed hepatic and splenic enlargement of 4 inches, spider naevi and flushed palms. Liver function was impaired: serum albumin 3.2 g. per cent, serum globulin

4.1 g. per cent, serum bilirubin 0.2 mg. per cent, colloidal gold 5. The blood count was normal except for a leucocytosis of 16,000 per cu.mm. Since 1955 the clinical and biochemical findings have remained unchanged but the haemoglobin has fallen to 60 per cent and the white cells have risen to 40,000 per cu.mm. - the majority of cells being polymorphonuclear.

In all 3 patients the clinical and biochemical picture was fully consistent with cirrhosis, and the diagnosis was confirmed by liver biopsy in case C44. The reason for the development of this uncommon complication of polycythaemia vera is uncertain. Two of the patients, C43 and C44, became jaundiced and it is possible that they suffered from subacute massive necrosis. As subacute necrosis may occur without jaundice, a similar explanation may hold for case C45.

Polycythaemia vera is not the only myeloproliferative disorder which is complicated by cirrhosis. Wetherley-Mein and Cottom (1956) have observed portal fibrosis in acute leukaemia and Leonard, Israels and Wilkinson (1957) have described the occurrence of cirrhosis in myelosclerosis. I have also been following the course of a man, aged 46 years, who ruptured his spleen on falling from a pedal-cycle in 1956. At operation the spleen was enlarged and subsequent investigation revealed a leuco-erythroblastic anaemia, slight hepatic enlargement and urobilinogenuria (14 mg/day). Liver function tests showed a reversal of the albumin-globulin ratio but were otherwise normal. Sternal and iliac crest punctures were

unsuccessful and a rib biopsy had to be performed. This showed features compatible with a diagnosis of early myelofibrosis. For 2 years the patient remained well, and was then re-admitted with haematemesis and ascites. There is now little doubt that he has cirrhosis.

The common factor to these 3 conditions - polycythaemia vera, acute leukaemia, and myelofibrosis - is infiltration of the liver by haemopoietic tissue and this must result in parenchymal damage with replacement fibrosis. Such is the possible sequence of events in the 3 cases under discussion.

A third and last explanation for the development of cirrhosis in polycythaemia vera is the occurrence of hepatic venous thrombosis (Budd-Chiari Syndrome). This syndrome is usually acute and rapidly fatal but a more chronic course has been described (Kelsey and Comfort, 1945). Nevertheless the survival in each case for several years is much against the diagnosis of the Chiari syndrome.

As all 3 patients are still alive at the time of writing the exact pathogenesis of the cirrhosis is still uncertain.

d) Rheumatic heart disease and nephritis.

The association of a renal disorder with hepatic cirrhosis is well known but little understood, and is thought to represent a variety of disorders including both glomerulo-nephritis and renal tubular disease. Patek, Seegal and Bevans (1951) observed an autopsy incidence of nephritis in 11.7 per cent of 60 cases of cirrhosis, and a clinical incidence in 7 per cent of 200 consecutive cirrhotic patients. These figures were

regarded as highly significant as the incidence of nephritis in the hospital population as a whole did not exceed 1 per cent. Three of the 49 patients with cryptogenic cirrhosis in this study had an undoubted renal lesion: case C13 (Fig. 11) had chronic glomerulo-nephritis and died of uraemia; case C37 had a clinical picture indistinguishable from the nephrotic syndrome, and case C39 had a chronic renal lesion of uncertain nature but which may have been chronic pyelonephritis. This patient, too, died of uraemia.

There have been no reports of the association of rheumatic heart disease and hepatic cirrhosis in the absence of chronic congestive cardiac failure, but the two conditions were present in 3 patients included in this study (cases C12, C16, and C20) and I have been observing a fourth patient for 5 years in whom the association may also be present. This case, a boy of 13, was first admitted in 1952 with mitral stenosis, splenomegaly, and iron deficiency anaemia. Repeated blood cultures and the E.S.R. were normal, and a satisfactory response occurred to oral iron therapy. While in the ward he developed transient pericardial friction and fever, but apart from this episode progress was uninterrupted. I have seen the patient at regular intervals since 1952, and, although in perfect health, the spleen has remained palpable. For 4 years liver function tests were entirely normal, but this year (1957) serum globulin has been consistently elevated to 4.0 g. per cent. He may have, therefore, both mitral stenosis and cirrhosis. A fifth patient with aortic valve disease, massive splenomegaly and oesophageal

varices has also been seen since the material for this thesis was completed. He gave no past history of rheumatism or of chorea but diet was poor and he drank to excess. The Wassermann Reaction was negative. None of these cases was in congestive cardiac failure and a cardiac cirrhosis was considered to be most improbable.

The incidence of rheumatic heart disease and nephritis among patients with cryptogenic cirrhosis is greater than one would expect, as only one of the 40 patients with alcoholic and post-hepatitis cirrhosis had a similar disorder, case J7, who was admitted with acute glomerulo-nephritis and died in hepatic coma. It is worth considering whether this association is more than fortuitous. Glomerulo-nephritis and rheumatic heart disease are both believed to result from allergy to the haemolytic streptococcus. In both conditions the acute episode may pass unnoticed by the patient, as was so in all the cases which I have mentioned above. The classical pathological feature of rheumatic fever is the Aschoff nodule, which lies in close relationship to small arteries, and represents an exudative lesion surrounding necrotic collagen. Such lesions heal by fibrosis. The classical pathological feature of acute glomerulo-nephritis is more directly vascular, consisting of proliferation of the endothelial cells lining the glomerular tuft. In some patients with hepatic cirrhosis the early pathological changes are confined to the region of the portal tracts, and the changes elsewhere in the liver are remarkably slight or non-existent. The majority of such patients with minimal hepatic lesions

present with haematemesis, and are often found to have splenomegaly and hypochromic anaemia, i.e. they resemble the cases described by Banti (e.g. cases C1, C2, C11 and C34). In such cases the pathological changes may be so slight that it is difficult to believe that portal hypertension is caused by excessive fibrosis or by hyperplastic nodules of liver tissue distorting the portal venous radicals. It would be much more credible if it was shown that portal hypertension was caused by a primary vascular reaction within the liver which produced partial portal obstruction. Splenomegaly might be the natural consequence of portal hypertension; alternatively it might be due to a similar inflammatory reaction within the highly vascular spleen. If allergy to the haemolytic streptococcus can produce such a reaction in the kidney, might it not do so in the liver and spleen as well? Such an explanation would also account for the increased incidence of nephritis among patients with cirrhosis, and for the occasional occurrence of rheumatic heart disease and cirrhosis.

I have only one piece of laboratory evidence to offer which is relevant to this theory. Baikie (1957), working on bile pigment metabolism in health and disease, has had occasion to measure faecal and urinary urobilinogen excretion during the course of acute rheumatism prior to the institution of salicylate therapy. He has observed, in certain cases, a fall in the faecal urobilinogen excretion but a very marked rise in the output of urinary urobilinogen. Such findings point to the occurrence of intrahepatic disease, but the precise nature of

the abnormality is unknown. I have myself observed transient slight icterus in a patient with acute polyarthritis, and also the advent of joint pains in a patient who appeared to have a clinically mild infective hepatitis.

The analogy between acute nephritis and an acute vascular reaction within the liver can be carried a stage further. Chronic nephritis is characterised by a granular contracted kidney, the result of prolonged renal ischaemia, glomerular and tubular atrophy, and replacement fibrosis. Might not chronic hepatitis, in certain instances, also result from purely ischaemic changes within the liver? I do not suggest that such an explanation is applicable to all cases of cryptogenic cirrhosis. Just as there are many causes for renal fibrosis and failure, so there are many conditions which may cause hepatic fibrosis and failure, and late pathological study may not be useful in elucidating the pathogenesis of the lesion. Prolonged and careful clinical study may be more rewarding in furthering our knowledge of the relationship between such apparently diverse conditions.

Although dietary deficiency, steatorrhoea, polycythaemia vera, and possibly allergy to the haemolytic streptococcus or to some product of gestation may initiate hepatic damage in certain patients with cryptogenic cirrhosis, it must be admitted that often no aetiological clue was apparent. It is evident, however, when the case histories are read, that some patients were singularly affected by the consequences of portal hypertension, while others had symptoms suggestive of active

parenchymal disease. The former group I have termed group A, and the latter group B. Examples of group A can be found in cases C1, 2, 8, 11, 16, 19, 23, 34, and 41 and with less certainty in cases C3, 7, 9, 10, 15, 17, 22, 28, 29, 31 and 46 (see appendix). In some of these patients haematemesis was the only symptom of ill health, and there was nothing in the past or present history to suggest active hepatic parenchymal disease. In others the symptomatology could be adequately accounted for by the presence of anaemia. This group of patients was remarkable in two further respects. Firstly, in certain instances the prognosis was reasonably good, provided that haemorrhage could be effectively treated. Two patients have survived for 14 years since the diagnosis was made, and at least 4 other patients have survived for 6 years. It must be presumed that parenchymal damage was not too extensive, for had it been so the occurrence of haemorrhage would have further depressed hepatic function and endangered life. My second point would tend to corroborate this statement, namely, that the mildness of the pathological picture in certain instances contrasted greatly with the severity of the clinical picture (e.g. cases C1, fig. 7; C11, fig. 10). In case C1 a preoperative percutaneous portogram had been performed and had shown no evidence of extra-hepatic portal obstruction. At operation a spleno-renal anastomosis was carried out and a liver biopsy taken. The pathological report was as follows: 'some portal fibrosis and small foci of hyperplasia, but the liver architecture is not sufficiently disturbed to justify a diagnosis of cirrhosis. Some portal

canals are infiltrated by inflammatory cells.' It was not uncommon for the surgeon to remark on the normality of the macroscopic appearance of the liver. Not all cases had such a mild histological picture; typical multilobular cirrhosis was sometimes observed (e.g. case C8, fig. 9).

These patients in group A were clinically quite distinct from the patients in group B who had many symptoms of ill health but who were seldom troubled by the consequences of portal hypertension (cases C5, 14, 21, 25, 26, 30, 37, 38 and 40 are examples of this group). Poor appetite, weight loss, at times of alarming extent and simulating gastro-intestinal neoplasm, energy loss and diarrhoea were common complaints and usually of 1 to 2 years duration. It would seem not unreasonable to associate this illness with subacute hepatitis, possibly of viral origin, as the symptomatology so closely resembled that given by patients with post-hepatitis cirrhosis before the advent of icterus. It will be recalled that in post-hepatitis patients such symptoms were occasionally present for weeks or months before jaundice was noticed. The course of the illness also resembled post-hepatitis cirrhosis, usually progressive but occasionally relapsing, and with a poor prognosis.

A third group of patients could also be described, group C. Such cases were usually admitted with extra-hepatic disease (Table 6) and certain of them have already been discussed. Others had symptomless cirrhosis.

It can serve no useful purpose to speculate further on aetiology, but in summary I wish to reiterate that the causes

TABLE 6

Thirteen patients with cryptogenic cirrhosis who presented because of extra-hepatic disease. (Group C patients : see text).

Case No.	Presenting Disease
6	Perforated duodenal ulcer.
12	Diabetes : Pneumonia : Rheumatic heart disease.
13	Chronic nephritis.
18	Carcinoma of the stomach.
24	Cardiac failure (degenerative).
33	Bronchitis : Early heart failure.
35	Bronchitis.
36	Steatorrhoea (Megaloblastic anaemia).
42	Steatorrhoea (Megaloblastic anaemia).
43	Polycythaemia vera.
44	Polycythaemia vera.
45	Polycythaemia vera.
47	Thyrotoxicosis with cardiac failure.

of cryptogenic cirrhosis may well be diverse. The clinical evidence for an association with viral hepatitis is applicable only to a small number of patients. In many others the disease would appear to be of insidious onset and to cause portal hypertension at a time when parenchymal function was little disturbed. It is also suggested that the association of cryptogenic cirrhosis with steatorrhoea, polycythaemia vera, nephritis, rheumatic heart disease, and possibly pregnancy may be more than fortuitous.

SUMMARY

Cirrhosis was of portal type in 89 per cent of 100 patients with cirrhosis admitted to one medical unit in Glasgow Royal Infirmary between 1946 and 1957. The cause of the disease was ascribed to alcoholism in 11 per cent of cases, to infective hepatitis in 34 per cent, and was unknown in the remainder.

Alcoholic cirrhosis was a disease of males. Half of the patients consumed a diet poor in protein, and the majority were in the lower social classes. Dietary deficiency alone was not considered to be responsible for the development of cirrhosis, although it is likely to have been a contributory factor.

Post-hepatitis cirrhosis differed from alcoholic cirrhosis in several respects. The age incidence was wider, the sex incidence equal, and half of the patients were in the upper

social classes. In the majority of cases the development of cirrhosis was ascribed to the severity of the infection, although in certain instances dietary deficiency, alcohol consumption, or intestinal malabsorption may have favoured the progression of the illness. An interval between the attack of jaundice and the recognition of cirrhosis was observed in half of the patients, while the other half had continuous jaundice. The history of infective hepatitis was sometimes atypical in that the duration of the pre-icteric stage was unduly long, or conversely that jaundice was apparently mild and attended by few symptoms.

Cryptogenic cirrhosis was commoner in females than in males, and was commoner over the age of 50 years. The dietary history was poor in 25 per cent of patients. The occurrence of the disease in association with steatorrhoea, polycythaemia vera, rheumatic heart disease and chronic renal disease is described, and also the association with pregnancy. It is suggested that these associations might not be coincidental, and that the aetiology of cryptogenic cirrhosis may be diverse. In a small number of patients the symptomatology and the subsequent course suggested a subacute hepatitis. In many others the clinical emphasis was on portal hypertension, but the aetiology of this group is still obscure.

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CHAPTER 2

Symptoms and Signs of Portal Cirrhosis.

It has been stated that the symptoms and signs of hepatic cirrhosis depend on three factors - the causal lesion, portal hypertension and hepatic cellular failure (Sherlock, 1955). This is undoubtedly true, but it is worth considering briefly the symptomatology in each of the three aetiological groups and noting the differences between them. The principal papers which have detailed the symptoms and signs of cirrhosis in recent years have mainly originated in the U.S.A., where the emphasis is on alcoholic cirrhosis of a much more florid nature than that which is seen in Britain (Patek and Post, 1941; Patek and Ratnoff, 1942; Patek, Post, Ratnoff, Mankin, and Hillman, 1948; Hall, Olsen and Davis, 1953; Zimmerman, 1955). Rolleston and McNee (1929) have given a comprehensive account of the clinical features of cirrhosis in this country, but the literature which they reviewed is largely concerned with alcoholic cirrhosis. Post-hepatitis cirrhosis was not recognised as an entity at that time. More recent clinical surveys, such as those of Kelsall, Stewart, and Witts (1947), Reynell (1954) and Sherlock (1948 and 1955) have all been concerned with liver disease in the southern part of Britain, and no comparable survey has originated from Scotland. It has therefore been considered worthwhile to give the symptomatology which was directly responsible for the admission of the patient, and the principal examination findings at that

time, together with a comment on any unusual feature.

The symptoms of alcoholic cirrhosis:

The principal symptoms which compelled the 10 patients with alcoholic cirrhosis to seek medical advice are shown in Table 1. The consequences of portal hypertension were responsible for the admission of 4 patients, and 2 patients presented in parenchymal failure (oedema and/or ascites). In the remaining 4 patients cirrhosis was an unexpected finding, extra-hepatic disease having been responsible for admission to hospital. Flatulent dyspepsia, anorexia, morning nausea and vomiting have long been regarded as the classical symptoms of alcoholic cirrhosis, but only 4 of the 10 patients would admit to gastro-intestinal upset of any kind. One of the 3 patients admitted with haematemesis complained of undue flatulence, but the other 2 patients were in excellent health until the onset of bleeding. Likewise one of the 2 patients who presented with severe oedema had been in good health until 3 weeks prior to admission. These facts illustrate the insidious nature of alcoholic cirrhosis.

The symptoms of post-hepatitis cirrhosis:

The principal symptoms which led to the admission of 30 patients with post-hepatitis cirrhosis are given in Table 11. Jaundice, regarded here as a symptom as well as a sign, was the presenting complaint of 11 patients, but it will be observed from the table that the incidence of jaundice was greater than the presenting complaint would suggest, 18 patients in all being jaundiced at the time of admission. Parenchymal

TABLE 1

Presenting Symptomatology of 10 patients with alcoholic cirrhosis

Presenting Feature	No. of patients	Percentage
A : Portal Hypertension		
1. Haematemesis	3	30
2. Symptoms of anaemia (iron deficiency)	1	10
B : Parenchymal Failure		
1. Abdominal swelling	1	10
2. Oedema with purpura on the legs	1	10
C : Incidental Disease		
1. Epileptic fit	1	10
2. Coma (Subdural haematoma)	1	10
3. Symptoms of pulmonary tuberculosis	1	10
4. Chest pain	1	10

failure was responsible for the admission of one third, and portal hypertension for one fifth of the patients.

In contrast to patients with alcoholic cirrhosis, symptoms were numerous (Table 111). Anorexia, nausea, flatulence, lassitude, and upper abdominal pain were frequent complaints. The high incidence of epigastric and right upper abdominal pain is worthy of note (40%) and a few patients complained of pain in the splenic region. Seven patients were subjected to laparotomy because of the inability to exclude underlying gall bladder disease. In only one of these patients were stones found, and in none was the cirrhosis of biliary type. Two of the 7 patients died post-operatively and 2 developed parenchymal failure. Baggenstoss and Stauffer (1952) also observed a high incidence of right upper abdominal pain and the harmful effects of exploratory laparotomy. It should be remembered that gall stones are a frequent coincidental finding in portal cirrhosis, occurring in 13.6 per cent of 500 cases (Bucalo, 1952). Two other prominent symptoms should be mentioned. Energy loss was complained of by 63 per cent of patients, and weight loss by 43 per cent. These two symptoms are frequently associated with active intrahepatic disease and cellular necrosis.

The symptoms of cryptogenic cirrhosis:

Gastro-intestinal bleeding and extra-hepatic disease were each responsible for the admission of 25 per cent of patients with cryptogenic cirrhosis. Symptoms of anaemia caused 20 per cent of patients to seek advice, and a further 20 per cent

TABLE 11

Presenting symptomatology of 30 patients with post-hepatitis cirrhosis.

Presenting Feature	No. of patients	Percentage
A : Portal Hypertension		
1. Haematemesis	5*	17
2. Anaemia	2	6
B : Parenchymal Failure		
1. Oedema and abdominal swelling	8+	27
2. Post-operative (appendix) coma.	1	3
C : Jaundice	11	37
D : Incidental Disease		
1. Symptoms of acute nephritis	1	
2. Symptoms of tuberculous pleural effusion	1	10
3. Symptoms of steatorrhoea	1	

TABLE 11 (Cont'd)

* 4 of the 5 patients were, or had recently been, jaundiced.

\+ 2 patients had continuous jaundice.

3 Persistent jaundice for 2 years prior to admission with tuberculous pleural effusion.

TABLE 111

Incidence of predominant symptoms in post-hepatitis cirrhosis.

Symptom	No. of patients	Percentage
Dyspepsia, anorexia, nausea, flatulence.	21	70
Loss of energy	19	63
Weight loss	13	43
Epigastric and right upper abdominal pain.	12	40
Intermittent diarrhoea	5	16

TABLE IV

Presenting features of 49 patients with cryptogenic cirrhosis.

Presenting Feature	No. of Patients	Percentage
Haematemesis	12	25
Anaemia (all types)	10	20
Oedema and/or ascites	5	10
Symptoms of gastro-intestinal disorder	10	20
Symptoms of incidental disease	12	25
1. Respiratory Infection	5	
2. Nephritis	2	
3. Polycythaemia Vera	2	
4. Cardiac Failure	1	
5. Thyrotoxicosis	1	
6. Perforated peptic ulcer	1	

presented because of gastro-intestinal symptoms other than bleeding. Only 10 per cent of patients were admitted because of troublesome oedema or ascites. (Table IV).

Many patients were in good health until the advent of the particular circumstance which led to hospital admission, and in this respect they resembled patients with alcoholic cirrhosis. Others had many complaints, and resembled those with post-hepatitis cirrhosis. These points have already been emphasised in chapter 1.

The Signs

It is extremely difficult to give a total incidence of the numerous signs that may occur throughout the complete natural history of portal cirrhosis principally because few patients were followed from beginning to end of the clinical sequence, and the majority were seen at various stages in the course of the disease. Fortunately, it serves no useful purpose to enumerate the total incidence of hepatomegaly, splenomegaly, ascites and the other features of cirrhosis, as the classical signs are all well known. It is of much greater interest to study the incidence of signs found when the patient first presented as a diagnostic problem, for by so doing a more realistic picture of the disease is built up in the mind of the clinician. In this country the majority of patients do not present with ascites, spider naevi, flushed palms and a trace of jaundice. These are the late features of a disease which few can fail to diagnose, but the problem may be very different when the patient first seeks advice.

The signs in each of the 3 aetiological groups have not been considered separately as it is more convenient to consider them as a whole. In Table V I have detailed the clinical features which were present when the patient was first admitted to hospital, or those found during the first interview at the out-patient department, and correlated these signs with the presenting complaint. In the following pages I shall briefly discuss each of the principal clinical features of cirrhosis.

1) The liver: Hepatic enlargement was the commonest physical sign of cirrhosis. In the whole series of 89 patients, 67 per cent had hepatomegaly when first seen, and in 26 per cent the enlargement was greater than 2 inches. The lowest incidence of hepatomegaly was found among those presenting with haematemesis (45 per cent) and the highest incidence among those presenting with jaundice (81 per cent). There was no absolute correlation between liver size and hepatic function, although decreasing size was often associated with parenchymal failure. Only 56 per cent of those presenting with oedema and ascites had hepatic enlargement, while 79 per cent of those whose complaints were of incidental disease, and in whom hepatic function was good, had hepatic enlargement. A cirrhotic liver may further enlarge in the presence of congestive cardiac failure or severe anaemia and regress when these abnormal states are corrected. A bruit was detected on auscultation beneath the xiphisternum in 2 patients. This sign has never been observed in hepatomegaly

TABLE V

Distribution of main physical signs according to presenting complaint (figures in per centage)

Presenting Complaint	No. of patients (actual)	Hepatic Enlargement 2 in. or less	Hepatic Enlargement more than 2 in.	Hepatic Enlargement total	Splenic Enlargement 2 in. or less	Splenic Enlargement more than 2 in.	Splenic Enlargement total	Jaundice	Oedema
Haematemesis	20	30	15	45	-	45	45	25	20
Jaundice	11	36	45	81	36	-	36	90*	18
Oedema and ascites	16	31	25	56	18	31	49	37	87
Anaemia	13	54	23	77	38	23	61	15	46
Gastro-intestinal symptoms	10	50	30	80	50	40	90	10	30
Incidental disease	19	53	26	79	26	37	63	21	31

* 1 patient complained of intermittent jaundice but was not jaundiced when first seen.

TABLE V (Cont'd)

Presenting Complaint	No. of patients (actual)	Ascites	Spider Angiomata	Finger Clubbing	Visible veins in abdominal wall	No clinical signs
Haematemesis	20	10	15	5	5	30 (6 patients)
Jaundice	11	9	18	-	36	9 (1 patient)
Oedema and ascites	16	75	37	37	-	-
Anaemia	13	7	23	7	-	-
Gastro-intestinal symptoms	10	-	10	20	20	-
Incidental disease	19	5	5	26	-	5 (1 patient)

due to metastatic cancer. The consistency of the liver was usually firm, occasionally hard but never stony hard. It was the exception rather than the rule to feel distinct nodularity.

2) The spleen: Splenic enlargement was found in 50 per cent of the whole series at the time of the first examination. Not uncommonly it was the one physical sign that aroused suspicion of cirrhosis, for by itself a palpable liver edge just below the costal margin may pass as a normal finding. The highest incidence of splenic enlargement occurred among those with predominantly gastro-intestinal symptoms, and the lowest incidence among those presenting with jaundice (90 per cent and 36 per cent respectively). It is generally accepted that splenic enlargement is caused by portal hypertension, and the highest incidence of splenomegaly over 2 inches occurred among those presenting with haematemesis. Nevertheless there was no absolute correlation between spleen size and the presence of varices, and, in fact, splenic enlargement has been encountered in the absence of portal hypertension as judged by manometry at the time of operation. It has been suggested that splenic enlargement may occasionally be associated with hepato-cellular necrosis (McMichael 1935; Himsworth, 1950) and I think that there is clinical evidence to support this theory. I have, for example, observed progressive splenic enlargement over a 2-year period in a patient with subacute necrosis, the weight of the spleen at death, which was from parenchymal failure, being over 2,000 g.

The liver was enlarged, and microscopically showed extensive cellular necrosis. No varices were observed in life or in death. Presumably such splenic enlargement is caused by reticulo-endothelial hyperplasia. The persistence of splenomegaly after recovery from jaundice or after correction of iron deficiency anaemia is often indicative of cirrhosis. It is not uncommon for a female patient to present with hypochromic anaemia and slight splenomegaly, and routine examination fail to reveal a cause for the clinical findings. The anaemia can be corrected by oral iron therapy but slight splenomegaly may persist. Such patients are often seen again, usually years later, with well established cirrhosis, and the presenting complaint is frequently haematemesis.

3) Jaundice: Jaundice was common in those patients with post-hepatitis cirrhosis, but was uncommon at the time of first examination in alcoholic and cryptogenic cirrhosis. All of the patients who presented complaining of jaundice were thought to have post-hepatitis cirrhosis, and of 18 other patients who were noted to be icteric when first examined, 9 had post-hepatitis cirrhosis. The increased incidence of icterus in those patients who presented with oedema and ascites is only partly explained by the fact that jaundice is a common sign of parenchymal failure, for the majority had post-hepatitis cirrhosis.

Transient icterus may occasionally suggest underlying liver disease in the absence of other physical signs. I have observed this occurrence after unexplained haematemesis, during

the course of pneumonia, and also following surgical repair of a hernia, in the latter instance transient icterus being associated with extensive bruising in the region of the wound, although the prothrombin time was not unduly prolonged when estimated several days after the operation. Subsequent investigations supported the clinical diagnosis of chronic liver disease in all of those patients. Recurrent slight icterus over many months or even years was commonly associated with the histological picture of subacute necrosis of liver. In some of those patients enlargement of the left lobe of liver was much more remarkable than that of the right.

4) Oedema and Ascites: Oedema and ascites are signs of hepato-cellular failure and are largely due to hypoproteinaemia and to disordered electrolyte balance. Portal hypertension is a contributory cause of lesser importance. Such signs occur late in the natural course of cirrhosis, and in this study only 13 per cent of patients presented with the complaint of abdominal swelling, while a further 5 per cent were found to have ascites at the time of the first examination. The incidence of oedema is not a true reflection of hepatic function as in many instances minor degrees of oedema were caused by anaemia and local vascular factors. Ascites is generally regarded as a bad prognostic sign, and this is borne out by the fact that 25 of 39 patients examined shortly before death had ascites. Ten of the remaining 14 patients died from haematemesis or post-operatively. Transient ascites may

occasionally occur after haemorrhage or after pregnancy, subsiding in the course of several weeks, and be compatible with a prognosis that is measured in years, unless a fatal haemorrhage should supervene.

5) Visible veins in the abdominal wall: Prominent dilatation of the subcutaneous veins in the abdominal wall is not a common physical sign in cirrhosis either early or late in the disease, and I have never seen a classical caput Medusae. Only one of 20 patients presenting with haematemesis had definite subcutaneous venous engorgement. Although this sign is indicative of portal hypertension it is generally seen late in the disease when there is parenchymal failure and a small amount of ascites, and is therefore of little use diagnostically.

6) Finger clubbing: Finger clubbing is a recognised physical sign of cirrhosis, but is reputed to be uncommon (Rolleston and McNee, 1929; Sherlock, 1955). In this series, 17 per cent of patients were noted to have clubbing of varied degree, but in only 11 per cent was it certainly attributable to cirrhosis, 5 patients having complicating disease which may have been responsible for the sign. The highest incidence occurred among those who presented with oedema and ascites (37 per cent) and in none of those patients was other disease detected which may have caused finger clubbing. Clubbing is said to be a feature of chronic obstructive jaundice (Sherlock, 1955), but the incidence among those with jaundice due to intra-hepatic disease was no higher than in those without

jaundice.

7) Spider angiomata: The incidence of spider angiomata may be slightly higher than recorded here, as the case sheets of the few patients not seen personally at the time of first admission to hospital did not always record the presence or absence of this sign. Nevertheless it can be said that it was not a particularly common feature at the time of the first examination being present in 16 per cent of patients. The highest incidence occurred among those presenting with signs of parenchymal failure (37 per cent). Flushed palms were even less common than spider naevi and were again more frequently seen late in the course of the disease.

8) Other signs: Certain other clinical features deserve to be mentioned. Facial telangiectases were as commonly present as spider naevi, but this sign is also frequently found in the absence of chronic liver disease. Glossitis was observed in 12 patients. Six of those patients had hypochromic anaemia, but none of the 3 patients with a megaloblastic anaemia had glossitis. This sign could not be correlated with dietary deficiency. Unexplained pyrexia was occasionally encountered, and cirrhosis should be kept in mind as a cause of unexplained fever. Pleural effusion was quite frequently associated with ascites, but I have seen one patient with histologically proven post-hepatitis cirrhosis (autopsy) who had a recurrent blood-stained pleural effusion in the absence of ascites.

Peripheral neuritis, with very marked calf tenderness

and diminution or loss of tendon reflexes in the legs, has occasionally been seen in cryptogenic cirrhosis, and generally occurs late in the course of the disease. Neuro-psychiatric phenomena were not common. One patient became manic after a haematemesis and had to be transferred to a mental observation ward because of his violent behaviour. He recovered from this episode and resumed his business life but died a year later from recurrence of bleeding. Portal-systemic encaphalopathy has also been seen in the terminal stages of liver failure, and in one patient after a porta-caval shunt. Neurological phenomena were never the presenting feature which led to admission.

Lastly it must be remembered that cirrhosis may be present when there are no physical signs, 9 per cent of the patients falling into this category. No less than 6 of the 20 patients presenting with haematemesis had no detectable physical signs when first admitted. From time to time post mortem examination on a patient dying of some other disease revealed what appeared to be a well advanced cirrhosis, unsuspected during life. It is likely that, in such cases, cirrhosis had been present for many years, perhaps for decades, and that compensatory hyperplasia of normal cells had made good the deficit caused by disease.

SUMMARY

The presenting symptomatology of 10 patients with alcoholic

cirrhosis was attributed to portal hypertension in 40 per cent, to parenchymal failure in 20 per cent, while 40 per cent were admitted with extra-hepatic disease. The classical symptoms of morning nausea and flatulence were the exception rather than the rule. The insidious nature of the disease is emphasised.

The presenting symptomatology of 30 patients with post-hepatitis cirrhosis was attributed to portal hypertension in 23 per cent of cases, to parenchymal failure in 30 per cent, and to incidental disease in only 10 per cent. The remaining 37 per cent of patients were admitted because of jaundice. Unlike alcoholic cirrhosis, symptoms were numerous, and in addition to anorexia and nausea, energy loss, weight loss and abdominal pain were common. Attention is drawn to the harmful effect of laparotomy.

The presenting symptomatology of 49 patients with cryptogenic cirrhosis was attributed to haemorrhage in 25 per cent and to anaemia in 20 per cent. Incidental disease was responsible for the admission of 25 per cent of patients, gastro-intestinal symptoms including weight loss for a further 20 per cent, while only 10 per cent were admitted because of oedema and ascites. The disease was commonly insidious, but a small number of patients had symptoms similar to those with post-hepatitis cirrhosis.

Hepatic and splenic enlargement were the commonest physical signs occurring in 67 and 50 per cent of all cases respectively, at the time of first admission. Jaundice was

a common presenting feature in post-hepatitis cirrhosis, but uncommon in alcoholic and cryptogenic cirrhosis. Ascites, finger clubbing, spider naevi and visible veins in the abdominal wall were all late features of cirrhosis, and a classical caput Medusa was never encountered. Nine per cent of patients had no signs indicative of cirrhosis. This assumes importance when the presenting feature is gastro-intestinal haemorrhage, and over one third of such patients had neither hepatic nor splenic enlargement. Certain of the less common physical signs are mentioned.

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CHAPTER 3

The Value of Ancillary Methods of Investigation in Portal Cirrhosis.

1. Liver function tests.

There are numerous biochemical tests which may reflect changes in liver function, and the most rational of these depend on alterations in the various fractions of the plasma proteins. Plasma albumin, α and β globulins, prothrombin and fibrinogen are all manufactured by the parenchymal cells, while y globulin is largely produced by cells of the reticulo-endothelial system (Martin and Neuberger, 1957). Unfortunately no single test is specific for liver disease, and results must be interpreted in the light of the clinical picture. Thus in almost all cases of hepatic parenchymal failure the plasma albumin is low, but a similar result may be obtained in chronic renal disease or in cachectic states whatever their origin may be. Similarly the prothrombin time depends not only on hepatic function but also on the availability of vitamin K. The flocculation tests of liver function are empirical, depending largely on alterations in the plasma globulins. Certain of these tests, such as the colloidal gold reaction, are positive when y globulin is in excess, and this may occur in certain inflammatory and sensitivity states which do not, so far as is known, affect the liver. Other flocculation tests, for example, thymol turbidity reaction, are abnormal when both β and y globulins are elevated, and are further favoured by depression of plasma albumin (Maclagan,

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1944). Flocculation tests may be positive in both acute and chronic liver disease. It will therefore be appreciated that the biochemical tests of liver function are no substitute for thorough clinical examination and for repeated assessments of the clinical state over a period of time.

In this chapter I shall discuss the value of the various tests in alcoholic, post-hepatitis and cryptogenic cirrhosis. Almost all of the tests were performed by the biochemistry department of Glasgow Royal Infirmary as part of the routine investigation of the patient; occasionally the colloidal gold reaction was performed personally. The minimal investigation was considered to be a determination of the plasma proteins (both albumin and globulin) together with a flocculation test, but usually both colloidal gold and thymol turbidity estimations were performed. Serum bilirubin was estimated in about three-quarters of the patients, plasma alkaline phosphatase and the prothrombin time in a little more than half. The prothrombin time will be discussed with the haematology of liver disease.

The usefulness and reliability of these tests as an aid to diagnosis may be considered in several ways. It is helpful to know how frequently the tests are positive or negative when a patient with cirrhosis is first seen. It is also of interest to know which of the various tests is most useful, and which the least helpful, and to consider whether the aetiology of cirrhosis, so far as it is known, has any influence on the results. Lastly I shall try to indicate

their worth as a diagnostic aid to the problem case, and their value in assessing the prognosis of portal cirrhosis.

A) The frequency of positive and negative results when a patient is first seen:

1) Where the diagnosis was made on clinical grounds only : 48 patients. This group contains a greater proportion of patients with well compensated cirrhosis as in certain instances the only findings were unexplained hepatic or splenic enlargement.

2) Where the diagnosis of cirrhosis was histologically proven : 34 patients. In this group there is a greater proportion of cases with decompensated cirrhosis as some patients were first seen in parenchymal failure, dying shortly afterwards, the histological proof being obtained at post-mortem.

These groups have been separated because results are perhaps more readily acceptable when the diagnosis is certain.

Nine per cent of the proven cases, 10 per cent of group (1), and 10 per cent of the total had no biochemical abnormality at the time of first examination. A further 18 per cent of the proven cases, 31 per cent of group (1), and 26 per cent of the total had only an abnormality of the plasma proteins (Table 1).

These findings are not altogether surprising as Sherlock (1955) has shown that well compensated cirrhosis may exist without biochemical abnormality. Follow-up of the 10 per cent with normal results has usually shown a gradual fall in

TABLE 1

Incidence of positive and negative results of liver function tests when patient was first seen.

a)	Total number of patients with histologically proven cirrhosis in whom adequate biochemistry was performed.	=	34
b)	Number in whom biochemical tests were wholly negative when first performed.	=	3 (9%)
c)	Number in whom some abnormality of plasma proteins was detected, but no abnormality of flocculation tests (or of serum bilirubin or alkaline phosphatase if these were estimated).	=	6 (18%)
d)	Total number of patients with clinically diagnosed cirrhosis in whom adequate biochemistry was performed.	=	48
e)	Number in whom no biochemical abnormality was detected when tests first performed.	=	5 (10%)
f)	Number in whom some abnormality of plasma protein was detected, but no abnormality of other tests of liver function.	=	15 (31%)

plasma albumin often accompanied by a rise in plasma globulin, while flocculation tests became positive less frequently. These changes are again referred to when the prognostic value of the liver function tests are considered.

B) The relative merits of the individual tests, and the influence of aetiology on tests of liver function:

Urobilinogenuria, depression of plasma albumin, and elevation of plasma globulin were the most constant biochemical abnormalities found in cirrhosis, being demonstrated in two thirds of the patients. In both alcoholic and post-hepatitis cirrhosis plasma globulin was commonly elevated (77 and 76 per cent respectively). In cryptogenic cirrhosis only 50 per cent of patients had a raised plasma globulin. Plasma albumin was depressed in 33 per cent of those with alcoholic cirrhosis, 86 per cent of those with post-hepatitis cirrhosis, and 61 per cent of those with cryptogenic cirrhosis, when the patient was first examined.

Colloidal gold precipitation was the better of the two flocculation tests in both alcoholic and cryptogenic cirrhosis, but thymol turbidity was slightly more frequently positive in post-hepatitis cirrhosis. For general use the colloidal gold test is to be preferred. Two thirds of the patients with post-hepatitis cirrhosis, half of those with alcoholic cirrhosis and less than half with cryptogenic cirrhosis had at least one flocculation test positive.

Both alkaline phosphatase and serum bilirubin were elevated in 50 per cent of patients with post-hepatitis

TABLE 11

The incidence of normal and abnormal results in the biochemical tests of liver function. The results are those obtained when the patient was first seen. The figures are given in per centage.

Biochemical Test	Alcoholic Cirrhosis		Post-hepatitis Cirrhosis.		Cryptogenic Cirrhosis		Combined incidence of abnormality in Portal Cirrhosis.
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Serum albumin	67	33	14	86	39	61	67
Serum globulin	22	78	24	76	50	50	62
Colloidal gold	44	56	36	64	56	44	52
Thymol turbidity	67	33	32	68	76	24	39
Alkaline Phosphatase	71	29	50	50	61	39	41
Serum bilirubin	78	22	50	50	81	19	29
Urobilinogenuria	33	67	7	93	39	61	73

cirrhosis, the results reflecting the degree of intra-hepatic biliary obstruction present at the time of the estimation. Rather surprisingly, alkaline phosphatase was elevated in 38 per cent of patients with cryptogenic cirrhosis, although serum bilirubin was elevated in only 19 per cent. Corresponding elevations were demonstrated in about a quarter of the patients with alcoholic cirrhosis. These results are presented in tabular form in Table 11.

The statement made in the opening paragraph of this chapter that no one test is sufficient to diagnose liver disease has been borne out by these results. Urinary examination and estimation of the plasma proteins will give useful information, but results require careful interpretation in the light of the clinical data. Unfortunately the highest proportion of biochemical abnormalities is to be found in those cases which are most easily diagnosed clinically, namely, post-hepatitis cirrhosis, while the exact converse is true for cryptogenic cirrhosis.

C) <u>The value of liver function tests in the diagnosis of the doubtful case</u>.

Thirty-two patients presented some difficulty in diagnosis when first examined, either because the disease was well compensated and the physical signs few, or because the clinical picture suggested certain alternative diagnoses. Histological proof has since been obtained in 38 per cent of those patients, and in others the sequence of events in time has made the diagnosis of cirrhosis certain. In Table 111 the

TABLE 111

The value of liver function tests in the diagnosis of the problem case.

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
A 2	Alcoholic male with hypochromic anaemia from bleeding haemorrhoids, and palpable spleen tip.	No	3.8	3.2 (2.9)	2	+ -	No change 2 years
A 3	Elderly man admitted with epilepsy. History of alcoholism: Liver palpable 3 inches.	No	3.0	3.8 (3.5)	0	0	Varices present
A 8	Palpable spleen incidental finding in a man with a respiratory infection. Heavy drinker.	No	3.8	3.9 (3.5)	1	0	-

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
A10	Ascites in an elderly man. Heavy drinker.	No	2.5	4.1 (2.9)	2	++	Died: No P.M. Lived 8 months after onset of ascites.
J17	Female: severe iron deficiency anaemia. Hepatic and splenic enlargement. Past history of jaundice.	No	3.3	4.1 (3.5)	4	0	-
J19	Male. Steatorrhoea. Past history of jaundice for 6 months. No hepatic or splenic enlargement.	No	2.3	4.7 (2.9)	6	++	Varices present
J23	Persistent jaundice in a man of 49. Neither liver nor spleen palpable.	Yes	1.7	2.3 (2.9)	3	++	Died : P.M.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
J25	Slight jaundice and ascites in a woman of 48. Liver and spleen not palpable.	Yes	1.8	2.8 (3.5)	0	0	Alive and much improved 1 year later. Taking ion-exchange resin and high protein diet.
J27	Male with splenomegaly and macrocytic anaemia.	No	3.4	3.9 (2.9)	3	++	Progression over 3 years. Ascites and hepatic coma.
J28	Unexplained hepatomegaly in a man of 38.	Yes	2.9	3.1 (2.9)	0	+	Lived 5 years. Jaundice and very large liver.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C 1	Female, aged 49. Hypochromic anaemia. Spleen tip palpable.	Yes	2.0	2.3 (2.9)	3	0	Varices present. Later developed hypersplenism.
C 4	Haemolytic anaemia in a man of 80. Liver 3 inches: spleen tip.	Yes	4.2	2.6 (2.9)	0	0	Died. P.M. Varices +
C 9	Female. 'Anaemia' for 12 years. Spleen 3 inches.	Yes	3.0	3.4 (2.9)	6	+++	Hypersplenism. Died. P.M.
C11	Haematemesis. No ulcer history. Liver and spleen not palpable.	Yes	2.9	1.9 (2.9)	0	0	Died. P.M.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C14	Woman of 64: weight loss. Liver 4 inches. Spleen tip.	Yes	4.5	4.2 (2.9)	0	0	Needle biopsy - cirrhosis. Died at home.
C18	Man of 59 with ascites. Liver and spleen not palpable.	Yes	2.7	4.1 (3.5)	0	0	P.M. Carcinoma of stomach and cirrhosis of liver.
C20	Rheumatic heart disease: splenomegaly: raised E.S.R.	No	3.2	5.0 (3.5)	5	++	Follow-up 7 months. No change in tests.
C21	Unexplained splenomegaly in a male of 67.	No	2.2	2.9 (3.5)	0	0	No change in spleen over 1 year. Blood and marrow normal.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C25	Hepato-spleno-megaly in a woman of 60	No	2.9	3.7 (2.9)	6	++	Cirrhosis observed at laparotomy. No biopsy taken.
C26	Female, aged 48: Ill-health for 1 year. Spleen just palpable.	Yes	5.3	2.9 (2.9)	2	-	Gradual development of classical picture of cirrhosis over 1 year. Ascites later.
C27	Unexplained hepato-megaly of 4 inches in a man of 48.	No	3.5	3.4 (2.9)	0	0	Alive 2 years later. No change in liver size.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C30	Female with gastric ulcer. Splenomegaly an incidental finding.	No	5.1	2.1 (2.9)	0	0	1 year later had classical picture of cirrhosis with ascites. Died in hepatic coma.
C33	Elderly man with chronic bronchitis. Spleen 1-2 inches.	No	3.7	4.0 (3.5)	0	0	No follow-up.
C35	Elderly man: chronic bronchitis Liver 3 inches: Spleen 6 inches.	No	3.7	2.9 (2.9)	0	0	Varices +ve. Died of haematemesis 3 years later.
C36	Male. Steatorrhoea. Persistent hepatic enlargement of 2 inches.	No	3.5	3.9 (3.5)	3	0	In good health: under treatment over 3 years.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C40	Middle-aged woman with weight loss. Liver and spleen not palpable.	Yes	3.4	3.8 (2.9)	0	+	6 years later has classical picture of decompensated cirrhosis with strongly positive flocculation tests.
C42	Elderly woman with megaloblastic anaemia which responded to folic acid but not to vitamin B12. Hepatic enlargement and spider naevi.	Yes	2.5	4.0 (3.5)	0	0	Died P.M.
C45	Polycythaemia Vera. Gradual development of clinical picture compatible with cirrhosis.	No	3.2	4.1 (2.9)	5	++	Remains unchanged. ? myelo-fibrosis.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

TABLE 111 (Cont'd)

Case No.	The Problem	Histological Proof	Plasma Albumin g.per cent	Plasma * Globulin g.per cent	Colloidal Gold	Thymol Turbidity	Comment
C46	Female with severe iron deficiency anaemia and splenomegaly of 1 inch.	No	3.9	4.1 (3.5)	2	0	Varices -ve. Anaemia corrected but spleen still palpable.
C47	Woman of 66: previously treated for toxic nodular goitre, auricular fibrillation and heart failure. Hepatomegaly 5"; spleen 2" incidental finding.	No	3.3	2.1 (2.9)	0	0	2 year follow up: No change.
C48	Male, aged 37: febrile illness with splenomegaly and hepatomegaly.	Yes	2.7	3.0 (2.9)	0	0	5 years later has ascites and chronic portal-systemic encephalopathy as a result of porta-caval shunt.

* Plasma globulin in parenthesis is the upper limit of normal at the time of the estimation.

problem which each case presented is stated, together with the liver function tests at that time. A comment on other helpful diagnostic features and on the further progress of the patient, when known, is also given. Analysis of these results has shown that in 10 per cent of cases biochemical tests were wholly normal, while in 47 per cent the diagnosis of cirrhosis was strongly supported by the finding of an abnormality in both plasma proteins and in flocculation tests. In many of the remaining cases, however, only a slight abnormality of plasma proteins was observed, a finding that was of little help in proving or disproving the diagnosis of cirrhosis. These results bear out Sherlock's (1955) opinion that when the diagnosis of cirrhosis is in doubt after careful clinical assessment, biochemistry is only of limited value in solving the problem, and some other measure such as liver biopsy is necessary to reach a final conclusion speedily.

It is of interest to note here the value of barium swallow examination in these problem cases. This investigation was performed in 23 of the patients with a positive result in 6 (26 per cent).

D) Prognostic value of liver function tests:

The prognosis of an individual case of cirrhosis does not depend solely on the state of liver function but also on the degree and effects of portal hypertension. Function may be normal and yet life imperilled by gastro-intestinal bleeding. This fact must be constantly remembered when

giving a prognosis in chronic liver disease. Notwithstanding these remarks, there are two biochemical results which are a useful guide to prognosis. Parenchymal failure is almost always associated with a low plasma albumin, and a rising serum bilirubin is an ominous but late sign in alcoholic and cryptogenic cirrhosis, but is not of much value in those cases with chronic hepatitis and long continued jaundice. The flocculation tests are of practically no value in determining progress or in assessing duration of life in established cirrhosis. Strongly positive tests are compatible with many years of good health, and death may occur from parenchymal failure when flocculation tests are negative. These facts are well illustrated by the results in two groups of patients: firstly a group of 18 patients who are alive, and in whom biochemical follow-up has been carried out for a period in excess of 1 year; secondly by the results which were obtained in 38 of the patients shortly before death. (Tables IV and V). Eleven of the 18 patients still alive had improved clinically during the period of follow-up, and in 10 of these patients improvement was accompanied by a rise in plasma albumin (Table IV). In 9 of these 11 patients the flocculation tests have remained either positive (4 cases) or negative (5 cases) while in 2 patients a positive result became negative. Four patients showed little change in their clinical state, and little change occurred in the biochemical tests. Three patients deteriorated, 2 of them markedly, and in both instances the

plasma albumin fell below 2 grams per cent. In the third patient deterioration was largely due to chronic portal-systemic encephalopathy, the unfortunate sequel of a shunt operation. In this patient plasma albumin has risen slightly but is still below the lower limit of normality.

In contrast are the biochemical results in the 38 patients shortly before death from liver disease (Table V). Plasma albumin was low in 29 of these patients, while flocculation tests were only slightly more frequently positive than negative. The cause of death in the 9 patients with normal plasma proteins is of some interest: 3 died from massive haemorrhage; 3 died post-operatively (porta-caval shunt 2 : splenectomy 1); 1 man of 80 died from congestive cardiac failure which may have been caused by over enthusiastic blood transfusion; and 2 died in hepatic coma. In both of the latter cases plasma albumin had fallen by over a gram in the few months preceding death, and in neither case was albumin estimated within 2 months of the date of death, so that the level may well have become abnormal.

A plasma albumin concentration below 2 grams per cent is usually associated with a fatal outcome, but occasionally remarkable improvement may take place. Case J25 is a good illustration of this; when first seen she had gross ascites with a plasma albumin level of 1.8 grams per cent. Treatment with an ion-exchange resin and a high protein diet resulted in complete absorption of ascitic fluid and a rise of plasma albumin to 5 grams per cent. She remained symptom free for

TABLE IV

Changes in liver function tests in 18 patients followed up for a period in excess of 1 year. All patients are still alive.

Clinical Assessment	Number of patients	Serum Albumin increased	Serum Albumin decreased	Serum Albumin No change
Improved	11	10	1	0
No change	4	1	1	2
Deteriorated	3	1	2	0

Clinical Assessment	Number of patients	Flocculations remained positive	Flocculations remained negative	Flocculations became negative	Flocculations became positive
Improved	11	4	5	2	0
No change	4	1	3	0	0
Deteriorated	3	1	0	0	2

TABLE V

Liver function tests estimated within 3 months of death in 38 patients

Estimation	Number of patients.	Normal	Low	High
Serum albumin	38	9	29	-
Serum globulin	38	16	-	22
Colloidal gold	36	16	-	20
Thymol Turbidity	29	13	-	16
Serum bilirubin	27	15	-	12

almost a year before ascites recurred. Such cases are unusual but provide much encouragement to the physician.

E) Liver function tests and assessment for operation:

Twenty-two patients had various elective operative procedures (splenectomy; operations to relieve portal hypertension; haemorrhoidectomy, etc.) and 9 died in the immediate post-operative period. This high mortality can only partly be attributed to operative complications. In some instances the biochemical tests suggested severe impairment of liver function, and the additional burden imposed on the liver by the anaesthetic and operation may well have proved too much for the meagre hepatic reserves. Eight of the 9 patients who died had strongly positive flocculation tests, and 4 had plasma albumin levels below 3 grams per cent. Thirteen patients survived operation; 7 had no abnormality or minimal disturbance of biochemical tests, and none of these patients suffered as a result of the operative procedure. Five patients had positive flocculation tests and 4 had plasma albumin levels below 3 grams per cent - and 3 of these patients showed evidence of parenchymal failure post-operatively.

These results should make one extremely cautious in recommending elective surgery to patients with cirrhosis, particularly when biochemical tests suggest parenchymal damage. The benefit to be gained by operation must be carefully weighed against the operative risk before a decision is made. A plasma albumin level of less than 3 g. per cent

should be regarded as a contraindication to elective surgery. Strongly positive flocculation tests are not such a clear contraindication, but operation is best avoided unless some definite benefit is to be gained. Pentothal induction of anaesthesia should never be used. Case J26 in this study went into fatal hepatic coma following pentothal anaesthesia for biopsy of a papilloma of the larynx. The papilloma proved to be a simple tumour.

2. Barium swallow for varices

Hepatic cirrhosis is much the commonest cause of oesophageal and gastric varices, and their demonstration lends great support to the diagnosis of the disease. The most reliable method for detecting varices is by oesophagoscopy, but this investigation is both dangerous and uncomfortable, and is seldom resorted to. It was performed in two cases in this study: in case C19 it confirmed the presence of oesophageal varices when radiological examination was unconvincing; and in case C8 no varices were observed although the patient had had numerous haematemeses. Further examination by gastroscopy suggested the presence of gastric varices.

Trans-splenic portal venography is also said to be a reliable method for the demonstration of varices, but the procedure is dangerous when the spleen is not enlarged. I have no experience of this technique.

Examination of the oesophagus by a barium emulsion is simple and safe but less reliable. Sherlock (1955) quotes

Templeton (1944) as stating that only 40 per cent of oesophageal varices can be detected by this method. Nevertheless the simplicity of the procedure makes it eminently suitable for routine use. Sixty-one patients in this study had a barium swallow examination, and the results are shown in Table VI. In 19 patients (31 per cent) varices were demonstrated. Varices were either strongly suspected on clinical grounds or demonstrated at post mortem in 6 of the 42 patients in whom barium swallow was negative. In a further 14 patients in whom barium examination was not performed for a variety of reasons, varices were demonstrated at autopsy. Thus in the whole series of 89 cases of 'portal' cirrhosis varices were demonstrated or strongly suspected on clinical grounds in approximately 42 per cent of cases.

The value of this radiological investigation as an aid to the diagnosis of the less certain case has already been referred to - in 26 per cent it proved of benefit, and in the remainder was not helpful.

3. Needle liver biopsy.

Needle liver biopsy has now an established place in the diagnosis of liver disease. With suitable selection of cases, the risk to life is small, and the procedure is not usually painful. A biopsy should not be performed unless the liver is palpably enlarged or liver dullness in the axillary line clearly demonstrable. When the prothrombin time is prolonged it should first be corrected, if possible,

TABLE VI

Results of barium swallow examination for oesophageal varices in 61 cases, together with certain post mortem observations.

Type of Cirrhosis	Barium Swallow positive for varices	Barium Swallow negative for varices	Barium Swallow negative but varices present at post mortem.	Barium Swallow not done. Varices present at post mortem.
Alcoholic	4	4	0	0
Post-hepatitis	5	15*	2	3
Cryptogenic	10	23[1]	0	4
Total	19	42	2	7

* 1 patient had a haematemesis although no varices were demonstrated.

1 1 patient had a haematemesis but recovered.
2 patients had haematemesis many months after the barium examination. It is possible that varices had developed in the interval between the barium examination and the occurrence of haemorrhage.

by the administration of vitamin K. (Sherlock, 1955).

Fifteen of the 89 patients in this study were subjected to needle biopsy without mishap. The diagnosis of cirrhosis was confirmed in 11 patients. In one patient no liver tissue was obtained, but subsequent follow-up has left no doubt as to the diagnosis. In 3 other patients the biopsy was technically successful but the histological appearances were not wholly compatible with cirrhosis. Thus in case J15 increased cellularity in the portal tracts was observed, but the lobular architecture was preserved. At operation for splenectomy the surgeon commented that the liver was 'hob-nailed' but unfortunately no biopsy was taken. Again in case C28 the appearance of the biopsy specimen was not abnormal, but at laparotomy cirrhosis was macroscopically obvious. This patient developed oesophageal varices and went into coma following haematemesis. The third patient (C34) was a young man with splenomegaly and oesophageal varices, in whom the differential diagnosis lay between cirrhosis and some extra-hepatic cause of portal hypertension. Liver function tests were normal and needle biopsy produced a small piece of apparently normal tissue. The evidence therefore favoured an extra-hepatic cause for portal obstruction and he was recommended to have a laparotomy. This advice was not taken and the patient went home. He was seen by request 7 years later. In the interval he had had one severe haematemesis following which he had developed a transient ascites. This had been tapped by his general practitioner

and had not recurred. Since then he had been well, but the plasma albumin had fallen to 2.8 grams per cent, and the globulin risen to 3.8 grams per cent. The urine contained urobilinogen in excess. It would seem most likely, therefore, that this patient has cirrhosis.

The reason for the normal or almost normal biopsy appearances in these cases can be found in the underlying pathology. When subacute necrosis is the forerunner of cirrhosis, necrotic and fibrotic areas lie side by side with areas which are normal. It is therefore not surprising that a normal biopsy is sometimes obtained. Diffuse fibrosis, on the other hand, involves every lobule, and the success of the biopsy depends solely on the ability to obtain a specimen of tissue.

Although needle liver biopsy may give an immediate solution to the problem of otherwise unexplained hepatomegaly it has been performed less frequently in recent years. There are four reasons for this:

1) It carries a small but definite risk.
2) When the portion of tissue is small it is not always easy to interpret the histological appearances. This is particularly true when the diagnosis lies between portal and biliary cirrhosis.
3) When routine radiological and haematological investigation have failed to explain the cause of chronic hepatic and splenic enlargement, the possibilities in this country are usually narrowed

down to cirrhosis and neoplastic infiltration. In neither instance can the disease be cured, and time will usually speedily provide the answer.

4) Needle biopsy is probably of greatest value in elucidating the cause of jaundice without having recourse to laparotomy. Even in this field, however, less use is being made of blind biopsy, and more of exploratory laparotomy, partly because of the increased safety of the latter procedure with modern anaesthesia, and partly because a speedy and certain conclusion is reached, and where possible a remedy applied.

Despite these considerations, needle biopsy is the most conclusive of all the ancillary methods of investigation performed in the medical ward. A certain diagnosis is frequently obtained and a reasonable assessment of the extent and severity of the hepatic damage can be made. Such knowledge will lead to a more positive attitude to treatment. The patient presenting with haematemesis and an enlarged liver who is shown to have cirrhosis can have vigorous treatment applied in the hope that a useful recovery will be made. On the other hand the patient with the same clinical pattern who is shown to have metastatic cancer will receive unreserved sedation. The solution to the problem case of jaundice may be easily obtained without the discomfort and dangers inherent to an abdominal operation. Needle biopsy may enable an opinion to be given on the cause of portal

hypertension - if a normal biopsy is obtained it is likely, but not certain, that an extra-hepatic cause is responsible and this may be relieved by surgical measures.

As with all ancillary methods, needle biopsy should be used critically and performed for a definite reason, and not simply to satisfy the curiosity of the clinician.

SUMMARY

The value of biochemical tests of liver function, radiological examination for varices, and needle biopsy have been considered. It is concluded that there is no infallible procedure available to the physician for diagnosing cirrhosis, and that needle liver biopsy will give the most conclusive results.

Liver function tests were frequently equivocal, and in 10 per cent of patients no abnormality was detected at the time of the first examination. Alteration in the plasma proteins was the commonest abnormality in all the aetiological groups. Flocculation tests were positive in two-thirds of the patients with post-hepatitis cirrhosis, half of those with alcoholic cirrhosis, and less than half of those with cryptogenic cirrhosis. Tests were most commonly positive when the diagnosis was not in doubt on clinical grounds, and were clearly positive in only 47 per cent of the problem cases. Flocculation tests were of no value in assessing

the prognosis of portal cirrhosis, but a falling serum albumin was a bad prognostic sign. A plasma albumin level of less than 3 g. per cent should be regarded as a contra-indication to elective surgery. Surgery should not be lightly recommended when flocculation tests are strongly positive even in the presence of a serum albumin level greater that 3 g. per cent.

Barium swallow examination successfully demonstrated oesophageal varices in a third of 61 patients so examined. In a further 13 per cent of cases in whom varices were almost certainly present, the barium examination was negative.

Needle liver biopsy was performed on 15 patients with a positive result in 11. Some explanation is given for the negative results.

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CHAPTER 4

Haematological Observations in Portal Cirrhosis

Hepatic cirrhosis is frequently accompanied by various haematological abnormalities. The peripheral blood picture, the bone marrow, the erythrocyte sedimentation rate (E.S.R.) and the chemical mechanism of haemostasis may all be abnormal in chronic liver disease. In this chapter the incidence and cause of these abnormalities will be considered in 78 patients with alcoholic, post-hepatitis and cryptogenic cirrhosis. Eleven patients have been excluded from this study because they suffered from some other disease which may have influenced the blood picture. These cases are listed in Table 1.

Methods and normal values:

a) Haemoglobin: In almost all patients haemoglobin concentration was measured in a photoelectric colorimeter, calibrated so that 100 per cent haemoglobin was equivalent to 14.8 g. haemoglobin per 100 ml. blood. In an occasional patient the haemoglobin was measured in a Haldane's haemoglobinometer. A figure of 90 per cent or more was considered normal for a man, and 85 per cent or more normal for a woman.

b) Red blood cells and white blood cells were counted in a haemocytometer by the usual standard technique. Normal values were:

Men:	R.B.C.	4.5 - 6.5 million per cu.mm.
	W.B.C.	4,000 - 11,000 per cu.mm.
Women:	R.B.C.	4.0 - 6.0 million per cu.mm.
	W.B.C.	as for men.

TABLE 1

11 patients excluded from haematological survey because of associated disease.

No.	Cause of Cirrhosis	Other disease
J 7	Hepatitis	Acute nephritis.
J13	Hepatitis	Carcinoma of pancreas.
C13	Cryptogenic	Chronic nephritis. Menorrhagia.
C18	Cryptogenic	Carcinoma of stomach with metastases.
C21	Cryptogenic	Prostatic enlargement. Uraemia.
C24	Cryptogenic	Congestive cardiac failure
C33	Cryptogenic	Chronic bronchitis. Congestive cardiac failure
C43	Cryptogenic	)
C44	Cryptogenic	) Treated polycythaemia) vera.
C45	Cryptogenic	)
C47	Cryptogenic	Thyrotoxicosis, hypertension and repeated epistaxes.

The normal range of lymphocytes in a differential white cell count was taken as 1,500 - 4,500 cu.mm. (Whitby and Britton, 1950).

c) Colour Index: Normal range 0.85 - 1.15 (Whitby and Britton, 1950).

d) Platelet Counts: Before 1953 platelets were counted by the method of Rees and Ecker (Tocantins, 1937) using capillary blood. Normal figures for this method were 130,000 - 250,000 cu.mm. Since 1953 Dacie's method has been employed using venous blood (Dacie, 1956). Normal values lie between 150,000 and 300,000 cu.mm. Only definite departures from normal have been regarded as significant.

e) Marrow: Marrow was obtained by either sternal or iliac crest puncture, and the granules smeared and stained with May-Grunwald and Giemsa. Occasionally smears were stained for iron by the Prussian blue method, but if section material was available this was stained for iron in preference to the smear. Sections were also stained with haematoxylin and eosin.

f) E.S.R.: Throughout this thesis the Westergren method has been used and readings taken at 1 hour. The upper limit of normal was taken as 10 mms.

g) Prothrombin time: Quick's one stage method was used. A reading of more than 3 seconds longer than a normal control was regarded as significant.

RESULTS

1. No disorder of the peripheral blood picture:

19 patients (24 per cent) had no disorder of the peripheral blood picture at any time during their attendance at this hospital. The bone marrow was not examined in any of these patients. Four other patients had constantly normal values for haemoglobin and for red cell counts, but had some abnormality of the white cells or platelets. One patient (Case C3) who had normal blood values on repeated occasions, had previously had a splenectomy performed at another hospital because of leucopaenia and thrombocytopaenia. The histology of the spleen was that of Banti's syndrome. Splenic enlargement was observed in 8 of the remaining 18 patients.

Symptoms and signs of hepatic parenchymal failure as judged by oedema and ascites were observed in 7 patients with a normal blood picture. Cirrhosis was well compensated in the other 12 patients.

A normal or abnormal blood picture is not related to the underlying aetiology of cirrhosis. Normal values were observed in 20 per cent of patients with alcoholic cirrhosis, 16 per cent of those with post-hepatitis cirrhosis and 26 per cent of those with cryptogenic cirrhosis.

It is concluded that a normal blood picture is not dependent upon a) good hepatic parenchymal function, b) the absence of splenomegaly, or c) any one aetiological type of cirrhosis.

2. <u>Disordered peripheral blood picture due to frank gastro-intestinal bleeding.</u>

Frank gastro-intestinal bleeding was responsible for

anaemia in 18 patients (24 per cent). As bleeding was usually recurrent, no proper assessment of the blood picture could be made. Thirty-one per cent of those with cryptogenic cirrhosis were so affected, 27 per cent of the alcoholics, but only 15 per cent of those with post-hepatitis cirrhosis. The spleen was palpably enlarged in 10 patients, markedly so in 7 of these patients. One patient had had a splenectomy in another hospital at a previous date.

Haematemesis was accompanied by a polymorphonuclear leucocytosis in 3 patients (2 of whom had splenic enlargement) and by a persistent leucopaenia in 5 patients, all of whom had splenic enlargement. Thrombocytopaenia was observed in 3 patients, and may have been a contributory cause of haemorrhage. All 3 patients had splenic enlargement.

It is noteworthy that 39 per cent of patients with portal hypertension severe enough to cause oesophageal varices did not have splenomegaly. On the other hand leucopaenia and thrombocytopaenia were constantly associated with an enlarged spleen.

The effect of occult blood loss on the peripheral blood picture is discussed under the headings of hypochromic and normochromic anaemia.

3. Hypochromic anaemia (colour index less than 0.85)

The association of hypochromic anaemia with portal cirrhosis has long been recognised and usually ascribed to blood loss from oesophageal varices and from haemorrhoids. Wintrobe (1936) concluded that the anaemia of cirrhosis was

always normochromic or macrocytic except when haemorrhage or infection complicated the clinical picture. Most of the pertinent literature regarding the peripheral blood picture in cirrhosis has come from the United States where it would appear that hypochromic anaemia is less common than it is in Glasgow. Jarrold and Viltner (1949), for example, made haematological observations on 30 consecutive patients with cirrhosis, finding that 24 were anaemic, but that in no patient was the anaemia hypochromic. Berman et al (1949), in a comprehensive study of 25 patients, reported that 21 (84 per cent) were anaemic, but that only 2 had a hypochromic anaemia, and that one of the 2 patients had both acute and chronic gastro-intestinal bleeding. These reports are in contrast to the findings in the Glasgow area where hypochromic anaemia was not uncommon. After exclusion of anaemia due to frank haemorrhage, 37 patients were anaemic, of whom 9 (11.5 per cent of the 78 patients) had a hypochromic anaemia. Details of the cases are given in Table 2.

Only 2 patients were male, and both had alcoholic cirrhosis. Seven patients were female, comprising 4 with cryptogenic cirrhosis and 3 with post-hepatitis cirrhosis. Female preponderance was greater in hypochromic anaemia than in normochromic anaemia, while males predominated when the anaemia was macrocytic.

The diet was extremely poor in 5 patients, and this was thought to be a contributory factor in the cause of the anaemia, and possibly of the cirrhosis as well.

TABLE 2

Observations on 9 patients with hypochromic anaemia

No.	Sex	Cause of Cirrhosis	Haemo-globin per cent.	R.B.C. millions cu.mm.	Colour Index	Diet	Faecal occult blood	Spleen size inches	Varices	Liver Function
A 2	M	Alcohol	50	4.5	0.55	Average	Positive	2	Negative	Good
A 3	M	Alcohol	80	4.9	0.8	Poor	Positive	Not palpable	Positive	Good
J 4	F	Hepatitis	63	4.2	0.76	Average	Positive	2	Negative	Decompensated
J17	F	Hepatitis	29	3.3	0.44	Poor	-	3	-	Good
J21	F	Hepatitis	44	4.1	0.53	Average	Positive	Not palpable	Positive	Good
C 1	F	Cryptogenic	36	2.5	0.72	Poor	Negative	2	Positive	Good
C 9	F	Cryptogenic	45	3.7	0.6	Poor	Positive	3	Negative	Good
C32	F	Cryptogenic	59	4.0	0.73	Average	Positive	Not palpable	Negative	Good
C46	F	Cryptogenic	30	2.8	0.53	Poor	Negative	1	Negative	Good

TABLE 3

Observations on the bone marrow in 8 patients with cirrhosis and hypochromic anaemia.

No.	Cellularity	Erythropoiesis	Myeloid Series	Plasma Cells	Iron
A 2	Increased	Active Normoblastic	Normal	No increase	absent
J 4	Average	Active Normoblastic	Increased number of early myelocytes	No increase	-
J17	Increased	Very active normoblastic	Normal	No increase	absent
J21	Hypocellular	Active Normoblastic	Normal	Increased	absent
C 1	Average	Active Normoblastic	Very active	No increase	absent
C 9	Increased	Very active normoblastic	Normal	No increase	-
C32	Average	Hypoactive Normoblastic	Normal	No increase	absent
C46	Increased	Active Normoblastic	Normal	No increase	absent

The benzidine test for faecal occult blood was applied in 8 patients with consistently positive results in 6. Both patients who gave negative results had marked dietary deficiency.

Oesophageal varices were demonstrated by barium swallow in 3 of 8 patients so examined; in 2 patients large haemorrhoids were present when varices were absent.

Splenic enlargement was present in 6 patients (66 per cent). Splenomegaly may be a feature of uncomplicated hypochromic anaemia, but the enlargement is usually slight, and the spleen regresses in size when the iron deficiency is corrected. Persistence of a firm splenomegaly after the haemoglobin has risen to normal should be regarded with suspicion as it may be the sole clinical finding in a well compensated cirrhosis.

Liver function was good in 8 of the 9 patients, a surprising finding in view of the severity of the anaemia in the majority of instances.

The gastric juice was examined in only 2 patients. One patient produced hydrochloric acid after 0.5 mg. histamine, while the other patient had an achlorhydria even after 2 mg. of histamine.

The marrow was examined in 8 patients. Cellularity was average or increased in all but one, and erythropoiesis was normoblastic in every case. The myeloid series was active without exception, and one patient had a predominance of early myelocytes. The marrow was stained for iron in 6

patients, with a negative result in every instance. These results are recorded in Table 3.

The response to oral iron therapy was adequate and usually prompt, so that malabsorption was an unlikely cause of the anaemia. It would appear that blood loss from the gastro-intestinal tract, or dietary deficiency, or both of these factors, satisfactorily explains the presence of hypochromic anaemia in cirrhosis.

4. Normochromic anaemia: colour index 0.85 - 1.15.

The colour index has a wide range of normality. It broadly divides those patients who are markedly iron deficient (colour index less than 0.85) from those with a normochromic macrocytic anaemia (colour index more than 1.15), the exception to this rule being the presence of spherocytes. Within the normal range fall those patients with lesser degrees of iron deficiency and those with a normochromic anaemia and normocytic or only slightly macrocytic cells. The true incidence of macrocytosis can only be measured with accuracy when a method more precise than the colour index is used, and, employing a suitable technique, Hall (1956) showed that the majority of patients with cirrhosis which he studied (in the United States) had macrocytosis, even when the blood values were normal. It is appreciated, therefore, that the present division on the basis of the colour index is somewhat rough and ready, but it is a standard clinical method of evaluating anaemia, and is of undoubted value from the clinical viewpoint when taken in conjunction with careful inspection of

a blood film.

Twenty patients in this study had a normochromic anaemia (Table 4). Female patients again predominated in the ratio of 3 to 2. Ten patients had post-hepatitis cirrhosis, 9 cryptogenic cirrhosis, and 1 alcoholic cirrhosis, so that this type of anaemia was relatively much commoner in post-hepatitis cirrhosis affecting one-third of this group of patients. In only 3 patients was the diet known to be inadequate. The benzidine test for occult blood was not routinely applied when iron deficiency was considered to be unlikely, but a positive result was obtained in 3 of 8 patients so tested. Oesophageal varices were demonstrated in 7 patients, and not demonstrated in 11 patients. All but 5 of the 20 patients had splenomegaly.

The bone marrow was examined in 13 patients (Table 5). Cellularity was average or above average in every case; erythropoiesis normoblastic in 11 patients and macronormoblastic in 2 patients; and the myeloid series was active or hyperactive in all patients. Maturation arrest of the myeloid series was observed on 3 occasions, and was associated with splenomegaly in every instance. A definite increase in plasma cells was observed only twice.

No single mechanism will explain the cause of normochromic anaemia in cirrhosis. It was once assumed that the anaemia was due to impaired liver function which resulted in retention of toxic products of metabolism and subsequent marrow depression. It has been clearly shown, however, that severe

TABLE 4

Observations on 20 patients with normochromic anaemia.

No.	Sex	Haemo-globin per cent.	R.B.C. millions cu.mm.	Colour Index	Diet	Faecal occult blood	Spleen Inches	Varices	Liver Function
A 5	M	88	4.1	1.07	Poor	Not tested	Not palpable	Negative	Compensated
J 3	F	76	3.3	1.15	Poor	Negative	2	Negative	Decompensated
J 5	M	74	3.8	0.97	Normal	Not tested	1	Positive	Progressive Hepatitis
J 6	F	80	3.5	1.14	Not known	Not tested	1	Negative	Progressive Hepatitis
J10	M	85	4.3	1.0	Normal	Not tested	Not palpable	Not known	Progressive Hepatitis
J11	M	80	3.5	1.14	Normal	Not tested	2	Negative	Compensated
J12	F	40	2.1	0.95	Normal	Not tested	1	Positive	Progressive Hepatitis
J15	F	78	4.2	0.92	Not known	Not tested	5	Negative	Compensated

TABLE 4 (Cont'd)

No.	Sex	Haemoglobin per cent.	R.B.C. millions cu.mm.	Colour Index	Diet	Faecal occult blood	Spleen Inches	Varices	Liver Function
J16	F	72	3.5	1.02	Normal	Not tested	Not palpable	Negative	Progressive Hepat[illegible]
J27	M	90	4.0	1.12	Normal	Positive	1	Positive	Compensated
J29	F	53	2.7	0.98	Normal	Not tested	3	Negative	Decompensated
C 4	M	51	2.3	1.1	Normal	Negative	1	Positive	Compensated.
C14	F	59	3.0	0.98	Normal	Negative	1	Negative	Decompensated
C20	F	70	3.5	1.0	Normal	Not tested	1	Negative	Compensated
C26	F	72	4.1	0.88	Poor	Negative	1	Positive	Decompensated
C28	M	80	4.3	0.93	Normal	Positive	Not palpable	Positive	Decompensated

TABLE 4 (Cont'd)

No.	Sex	Haemo-globin per cent.	R.B.C. millions cu.mm.	Colour Index	Diet	Faecal occult blood	Spleen Inches	Varices	Liver Function
C31	F	55	3.0	0.91	Normal	Positive	3	Negative	Compensated
C40	F	74	4.1	0.9	Normal	Not tested	Not palpable	Negative	Decompensated
C41	F	70	3.3	1.06	Normal	Not tested	6	Positive	Compensated
C49	F	66	2.99	1.1	Normal	Negative	8	Not known	Decompensated

TABLE 5

Observations on the bone marrow of 13 patients with normochromic anaemia

No.	Cellularity	Erythropoiesis	Myeloid Series	Plasma Cells
J 3	Average	Active Normoblastic	Active with late forms predominating	No increase
J 6	Hypercellular	Active Normoblastic	Active with some maturation arrest	Slight increase
J12	Hypercellular	Normoblastic	Active normal	No increase
J15	Hypercellular	Active Normoblastic	Active with maturation arrest	No increase
J27	Hypercellular	Very active normoblastic	Active normal	No increase
J29	Hypercellular	Active Normoblastic	Active normal	No increase
C 4	Hypercellular	Very active macronormoblastic	Hyperactive at all stages of development	No increase

TABLE 5 (Cont'd)

No.	Cellularity	Erythropoiesis	Myeloid Series	Plasma Cells
C14	Average	Normoblastic	Active normal	No increase
C20	Average	Normoblastic	Active normal	No increase
C31	Hypercellular	Very active normoblastic	Very active. Late forms predominated.	No increase
C40	Hypercellular	Macronormoblastic	Active normal	Increased
C41	Hypercellular	Active Normoblastic	Active with maturation arrest	No increase
C49	Hypercellular	Very active normoblastic	Active normal	No increase

hepatic parenchymal failure may occur without anaemia, and almost half of the patients at present under consideration had well compensated cirrhosis.

There are at least 4 possible explanations for the occurrence of normochromic anaemia in cirrhosis, namely, a) occult blood loss with active regeneration, b) hypersplenism, c) chronic infection and d) an increase in plasma volume. Each of these will be discussed:

a) Anaemia from occult blood loss:

This was the cause of anaemia in only a small number of patients. The benzidine test for faecal occult blood was positive in 3 of 8 patients tested, and one patient had a persistent reticulocytosis without other evidence of haemolysis, thus indicating active blood regeneration. Only two patients responded well to oral iron therapy (Cases C26 and C31) and both these patients had a colour index below 1. In 11 of the 20 patients the colour index was 1 or above unity.

It is notable that few patients with normochromic anaemia had such low haemoglobin values as those with hypochromic anaemia.

b) Hypersplenism:

The term hypersplenism is used to denote a decrease in one or more of the formed elements of the peripheral blood in the presence of an enlarged spleen and a hyperplastic bone marrow, the latter containing an abundance of the precursors of those elements which are deficient in the blood. The role of the spleen in this condition is still uncertain, and there

are two main schools of thought. Doan (1949) believes that splenic enlargement is principally due to reticulo-endothelial hyperplasia, and that the phagocytic potential of the spleen is increased. Dameshek (1948), on the other hand, believes that the spleen produces 'a hormone' which acts on the bone marrow regulating either the maturation of immature cells or the release of mature elements into the circulation. Both explanations account for the cardinal features of the condition, but it is to be noted that Doan's theory is more comprehensive as it will include a haemolytic process. It is still uncertain which of these theories is correct.

Much of the evidence regarding haemolysis is conflicting. Jarrold and Viltner (1949), for example, observed normal urobilinogen excretion in 11 patients with normochromic or macrocytic anaemia attributed to cirrhosis, while Jandl (1955) found increased urobilinogen excretion in the majority of 20 patients with alcoholic cirrhosis which he carefully studied under ideal conditions. Jones and his colleagues (1955), using red cells labelled with radio-active sodium chromate, found an abnormal red cell half life in 8 of 15 patients, only 3 of whom were anaemic. They were of the opinion that urobilinogen studies were not sensitive enough to detect a mild haemolytic process.

There was unequivocal evidence of hypersplenism in 6 of the 20 patients in this study (Table 6). All had anaemia, thrombocytopaenia and splenic enlargement, and 3 of the 6 had leucopaenia. The marrow was examined in 5 of these patients,

TABLE 6

Data on 6 patients with hypersplenism

No.	Spleen g. or inches	W.B.C. cu.mm.	Platelets cu.mm.	Marrow
A 5	520g.	Normal	93,000	Died shortly after admission.
J15	5"	1,800	33,000	Hypercellular. Megakaryocytes numerous Myeloid maturation arrest.
J29	3"	Normal	92,000	Hypercellular. Megakaryocytes numerous.
C 4	1"	2,000-4,000	86,000	Extremely cellular. All elements affected.
C41	6"	1,400	39,000	Hypercellular. All elements affected.
C49	8"	Normal	97,000	Extremely cellular. Normoblasts specially numerous.

and was hyperplastic in each case. Two patients underwent splenectomy; a complete haematological recovery was obtained in one (Case C41) while the other (Case J15) died a few hours after operation. Four of these 6 patients had more detailed study to determine whether or not the rate of red cell destruction was increased (Table 7). In 2 patients (Cases C4 and C49) faecal urobilinogen excretion was high, and both patients were regarded as having haemolytic anaemia. In the other 2 patients (Cases J29 and C41) faecal urobilinogen excretion was low, and the anaemia was thought not to be haemolytic. Nevertheless one of these patients responded well to splenectomy. Deductions cannot be made from such a small study, but the results would suggest that there might be truth in the theories of both Doan and Dameshek.

c) Anaemia due to chronic infection:

The association of anaemia with infection is well recognised, and is usually normochromic and normocytic (Whitby and Britton, 1950).

Ten patients with post-hepatitis cirrhosis had a normochromic anaemia and in 8 of these patients jaundice was persistent or recurrent. It is possible that the high incidence of normochromic anaemia was due to the presence of chronic infection.

d) An increase in blood volume causing an apparent anaemia:

Bateman, Shorr, and Elgvin (1949) investigating 7 patients with alcoholic cirrhosis (only one of whom had

TABLE 7

Urobilinogen excretion, serum bilirubin and haemoglobin percentage in 4 patients with hypersplenism.

No.	Faecal Urobilinogen mg. per day.	Urinary Urobilinogen mg. per day.	Serum Bilirubin mg%.	Haemoglobin %
J29	39	11.7	1.0	53
C 4	352	-	0.6	58
C41	67	9	1.0	70
C49	1027	-	3.2	45

splenomegaly) observed a marked increase in total blood volume with a relatively greater increase of plasma volume than of the cell mass. They suggested that this caused an apparent anaemia, and that the normal cell mass accounted for the poor response to haematinics. This explanation can be accepted when the anaemia is of moderate degree, but Sherlock (1955) has remarked that the volume changes are insufficient to account for the anaemia in the majority of cases. Eisenberg (1956), using a radio-active chromium labelled cell technique, found a significant increase in plasma volume only in patients with oesophageal varices and/or cyanosis. In the absence of these features the results were normal. If these results are confirmed, hypervolaemia may account for anaemia in a minority of patients.

Normochromic anaemia was often resistant to therapy, possibly through failure to consider the precise aetiology in an individual case. Haematinics were administered to 14 patients with generally poor results. Choline, yeast, and methionine were given to 5 patients for many weeks without response, and a 6th patient had, in addition, folic acid, vitamin B12, and ascorbic acid, still without response. Three patients given proteolysed liver had a rise in reticulocytes and the red cell count, but 2 of the 3 also had iron therapy. Iron alone was given to 4 patients with a colour index below unity with a good result in one case, a slight response in a second, and no response in the other two. One patient, who had macrocytic cells in a peripheral blood film

and a colour index at the upper limit of normal, was given vitamin B12 by his practitioner and the blood values improved. This patient unfortunately refused all further investigation. As previously stated splenectomy was performed on 2 patients, with a good result in one and a fatal result in the second.

From the practical viewpoint, all patients with a colour index below unity should receive iron, and all with a colour index above unity should receive proteolysed liver as a supplement to a high protein diet. Hypersplenism should always be considered when the spleen is enlarged and appropriate investigations undertaken to substantiate such a diagnosis. Splenectomy should only be considered if liver function is good and the health of the patient seriously disturbed by the haematological abnormality.

5. Macrocytic anaemia with colour index greater than 1.15.

Eight patients had a macrocytic anaemia with a colour index ranging from 1.2 to 1.57. 5 patients were male and 3 female. 4 patients had cryptogenic cirrhosis, 2 alcoholic cirrhosis, and 2 post-hepatitis cirrhosis. Hepatic parenchymal failure was present in 6 patients, and the remaining two patients had proven steatorrhoea. The spleen was very large in two patients, a third had previously been splenectomised, and 5 patients had no splenomegaly. The diet was normal in all but one patient - an alcoholic male. The clinical and haematological data are given in Table 8, and the marrow findings in Table 9. Marrow cellularity was increased in 6 of the 7 patients. Erythropoiesis was

megaloblastic in 3 patients, two of whom had proven steatorrhoea, macronormoblastic in 1 patient, and normoblastic in the other 3. The myeloid series was normal in 5 patients, depressed in one, and showed maturation arrest in one patient. Plasma cells were greatly increased in 3 patients, all of whom had increased plasma globulin.

All 3 patients with megaloblastic erythropoiesis had free hydrochloric acid in the gastric juice. In two of these patients the fat balance was abnormal (Case J19 - 70 per cent absorption; Case C36 - 89 per cent absorption), but in the third patient the diagnosis of malabsorption remained a clinical one as the patient was unable to tolerate the special diet necessary for fat balance. Two patients responded to vitamin B12; Case J19 by only slight improvement in the peripheral blood count, but by definite conversion of megaloblastic to normoblastic erythropoiesis; Case C36 had a more dramatic response to vitamin B12 although the marrow conversion was slower than is usual in pernicious anaemia. In the third patient (Case C42) no response was obtained to vitamin B12, but a prompt response occurred when folic acid was administered.

Although macrocytic anaemia is a common finding in cirrhosis, megaloblastic erythropoiesis is rare. Berman et al (1949) were of the opinion that uncomplicated cirrhosis was never responsible for a megaloblastic anaemia. Jarrold and Viltner (1949) observed megaloblasts in the marrow of 3 patients out of 30 studied. All 3 patients had severe

TABLE 8

Observations on 8 patients with cirrhosis and a macrocytic anaemia.

No.	Sex	Cause	Haemoglobin per cent.	R.B.C. millions cu.mm.	Colour Index	Diet	Test Meal	Spleen Inches	Compensated or Decompensated
A 1*	M	Alcohol	97	4.0	1.21	Normal	-	4	Decompensated
A10*	M	Alcohol	110	4.4	1.25	Poor	-	Not palpable	Decompensated
J18	F	Hepatitis	75	3.0	1.25	Normal	-	Not palpable	Decompensated
J19	M	Hepatitis Steatorrhoea	66	2.1	1.57	Normal	HCl present	Not palpable	Compensated
C 5	M	Unknown	36	1.25	1.45	Normal	-	5	Decompensated
C36	M	Unknown Steatorrhoea	33	1.35	1.22	Normal	HCl present	Not palpable	Compensated.
C39	F	Unknown	86	3.3	1.2	Normal	-	splen-ectomy	Decompensated
C42	F	Unknown ?Steatorrhoea	50	1.8	1.38	Normal	HCl present	Not palpable	Decompensated

* Although the haemoglobin percentage was normal the red cell count was low and macrocytic cells were observed on examination of a blood film.

TABLE 9

Observations on the bone marrow of 7 patients with cirrhosis and a macrocytic anaemia.

No.	Cellularity	Erythropoiesis	Myeloid Series	Plasma Cells
A 1	Hypercellular	Active normoblastic	Normal	Increased
J18	Hypercellular	Active normoblastic	Normal	No increase
J19	Hypercellular	Megaloblastic	Normal	Increased
C 5	Hypercellular	Macronormoblastic	Maturation arrest	Increased
C36	Hypercellular	Megaloblastic	Depressed	Normal
C39	Hypocellular	Hypoactive normoblastic	Hypoactive	Normal
C42	Hypercellular	Megaloblastic	Normal	Normal

dietary deficiency and it was thought that they were deficient in extrinsic factor. One of the 3 showed a partial response to ground beef orally, but the other two were too ill for experimental therapy, though they showed a response to liver extract parentally. One of the 6 cases of haemochromatosis recorded in chapter 9 also developed a megaloblastic anaemia associated with severe dietary deficiency and scurvy. A satisfactory haematological response was obtained when ascorbic acid was administered alone. This patient has been reported by Brown (1955). Movitt (1949) recorded 2 patients with cirrhosis, megaloblastic anaemia and free hydrochloric acid in the gastric juice. One patient responded to liver extract but the other did not. Jandl (1955) observed megaloblastic anaemia in 4 of the 20 cases of alcoholic cirrhosis which he studied, all of whom responded to folic acid.

I have previously stated that the association of steatorrhoea and cirrhosis is probably more than fortuitous, but this association was not excluded in any of the above reported cases. In the Western hemisphere pernicious anaemia, pregnancy, and intestinal malabsorption are the only common causes of megaloblastic erythropoiesis, and until they have been excluded the diagnosis of a megaloblastic anaemia due to cirrhosis cannot be accepted. When diet is defective pure extrinsic factor deficiency or ascorbic acid deficiency should also be carefully excluded as the cause of megaloblastosis. In my experience liver disease alone has never been responsible

with certainty for a megaloblastic anaemia.

One patient had macronormoblastic erythropoiesis (Case C5). He was given both proteolysed liver and folic acid, as well as all the other usual haematinics including vitamin B12 without change in the marrow picture. This patient ran a progressive course over 2 years, with increasing anaemia, leucopaenia, thrombocytopaenia, and splenomegaly. Urobilinogen studies later demonstrated that haemolysis was taking place (see below). Unfortunately the patient was never well enough to have splenectomy performed.

Case No.	Faecal Urobilinogen mg/day	Urinary Urobilinogen mg/day	Serum Bilirubin mg%	Reticulocytes %	Hb %
C5	226	6.6	0.4	7	40

The treatment of macrocytic anaemia in cirrhosis depends to some extent on the cause. When it is associated with intestinal malabsorption and a megaloblastic bone marrow, the majority of cases will respond to folic acid, although vitamin B12 may also have to be given. When the marrow is normoblastic, proteolysed liver and a high protein diet may be beneficial. Splenectomy should be performed when there is satisfactory evidence of hypersplenism, provided that the general condition of the patient is suitable for operation.

6. White blood cells.

In the absence of splenic enlargement, hepatic cirrhosis is seldom accompanied by an alteration in the white cell count. Following acute haemorrhage there may be a transient rise in the count, and there is usually a leucocytosis in

response to active infection, although this may not occur in some patients who are leucopaenic. Only one patient in this study had an elevated white cell count in the absence of haemorrhage or extra-hepatic infection, and this occurred with severe progressive hepatitis (Case J23). The spleen was not enlarged.

Leucopaenia is not uncommon when the spleen is enlarged, and may be either constantly or intermittently present. It was observed in 10 patients in this study, 9 of whom were also thrombocytopaenic (Table 10). The spleen was enlarged in every instance, and the marrow was either normally cellular (5 patients) or hypercellular (5 patients). In two patients myeloid maturation arrest was observed. All of these patients were regarded as having hypersplenism, and 6 were subjected to splenectomy. Only 2 survived the immediate post-operative period and both had the peripheral blood picture restored to normal (Cases A9 and C41). The poor results are attributed to the selection of patients with severe liver damage.

Berman et al (1949) drew attention to the finding of an absolute lymphopaenia in cirrhosis. In a series of 25 patients, the majority of whom were alcoholic, 64 per cent had an absolute lymphopaenia below 1,500 cu.mm., regardless of whether the total count was normal, low, or elevated. This finding has been confirmed (Table 11). Differential white cell counts were performed on 25 patients, all of whom had some abnormality of the peripheral blood picture. An

TABLE 10

Observations on 10 patients with cirrhosis and leucopaenia

No.	W.B.C. cu.mm. Range.	Anaemia	Thrombocytopaenia	Spleen Size. Inches	Marrow. Myeloid Series	Splenectomy
A 7	1,000-3,600	Haematemesis	Yes	4	Normal	Yes : Died
A 9	1,800-3,200	Haematemesis. not anaemic on recovery.	Yes	5	Normal	Successful
J 4	2,200-4,400	Hypochromic	Yes	2	Normal	Yes : Died
J15	1,800-3,800	Normochromic	Yes	5	Maturation arrest	Yes : Died
C 4	2,000-4,000	Normochromic	Yes	1	Hyperplastic	No
C 5	1,000-2,000	Macrocytic	Yes	5	Maturation arrest	No
C 9	1,200-2,600	Hypochromic	Yes	3	Hyperplastic	Yes : Died

TABLE 10 (Cont'd)

No.	W.B.C. cu.mm. Range.	Anaemia	Thrombocytopaenia	Spleen Size. Inches	Marrow. Myeloid Series	Splenectomy
C16	1,400-3,800	Haematemesis	Yes	5	Normal	No
C31	2,200-4,800	Normochromic	No	3	Hyperplastic	No
C41	1,400-2,000	Normochromic	Yes	6	Hyperplastic	Yes : Successful

TABLE 11

Absolute Lymphocyte counts on 25 patients with cirrhosis

Less than 1,500 cu.mm.	1,500-4,500 cu.mm.	More than 4,500 cu.mm.
Total : 15 patients	Total : 10 patients	None
5 alcoholic cirrhosis	1 alcoholic cirrhosis	
3 Post-hepatitis cirrhosis	8 Post-hepatitis cirrhosis	
7 Cryptogenic cirrhosis	1 Cryptogenic cirrhosis	

absolute lymphopaenia was found in 15 patients (60 per cent), 10 patients had a normal lymphocyte count, and no patient had a lymphocytosis. The finding of an absolute lymphopaenia may be helpful diagnostically.

7. Blood Platelets

Platelet counts were performed on 28 patients. In all other cases a blood film was studied and platelets noted to be present, but as this is a rather rough and ready assessment, minor degrees of thrombocytopaenia may have been missed. Platelet counts of under 110,000 cu.mm. were observed in 15 patients, 9 of whom have already been considered in the discussion of leucopaenia (See Table 10). In the remaining 6 patients the spleen was also enlarged, so that leucopaenia and thrombocytopaenia were both constantly associated with splenomegaly. Two patients had the platelet count restored to normal by splenectomy, and one patient (Case C49), who also had haemolytic anaemia, had the platelet count restored to normal by cortisone therapy.

Only 2 patients had platelet counts of under 40,000 cu.mm. and purpura was seldom observed. One patient presented with purpura on both lower limbs in association with severe oedema. The platelet count was 95,000 cu.mm. Both oedema and purpura disappeared when the patient was placed on a low salt high protein diet, but the platelet count remained below normal (Case A1). Epistaxis is a well recognised feature of cirrhosis. It occurred repeatedly in Case J15, and was attributed to thrombocytopaenia. Six other patients with

abnormally low platelet counts had gastro-intestinal bleeding, but as varices were believed to be present in every case, it is uncertain whether thrombocytopaenia was in any way responsible for the bleeding.

8. E.S.R.

The E.S.R. was routinely performed on almost all patients. The Westergren method was used, and results above 10 mms. in 1 hour were considered abnormal. Sixteen patients with extra-hepatic disease likely to influence the E.S.R. have been excluded from this study: 3 with tuberculosis, all of whom had a raised E.S.R.; 3 with steatorrhoea and megaloblastic anaemia, all of whom had a very rapid sedimentation rate; and 10 of the 11 patients previously excluded from the haematological study because of the diseases detailed in Table 1. One patient excluded from the blood survey has been included in this section (Case C21) because the associated disease - uraemia caused by benign prostatic enlargement - was not thought to influence the E.S.R.

The results in 63 patients are given in Table 12. In this table a comment is made as to the presence or absence of anaemia, and when anaemia was present the type is stated. Serum albumin and globulin results are also given. Until 1956 the upper figure of normality for serum globulin in the biochemistry department of this hospital was 2.9 g. per cent, but in 1956 the method of estimation was changed, and the upper limit of normal rose to 3.5 g. per cent. For this reason I have put the normal figure in parenthesis in the

table.

Approximately one third of patients had a normal and two thirds a raised E.S.R. (22 patients and 41 patients respectively). Active hepatocellular damage was usually associated with a raised sedimentation rate, and it will be observed that almost all the patients with post-hepatitis cirrhosis had a definite increase. Conversely, apparently quiescent disease was often associated with a normal E.S.R., the patient having few symptoms related to hepatic dysfunction, although the consequences of portal hypertension were sometimes troublesome. Unfortunately the E.S.R. cannot be taken as an absolute guide to the activity or otherwise of hepatic disease as so many other factors, some related to liver function and some not, influence it. A few of these will be considered.

A) Anaemia and the E.S.R. : Anaemia is an inconstant factor in its effect on the sedimentation rate. It is well recognised that severe anaemia may co-exist with a normal E.S.R., particularly when the cause is simple iron deficiency or after haemorrhage (Davis, 1946; Terry, 1950), and for this reason correction charts for the E.S.R in anaemia are valueless. On the other hand certain types of anaemia are frequently associated with a raised E.S.R. - e.g. pernicious anaemia or the anaemia secondary to leukaemia. It can be seen from the results presented here that the E.S.R. was often normal in patients who were either not anaemic or who had a hypochromic anaemia, and that it was usually raised when the anaemia was

normochromic or macrocytic. The relationship, however, is by no means clear, and probably reflects other facets of altered liver function - e.g. alteration in the plasma proteins, as well as alterations in the red cells.

a) No anaemia : 18 patients.

E.S.R. normal : 8 patients.

E.S.R. raised : 10 patients. Range 16 - 57 mms.

b) Hypochromic anaemia : 9 patients.

E.S.R. normal : 6 patients.

E.S.R. raised : 3 patients. Range 34 - 100 mms.

c) Normochromic anaemia : 20 patients.

E.S.R. normal : 4 patients.

E.S.R. raised : 16 patients. Range 11 - 108 mms.

d) Macrocytic anaemia : 4 patients.

E.S.R. normal : 0 patients.

E.S.R. raised : 4 patients. Range 20 - 110 mms.

e) Anaemia from frank gastro-intestinal bleeding :

12 patients.

E.S.R. normal : 4 patients.

E.S.R. raised : 8 patients. Range 11 - 86 mms.

B) <u>E.S.R. and plasma proteins</u> : Alterations in the plasma proteins are known to influence the E.S.R., and increases in the globulin and fibrinogen fractions are particularly active in this respect. Electrophoresis of proteins was not performed, and only results for albumin and globulin are available. The results show that a high plasma globulin was frequently associated with a raised E.S.R. (33 out of 41 patients), although the

correlation was not absolute as 12 of 21 patients with a normal E.S.R. also had a raised plasma globulin.

C) E.S.R. and liver function : Mention has already been made of the association between active hepato-cellular damage and a raised E.S.R. When an approximate division was made between those with well compensated cirrhosis on the one hand, and those with apparently active hepatitis or decompensated disease on the other, it was found that the E.S.R. was raised in 14 out of 30 patients in the former group and in 28 out of 33 in the latter.

The factors which influence the sedimentation of red blood cells is a study in itself, and no one cause can explain the high rate in many cases of cirrhosis.

9. Prothrombin time.

Prothrombin is a plasma protein which is manufactured in the liver. In the presence of hepatic parenchymal failure prothrombin levels fall, and there is an increased tendency to bleed. Vitamin K, a fat soluble vitamin, is required for the biosynthesis of prothrombin. When fat is inadequately absorbed from the small intestine, as in regurgitant jaundice, vitamin K absorption is defective and the prothrombin time rises. In hepatic cirrhosis the prothrombin time is often normal, but it may be prolonged either because of hepato-cellular failure or because of jaundice. In the former instance correction is often not obtained by the administration of vitamin K.

The prothrombin time was estimated in 54 patients with

TABLE 12

The erythrocyte sedimentation rate (E.S.R.) in alcoholic, post-hepatitis and cryptogenic cirrhosis. Serum albumin and globulin levels are given with normal value for serum globulin in parenthesis. The presence or absence of anaemia, with its type when present, is also recorded.

No.	E.S.R. mms. in 1 hour	Serum Albumin g. per cent	Serum Globulin g. per cent	Type of Anaemia when present
A 1	85	3.9	5.5 (2.9)	Macrocytic
A 2	6	3.8	3.2 (2.9)	Hypochromic
A 3	84	3.0	3.8 (3.5)	Hypochromic
A 4	10	3.6	3.3 (3.5)	Haematemesis
A 5	13	-	-	Normochromic
A 7	40	3.7	5.2 (2.9)	Haematemesis
A 8	6	3.8	3.9 (3.5)	Not anaemic
A 9	2	4.6	2.1 (2.9)	Not anaemic
A10	20	2.5	4.1 (2.9)	Macrocytic
J 1	24	2.2	5.5 (2.9)	Not anaemic
J 2	57	1.5	5.4 (2.9)	Not anaemic
J 3	14	2.0	3.5 (2.9)	Normochromic
J 4	7	2.8	2.2 (2.9)	Hypochromic
J 5	25	3.2	3.6 (2.9)	Normochromic
J 6	108	2.7	5.8 (2.9)	Normochromic
J 8	20	1.3	3.6 (2.9)	Not anaemic
J 9	28	2.6	4.2 (2.9)	Not anaemic
J10	78	1.5	6.8 (3.5)	Normochromic
J14	36	2.8	2.6 (2.9)	Haematemesis
J15	4	3.2	1.6 (2.9)	Normochromic

TABLE 12 (Cont'd)

No.	E.S.R. mms. in 1 hour	Serum Albumin g. per cent	Serum Globulin g. per cent	Type of Anaemia when present
J16	76	1.6	4.5 (3.5)	Normochromic
J17	8	3.3	4.1 (3.5)	Hypochromic
J18	76	2.2	4.8 (3.5)	Macrocytic
J19	130	2.3	4.7 (2.9)	Macrocytic
J20	2	4.0	3.5 (2.9)	Not anaemic
J21	34	3.1	4.0 (2.9)	Hypochromic
J23	4	1.7	2.3 (2.9)	Not anaemic
J25	16	1.8	2.8 (3.5)	Not anaemic
J26	62	3.4	2.4 (2.9)	Haematemesis
J27	44	3.4	3.9 (2.9)	Normochromic
J28	35	2.9	3.1 (2.9)	Not anaemic
J29	111	1.8	4.7 (2.9)	Normochromic
J30	33	3.1	6.0 (3.5)	Not anaemic
C 1	7	4.0	4.2 (3.5)	Hypochromic
C 2	28	3.6	2.9 (2.9)	Haematemesis
C 3	55	2.4	3.9 (2.9)	Not anaemic
C 4	12	4.2	2.6 (2.9)	Normochromic
C 5	110	2.1	4.3 (2.9)	Macrocytic
C 6	8	-	-	Not anaemic
C 7	17	2.9	2.1 (2.9)	Haematemesis
C 8	8	3.3	2.2 (2.9)	Haematemesis
C 9	100	3.0	3.4 (2.9)	Hypochromic
C11	6	2.9	1.9 (2.9)	Haematemesis

TABLE 12 (Cont'd)

No.	E.S.R. mms. in 1 hour	Serum Albumin g. per cent	Serum Globulin g. per cent	Type of Anaemia when present
C14	16	4.5	4.2 (2.9)	Normochromic
C16	11	4.5	2.7 (2.9)	Haematemesis
C17	17	-	-	Haematemesis
C20	35	3.2	5.0 (3.5)	Normochromic
C21	8	2.2	2.9 (3.5)	Normochromic (uraemia)
C22	86	3.2	4.5 (3.5)	Haematemesis
C25	19	2.9	3.7 (2.9)	Not anaemic
C26	20	5.3	3.0 (2.9)	Normochromic
C27	2	3.5	3.4 (2.9)	Not anaemic
C28	45	1.4	5.5 (2.9)	Normochromic
C29	8	1.4	6.6 (2.9)	Haematemesis
C30	2	3.3	2.4 (2.9)	Not anaemic
C31	11	-	-	Normochromic
C32	7	3.8	3.8 (3.5)	Hypochromic
C37	116	1.8	5.0 (3.5)	Not anaemic
C38	9	3.0	4.5 (3.5)	Not anaemic
C40	104	3.4	3.7 (2.9)	Normochromic
C41	5	3.2	3.6 (3.5)	Normochromic
C42	130	2.5	4.0 (3.5)	Macrocytic
C46	7	3.9	4.1 (3.5)	Hypochromic
C48	8	3.3	3.8 (3.5)	Normochromic
C49	63	2.4	3.6 (3.5)	Normochromic

cirrhosis. A result within 3 seconds of the control prothrombin time was considered to be normal. 32 patients gave a normal result, 13 patients had a prolongation of 4 - 6 seconds longer than a control, and 10 patients a prolongation of more than 6 seconds. In 4 patients no correction was obtained when vitamin K or K1 was administered, and in 2 patients, neither of whom was jaundiced, correction was obtained.

The prothrombin time was measured in 8 patients admitted with haematemesis. A normal result was obtained in 5 patients and a prolongation in 3 patients.

It is concluded that the prothrombin time is not a sensitive index of hepatic function. Nevertheless it should be measured routinely in all cases of cirrhosis admitted to hospital, and, if bleeding should occur, vitamin K should be administered.

SUMMARY

Haematological observations were made on 78 patients with portal cirrhosis. Some disorder of the peripheral blood picture was detected in 76 per cent of these cases.

Anaemia was the result of frank gastro-intestinal bleeding in 18 patients (24 per cent). A further 9 patients (11.5 per cent) had an iron deficiency anaemia which was attributed to occult blood loss, dietary deficiency or to

both of these factors.

The spleen was enlarged in approximately two-thirds of the patients who had gastro-intestinal bleeding, occult or overt.

A normochromic anaemia was detected in 20 patients (26 per cent). This group contained a preponderance of patients with post-hepatitis cirrhosis. Several factors were responsible for the anaemia. Hypersplenism, in the widest sense to include haemolysis, and iron deficiency were proven causes. Other possible factors were thought to include active hepatitis and an increase in plasma volume. The spleen was enlarged in 75 per cent of these patients.

A macrocytic anaemia was present in 8 patients (10 per cent). In 2 of these patients the count was only slightly below normal although macrocytes were present in the peripheral blood. Three of the 8 patients had megaloblastic erythropoiesis and free hydrochloric acid in the gastric juice. Malabsorption of fat was proven in 2 of the 3 patients. Splenomegaly was detected in only one-third of cases.

Ten patients had a leucopaenia (12 per cent) and 15 patients a thrombocytopaenia (19 per cent). In 9 patients leucopaenia and thrombocytopaenia co-existed. The spleen was palpably enlarged in every patient with leucopaenia and thrombocytopaenia.

The E.S.R. was raised in approximately 66 per cent of patients. It was commonly elevated when plasma globulin

was raised, when anaemia was normochromic or macrocytic, or when hepatic function was failing, but no absolute correlation with any of these factors could be made.

The prothrombin time was prolonged in 43 per cent of 54 patients. Five of 8 patients admitted because of gastro-intestinal bleeding had a normal prothrombin time.

The treatment of the various haematological abnormalities is dependent on the cause, and haemolysis should not be overlooked as a possible explanation of anaemia. Leucopaenia and thrombocytopaenia were never of such severity as to demand urgent treatment by transfusion or splenectomy. The prothrombin time was occasionally corrected by the administration of vitamin K.

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CHAPTER 5

The prognosis of portal cirrhosis

Cirrhosis of the liver is generally associated in the lay mind with alcohol and a poor prognosis. The latter, if not the former, is certainly correct, at least once the symptoms of the disease have forced the patient to seek medical advice. In certain instances the incidental finding of hepatic or splenic enlargement in a patient with no complaint referable to hepatic dysfunction may enable the correct diagnosis to be made during the latent or asymptomatic phase of the disease, and this may last, if the patient is fortunate, for 5 or more years. More usually, however, the diagnosis is not made until the consequences of portal hypertension or parenchymal failure, or both, have become obvious, and thereafter the outlook is bad. The poor prognosis is well illustrated by the figures given by Patek and his colleagues (1948). Their patients were divided into two groups, those who received no specific treatment, and those who were treated by appropriate dietary measures. Seventy per cent of the former and 35 per cent of the latter were dead at the end of 1 year, and 93 per cent of the former and 70 per cent of the latter were dead at the end of 5 years. Over three-quarters of their patients were alcoholics, and it is generally stated that the life expectancy for alcoholic cirrhosis is slightly more favourable than that for other causes of the disease provided the patient can be induced to stop drinking. I have been unable to find corresponding

figures for post-hepatitis and cryptogenic cirrhosis, but all authors are agreed that once liver cell failure has occurred the prognosis is poor.

The purpose of this chapter is to give in a little more detail the prognosis of the 89 patients with portal cirrhosis who have already been under consideration. Initially I shall discuss the prognosis in portal cirrhosis as a whole, and then elaborate on the different aetiological groups.

1) <u>The prognosis in portal cirrhosis as a whole.</u>

The fate of 78 of the 89 patients is known at the time of writing (1957) and the prognosis is illustrated in Tables 1 and 2.

Thirteen patients (16.6 per cent) died during their first admission to the Royal Infirmary, and a further 13 patients (16.6 per cent) were dead by the end of 1 year's follow-up. An additional 6 patients (8 per cent) died post-operatively, the operation having been carried out during their first admission or shortly thereafter. The total mortality by the end of 1 year was therefore 41 per cent of 78 patients. Twenty-nine patients were followed up for 5 years or more, or until death, and the mortality rate by the end of 5 years was 72 per cent (Table 2). Three patients who were untraced after repeated attempts had been made to find them were regarded as deceased. In Table 1 the poor prognosis is slightly exaggerated by the fact that 5 patients had been diagnosed as having cirrhosis or splenic anaemia in other hospitals at a date prior to their admission to the Royal Infirmary.

It will be noted that there is very little difference

TABLE 1

The prognosis of 89 patients with portal cirrhosis

Year	No. of cases admitted or seen in that year.	No. Dead in 1957.	No. alive in 1957.	No. Untraced in 1957.
1946	4	3	-	1
1947	4	4	-	
1948	2	2	-	
1949	3	3	-	
1950	4	3	1	
1951	5	2	3	
1952	7	4	1	2
1953	14	10	3	1
1954	10	6	3	1
1955	8	5	2	1
1956	21	6	11	4
1957	7	1	5	1

TABLE 2

The 5-year survival rate of 29 patients with portal cirrhosis.

Year	No. of patients admitted.	No. alive 5 years later
1946	4	2
1947	4	0
1948	2	0
1949	3	0
1950	4	1
1951	5	4
1952	7	1
Total	29	8

Percentage survival after 5 years = 28 per cent.

between these figures and those given by Patek (1948).

2) The prognosis in alcoholic cirrhosis (10 patients).

The numbers involved in this group are small and unsuitable for close comparison with post-hepatitis and cryptogenic cirrhosis, but it would appear that the prognosis in portal cirrhosis whatever the cause is always poor once a patient has passed from the asymptomatic phase into the symptomatic phase of the disease, with the exception of those patients with cryptogenic cirrhosis whose symptoms are predominantly due to portal hypertension (See later).

5 patients are alive, 4 dead, and one is untraced (Table 3). The longest survival period from diagnosis to death was 7 years; the other 3 patients dying 6 months, 1 year and 3 years after diagnosis. The patient who died 1 year after diagnosis succumbed to operation, but this was a procedure carried out in an endeavour to stop recurrent bleeding with failing hepatic function. Three of the 5 living patients have been followed up for approximately 2 years, the other 2 for lesser periods.

3) The prognosis in post-hepatitis cirrhosis (30 patients).

Twenty-one of the 30 patients in this group have died, and only 2 of these 21 patients survived for more than 3 years from the time of hospital admission. The longest period of follow-up has been 7 years, and this patient is still alive (Table 4). The prognosis in post-hepatitis cirrhosis is of particular interest because the onset of cirrhosis can be approximately dated to the onset of jaundice, and therefore

TABLE 3

The prognosis in alcoholic cirrhosis. Follow-up until the summer of 1957.

	Number of patients	Year of follow-up <1	1	2	3	4	5	Comment
Died first admission	1							Hepatomegaly detected 7 years previously.
Died post-operatively	1							Hepatomegaly detected 1 year previously.
Dead	2	1			1			
Alive	5	1	1	3				
Untraced	1		1					

TABLE 4

The prognosis in post-hepatitis cirrhosis. Follow-up until the summer of 1957.

	Number of patients	Year of follow-up						
		<1	1	2	3	4	5	More than 5
Died first admission	5							
Died post-operatively	5			1	1			
Dead	11	1	2	5	1	1	1	
Alive	6	1	2	2				1 (7 years)
Untraced	3	2	1					

the whole course of the disease is known. Baggenstoss and Stauffer (1952) have pointed out that hepatic fibrosis may be observed within a few weeks of the acute phase of hepatitis. If jaundice is taken as the starting point of the disease, cases could be divided into 2 equal groups - one with continuous jaundice and a prognosis which was always short of 6 years and often short of 3 years, and a second group in whom there was a latent asymptomatic non-icteric phase which usually lasted from 1 to 6 years, but occasionally longer, and which was followed by a symptomatic phase lasting from 1 to 4 years (See Tables 3 and 4, chapter 1). The latent period was occasionally broken by an episode which suggested underlying liver disease, such as the occurrence of ascites after pregnancy. The length of the latent phase cannot be predicted, but, unfortunately, a poor prognosis is almost certain once the symptomatic phase has been reached. This poor prognosis is well illustrated by the fact that of 21 fatal cases only 2 survived for more than 3 years and none for more than 5.

4) <u>The prognosis in cryptogenic cirrhosis.</u>

In chapter 1 I have given reasons for believing that cryptogenic cirrhosis should not be regarded as a uniform entity, but rather to be composed of 2 main groups, Group A resembling Banti's syndrome because of the emphasis on splenomegaly and portal hypertension, and Group B resembling post-hepatitis cirrhosis because of the predominance of symptoms and signs attributable to parenchymal dysfunction.

A third group of patients (Group C) was described, consisting of patients admitted with extra-hepatic disease in whom cirrhosis was also detected.

In Table 5 the prognosis is given for 22 patients from Group A (See Chapter 1). Twelve of these 22 patients are dead, 1 is untraced, and 9 are alive. Three deaths occurred during the first admission to the Royal Infirmary, but cirrhosis had been suspected in one of these patients 2 years previously. There were also two post-operative deaths. Although the prognosis for these patients was often extremely bad because of the constant threat of massive haemorrhage, some patients did survive for an encouraging length of time, and the prognosis was better than that for any other group of cirrhotics. Six patients survived for more than 5 years, two of them for fourteen years and two for eight years. The follow-up periods are detailed in Table 5. It is in this group of patients that operative treatment for the relief of portal hypertension is most valuable, and 4 of the 22 patients had porta-caval shunts, and 4 others had splenectomy. Such treatment may have had a bearing on the better prognosis, although it also accounted for 2 of the deaths.

The prognosis for 10 patients in Group B is in contrast to the good prognosis for Group A. Seven of these patients are dead or untraced, and 3 are alive. Two of the survivors appeared to run a remitting course, but now, 5 and 6 years from the onset, both are in parenchymal failure. The others ran a progressive course, and no patient is known to have

TABLE 5

Cryptogenic cirrhosis. The prognosis of 22 patients in whom portal hypertension was the predominant feature (Group A). Follow-up until Summer of 1957.

	Number of patients	Year of follow-up						
		< 1	1	2	3	4	5	More than 5
Died first admission	3*							
Died post-operatively	2							
Dead	7	1	2	1		1		2 (8 and 14 years)
Alive	9	1	2	1	1	1		3 (6,6, and 14 years)
Untraced	1							1 (8 years)

* 1 patient had a haematemesis 2 years previously. Investigation in another hospital had revealed no abnormality.

TABLE 6

Cryptogenic cirrhosis. The prognosis of 10 patients in whom symptoms and signs of parenchymal disease predominated (Group B). Follow-up until Summer of 1957.

	Number of patients	Year of follow-up						
		< 1	1	2	3	4	5	More than 5
Dead	5	2	2	1				
Alive	3	1					1	1 (6 years)
Untraced	2		1					

TABLE 7

Cryptogenic cirrhosis. The prognosis of 13 patients admitted because of extra-hepatic disease in whom cirrhosis was incidental (Group C). The table also incorporates 4 patients in whom grouping was uncertain (See Chapter 1). Follow-up until Summer of 1957.

	Number of patients	Year of follow-up						
		<1	1	2	3	4	5	More than 5
Died first admission	4							
Dead	3		2	1				
Alive	6	2	1		1	2		
Untraced	4			1				

survived for more than 2 years from hospital admission (See Table 6).

The prognosis in the third group, C, admitted because of extra-hepatic disease, is given in Table 7. Again there were no known survivors beyond 5 years, but death was not always due to cirrhosis.

5) The prognosis after the occurrence of ascites.

The poor prognosis associated with ascites is well known and has been referred to in chapter 2. Persistent or shortly recurrent ascites was observed in 29 patients, all but 4 of whom are dead. None of the surviving patients has been followed for more than 1 year. The survival time after ascites was detected in the remaining 25 patients was as follows:

1 - 3 months	:	11 patients
5 - 12 months	:	8 patients
18 months	:	1 patient
Recurrent ascites over 7 years	:	1 patient
Post-operative deaths	:	2 patients
Untraced after ascites detected	:	2 patients

Transient ascites may occur after sudden severe blood loss, pregnancy, and during a severe attack of infective hepatitis. If the precipitating event can be adequately treated, the prognosis thereafter is not necessarily very bad. Case A4 developed massive ascites after a haematemesis. Ascites persisted for one month and then cleared completely.

The patient returned to full employment, and although follow-up is short of a year, he has remained well. Case J27 had an atypical illness associated with jaundice and transient ascites 4 years before his death from hepatic failure. Ascites did not recur until a few months before death. Reference has already been made in chapter 1 to survival times of 14 and 12 years following transient ascites in the post-partum period.

6) The prognosis after gastro-intestinal bleeding.

Twenty-five patients had frank haematemesis or melaena. (This figure excludes those who had terminal vomiting of blood, death being almost entirely due to parenchymal failure). Seven of these patients are alive, 3 of whom have had operative procedures designed to relieve portal hypertension. The survival time of these 7 patients ranges from 4 years to less than 1 year after the occurrence of haemorrhage. The 3 patients who had surgical treatment have survived for 3, 1 and less than 1 year after operation.

The survival period from the occurrence of haemorrhage to death in the 18 fatal cases was as follows:

Died from first haemorrhage	:	3 patients
Died in 1st year of follow-up	:	4 patients
Died in 2nd year of follow-up	:	3 patients
Died in 3rd year of follow-up	:	3 patients
Died in 4th year of follow-up	:	1 patient
Died in 8th year of follow-up	:	1 patient
Untraced after 8 years	:	1 patient

Post-operative deaths : 2 patients (both had recurrent haemorrhage over several months.)

Three of the fatal cases had shunt operations, surviving for 4 years, 3 years and 1 year thereafter.

The prognosis following gastro-intestinal haemorrhage from varices is not good, although better than after the development of ascites. Little can be done to improve the prognosis in the latter instance, as it is usually associated with severe parenchymal decompensation, but something may be done surgically to improve the prognosis after the recognition of portal hypertension. If suitable cases are chosen for operation the operative mortality is low and the prognosis good. Walker (1957) has recently given figures for his results in 56 patients subjected to porta-caval anastomosis. Three patients died post-operatively. Fifty patients have been followed up for periods extending to over 5 years, and no case who had not had a previous operation involving the portal vein had a recurrence of haemorrhage. The majority of these patients had cryptogenic cirrhosis.

S U M M A R Y

The mortality rate in portal cirrhosis 1 year after hospital admission was 41 per cent, and by the end of 5 years was 72 per cent.

There were 10 cases of alcoholic cirrhosis of whom 5 are alive and 5 dead. The longest course from diagnosis until death was 7 years, and the other 4 patients died within 4 years of diagnosis.

There were 30 cases of post-hepatitis cirrhosis of whom 6 are alive and 24 dead or untraced. The longest course from diagnosis until death was 5 years, but one surviving patient has been followed for 7 years. Of the 21 deceased only 2 survived for more than 3 years. When jaundice was continuous from onset until death few patients survived for more than 3 years. In those who were fortunate enough to have a non-icteric phase, cirrhosis usually remained asymptomatic for 1 to 6 years. Thereafter the prognosis was similar to those who had continuous jaundice.

The prognosis of cryptogenic cirrhosis cannot be stated so simply. Of 22 patients who had a clinical picture resembling Banti's syndrome (Group A), 6 survived for more than 5 years, 2 of them for 14 years. In contrast only 1 of 10 patients who had symptoms suggestive of subacute hepatitis has survived for more than 5 years. This patient is in severe parenchymal failure in the 6th year of follow-up. The prognosis for the third group of patients who presented with extra-hepatic disease was also poor but death was not always due to cirrhosis.

The prognosis after the onset of ascites was very bad and 19 of 29 patients so affected died within 1 year. Transient ascites associated with a reversible cause (such as haematemesis)

need not be associated with such a depressing outlook.

The prognosis after gastro-intestinal haemorrhage is illustrated by 18 cases followed from onset of bleeding until death. 7 died within a year and 16 within 5 years. Surgical treatment on appropriately selected cases may improve the prognosis of portal hypertension.

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CHAPTER 6

The Treatment of Portal Cirrhosis

From the account given in the previous chapter it would appear that neither medicine nor surgery are effective forms of therapy for portal cirrhosis. This is not wholly true, for, although the disease cannot be cured, the course of the disease may be altered and symptoms may be relieved. The rationale behind the various therapeutic regimes has been fully discussed by other authors and will not be dealt with here. Patek and his colleagues (1941, 1948) have shown in a practical manner the benefit to be obtained from a nutritious diet, and Himsworth (1950) has marshalled the experimental evidence to justify such dietary regimes. Sherlock and her co-workers (1956) have described the cause and management of mental derangement in cirrhosis. The good results obtained by Walker (1957) in the surgical management of portal hypertension have already been quoted, and similar results have been obtained in America by Ellis, Linton and Jones (1956).

In this chapter I shall briefly comment on my own experience in the treatment of portal cirrhosis.

1) The treatment of well compensated cirrhosis without symptoms attributable to portal hypertension.

All patients in this category were prescribed a high protein diet with additional Vitamin B and advised to abstain from alcohol completely. Such advice was seldom taken by those in good health. Abstinence from alcohol generally meant the breaking of valued social contacts, and, in the

absence of symptoms and signs of disease, few patients were prepared to lose their friends and change their social habits. A high protein diet was often an economic impossibility, and not unnaturally most patients were unwilling to take a high protein diet while the rest of the family existed on lesser fare. The only effective method of ensuring a high protein intake was to prescribe it as a medicine, 'Bemax', Casilan, 'Complan' and other preparations being used. Although there was no certain evidence that the course of portal cirrhosis was altered by this treatment, it was thought that both clinical and experimental evidence justified such a regime, which, apart from a little self-denial, caused no hardship to most patients.

2) <u>The treatment of well compensated cirrhosis with significant portal hypertension.</u>

In the previous chapter I have indicated that the prognosis after the occurrence of bleeding from oesophageal and gastric varices is often, indeed usually, poor, although occasionally a patient may survive for many years before succumbing to a massive bleed. The treatment in the acute phase of bleeding should be along routine lines, and transfusion should be adequate to replace blood loss and thus maintain liver function. Since 1955 the use of a tri-lumen tube for compression of oesophageal and gastric varices by balloon tamponade has been routine practice. It was found to be of limited value, partly because bleeding from gastric varices was not adequately controlled, and partly because the

presence of the tube was not well tolerated by an anxious, restless patient. Nevertheless it was sometimes of temporary value and I think it should always be given a trial.

All patients who survive the acute stage of bleeding should be considered for portal anastomotic operation to relieve portal hypertension. If parenchymal function is good then operation should be proceeded with. The danger from a policy of waiting to see if bleeding will recur would appear to be every bit as dangerous as the operation, always provided that only cases with good liver function are selected for surgical treatment. In this series 6 patients had porta-caval or spleno-renal shunts performed, and 1 patient had a direct excision of varices. Four of these patients had well compensated disease with no oedema or ascites and a plasma albumin level greater than 3.5 g. per cent. A fifth patient had ascites demonstrable in a hernial sac but was otherwise in good compensation. All five patients survived the operation. Two patients with decompensated cirrhosis were operated on because it appeared that the danger from recurrent bleeding was as great as the danger from operation. Both patients died in the immediate post-operative period, further bleeding being followed by fatal coma. Selection of cases for shunt operations must be rigorous and it is noteworthy that no patient with post-hepatitis cirrhosis was thought to be suitable for this procedure. All patients selected for portal shunt surgery should be able to tolerate a high protein diet without adverse effect.

3) The treatment of decompensated cirrhosis and portal-systemic encephalopathy.

It is now generally accepted that hypoalbuminaemia is the principle cause of oedema and ascites in portal cirrhosis and treatment by means of a diet rich in protein but low in salt, combined with the administration of a diuretic which increases sodium excretion, is rational. Alcohol must be forbidden. This treatment is successful in a minority of cases. I have already indicated that once ascites has appeared the prognosis is often but a few months and seldom more than a year. The prognosis is better when there is oedema without ascites, and better in alcoholic cirrhosis, by all accounts, than in post-hepatitis cirrhosis. One alcoholic patient in this series, who presented in 1955 with gross oedema of his legs, purpura on dependent parts, hepatomegaly and splenomegaly, has been maintained in good health by dietary measures alone for over 2 years. Such a result is most encouraging, and emphasises that standard methods of treatment should always be adequately tried. Too often, however, ascites persists and frequent paracenteses may be required. Frequent abdominal paracenteses should be avoided until the terminal stage of the disease, as the course thereafter is usually speedily progressive. Ion-exchange resins are worth a trial when diuretics have failed. I have found this medicine poorly tolerated, and as there was usually a latent period of 3 - 4 weeks before the effect of the resin became apparent, it was often difficult to persuade the

patient to persist with treatment. My experience has not been large, but of 6 patients so treated, 2 had satisfactory results, one being free from ascites for over a year. No complications attributable to disordered electrolyte balance were encountered.

When decompensated cirrhosis is attended by ascites and by mental symptoms, treatment becomes extremely difficult. A high protein intake aggravates the mental changes, and a low protein intake aggravates the ascites. Mersalyl is helpful but ion-exchange resins are seldom tolerated. I have found that the continuous administration of an oral antibiotic such as tetracycline or streptomycin will abolish the disturbing drowsiness and hallucinations, and at the same time permit of a moderate protein intake. The increased well-being which is experienced for a short time may be quite dramatic, although it is doubtful if there is a significant prolongation of the period of survival.

I have only once encountered severe neuro-psychiatric disturbance in the absence of severe parenchymal failure, and this occurred as a sequel to a porta-caval anastomosis. The mental abnormality was relieved when the diet contained less than 40 g. protein, and recurred when protein intake was increased beyond this figure.

The treatment of hepatic coma by means of protein deprivation and the administration of a broad spectrum antibiotic may be life saving. The most striking benefit which I have witnessed occurred in a business manager who both drank heavily and had a past history of severe hepatitis. For some

months he had not felt well, and on the advice of his practitioner he took a barbiturate sedative. He was admitted in coma and found to have jaundice, oedema, ascites and numerous spider naevi. There was thought to be little hope of recovery, but he walked out of hospital 6 weeks later, still with oedema, but with the ability to get about in comfort.

Intravenous glutamic acid has been given to 3 patients in hepatic coma without certain benefit.

The treatment of chronic liver disease must, by its very nature, be palliative, but something can be done to improve the physical and mental well-being of the patient. In the late stages of the disease, therapeutic success is generally short-lived, but in the early stages the correction of iron deficiency anaemia and the relief of portal hypertension may be followed by years of good health.

SUMMARY

The treatment of portal cirrhosis is palliative, but the prognosis can be improved in selected cases. A full assessment of liver function must be performed, the degree of portal hypertension evaluated, and an enquiry made into the cause of the cirrhosis, before a decision on definitive treatment is made.

1) When cirrhosis is well compensated and there are no

symptoms attributable to portal hypertension, a high protein nutritious diet should be prescribed together with Vitamin B and, if necessary, an appropriate haematinic drug. Alcohol must be forbidden.

2) When cirrhosis is well compensated but portal hypertension is responsible for symptoms, an endeavour should be made to reduce portal pressure. This is best done by a porta-caval anastomosis. Oesophageal balloon tamponade is of some value during the acute phase of bleeding.

3) Decompensated cirrhosis without portal-systemic encephalopathy is treated by a high protein, low salt diet and diuretics. Ion-exchange resins are sometimes of value when diuretics fail to control oedema and ascites.

4) Decompensated cirrhosis with portal-systemic encephalopathy is treated by the methods described by Sherlock (1956). Minor neuro-psychiatric abnormalities may be held in abeyance by continuous 'broad-spectrum' antibiotic therapy together with a diet of moderate protein content.

The place of splenectomy in the treatment of hypersplenism is considered in chapter 4.

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C H A P T E R 7

Some Pitfalls in the Diagnosis of Cirrhosis

In any study involving the follow-up of a large number of patients, errors in diagnosis will be encountered. As experience grows the pitfalls are recognised and avoided. In this chapter I have selected for discussion certain cases which presented some problem in diagnosis. In most instances the clinical picture was compatible with cirrhosis but the correct diagnosis proved otherwise.

1) Polycythaemia Vera:

Similarities may exist in the clinical pictures of cirrhosis and polycythaemia. Hepatic enlargement, splenic enlargement, and facial telangiectasis are common to both conditions, and the diagnosis of polycythaemia may rest entirely on the haematological findings. Occasionally, however, a polycythaemic patient may become anaemic, either because of blood loss or because of deficiency of a specific haematinic. Under such circumstances the red cell mass will fall and the diagnosis, if not already known, may be completely obscured. The following 4 case reports will illustrate certain of the difficulties. In the first case the diagnosis was not in doubt, but it might well have been had information from another hospital not been available.

Case 1: A man, aged 45, was referred from another hospital in March, 1956. A diagnosis of polycythaemia vera had been made in 1954 on the basis of the clinical findings and a peripheral blood examination, and he had

been treated by frequent venesection. There was a past history of occasional dyspepsia, and haematemesis had occurred on two occasions. On examination in March, 1956 the spleen was enlarged 5 inches and the liver one inch. The blood pressure was normal. Peripheral blood findings were as follows: Haemoglobin 70 per cent, red blood cells 6 million per cu.mm., white blood cells 17,000 per cu.mm., and platelets 450,000 per cu.mm. The red cell mass as estimated by a radioactive chromium (Cr^{51}) technique was 33.6 ml/Kg; the average normal result is 30.3 ml/Kg. Observation over 9 months showed little change in these values. The patient was then given oral iron, and within 5 weeks the haemoglobin had risen to over 100 per cent, the red blood cells to 6,750,000 per cu.mm., and the red cell mass to 47.8 ml/Kg, a result well within the polycythaemic range.

It is not generally known that the diagnosis of polycythaemia vera may be masked in this manner. In the following 2 patients the true diagnosis was not immediately apparent, and a presumptive diagnosis of cirrhosis was made.

Case 2: A woman, aged 51, was admitted to hospital in December, 1955, complaining of lassitude, anorexia, and weight loss of 6 months duration. For two months she had experienced undue breathlessness on exertion. There was a past history of rheumatic fever in 1930, of haemorrhage after tooth extraction lasting 3 days in 1950, and of a transient left-hemiparesis in 1952. There was no past history of jaundice or of alcoholism. On

examination the patient was slightly icteric. The spleen was enlarged 4 inches below the left costal margin and was firm and bulky. The liver was palpable 3 inches below the right costal margin but was soft. The tendon reflexes were increased on the left side as compared with the right, and the left plantar response was extensor. Clinical examination was otherwise negative.

Investigation: Haemoglobin 52 per cent (100 per cent Haemoglobin = 14.8g. per cent), red blood cells 1,900,000 per cu.mm., white blood cells 4,200 per cu.mm. The appearance of the red cells in a stained film was consistent with pernicious anaemia. Sternal marrow examination revealed frankly megaloblastic erythropoiesis. No free hydrochloric acid was secreted into the stomach even after 2 mg. histamine had been given. Liver function tests were normal and a barium swallow and meal showed no abnormality.

It was considered that neither the degree nor the firmness of the splenic enlargement could be explained by pernicious anaemia alone, and the patient was considered to have a well compensated cirrhosis in addition to pernicious anaemia.

Progress and treatment: A satisfactory haematological response was obtained following injection of vitamin B12, and by March, 1956, the blood levels were haemoglobin 109 per cent, red blood cells 5,600,000 per cu.mm., and packed cell volume (P.C.V.) 57 per cent. Splenomegaly

was unchanged. In September, 1956, the patient again had undue bleeding after tooth extraction and the result of blood examination suggested polycythaemia: haemoglobin 98 per cent, red blood cells 6,500,000 per cu.mm., white blood cells 24,000 per cu.mm., and platelets 1,750,000 per cu.mm., P.C.V. 55 per cent. Blood volume studies were undertaken, and the cell mass as determined by radio-active chromium (Cr^{51}) was clearly in the polycythaemic range - 45 ml/Kg. This patient has been successfully treated with radio-active phosphorus (P^{32}) and continues to receive vitamin B12.

Comment: The association of polycythaemia vera and pernicious anaemia has previously been reported but must be extremely uncommon (Galt et al, 1952). Certain features in the past history might have suggested the correct diagnosis, such as the undue bleeding after tooth extraction and the transient hemiparesis. A haemorrhagic tendency is sometimes encountered in cirrhosis but it is almost always due to severe impairment of liver function with prolongation of the prothrombin time. Nevertheless a provisional diagnosis of hepatic cirrhosis was quite justified, as it is much the commonest cause of symptomless splenomegaly in this country. The importance of adequate follow-up of a patient in whom some incongruous feature has been detected is well illustrated.

Case 3: A woman, aged 66, was admitted to hospital complaining of dyspnoea on exertion of 3 years duration

and of low back pain for 6 months. There was a history of haematemesis 5 years previously and of a recurrence one month before admission. The skin and mucosae were pale. The liver was enlarged 3 inches and the spleen 5 inches below the costal margins. Apart from a marked kyphosis of the dorsal spine no other abnormality was detected.

Investigations: Haemoglobin 44 per cent, red blood cells 3,400,000 per cu.mm., white blood cells 68,000 per cu.mm., platelets 830,000 per cu.mm. In stained blood films there was hypochromia of red cells and a polymorphonuclear leucocytosis. No primitive white cells were present in the peripheral blood. Smears of sternal marrow were hypercellular with hyperplasia of both myeloid series and megakaryocytes. Bleeding time, clotting time, and the result of the Hess test of capillary fragility were all normal. Liver function tests were normal. Barium swallow and meal revealed neither oesophageal varices nor peptic ulcer. Radiological examination of the bones showed changes of Paget's disease in the pelvis.

Progress and treatment: On iron therapy by mouth a rapid rise of red cell and haemoglobin values occurred to red blood cells 6,900,000 per cu.mm., and haemoglobin 89 per cent. Blood volume studies were then performed, using Evans Blue and calculating the red cell mass from the venous haematocrit, assuming the relationship body haematocrit/venous haematocrit = 0.9. The results were clearly in the polycythaemic range, the red cell mass

being 58.9 ml/Kg. Further haematemesis occurred some months later, and the patient succumbed to pneumonia.

Comment: Both cases 2 and 3 illustrate the haemorrhagic tendency which is frequently associated with thrombocythaemia (Hardisty and Wolff, 1955). The reason for this is uncertain, but it would appear that platelets in high concentration may inhibit thromboplastin formation (Spaet et al, 1956; Baikie et al, 1958). The correct diagnosis was suggested by the finding of a high white cell and platelet count, but until the anaemia had been partially corrected by the administration of oral iron, the alternative diagnosis of cirrhosis with oesophageal varices appeared likely, despite the failure to demonstrate varices radiologically. A leucocytosis of this degree is much against the diagnosis of cirrhosis, for, even after haemorrhage, counts above 20,000 cu.mm. are exceptional. I have never encountered thrombocythaemia in cirrhosis. It must be emphasised, however, that the true diagnosis may be completely masked by anaemia, and that blood volume studies can be misleading while iron deficiency exists.

The fourth patient whom I report is illustrative of yet another and more complex problem in the differential diagnosis of polycythaemia and cirrhosis.

Case 4: A man, aged 46, was admitted to hospital complaining of left upper abdominal discomfort of 2 years duration. For 10 years he had been troubled by inter-

mittent dyspepsia and melaena stools had been observed from time to time. For 4 years he had been troubled by haemorrhoids which had bled repeatedly. On examination he was a small man with rachitic deformity of his legs and telangiectasis on his cheeks. The spleen was enlarged 3 inches below the left costal margin, and the liver 2 inches below the right. Large haemorrhoids were present, and bleeding was observed during proctoscopic examination.

Investigation: Haemoglobin 70 per cent, red blood cells 3,700,000 per cu.mm., white blood cells varied from 1,500 - 4,500 per cu.mm., platelets 145,000 per cu.mm., and P.C.V. 38 per cent. A stained blood film showed slight hypochromia of the red cells and undue anisocytosis. A differential white cell count was normal. Marrow smears were hypercellular with active normoblastic erythropoiesis, myeloid hyperplasia and numerous megakaryocytes. The E.S.R. was 2 mms in 1 hour. Barium swallow and meal were both negative and liver function tests were normal. Radiological examination of the bones was negative apart from evidence of old rickets.

Progress: It was considered that this patient had a well compensated cirrhosis with hypersplenism. Splenectomy was seriously considered, but as the patient was extremely well during his stay in hospital it was decided to treat the haemorrhoids, and to reconsider splenectomy at a later date.

In January, 1957, one month after haemorrhoidectomy,

he was re-admitted to the surgical ward with acute upper abdominal pain. The cause of this was uncertain, so laparotomy was performed and splenic infarction observed. The spleen was removed and a liver biopsy taken. Following operation an immediate rise in blood values was observed to haemoglobin 90 per cent, white blood cells 60,000 per cu.mm., platelets 1,169,000 per cu.mm., and P.C.V. 51 per cent. Almost all the white cells were neutrophil polymorphonuclears and an occasional nucleated red cell was observed in the peripheral blood. The pathological report on the liver and spleen was as follows:

Spleen: 2,000 g. Several infarcts present. Normal splenic architecture replaced by cells of mature and immature structure with numerous polymorphonuclear leucocytes and also many undifferentiated stem cells. No increase in fibrous tissue.

Liver: Groups of undifferentiated cells are present in small numbers in the hepatic sinuses, but periportal infiltration is not marked.

The pathologist considered leukaemia to be the most probable diagnosis, but suggested further haematological investigation before a confident diagnosis was made. The patient was re-admitted in May, 1957, with right upper abdominal pain. The complexion was now ruddy, and the liver very markedly enlarged to 5 inches below the costal margin. Friction was palpable on respiration over the

enlarged liver. Blood values were haemoglobin 100 per cent, red blood cells 6,240,000 per cu.mm., white blood cells 80,000 per cu.mm., platelets 910,000 per cu.mm., P.C.V. 54 per cent. Stained films showed a neutrophil leucocytosis. An occasional myelocyte and quite numerous nucleated red cells were also observed. Platelets varied greatly in size. A sternal marrow smear again showed myeloid hyperplasia and active normoblastic erythropoiesis. Blood volume studies were in the polycythaemic range, with a red cell mass of 46.7 ml/Kg. body weight. This patient has been treated with radio-active phosphorus (P^{32}) and further follow-up is in progress.

Comment: The final diagnosis in this patient is still uncertain, but cirrhosis can definitely be excluded. Initially the features of splenomegaly, hepatomegaly, haemorrhoids, anaemia and intermittent leukopaenia suggested that cirrhosis was the most probable diagnosis, but this opinion had to be abandoned as a result of the histological findings. On the basis of the pathological report, myeloid leukaemia would appear to be the likely diagnosis, and this cannot with certainty be excluded. Erythraemia, leucocytosis and thrombocythaemia are common to both chronic myeloid leukaemia and polycythaemia vera, but several features in this patient are against a diagnosis of myeloid leukaemia. Firstly, aleukaemic myeloid leukaemia is an uncommon disease. Follow-up of patients in whom this diagnosis has been made almost always discloses some other pathological condition

responsible for splenic enlargement and myeloid hyperplasia. Secondly, no immature white cells were present in the peripheral blood before splenectomy, and since splenectomy only an occasional myelocyte has been observed. It is thought that this is also against a diagnosis of chronic myeloid leukaemia. Thirdly, hypersplenism must must be as rare in chronic myeloid leukaemia as it is in polycythaemia vera, so that this occurrence favoured neither diagnosis. The finding of an increased red cell mass indicated that polycythaemia was present, and fortunately radio-active phosphorus is a satisfactory treatment for both polycythaemia vera and chronic myeloid leukaemia. Sufficient time has not elapsed to observe the effect of this therapy.

These 4 patients illustrate the manner in which polycythaemia vera and cirrhosis may be confused. It will be recalled that 3 other patients were thought to have both diseases. It is therefore apparent that polycythaemia should be kept in mind when the clinical picture of cirrhosis is atypical.

2) Haemolytic Anaemia:

In chapter 4 I have described the different types of anaemia which may complicate cirrhosis, and the aetiology has been discussed. Haemolytic anaemia may occur in a patient with asymptomatic cirrhosis, and one patient is described in whom the diagnosis of cirrhosis was not definitely established until after death, the only clinical manifestation of the

disease being slight hepatic enlargement (Case C4, see Appendix).

Some years ago my attention was drawn to the possible error of diagnosing cirrhosis on the grounds of splenic enlargement associated with strongly positive flocculation tests, and overlooking an acquired haemolytic anaemia which was responsible for the patient's symptomatology. Since then I have observed 2 similar cases in whom the diagnosis of cirrhosis was doubtful, despite the biochemical evidence of disordered liver function, but unfortunately I have been unable to obtain pathological proof in either instance. The flocculation tests of liver function depend on alterations in the plasma proteins, particularly globulin, and positive results may be obtained in extra-hepatic disease (Lichtman, 1949). As abnormalities of plasma globulin may also be responsible for acquired haemolytic anaemia (Dacie, 1954), the association of splenomegaly and positive flocculation tests in the latter disease would appear to be not unreasonable. In the following 2 patients the illness was predominantly, if not entirely, due to haemolysis.

Case 1: A woman, aged 66, was admitted to hospital in 1954 complaining of tiredness, breathlessness, angina of effort, poor appetite, weight loss, and a sore tongue. She had been treated for anaemia intermittently for 14 years, and had received liver injections. On examination she was a pale, thin woman with glossitis, splenic enlargement of 4 inches and a soft hepatic enlargement

of 3 inches.

Investigation: Haemoglobin 80 per cent, red blood cells 2,600,000 per cu.mm., white blood cells 6,400 per cu.mm., reticulocytes 8 per cent, platelets 220,000 per cu.mm. Spherocytic cells were noted on examination of a blood film and red cell fragility was increased (lysis commenced 0.64 per cent saline, complete 0.36 per cent saline. A control specimen commenced to lyse at 0.48 per cent saline and was complete at 0.28 per cent saline). No spherocytic cells were present in the blood of the patient's son. The direct Coombs test was positive at 4°C and 37°C. Sternal marrow smears were hypercellular with normoblastic erythropoiesis. The E.S.R. was 156 mm in 1 hour, and liver function tests were strongly positive: serum albumin 2.7 g. per cent, serum globulin 4.6 g. per cent, serum bilirubin 1.5 mg. per cent, and Colloidal gold 6. An X-ray of chest showed a rounded opacity in the left infraclavicular field; barium swallow was normal. No L.E. cells were found in the blood or marrow. An E.C.G. showed the changes of posterior myocardial ischaemia.

A diagnosis of symptomatic haemolytic anaemia secondary to cirrhosis was made. Treatment with cortisone 300 mg. daily was started and the response was excellent. Haemoglobin rose to 90 per cent, reticulocytes fell to 1-3 per cent, the rounded opacity in the left infraclavicular lung field disappeared, and both liver and spleen regressed in size, the liver to the right costal margin, the spleen to 1-2 inches below the

left costal margin. The E.S.R. remained high, Coombs test and flocculation tests positive. Reduction in the dose of cortisone below 50 mg. daily resulted in sharp relapse, but for 3 years the patient was maintained in fair health on this dose or its equivalent of prednisone. Breathlessness and angina were the main complaints, and splenomegaly the only sign, but apart from a rise in serum albumin to normal, the biochemical findings remained unaltered. The patient died in her sleep in April, 1957, having been active until the day of her death.

Comment: It is uncertain whether this patient had an idiopathic acquired haemolytic anaemia with positive liver function tests, or a symptomatic haemolytic anaemia secondary to cirrhosis. Certain events throw doubt on the latter diagnosis. The liver, for example, was soft and quickly reduced in size when anaemia was controlled, enlarging again when anaemia relapsed. The complete absence of signs of parenchymal failure over a period of 3 years despite an initially low plasma albumin was also against the diagnosis of cirrhosis. Spherocytosis, too, is very uncommon in the haemolytic anaemia which may complicate cirrhosis, although there is no reason why it should not occur. Whatever the true diagnosis may have been, the lesson that is learnt from this patient is that hepatic and splenic enlargement associated with strongly positive flocculation tests and a moderate degree of anaemia should not lead to the assumption that the patient has cirrhosis and an anaemia which is likely to be

irreversible. Instead, evidence of haemolysis should be sought by routine haematological investigation. If haemolysis exists, there is good opportunity for effective therapy.

The second patient illustrated a similar problem, and unfortunately the diagnosis is again in doubt.

Case 2: A woman of 60 was admitted to a fever hospital in December, 1953, with pyrexia, abdominal discomfort, malaise and listlessness. An ill defined mass was present in the left upper abdomen, but examination was otherwise normal. No abnormality was noted in the urine or faeces, and blood cultures were negative. The E.S.R. was elevated to 60 mm and the haemoglobin reduced to 65 per cent. In February, 1954, she was transferred to the medical unit for further investigation. By this time the temperature was normal and she felt well. On examination there was undue pallor and a palpable mass in the left hypochondrium which was difficult to define. Radiological investigation by straight X-ray, barium meal, barium enema and intra-venous pyelogram suggested that the mass was an enlarged spleen. The urine contained urobilinogen but no bile. Liver function tests were abnormal with serum albumin 3.5 g. per cent, serum globulin 3.7 g. per cent and Colloidal gold 6. Haemoglobin was 64 per cent, red blood cells 3,100,000 per cu.mm., white blood cells 5,800 per cu.mm., reticulocytes 4-8 per cent and E.S.R. 70 mm in 1 hour. Sphero-

cytic cells were noted on examination of a blood film, and saline fragility was slightly increased (lysis commenced at 0.52 per cent saline and was complete by 0.28 per cent saline. In a control specimen lysis commenced at 0.44 per cent saline and was complete by 0.28 per cent saline). Sternal marrow was hypercellular with very active normoblastic erythropoiesis. Faecal urobilinogen was 97 mg./day.

The clinical and haematological evidence suggested that this patient had both a hepatic lesion and haemolysis although the low faecal urobilinogen result contradicted the other data suggesting haemolysis. Within the next 4 weeks haemoglobin rose spontaneously to 84 per cent and reticulocytes fell to 1-2 per cent. Urobilinogen disappeared from the urine, but liver function tests were unchanged, and the E.S.R. actually rose to 100 mm in 1 hour. She was discharged home with a presumptive diagnosis of hepatic cirrhosis complicated by a transient haemolytic episode.

The patient was seen again in May, 1954, by which time the E.S.R. had fallen to 10 mm in 1 hour, colloidal gold to 2, and blood levels had further improved. By July, 1954, complete recovery had taken place. Clinical, biochemical and haematological examination revealed no abnormality. The patient is still in perfect health (1957) and is able to nurse an invalid sister.

Comment: This patient had an illness characterised by fever, abdominal discomfort, splenomegaly, urobilinogen-

uria, anaemia, reticulocytosis, a slight increase in red cell fragility, marked elevation of the L.D.H., and positive flocculation tests. The illness lasted for several months but an apparently complete recovery has taken place. There would appear to be a choice of 3 diagnoses:

1) That haemolytic anaemia complicated established cirrhosis. This is considered to be unlikely in view of the spontaneous and permanent recovery.

2) That the primary illness was either a subclinical infectious hepatitis or subacute massive necrosis of the liver, and that the anaemia was either the anaemia of infection or a haemolytic anaemia complicating infection. There is scanty evidence that a virus may occasionally be responsible for acquired haemolytic anaemia, and the contradictory opinions on this have been reviewed by Dacie (1954).

3) That haemolytic anaemia alone was responsible for the clinical picture and that the positive liver function tests were entirely due to a primary disturbance of the plasma proteins, and not secondary to liver disease. Whatever the correct diagnosis may be, it is apparent that haemolysis must be thought of in every patient who presents with an enlarged spleen and positive liver function tests, and routine haematological observations should be made.

This problem is not a common one, but it is important. It would be of great interest to know for certain whether the

clinical and biochemical picture of cirrhosis can be produced entirely by acquired haemolytic anaemia.

3) Subacute bacterial endocarditis:

Splenomegaly is not a recognised feature of active rheumatism or of rheumatic heart disease, and the association of ill health, splenic enlargement and a valvular lesion necessitates a diagnosis of subacute bacterial endocarditis until proved to the contrary. On 3 occasions in the past 5 years I have encountered this syndrome in the absence of bacterial infection. In one patient (Case C16) the spleen was very large and there was a history of haematemesis, so that no real problem in diagnosis existed, but in the other two patients the spleen was small and the true diagnosis did not become apparent for some time. In none of these patients was the liver enlarged. The first patient has not been included in the general series because the diagnosis of cirrhosis remains in some doubt, but the case history has been quoted in chapter 1.

Case 1: A boy of 15 was admitted to hospital in October, 1952. For 1 year he had become increasingly breathless on exertion, and his friends had remarked on his pallor. There was no past history of rheumatism, growing pains, scarlet fever, chorea or jaundice. On examination there was marked pallor but no finger clubbing or petechiae. A diastolic thrill was felt at the cardiac apex and the classical findings of pure mitral stenosis were found on auscultation. The spleen was palpable 1 inch below the costal margin and was firm. The urine contained no

abnormality.

Investigations: Haemoglobin 93 per cent, red blood cells 4,500,000 per cu.mm., white blood cells 6,200 per cu.mm., E.S.R. 4 mm in 1 hour. A blood film showed marked hypochromia of the red cells; white cells were normal. Seven blood cultures were negative. Faecal urobilinogen was 93 mg. per day. Screening of the heart revealed enlargement of the left auricle and right ventricle.

Progress and treatment: The patient was treated with oral iron, and the haemoglobin rose to 97 per cent within 2 months. While under treatment he developed intermittent pyrexia, and pericardial friction was heard. Salicylates were given and fever settled. The E.S.R. had remained normal throughout.

Since 1952 the patient has been observed at regular intervals. There has been no recurrence of ill health and he has remained in full employment. The cardiac findings are unchanged and he is now awaiting valvotomy (1957). The spleen remains palpable 1 inch below the costal margin on inspiration. Liver function tests, which had previously been repeatedly normal, have now shown a slight abnormality in that plasma globulin has risen to 4.2 g. per cent. Flocculation tests are negative. The diagnosis of cirrhosis remains presumptive.

Case 2: (Case C20). A married woman of 45 complained of undue dyspnoea, poor appetite and weight loss of 9 months duration. She stated that all her symptoms had

commenced after a 'flu-like illness in January, 1956. Amenorrhoea had been present for 3 months prior to admission. Ten years previously she had had rheumatic pains in her back, but had never had rheumatic fever, chorea, or jaundice. On examination she appeared unwell and there was early finger clubbing. The cardiac findings were those of mitral stenosis and aortic incompetence, and the blood pressure was 140/80 mm.Hg. The spleen was palpable on inspiration, but the liver was not palpable. Urine contained urobilinogen but no other abnormality.

Investigation: Haemoglobin 80 per cent, red blood cells 4,100,000 per cu.mm., white blood cells 8,800 per cu.mm., E.S.R. 35 mm in 1 hour. Screening of the heart showed enlargement of the left auricle. The enlarged spleen was also noted on radiography. Blood cultures were negative.

Progress and treatment: Despite consistently negative blood cultures, it was decided that the clinical evidence justified a diagnosis of bacterial endocarditis and she was treated with parenteral penicillin for 4 weeks. At the end of this period there was no change in the clinical findings and the E.S.R. was 33 mm. Liver function tests were now performed and found to be abnormal; serum albumin 3.2 g. per cent; serum globulin 5.0 g. per cent; colloidal gold 5; and thymol turbidity 9.5 McLagan units.

This patient has now been observed for 9 months. Auricular fibrillation developed shortly after discharge

from hospital and she was re-admitted for digitalisation, but otherwise she has remained well. The clinical and biochemical findings have not altered, and the E.S.R. remains between 30-40 mm in 1 hour.

Comment: It is certain that Case 1 did not have subacute bacterial endocarditis, and the persistent splenomegaly cannot be explained on the basis of iron deficiency anaemia which promptly responded to treatment. Likewise there has never been any suspicion of haemolysis, and a well compensated cirrhosis would appear to be the most likely diagnosis. The recent rise in serum globulin suggests that further developments may yet take place in the clinical picture.

It is almost certain that Case 2 did not have bacterial endocarditis although penicillin was given and follow-up is still short. The possibility of cirrhosis was not considered until antibiotic therapy had failed to influence the splenic enlargement and the E.S.R. The diagnosis rests very largely on the positive liver function tests.

4) Amyloid disease:

Amyloid disease is an uncommon condition, but one which may cause both hepatic and splenic enlargement. It therefore enters into the differential diagnosis of cirrhosis, particularly of those patients with cryptogenic cirrhosis in whom there is a high incidence of associated ill-health. Twelve per cent of patients with cryptogenic cirrhosis in this

study had chronic bronchitis, and in some of these patients bronchiectasis was not excluded. The incidence of pulmonary tuberculosis is also increased in cirrhosis, although only 4 patients in this study were thought to have active lesions. There is therefore reason for consideration of amyloid disease when the diagnosis of cirrhosis appears to be uncertain. The following patient was probably a diagnostic error, although hepatic cirrhosis was not positively excluded.

A female patient, aged 61, was admitted to hospital in 1953 for investigation of splenic enlargement. For many years she had had a morning cough and spit, and for 7 years she had received liver injections for alleged pernicious anaemia. Her symptoms at the onset of the illness which led to the latter diagnosis were of sore mouth and tongue, anorexia and ankle swelling. Glossitis had not recurred since treatment had been started. On two occasions in the 5 years preceding admission she had had pneumonia.

On examination both the liver and spleen were enlarged 3 inches and there was slight ankle oedema. Air entry was impaired at both lung bases and crepitations were heard over these areas. Examination of the blood revealed only a slight anaemia with haemoglobin 80 per cent and red blood cells 4,500,000 per cu.mm. The E.S.R. was 5 mm in 1 hour. Sternal marrow smears showed normoblastic erythropoiesis and free hydrochloric acid was present in the gastric juice after histamine had been given. Liver function tests were entirely normal and the urine contained neither albumin nor urobilinogen.

X-ray of chest showed basal inflammatory changes. A clinical diagnosis of bronchiectasis was made and the patient treated by postural drainage and antibiotics. In addition it was supposed that she had a well compensated cirrhosis.

A year later the patient was admitted to another hospital with pneumonia. The clinical findings were as before. A gum biopsy was performed and this showed the presence of amyloid.

Comment: It is appreciated that both amyloid disease and cirrhosis may have been present in this patient, and that liver biopsy might have been more informative. Gum biopsy is, however, an extremely simple procedure and carries no risk to the patient. It is said to give a high incidence of positive results in amyloid disease (Selikoff and Robitzek, 1947). It has been performed in 2 other patients in this series in whom the possibility of amyloidosis was considered, with a negative result in both instances.

5) Cancer and cirrhosis:

It can be extremely difficult to differentiate between cirrhosis and cancer by clinical examination alone, and such a problem is not uncommon. In chapter 1 I have described how the symptoms of subacute massive necrosis may mimic those of cancer, particularly with regard to profound weight loss, and how liver biopsy may be required to establish the diagnosis. Several instances of this have already been cited - e.g. Case C14 and Case C40, both of whom had extensive investigation before the correct diagnosis was reached. Cancer and cirrhosis may coexist, and this has

been observed on two occasions, in one patient the problem being persistent jaundice (J13), and in the other, ascites (C18). Three other patients were of interest. In the first the patient had jaundice, an enlarged liver, oesophageal varices, but did not have cirrhosis. The second patient had a blood stained pleural effusion and an enlarged and irregular liver but did not have cancer. The third patient is illustrative of a more usual problem, namely that of haematemesis in the presence of an enlarged liver and a past history of alcoholism.

Case 1: A woman, aged 65, attended the out-patient department complaining of undue tiredness and breathlessness on exertion. Appetite was good, weight steady, and there was no history of blood loss. On examination she was extremely pale and the spleen was enlarged 2 inches. Blood examination revealed a severe hypochromic anaemia with haemoglobin 30 per cent. The E.S.R. was 7 mm in 1 hour. On oral iron therapy the haemoglobin rose to 70 per cent within one month, and the spleen became impalpable.

The patient was not seen again for 2 years. For 18 months she had remained well, but for 6 months she had lost appetite and weight and had vomited frequently. On examination she was slightly icteric and had obviously lost weight. The liver was enlarged 3 inches, the spleen 2 inches, and there was a little oedema. The blood picture was normal with haemoglobin 95 per cent, but the E.S.R. was 44 mm in 1 hour. Tests of liver function suggested parenchymal damage although the flocculation tests were negative: serum albumin 3 g. per cent, serum

globulin 4.7 g. per cent, serum bilirubin 1.6 mg. per cent, colloidal gold 0, and alkaline phosphatase 17.5 Bodansky units. Oesophageal varices were demonstrated by barium swallow.

The course of the illness was progressive and the patient died in hepatic coma two months after admission.

At post mortem a primary carcinoma of liver was found. The parenchyma was almost completely replaced by tumour and there was a solitary metastases in the skull. There was no evidence, either macroscopically or microscopically, of cirrhosis, but the presence of oesophageal varices was confirmed.

Case 2: A man, aged 55, was admitted to hospital with a history of cough, spit, pain in the right side of the chest and intermittent pyrexia of 3 months duration. He had always been a heavy cigarette smoker, and alcohol consumption was as heavy as he could afford. On examination he was found to have a right-sided pleural effusion, finger clubbing and hepatic enlargement. Blood stained fluid was obtained by paracentesis of the chest. X-ray of the chest following a maximal aspiration of the fluid revealed underlying consolidation which was thought to be neoplastic. The E.S.R. was 118 mm in 1 hour and serum globulin was raised, but other tests of liver function were negative. A liver biopsy showed bile retention but no definite evidence of cirrhosis and no tumour cells. A clinical diagnosis of bronchogenic

neoplasm with metastatic spread to the pleura and liver was made, and because of intermittent pyrexia both penicillin and streptomycin were administered without immediate effect on the fever. Over the ensuing weeks, however, spontaneous improvement took place, and he was able to return home.

Little change in his condition occurred over the following year. An encysted pleural effusion and gross hepatic enlargement persisted. During this period he lived in a corporation lodging house on a diet which was extremely poor. He was readmitted with scurvy and a megaloblastic anaemia, both of which responded to oral ascorbic acid. A second liver biopsy revealed the presence of cirrhosis.

For a further 2 years the patient remained in fair health, and was then readmitted with active pulmonary tuberculosis. Despite the administration of anti-tuberculous drugs, his condition gradually deteriorated, ascites developed, and he died from rupture of an oesophageal varix.

At post-mortem an extensive right-sided fibro-caseous pulmonary tuberculosis was found. The liver was cirrhotic, and biopsy specimens of liver, pancreas, and aortic lymph nodes showed extensive deposits of iron. The histological diagnosis was of haemochromatosis. A green reduction to Benedict's reagent had been noted in his urine during the final admission when he was receiving para-amino-salicylic acid, but there were no

other features to suggest diabetes.

Case 3: A woman of 70 was admitted following a haematemesis. Appetite had been poor for 5 weeks. For many years, particularly in her younger days, she had been a heavy intermittent drinker. On examination she was slightly jaundiced, and the liver was enlarged, firm and irregular. The differential diagnosis lay between hepatic cirrhosis with a ruptured oesophageal varix, and carcinoma of the stomach with secondary deposits in the liver. She was treated by blood transfusion and by the passage of a balloon tampon into the oesophagus. This appeared to control the bleeding, and after 48 hours the oesophageal tube was removed. A week later she developed a right hemiplegia, became comatose, and died.

At post mortem she was found to have a gastric carcinoma with secondary deposits in the liver. There was no cirrhosis and no varices were demonstrated.

Comment: In the absence of hepatic and splenic enlargement the differential diagnosis of haematemesis usually lies between peptic ulcer, ruptured varix, and carcinoma of the stomach. In an elderly patient recurrent bleeding from a peptic ulcer carries a poor prognosis when medical treatment is employed, and gastrectomy is recommended by most authorities if bleeding is not speedily controlled by transfusion. Laparotomy is advised in all such patients to establish the diagnosis (see Cases C11 and C15). When, however, the liver is enlarged and irregular, peptic ulcer becomes much less likely, and for

practical purposes the diagnosis can be narrowed to the other two causes of haematemesis. Such patients should be regarded as having cirrhosis with varices and treated accordingly, as there is something to be gained by this management and nothing to be lost if the diagnosis is a disseminated cancer. Tests of liver function may be helpful if strongly positive, but time must elapse before results are available and often they are not helpful, principally because they may be normal in cirrhosis, occasionally because albumin/globulin reversal and a mild positive colloidal gold may be found with tumour metastases in the liver. The prothrombin time is sometimes of value in deciding the diagnosis. When the prothrombin time is prolonged and is not speedily corrected by a parenteral injection of vitamin K1, the diagnosis of cirrhosis becomes much more certain. This test has the merit of being simple, speedy and of being performed in many ward laboratories. Unfortunately the test has only a limited application as many patients with cirrhosis have a normal prothrombin time.

The cases described in this chapter were commonly diagnostic errors. In some instances the correct diagnosis was obtained in life, in other after death, and in a few the correct diagnosis is still uncertain. The final diagnosis was often by no means obvious even when these cases were looked at in retrospect. It is therefore essential to review periodically the atypical case of cirrhosis with an open mind if the pitfalls in diagnosis are to be avoided.

S U M M A R Y

Twelve cases, all of whom presented some problem in diagnosis, are described. In most instances the clinical picture resembled cirrhosis but the diagnosis proved to be otherwise.

1. Polycythaemia Vera: Four cases are described, in three of whom a tentative diagnosis of cirrhosis was originally made. In two cases polycythaemia was masked by a specific deficiency, of iron in one and of vitamin B12 in the other. Under such circumstances polycythaemia cannot be diagnosed until the deficiency is corrected.

2. Haemolytic anaemia: Two patients with haemolytic anaemia, splenomegaly and positive liver function tests are described. One patient was maintained in good health by cortisone, the other made a spontaneous recovery. It is uncertain whether these patients had an idiopathic acquired haemolytic anaemia with a disturbance of plasma proteins, or a symptomatic haemolytic anaemia secondary to cirrhosis. The evidence available favoured the former diagnosis.

3. Bacterial endocarditis: Two cases are described who were first considered to have bacterial endocarditis on the finding of a valvular lesion and splenomegaly. Subsequent investigation and follow-up has made this diagnosis improbable and both are considered to have rheumatic heart disease and portal cirrhosis.

4. Amyloid disease: One patient is described with

bronchiectasis and an enlarged spleen. A gum biopsy showed the presence of amyloid.

5. Cancer and cirrhosis: In the Appendix 2 cases are described in whom cancer and cirrhosis co-existed (Cases J13 and C18). Three cases are described in this chapter in whom the differential diagnosis lay between cancer and cirrhosis. One patient with jaundice, an enlarged liver and oesophageal varices proved to have a primary cancer of the liver. There was no pathological evidence of cirrhosis. The second patient had an enlarged liver and a blood stained pleural effusion. The pathological diagnosis was of pulmonary tuberculosis and haemochromatosis. The third patient represented the more common problem of alcoholism, and enlarged liver and haematemesis. The pathological diagnosis was carcinoma of the stomach.

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CHAPTER 8

Biliary Cirrhosis

Biliary cirrhosis is much less common than portal cirrhosis, and accounted for only 6 per cent of cases in this study. This is probably not an accurate reflection of the comparative incidence of the two diseases as many patients with obstructive jaundice, the usual precursor of biliary cirrhosis, are admitted directly to surgical wards, while all the cases considered here were admitted to a medical unit. The bias is therefore in favour of portal cirrhosis.

Biliary cirrhosis is almost always caused by an ascending cholangitis, the sequel to obstruction of the hepatic or common bile ducts. This form of cirrhosis is usually termed secondary biliary cirrhosis. Occasionally biliary cirrhosis may develop in a jaundiced patient in whom no obstructive process can be demonstrated, and such cases are generally designated primary biliary cirrhosis.

Himsworth (1950) has given a clear account of the development of secondary biliary cirrhosis. Obstruction to the bile ducts may be caused by stone, benign or malignant neoplasm, or by an inflammatory structure. Obstruction alone is not sufficient to cause cirrhosis; there must be, in addition, infection of the fine biliary ducts within the liver substance. This infection may be acute, subacute or chronic, persistent or intermittent. Occasionally the pathological process may be so insidious that the patient is hardly aware of ill-health until

the onset of parenchymal failure. More commonly the symptoms and signs of obstructive jaundice dominate the clinical picture until the onset of oedema, ascites or mental lethargy. It is important to make a precise diagnosis in all such cases as relief of extra-hepatic obstruction may prevent or delay the progression of liver damage.

Primary biliary cirrhosis has a variety of pseudonyms such as chronic intra-hepatic obstructive jaundice, cholangiolitic hepatitis or cirrhosis, and xanthomatous biliary cirrhosis. The affection is one of the small intra-hepatic bile canaliculi, or of the larger ducts into which they drain. The cause of this condition is unknown, and the evidence so far available suggests that several pathological processes may give rise to the same clinical picture. There is growing evidence that the virus of infective hepatitis may be responsible for primary biliary cirrhosis. It is almost certain that this virus may cause prolonged obstructive jaundice, and Shaldon and Sherlock (1957) have reported 12 cases so affected, all of whom recovered. It would appear that all patients are not so fortunate for 4 of the 8 patients with progressive cholangiolitic hepatitis reported by Watson and Hoffbauer (1946) had been in contact with a person suffering from infective hepatitis, and 1 of the 6 patients with primary biliary cirrhosis reported by McPhee (1956) had received an intravenous injection 3 months before the onset of jaundice. These facts suggest a causal relationship between infective hepatitis, primary intra-hepatic biliary obstruction and

primary biliary cirrhosis.

There is also evidence to suggest that bacterial infection may cause a similar clinical picture without extra-hepatic obstruction as a precursor. Himsworth (1950) has described such a case under the title of subacute cholangio-hepatitis. A pure growth of B. coli was obtained from the bile at operation but no obstruction was found. The illness continued until death following an accident 8 months later. At autopsy no obstructing lesion could be demonstrated. Moschowitz (1952) has described a similar case, the infecting organism being staphylococcus aureus.

A further possible cause of primary biliary cirrhosis is prolonged obstructive jaundice due to the toxic action of certain drugs, notably chlorpromazine and methyl testosterone. Eosinophilia is said to be not uncommon in such cases and suggests an allergic reaction to the specific agent (Jones, 1956).

Attention has also been drawn to the predominance of female patients in reported series of primary biliary cirrhosis. This has naturally suggested some endocrine cause for the disease, but no particular gland has been incriminated.

The 6 cases which are reported illustrate certain of the diagnostic problems in both primary and secondary biliary cirrhosis. The points of interest and the management of the problems are dealt with in the discussion. The principal clinical and laboratory features of these cases are summarised in Tables 1 and 2.

TABLE 1

Clinical features of 6 patients with biliary cirrhosis

Case No.	Age	Sex	Diet	Alcohol	Jaundice	Liver Inches	Spleen Inches	Xanthomata	Aetiology
1	39	F	Normal	No	Slight	2	2	Present	Operative damage to common bile duct.
2	68	M	Normal	£2-£5 week	Yes	4	1	Absent	Primary carcinoma of bile duct.
3	53	M	Normal	No	Yes	3	No	Absent	Primary carcinoma of bile duct.
4	72	F	-	No	No	3	No	Absent	Gall stones ?
5	44	F	Normal	No	Yes	3	No	Present: numerous	Primary biliary cirrhosis.
6	51	F	Normal	No	Yes	4	4	Present	Primary biliary cirrhosis ?

TABLE 2

Liver function tests on 6 patients with biliary cirrhosis on first admission to hospital. The values given for plasma cholesterol are not those obtained at that time.

Case No.	1	2	3	4	5	6
Urine Bile	+	+	+	-	+	+
Urobilinogen mg/day	21	2.4	0.8	+	9.5	45.5
Faecal Urobilinogen mg/day	20	55	3.0	-	41	37.0
Serum Albumin g%	2.9	3.1	2.6	5.7	2.6	4.0
Serum Globulin g%	5.0	2.3	4.6	5.0	3.1	2.6
Colloidal Gold	0	0	0	2	0	3
Alkaline Phosphatase Bodansky Units Normal 1-4 units	10.5	25.9	91.0	7.9	31.0	3.3
Prothrombin Time Patient	25	19	20	24	18	19
Control	13	14	15	15	15	14
Serum Bilirubin (mg%)	2.3	9.3	20	-	4.5	12.8
Cholesterol (mg%)	-	420	930	-	2,000	222
E.S.R. mm in 1 hour	35	65	76	30	120	108

Case 1. Secondary biliary cirrhosis : stricture of the common bile duct.

A female patient, aged 39 years, had her gall bladder explored in 1948 following an attack of biliary colic. During the operation it was thought that the common bile duct had been accidentally cut, and a cholecyst-gastrostomy was performed. Following the operation jaundice occurred, with dark urine and clay stools, but without malaise. As jaundice persisted the cholecyst-gastrostomy was undone and a cholecyst-jejunostomy performed. Mild jaundice persisted. By 1949 she had lost weight, had frequent, bulky, pale offensive stools, and menorrhagia of such severity that transfusion was required. A year later she was treated for night blindness, and xanthomata were first observed. In 1951 she complained of bone pain and difficulty in walking, but it was not until 1954 that she first attended a medical unit complaining of weight loss, vomiting, abdominal pain and severe backache.

On examination she was a small, emaciated woman with slight jaundice. Xanthomatous deposits were present beneath the eyes. The back was stiff and she had difficulty in walking. There was no finger clubbing. Both liver and spleen were palpable 2 inches below their respective costal margins.

Investigations: Urine contained both bile and urobilinogen. Faecal urobilinogen was 20 mg./day, and urinary urobilinogen 21 mg./day. Blood examination showed a hypochromic anaemia, haemoglobin 50 per cent, red blood cells 4,000,000

per cu.mm., white blood cells 3,600 per cu.mm., and E.S.R. 35 mm in 1 hour.

Liver function tests were indicative of parenchymal damage and biliary obstruction: serum albumin 2.9 g. per cent, serum globulin 5.0 g. per cent, colloidal gold and thymol turbidity were normal. Serum bilirubin was 2.3 mg. per cent and alkaline phosphatase 10.5 Bodansky units. Prothrombin time was 25 seconds to a control of 13 seconds, but was corrected following the administration of Vitamin K1. Serum calcium was 8.2 mg. per cent and phosphorus 1.8 mg. per cent.

X-rays of spine and long-bones showed generalised decalcification. Barium examination of the small intestine revealed an appearance consistent with steatorrhoea. Fat balance was unsuccessful as the patient could not tolerate the diet.

Progress: Abdominal pain was severe and required both pethidine and Eumydrine for relief. The temperature rose occasionally to 100°F. Nevertheless she gained weight on a high protein low fat diet, and the haemoglobin rose to 70 per cent under the influence of iron and folic acid.

She remained well for some months and then developed small bowel obstruction from adhesions, and a further operation was required. Shortly afterwards she began to have tetanic spasms which were not well relieved by intramuscular calciferol and oral calcium. Her condition slowly worsened and she died in 1955.

At post-mortem the liver was large, green, and

surrounded by adhesions. A loop of jejunum had been sutured to the liver in the region of the gall bladder, but the common bile duct appeared to be intact. The point of entry of the bile duct into the duodenum showed extreme stenosis and would admit only the tip of a fine probe (1-2 mm). The histology of the liver was that of biliary cirrhosis.

Case 2. Secondary biliary cirrhosis : primary carcinoma of the bile duct.

A man, aged 68 years, developed painless jaundice in October, 1956, but was otherwise in good health. He admitted to heavy alcohol consumption over many years, spending £2 - £5 per week on whisky. In November he was admitted to another hospital where laparotomy was performed. No extra-hepatic biliary obstruction was found, and he was thought to have 'hepatitis'. Liver biopsy revealed bile retention with an inflammatory reaction round the portal tracts and early fibrous tissue formation.

Examination in January, 1957, revealed a deeply jaundiced man with skin excoriation from scratching. Early clubbing of the fingers was noted. The liver was enlarged 4 inches below the costal margin, and the spleen tip was also palpable. Examination of other systems was negative.

Investigations: Urine contained bile but not urobilinogen. Faecal urobilinogen was 55 mg./day and urinary urobilinogen 2.4 mg./day. Blood examination was normal except for the E.S.R. which was 65 mm in 1 hour.

Liver function tests were consistent with obstructive jaundice: serum albumin 3.1 g. per cent, globulin 2.3 g. per cent, colloidal gold and thymol turbidity normal, alkaline phosphatase 26 Bodansky units. Serum bilirubin was 9.3 mg. per cent, and serum cholesterol 420 mg. per cent. Prothrombin time was prolonged to 19 seconds as compared to a control of 14 seconds. This defect was corrected by vitamin K1.

Progress: Itch was effectively relieved by methyl testosterone sublingually. As cholangiography had not been performed at the previous laparotomy, the patient was advised to have a further exploration. Again no extra-hepatic lesion was visible or palpable, but the cholangiogram revealed a filling defect at the hilum of the liver involving the right hepatic duct. The left hepatic duct was not filled. It was not possible to dilate this stricture, but a biopsy was obtained. The histology was that of a primary carcinoma of the bile duct.

Case 3. Secondary biliary cirrhosis : primary carcinoma of the bile ducts.

A 53-year old man developed laryngitis in January, 1956, for which he was treated with penicillin. In February he became jaundiced complaining of anorexia and nausea but not of pain. In March he was admitted to the surgical ward of another hospital where laparotomy was performed. No extra-hepatic biliary obstruction was found. Liver biopsy was reported to show an early biliary cirrhosis, possibly of the primary type.

Between March and October, 1956, he remained deeply jaundiced, and was greatly troubled by itch. He complained of periodic epigastric discomfort and of occasional diarrhoea, and he had lost 3 stones in weight. Despite the jaundice he was well enough to be up and about.

Examination in October, 1956, revealed a deeply jaundiced man with skin excoriation from scratching. The liver was enlarged 3-4 inches, but the spleen was not palpable and there was no ascites.

Investigations: The urine contained bile but not urobilinogen. Faecal urobilinogen was 3 mg./day and urinary urobilinogen 0.8 mg./day. Blood examination revealed a slight normochromic anaemia with haemoglobin 80 per cent, red blood cells 3,800,000 per cu.mm., white blood cells 9,600 per cu.mm., and E.S.R. 76 mm. Liver function tests were indicative of obstructive jaundice and parenchymal damage: serum albumin 2.6 g. per cent, serum globulin 4.6 g. per cent., colloidal gold and thymol turbidity negative, alkaline phosphatase 91 Bodansky units, serum bilirubin 16-20 mg. per cent, and cholesterol 930 mg. per cent. Prothrombin time was 20 seconds to a control of 15 seconds, but was corrected following the administration of vitamin K1. Barium swallow and meal were negative.

Progress: There was an occasional rise of temperature to 100°F and itch was troublesome but effectively relieved by methyl testosterone sublingually. A further exploration was advised. Once again no extra-hepatic obstructive

lesion was apparent, but an operative cholangiogram outlined strictures of the three main hepatic ducts, with gross dilatation of the ducts beyond the stricture. A catheter was passed beyond the point of narrowing in the right main hepatic duct and bile was allowed to drain into the common bile duct through an aperture in the catheter wall. The catheter was brought out on the surface of the abdomen through a stab wound. (Operation by Mr. C. J. Longland). A biopsy of the duct in the region of the stricture showed only chronic inflammatory tissue.

The patient speedily improved in the weeks following the operation. Jaundice faded, appetite increased, and he gained weight. Serum bilirubin fell from 20 mg. per cent to 3 mg. per cent. This improvement was maintained for 3 months when jaundice again deepened, the patient became drowsy and finally comatose.

At post mortem the obstructing lesion was found to be a primary carcinoma of the large intra-hepatic bile ducts. Advanced biliary cirrhosis was also present. (See fig. 14 at end of appendix).

Case 4. A common problem : cholelithiasis and secondary biliary cirrhosis or portal cirrhosis?

A female patient, aged 72 years, gave a history of 3 attacks of painless jaundice in the 8 months preceding admission, each attack accompanied by pale stools and dark urine. Undue flatulence, weakness, and weight loss had been observed over this period. For 3 weeks prior to

admission she had complained of continuous aching pain in the right upper abdomen and had vomited frequently.

Slight jaundice was present on admission to hospital but quickly faded. The liver was enlarged 3 inches below the costal margin, and firm. The spleen was not palpable.

Investigations: Urine contained urobilinogen but not bile. Blood examination was normal apart from the E.S.R. which was 30 mm in 1 hour. Serum albumin was 5.7 g. per cent, serum globulin 5 g. per cent, colloidal gold 2, and alkaline phosphatase 8 Bodansky units. Prothrombin time was 24 seconds to a control of 15 seconds.

Liver biopsy was productive of only a small piece of tissue. There was an obvious increase in fibrous tissue, but the interpretation of the type of cirrhosis was uncertain.

A cholecystogram was not helpful as the gall bladder was not outlined.

Progress: A provisional diagnosis of cholelithiasis and biliary cirrhosis was made, and the patient advised to have a cholecystectomy. This advice was refused and she went home. Five years later she was still alive and well. There had been no recurrence of jaundice or of abdominal pain.

Case 5. Primary biliary cirrhosis.

A female patient, aged 44, was admitted to hospital in June of 1954. She had been jaundiced for 6 months, and at the onset had complained of poor appetite and

nausea. Between 1940 and May, 1953, she had received liver injections for an anaemia erroreously believed to be pernicious. Examination revealed a deeply jaundiced but well nourished woman. The liver was palpable 3 inches below the costal margin but the spleen was not palpable. Examination of other systems was negative.

Investigations: Urine contained both bile and urobilinogen. Faecal urobilinogen was 41 mg./day and urinary urobilinogen 9.5 mg./day. Blood examination revealed a normochromic anaemia with haemoglobin 70 per cent, red blood cells 3,500,000 per cu.mm., white blood cells 6,200 per cu.mm., and E.S.R. 120 mm in 1 hour. Liver function tests suggested a predominantly obstructive lesion with impairment of parenchymal function: serum albumin 2.6 g. per cent, globulin 3.1 g. per cent, colloidal gold 0, alkaline phosphatase 31 Bodansky units and serum bilirubin 4.5 mg. per cent. The prothrombin time was 18 seconds to a control of 15 seconds. Barium swallow was negative.

Progress: At all times the patient was afebrile. A tentative diagnosis of post-hepatitis cirrhosis was made, based on the history and the constant finding of a high output of urobilinogen in the urine, which was thought to be much against an extra-hepatic obstructing lesion even in the presence of a high alkaline phosphatase.

In 1955 she reported complaining of itch and of very extensive subcutaneous deposits of cholesterol. Serum bilirubin had risen to 9 mg. per cent, and blood cholesterol was 2,000 mg. per cent. Pruritis was effectively relieved

by methyl testosterone. A few months later the patient was admitted to another hospital with pneumonia. On recovery a laparotomy was performed, but no obstructing lesion found. By 1956 she had developed parenchymal failure with oedema and later ascites. Flocculation tests were now strongly positive. She died in hepatic coma, and at post mortem the liver showed an advanced biliary cirrhosis. A few foci of round cell infiltration were present, but were not sufficiently numerous to suggest recent active inflammation. There was no obstruction of the main biliary passages.

Case 6. Diagnosis uncertain : possibly primary biliary cirrhosis.

A 51-year old female became jaundiced in 1951. The onset was insidious and she was not admitted to a hospital until 1952. At that time a diagnosis of post-hepatitis cirrhosis was made on clinical grounds. She remained jaundiced but comparatively well until 1954 when she developed symptoms of anaemia and attended the Royal Infirmary. On examination she was found to be deeply jaundiced and had very pale mucosae. There was oedema of both ankles, and slight ascites was present. Both liver and spleen were enlarged 4 inches below the respective costal margins.

Investigations: The urine contained bile and urobilinogen. Faecal urobilinogen was 37 mg./day and urinary urobilinogen was 45.5 mg./day. The haematological findings were consistent with pernicious anaemia: haemoglobin 33 per

cent, red blood cells 1,200,000 per cu.mm., white blood cells 1,200 per cu.mm., platelets 100,000 per cu.mm., while the red cells showed poikilocytosis and macrocytosis. The E.S.R. was 172 mm in 1 hour. Examination of the sternal marrow revealed frankly megaloblastic erythropoiesis, and there was a histamine-fast achlorhydria. Liver function tests were consistent with an active intrahepatic lesion, but when anaemia was corrected the flocculation tests became negative: serum albumin 4.0 g. per cent, serum globulin 2.4 g. per cent, colloidal gold 3, alkaline phosphatase 3 Bodansky units and serum bilirubin 12.8 mg. per cent. The prothrombin time was 19 seconds to a control of 14 seconds.

Progress: Treatment with vitamin B12 evoked a sharp reticulocyte response and haemoglobin rose to 85 per cent. Ankle oedema and ascites disappeared but jaundice was unchanged. She continued to run an intermittent fever.

She was re-admitted in 1956 with persistent bleeding from an abrasion on the tongue. The prothrombin time was 63 seconds to a control of 16 seconds, but was quickly corrected by intravenous vitamin K1. The patient was still deeply jaundiced and now had flushed palms and xanthomata around the eyes. Liver and spleen were both palpable 3 inches below the costal margins and there was a moderate ascites. She again had intermittent pyrexia. Urine contained both bile and urobilinogen and urinary urobilinogen was 32 mg./day. Serum albumin was 3.0 g. per cent, globulin 3.1 g. per cent, colloidal gold negative,

alkaline phosphatase 17 Bodansky units and blood cholesterol 222 mg. per cent. Blood values had dropped despite large doses of vitamin B12 to haemoglobin 70 per cent and red blood cells 3,300,000 per cu.mm.

This patient is still alive but in very poor health.

D I S C U S S I O N

These 6 cases illustrate the clinical picture of biliary cirrhosis and the diagnostic problems connected with this diagnosis. In Case 1 the diagnosis was obvious, cirrhosis following biliary obstruction and ascending cholangitis. Although this patient was never deeply jaundiced, biliary obstruction was prolonged and she suffered a very frank malabsorption syndrome with overt deficiency of vitamins A, D, and K and the minerals calcium and iron. Death was primarily due to electrolyte disturbance and not to liver failure.

Cases 2 and 3 had already been subjected to laparotomy before admission to the medical ward, and no cause had been found for their jaundice. In both instances the clinical and biochemical picture suggested obstructive jaundice. A further exploration failed to reveal an obvious obstructing lesion, but operative cholangiograms successfully demonstrated stenosis of the hepatic ducts high up within the liver substance. The diagnosis in both patients was unfortunately that of a primary malignant tumour but this does not detract from the value of operative cholangiography for, had the lesion been a simple one, obstruction might have been effectively

relieved. This method of investigation should be available to all patients who undergo a laparotomy to establish the cause of jaundice.

Case 4 is an example of the problem case. A patient past middle life has several attacks of painless jaundice accompanied by undue flatulence and weight loss. The only positive feature on clinical examination is an enlarged liver. The differential diagnosis embraces cholelithiasis with secondary biliary cirrhosis, cholelithiasis and cryptogenic cirrhosis, post-hepatitis cirrhosis, and, less likely, carcinomatous metastases within the liver. The importance of an exact diagnosis lies in the remediable nature of secondary biliary cirrhosis. In Case 4 an exact diagnosis was not made, routine investigation including liver biopsy failing to establish beyond doubt the cause of the jaundice. The patient refused operation. It was considered at the time of her admission that secondary biliary cirrhosis was the most likely diagnosis on the grounds of age (72 years), right upper abdominal pain and flatulent dyspepsia, prolongation of the prothrombin time without evidence of liver failure, and the raised alkaline phosphatase. Nevertheless all of these features are consistent with a diagnosis of portal cirrhosis complicated by a stone in the common bile duct, and the final diagnosis must remain in doubt. There has been no personal follow-up owing to the patient's unwillingness to return to hospital, but for 5 years she was followed up by communication with her practitioner. During that period there was no recurrence of jaundice or of abdominal pain. If the clinical diagnosis was

correct it must be presumed that obstruction has been relieved and that the restoration of a free biliary flow has prevented the progression of her cirrhosis.

Case 5 is the only certain example of primary biliary cirrhosis. When the patient was first seen jaundice had been present for 6 months and there was substantial evidence of parenchymal dysfunction in that plasma albumin was less than 3 g. per cent and urinary urobilinogen excretion was high. Laparotomy was not performed because of these findings. Nevertheless the flocculation tests were negative and serum alkaline phosphatase was high, so that, in retrospect, the correct method of investigation should have been an operative cholangiogram and a generous liver biopsy. A needle liver biopsy, the safest procedure in the presence of parenchymal failure, is of uncertain value in differentiating primary and secondary biliary cirrhosis, and it may even be difficult to be certain that the cirrhosis is biliary rather than portal (Moschowitz, 1952), although the finding of large bile lakes greatly favours secondary biliary cirrhosis (Movitt, 1956). This patient was subjected to a laparotomy at a later date, but although no obstruction to the extra-hepatic biliary system was found, the diagnosis remained in doubt until her death as cholangiograms had not been performed.

Absence of fever is said to favour a diagnosis of primary biliary cirrhosis (Sherlock, 1955; Snell, 1956) and Case 5 was the only patient in whom no pyrexia was recorded during the stay in hospital. It is also worth recording that in no other patient did the blood cholesterol exceed 1,000 mg. per

cent, and no other patient had such extensive xanthomatous deposits. The latter were particularly numerous on the hands and face, and one deposit had to be removed surgically because of pain and sepsis.

The last patient, Case 6, was of interest because she developed classical Addisonian pernicious anaemia during the course of her illness. Initially the clinical and biochemical picture was consistent with intra-hepatic disease: flocculation tests were positive, alkaline phosphatase was normal, and urinary urobilinogen excretion exceeded faecal urobilinogen excretion. The diagnosis of post hepatitis cirrhosis, which had previously been made elsewhere, was accepted. Gradually the picture changed with deepening jaundice, troublesome bleeding from reversible hypoprothrombinaemia, and the appearance of xanthomata on the face. Moreover the flocculation tests, which were initially positive, had become negative and alkaline phosphatase had risen to many times normal. The diagnosis is still uncertain but the clinical picture is sufficiently like that of Case 5 to justify a diagnosis of primary biliary cirrhosis. The initial liver damage may well have been due to viral hepatitis even if the present diagnosis is correct.

The absence of portal hypertension in all these patients is notable. No patient had haematemesis or demonstrable varices but splenomegaly was observed in 3 of the 6 patients, two of whom had long-standing jaundice. Sherlock (1955) has observed that the splenic enlargement associated with biliary

cirrhosis may occur when the portal pressure is normal. Although the precise cause of splenic enlargement is not known, it would appear to be related to intra-hepatic infection and is therefore analogous to the enlargement which sometimes occurs in severe infective hepatitis.

Biliary cirrhosis is not a common disease in Britain but it should be kept in mind when the diagnosis of cirrhosis is made. Successful relief of biliary obstruction may eradicate biliary infection, and if hepatic fibrosis is not too extensive complete and permanent relief of symptoms may be achieved. If the lesion is not amenable to curative surgery, palliative biliary drainage will relieve both jaundice and troublesome pruritus.

SUMMARY

The incidence of biliary cirrhosis in this study of 100 patients with cirrhosis was 6 per cent. Three patients had proven secondary biliary cirrhosis and in the fourth patient this diagnosis was presumptive. Case 5 had primary biliary cirrhosis and in Case 6 this diagnosis was probable but not certain.

In the 4 patients with secondary biliary cirrhosis the obstructing lesions were (1) inflammatory stricture of the common bile duct; (2) and (3) primary carcinoma of the bile ducts; and in case (4) gall stones were regarded as probable but not proven. In both cases (2) and (3) laparotomy had

previously been performed and no lesion discovered. Further investigation by means of operative cholangiography outlined filling defects in the main hepatic ducts within the liver substance, and in case (3) a catheter was passed beyond the obstruction, successfully relieving the jaundice for several months. The value of this method of investigation is stressed.

Primary biliary cirrhosis in case (5) was characterised by continuous jaundice with both bile and urobilinogen in the urine. The symptoms at onset suggested hepatitis. Alkaline phosphatase and blood cholesterol were greatly elevated and subcutaneous deposits of cholesterol were disfiguring. The duration of the disease from onset until death was 2 years. The second patient, case (6), who was also presumed to have primary biliary cirrhosis, had a similar clinical picture with continuous jaundice and urobilinogen in the urine. Initially the diagnosis was that of post-hepatitis cirrhosis, but, as the disease progressed, features of biliary obstruction became more prominent - deepening jaundice, pruritus, elevation of the alkaline phosphatase, and hypoprothrombinaemia with troublesome bleeding, speedily controlled by the administration of vitamin K. This patient is still alive 6 years after the onset of jaundice, but is now in parenchymal failure. An interesting feature was the development of Addisonian pernicious anaemia during the course of the illness.

It is thought that both examples of primary biliary cirrhosis may be clinical variants of post-hepatitis cirrhosis.

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CHAPTER 9

Haemochromatosis

Haemochromatosis was diagnosed in 5 of the 100 patients in this study. The incidence of haemochromatosis in any study of portal cirrhosis depends to a large extent on the criteria accepted for the diagnosis of the condition. Bell (1955) reviewed the autopsy reports of 932 cases of portal cirrhosis. Sections were stained for iron in 733 cases. He reported that only 1 per cent had classical bronzed diabetes, 2 per cent had siderotic cirrhosis and diabetes without skin pigmentation, and an additional 3 per cent had portal cirrhosis with very extensive deposits of iron within the liver, but without the other two features of the disease. In the whole series, however, 34 per cent of the male patients and 23 per cent of the female patients had hepatic haemosiderosis of variable degree, but this finding alone is not sufficient to justify a diagnosis of haemochromatosis unless the amount is very great and no alternative explanation exists, such as known haemolysis, to account for the deposition of iron. Almost all cases of haemochromatosis have at least two of the classical features by the time the diagnosis is made, and in the 5 cases included in this study, 3 had the classical triad and 2 had cirrhosis and pigmentation but were not diabetic.

At one time the disease was regarded as a rarity, but in 1935 Sheldon published a monograph based on the clinical, laboratory and autopsy findings of 311 cases reported in the

literature or known to himself, and Houston (1953) has been able to add a further 222 cases to this list. Haemochromatosis is therefore uncommon but not rare.

The disease is one of uncertain aetiology, but is thought to be due to an inborn error of iron metabolism. There have been a few reports of the occurrence of the same clinical picture after multiple blood transfusions (Morningstar 1955, Davies 1955) and its occurrence in pellagrinous natives in South Africa has been well documented (Gillman and Gillman, 1945).

Normally the absorption of iron takes place through the mucous membrane of the duodenum and small intestine, and the amount absorbed depends on body requirements. Iron, in the ferrous state, combines with a protein, apoferritin, in the mucosal cells to form ferritin, and when conversion to the latter compound is complete, no further iron is absorbed from the gut. Iron is removed from the intestinal mucosa as a ferric ion attached to a plasma globulin fraction, and is transported to the iron storage depots notably in the liver, spleen, and bone marrow. Normally plasma globulin is capable of combining with about 300 micrograms of iron per 100 ml of blood, but in health only one third of the available globulin is utilised, giving a serum iron of 100 micrograms per 100 ml. In haemochromatosis there is thought to be a disturbance of the regulatory mechanism in the duodenal and intestinal mucosae whereby iron is absorbed without regard to the body requirements. Serum iron is increased and the binding

capacity of the globulins is correspondingly reduced. This abnormality is almost certainly present from birth or from early life, and iron slowly accumulates in the tissues, notably in the liver, spleen, marrow, pancreas, heart muscle, anterior pituitary and in the dermis of the skin. There is some evidence that the abnormality is inherited as a recessive characteristic, and a familial incidence has been quoted by Sheldon (1935), Althausen, Doig, Weiden, Motterbam, Turner, and Moore (1951) and by Houston (1957).

It has never been fully explained why fibrosis should occur in those tissues in which excessive iron is deposited. Large quantities of iron are found in the liver of almost all patients with haemolytic anaemia or with aplastic anaemia maintained by blood transfusion, but cirrhosis is extremely rare. The explanation may lie in the very long duration of the accumulation, and it is perhaps noteworthy that in certain tissues, e.g. skin and testes, heavy deposits of iron occur in the endothelial lining of capillaries, and thus may cause ischaemic changes in the affected tissues, with fibrous replacement of more specialised cells.

In the early stages of the disease the pathological changes in the liver may be limited to slight fibrosis round the portal tracts (Sherlock, 1955), but later the picture may closely resemble that of subacute hepatitis with nodular hyperplasia, except for the presence of great quantities of iron within the liver cells.

The 5 patients with this disease who were admitted to one medical unit of Glasgow Royal Infirmary during the past 12

years exhibited most of the features of the condition. The case history of one patient has already been recorded in chapter 7, and a second illustrative case will be given, that of a woman, because of the rarity of the disease in the female sex.

Age and Sex: Haemochromatosis is predominantly a disease of middle life, the majority of cases being diagnosed between the age of 40 and 60 years (Sheldon 1935). In this study all 5 patients were in the 6th decade when the diagnosis was made, but only 2 of these patients presented with symptoms directly attributable to haemochromatosis, the other 3 being admitted with incidental disease.

Haemochromatosis is very rare in women, and by 1953 only 33 cases had been reported of which 3 were under the age of 45 years (Houston, 1957). The rarity of the disease in women is attributed to the physiological loss of iron during menstruation and in pregnancy, which slows the progress of the disease and prevents clinical recognition until a later age. One female patient was encountered in this study:

> A married woman, aged 51 years, developed diabetes shortly after emigrating from Glasgow to South Africa in 1948. Her skin had always been dark, but became much darker about the time of onset of diabetes. In 1950 she was admitted to the medical wards of the University of Witwatersrand in diabetic coma, and at this time the diagnosis of haemochromatosis was clearly established by liver biopsy and radio-iron studies. The diabetes was extremely difficult to control, and the daily dose of

soluble insulin varied from 400 to 600 units.

In 1953 she returned to Glasgow, and was admitted under the care of Professor Davis for stabilisation of diabetes. The menstrual history obtained at this time was that periods had been scanty for many years and had ceased completely in 1947 when aged 50. She had never been pregnant. On examination the clinical features were skin pigmentation of a blue-grey colour, hepatic enlargement of 2 inches, and severe diabetes. Laboratory investigations revealed a serum iron of 248 microgrammes per 100 ml., while the serum iron binding capacity was nil. Smears of sternal marrow contained an excessive amount of iron. Liver function tests and haematological examination were both normal.

Diabetes was extremely difficult to control, and even while in the ward she became ketotic, requiring 1,500 units of soluble insulin with 36 hours to re-stabilise her. Control was eventually achieved on a low iron diet of approximately 1,000 calories with 250 units of insulin zinc suspension (lente) in the mornings.

Treatment by means of repeated venesection had been commenced in South Africa, 11 litres having been withdrawn over several months. This treatment was continued, and between December 1953 and March 1956 a further 46 litres of blood were removed. At one stage the haemoglobin fell to 65 per cent (100 per cent haemoglobin = 14.8 g. haemoglobin per 100 ml.), but rose again to 100 per cent within a month when venesections were discontinued. At

this stage the serum iron fell to nil, and then slowly rose again to 100 microgrammes per 100 ml. This treatment has resulted in general improvement with increased energy and wellbeing. Skin pigmentation has become notably less, and the liver is slightly smaller (1 inch). Liver function tests, however, show a slight deterioration in that colloidal gold has risen to 2, and serum globulin now exceeds serum albumin. Diabetes is still severe and she receives 180 units of lente insulin daily.

Symptomatology: It has been stated that patients generally seek advice because of the symptoms of diabetes, or because of lethargy, weight loss, upper abdominal pain, skin pigmentation or impotence. (Sheldon, 1935; Finch and Finch, 1955). Symptoms and signs of hepato-cellular failure are a late feature of the disease and haematemesis is much less common than in Laennec's cirrhosis (Sherlock, 1955). As already stated, it has been my experience that some patients present because of disease apparently unrelated to haemochromatosis. In this small series one patient presented with a perforated duodenal ulcer, and the liver was noted to be cirrhotic at the time of operative repair. Liver biopsy established the diagnosis in this patient. A second patient, who also had a duodenal ulcer, was admitted because of a right-sided hemiplegia, presumably caused by a cerebral thrombosis. A third patient was admitted with a respiratory infection, but although cirrhosis was diagnosed in life, haemochromatosis was not recognised until autopsy. Two patients were admitted because of diabetes, but in one of these patients hepatic

cirrhosis and skin pigmentation had been observed 4 years previously while in a surgical ward for treatment of chronic dyspepsia. The high incidence of dyspepsia and duodenal ulceration is worthy of comment. It is well recognised that upper abdominal pain may precipitate admission, and this pain is generally attributed to distension of the liver capsule, or to the advent of primary carcinoma of the liver, a not uncommon complication of this disease. It is not appreciated that chronic duodenal ulcer is also common. All 4 male patients in this study complained of dyspepsia; two had proven duodenal ulceration, while a third, who had a 20-year history of intermittent pain and vomiting 3 hours after food with relief from alkali, had a gastro-jejunostomy performed. At operation the pylorus was noted to be firm and thickened. Death occurred from hepatic coma 4 years later, and at post-mortem no abnormality was detected in the stomach or duodenum. Four of 7 male patients with haemo-chromatosis recently reported by McAllen, Coghill and Lubran (1957) had duodenal ulceration, but Sheldon (1935) cites but one instance of this association. The duodenum is the principal site of iron absorption, and the usual pathological findings are heavy pigmentation of Brunner's glands with deposition of iron in the smooth muscle of the duodenum (Sheldon 1935). It is possible that vascular changes result in mucosal ischaemia and initiate ulceration.

Diabetes occurs in about 80 per cent of patients with haemochromatosis, but is probably a late feature of the disease (Finch and Finch, 1955; Dubin, 1955). Only half

of the patients with diabetes require insulin therapy (Sherlock 1955) while others are extremely severe diabetics. Three of the 5 patients in this series were diabetic, two of them severe and unstable, while the third had only occasional glycosuria although the fasting blood sugar was 150 mg. per cent, and the oral glucose tolerance curve typical of diabetes mellitus.

Weakness and weight loss have been prominent symptoms in most of the large series of cases (Sheldon 1935; Finch and Finch, 1955) but was not specifically noted in this study before the onset of diabetes.

SIGNS

1) The Liver: Hepatomegaly is one of the most constant physical signs encountered in haemochromatosis, and has been found in 93 per cent of cases (Finch and Finch, 1955). It must be remembered, however, that during the long asymptomatic period the liver may not be enlarged, and other signs, notably skin pigmentation, may precede hepatomegaly by many years. Four of the 5 patients in this study had hepatic enlargement, but the 5th patient, who presented with a perforated duodenal ulcer, had a liver that was only just palpable beneath the costal margin on inspiration. Three of the 5 patients were observed over a period of years; progressive hepatic enlargement was noted in 2 of these patients, but in the third, who was treated by repeated venesection, the liver became smaller. Hepatic pain was not a feature in any of the 5 patients nor was primary carcinoma of the liver encountered. The sudden onset of hepatic pain and weight loss should lead one to suspect the

latter occurrence.

2) The Skin: Excessive skin pigmentation has been found in 90 per cent of cases at the time of diagnosis, but in 30 per cent of these cases the pigmentation is slight (Finch and Finch, 1955). Pigmentation is usually generalised, but exposed parts are more severely affected. Buccal pigmentation has been occasionally reported. Three factors are responsible for pigmentation: excessive melanin deposition which gives a brown colour to the skin; excessive iron deposits which give a blue-grey tint; and atrophy of the epidermis which enables pigment to be more readily seen. Melanin pigmentation is usually the most prominent feature, and the amount of iron noted in a skin biopsy from a pigmented area may be quite small.

All 5 patients in this study were pigmented. Three were bronzed and two slaty grey. Pigmentation may be of very long standing. Thus one patient stated that he had been pigmented for as long as he could remember, a second dated the onset of pigmentation to military service in the East 30 years before, while the female patient thought her skin had always been darker than normal, but that pigmentation had increased shortly before the onset of symptoms of diabetes. It is quite possible that skin pigmentation may be the earliest clinical sign of the disease, as the pathological changes commence in early life. Sheldon (1935) has also quoted 16 cases from the literature in which pigmentation had been present for many years before the onset of symptoms.

3) The spleen: Splenomegaly has been reported in 40 - 60 per cent of cases (Dubin, 1955) but was not a feature in any of the 5 cases seen personally.

4) Ascites: Now that effective insulin control has lessened the risk to life from diabetes, parenchymal failure is a common cause of death. Three of the 5 patients in this study have died and two had terminal ascites.

5) Oesophageal varices: Oesophageal varices are surprisingly uncommon in haemochromatosis. This is a curious feature of the disease as both the chronicity of liver damage and the histological picture in the later phases of the condition would suggest that varices might be common. Varices were not demonstrated radiologically in any of the 5 patients under study, but one patient had a small haematemesis terminally, and varices were demonstrated at post-mortem.

6) Gonad function: Hypogonadism is a prominent feature in many of the reported cases and has been attributed to haemosiderin infiltration of the anterior pituitary. I have not specifically noted hypogonadism in any case, but no special studies were performed. Two of the 4 male patients had a normal beard growth. I do not have adequate records of this point in the other two cases.

7) Heart disease: The myocardium is one of the tissues which may become heavily infiltrated with haemosiderin, and the ensuing muscle damage is responsible for cardiac failure. In one series of 21 fatal cases reported by Dubin (1955) 11 had died of cardiac failure. Finch and Finch (1955) also stated that one-third of patients die from heart disease, and that many of the early deaths may be attributed to heart failure. None of the three fatal cases in this series died of heart disease, but one had complained of angina of effort for several years.

Electrocardiographic changes of myocardial ischaemia were noted in 2 patients.

8) Other diseases: Two of the 5 patients had pulmonary tuberculosis; only one of the two was a diabetic. Reference has already been made to the incidence of duodenal ulcer.

Liver function tests: The majority of patients with haemochromatosis have remarkably good liver function, and the biochemical tests are frequently normal or almost so. Liver function tests were performed in 4 of the 5 patients. One patient, the female, had completely normal tests when first admitted, but now, 4 years later, globulin is increased, albumin slightly reduced and colloidal gold flocculation is mildly positive. The other 3 patients had slight depression of plasma albumin and elevation of globulin when first seen, and this abnormality has persisted. Two of the 3 had normal flocculation tests, but the third had a positive colloidal gold reaction. The E.S.R. was elevated in all 5 patients, but when the two patients with pulmonary tuberculosis are excluded, the elevation was only slight (13, 14, and 17 mm in 1 hour, Westergren).

Diagnosis: There are numerous confirmatory tests to substantiate a diagnosis of haemochromatosis, the best of which are liver biopsy, estimation of serum iron and serum iron binding capacity, and the staining of marrow smears and sections for haemosiderin. Tests which are of less value include skin biopsy, Rous test for stainable iron in the urinary sediment, and gastric mucosal biopsy for the presence of iron.

Liver biopsy is the most conclusive of all the ancillary

investigations, for the liver is always involved and both cirrhosis and the excessive iron deposition may be demonstrated. Four of the 5 patients underwent liver biopsy either by needle or at laparotomy, and in all 4 very large amounts of haemosiderin were noted to be present. As mentioned earlier in this chapter iron is often present in the liver affected by portal cirrhosis, but the quantity is seldom as great as that found in haemochromatosis. In one patient already reported in chapter 1 (Case C4) cirrhosis was associated with chronic haemolytic anaemia, and amounts of iron comparable to those found in haemochromatosis were found in the liver. The same difficulty is encountered in the interpretation of a marrow biopsy. Large quantities of iron in the marrow are not diagnostic of haemochromatosis, and may be found in haemolytic anaemia, pernicious anaemia and in aplastic anaemia. The findings therefore require interpretation in the knowledge of the clinical picture. Three patients in this study had marrow stained for iron, and in all 3 an abundance of haemosiderin was noted.

Estimation of serum iron and serum iron binding capacity is a most useful diagnostic test, but again it is not infallible and the technique is somewhat tedious. In 88 per cent of cases reported in the literature serum iron was elevated, but in the remaining 12 per cent in whom serum iron was normal, the diagnosis appeared to be well substantiated (Finch and Finch 1955). The latter authors have noted sharp depression of serum iron in association with infection, and this is a possible explanation for a normal result in certain cases.

In the present study serum iron was estimated in 3 patients and serum iron binding capacity in 2 (Dr. R. Pirrie). Two patients had extremely high levels for serum iron in association with a very low combining capacity, but the third patient, in whom the iron binding capacity was not estimated, had a normal serum iron (115 microgrammes per 100 ml.).* This patient presented with a perforated duodenal ulcer, and the diagnosis appeared to be well founded on the grounds of liver biopsy, iron in the marrow, and the clinical picture. Apart from a mild post-operative pulmonary infection there was no apparent cause for the anomalous finding of a normal serum iron.

Skin biopsy is a less conclusive investigation, but even when the quantity of stainable iron is small the diagnosis of haemochromatosis is likely when excessive melanin pigmentation is found in association with atrophy of the epidermis. This investigation was performed in 2 patients. In one the quantity of iron was large, but in the other, a well pigmented man, only a small amount of haemosiderin was noted in the superficial layers of the dermis.

Prognosis: Haemochromatosis is a disease which probably exists from birth until death, and may vary in severity. In Sheldon's studies (1935) the average survival time after diagnosis had been made was 18½ months, but many of these cases were recorded before the introduction of insulin, and diabetic coma was responsible for 50 per cent of deaths. Nevertheless Finch and Finch (1955) have observed that even in the post-insulin era the average duration of life after

* The result 1 year later was 285 µg.

diabetes had developed was only 3 years. Diabetes was often a late manifestation of the disease, and the average duration of life as a whole after the diagnosis had been made was 4.4 years. There were on record, however, a few patients who had lived for as long as 20-30 years after diagnosis. The principal causes of death in the cases reported by Finch and Finch were cardiac failure, hepatic coma, haematemesis and hepatoma.

In this small series no true assessment can be made of prognosis. Only one patient has been treated by repeated venesection and she would appear to have benefited from this therapy, having survived for 7 years since treatment was commenced. It can be said with certainty that she would have died had it not been for the use of insulin. The follow-up period for 2 of the 3 fatal cases was 3 years, while the third patient died after 5 months. The diagnosis of cirrhosis in the latter case had been made at operation 4 years before, but at that time he had no symptoms referable to liver disease. Two patients died of hepatic parenchymal failure and the third patient of haemorrhage from an eroding duodenal ulcer.

Treatment: Until recent years there has been no effective treatment for haemochromatosis. The various therapeutic regimes, such as a low iron diet, or a diet rich in phosphorus to delay absorption of iron, have met with little success, and this is not surprising as large quantities of iron have accummulated in the body by the time that the disease is productive of symptoms. The only rational method of effecting improvement is to remove iron from the affected tissues, and

to this end British-anti-lewisite (B.A.L.) has been given, but with little success. Repeated venesection was then attempted (Finch 1949) with much better results, for each pint of blood contains 250 mg. of iron. Following venesection mobilisation of body iron is rapid, and many litres can be withdrawn without the occurrence of anaemia. This is almost a specific test for haemochromatosis, for I know of no other disease in which 20-40 pints of blood can be removed in as many weeks without the development of hypochromic anaemia. It is usual to bleed the patient at weekly intervals, removing 1 pint of blood on each occasion, and some authors recommend that the plasma be returned by intravenous infusion. Finch and Finch (1955) have not found this necessary except in those patients who were found to have oedema or ascites. Control of therapy is maintained by repeated estimations of serum iron and by the blood count. When the iron stores have been exhausted the frequency of phlebotomy is reduced to 3 monthly intervals. It has been demonstrated by serial liver biopsy that by this regime iron is removed from the liver, and there have been convincing reports of clinical improvement (Davis and Anowsmith, 1952; McAllen, Coghill and Lubran, 1957). In the female patient reported here serum iron was reduced from 248 microgrammes per 100 ml. to nil by weekly venesections over a period of 2 years. Frequently a litre of blood was withdrawn. The patient is now maintained with only an occasional venesection and serum iron is normal. Perhaps the most important observation in this case is that improvement has occurred over a 5-year period when deterioration would

otherwise have been expected. As venesection is the only useful treatment for the disease care should be taken to preserve the veins for the long therapeutic regime.

Treatment of the liver disease should not be forgotten. Alcohol must be forbidden and hepato-toxic occupational hazards avoided. The diet should be rich in protein even at the expense of the iron content, which can easily be removed by venesection. The usual measures should be employed to treat parenchymal failure and the consequences of portal hypertension.

SUMMARY

The incidence of haemochromatosis in this study was 5 per cent. Four of the patients were male and one female. Haemochromatosis is extremely rare in a woman, only 33 other cases having been described. The clinical features of the disease and the methods of confirming the diagnosis are discussed. Attention is drawn to the high incidence of dyspepsia with duodenal ulceration.

Repeated venesection is now accepted as the most rational therapeutic procedure, and one patient (the female) was so treated, 55 litres of blood being removed over a period of 3 years.

The prognosis of the untreated case, once symptoms have arisen, is bad (5 months to 3 years in the 3 fatal cases reported here) but may be greatly improved by venesection.

The one patient treated by this method is still in good health 7 years after the diagnosis was established.

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A P P E N D I X

Case reports of 89 patients with portal cirrhosis

Alcoholic Cirrhosis

Case No. Al.

Male, aged 39 years. In good health until 3 weeks before admission to hospital when he observed swelling of his legs and a purpuric rash on his lower limbs. No history of gastro-intestinal upset. Excessive alcohol consumption for 16 years. No history of jaundice. Diet average.

Examination : Gross oedema of legs; purpuric rash on legs; palms flushed; spider naevi present; slight icterus; liver enlarged 6 inches; spleen 3 inches.

Radiology : X-ray chest and barium swallow normal.

Liver function tests : Serum albumin 3.9 g.%; serum globulin 5.5 g.%; colloidal gold 6; thymol turbidity positive; alkaline phosphatase 2.4 Bodansky units; serum bilirubin 1.6 mg.%.

Progress : Treated by high protein diet. Follow-up for 3 years. Well and working until beginning of 1958 when he again became unwell. Drinking habits had been resumed. Re-admitted in hepatic coma March, 1958 but responded to treatment (intravenous fluids and broad-spectrum antibiotics).

Case No. A2.

Male, aged 55 years. Complained of undue tiredness for 6 months. Bleeding from haemorrhoids for 15 years. Cough and undue breathlessness on exertion for 10 years. Excessive alcohol consumption for 35 years, very heavy for 15 years. Diet average. No jaundice.

Examination : Pale (Hb=50%). No oedema; normal palms; no naevi; no jaundice; liver edge palpable on inspiration; spleen palpable 2 inches; haemorrhoids.

Radiology : X-ray chest and barium swallow negative.

Liver function tests : Serum albumin 3.8 g.%; serum globulin 3.2 g.%; colloidal gold 0; thymol turbidity negative; alkaline phosphatase normal; serum bilirubin 0.2 mg.%.

Progress : Anaemia responded to oral iron. Patient refused to report again, but follow-up by letter to own practitioner indicated that the patient was still alive 2 years later. The diagnosis in this case was a clinical one, based on the alcoholic history and the finding of a firmly enlarged spleen.

Case No. A3.

Male, aged 61. Admitted following an epileptiform convulsion. Alcohol consumption had always been as much as he could afford. Diet very poor. No history of jaundice.

Examination : No oedema; no naevi; no jaundice; palms normal; liver enlarged 3 inches and firm; spleen not palpable.

Radiology : Varices demonstrated by barium swallow.

Liver function tests : Serum albumin 3.0 g.%; serum globulin 3.8 g.%; colloidal gold 0; thymol turbidity negative; serum bilirubin 0.4 mg.%.

Progress : Follow-up 9 months. No change in condition.

Case No. A4.

Male, aged 39 years. Admitted following a sudden haematemesis. No previous history of dyspepsia. Appetite always good. Diet normal. Heavy alcohol consumption at week-ends for over 15 years. No history of jaundice.

Examination : Entirely normal at time of admission. Ascites developed 1 week later and persisted for about one month. Liver and spleen not palpable.

Radiology : Oesophageal varices demonstrated by barium swallow.

Liver function tests : Serum albumin 3.6 g.%; serum globulin 3.3 g.%; colloidal gold 5; thymol turbidity negative; alkaline phosphatase normal; serum bilirubin 0.4 mg.%.

Progress : Follow-up less than a year. Alive, well and working.

Case No. A5.

Male, aged 44 years. Admitted in a drowsy state, complaining of headache. The previous day he had fallen out of bed while drunk. He had taken excessive quantities of alcohol for 10 years, and hepatomegaly had been observed in another hospital 7 years previously. Recently, appetite had been poor and morning vomit was sometimes blood-stained. Diet generally poor.

Examination : Ankle oedema; slight jaundice; no naevi; palms normal; liver enlarged 2 inches; spleen not palpable. No focal neurological signs.

Radiology and liver function tests not performed.

Progress : Increasing drowsiness over 48 hours to coma and death.

Post-mortem : Laceration of brain with haemorrhage.
Portal cirrhosis.
No oesophageal varices demonstrated.

Case No. A6.

Male, aged 32 years. Admitted to hospital with a tuberculous right pleural effusion. Morning anorexia and diarrhoea for 3 months. Alcoholic for many years, and had been in a psychiatric ward with delirium tremens a year previously. Diet poor. No history of jaundice.

Examination : The only positive feature besides the pleural effusion was hepatomegaly of 5 inches.

Radiology : Barium swallow negative for varices.

Liver function tests : Serum albumin 3.8 g.%; serum globulin 4.3 g.%; colloidal gold and thymol turbidity negative; alkaline phosphatase normal; serum bilirubin 0.8 mg.%.

Progress : Transferred to a Sanatorium but discharged after 6 months for domiciliary treatment. Resumed drinking. Seen again eighteen months after original admission when he was found to have bilateral apical tuberculosis and hepatic enlargement of 4 inches. No signs of parenchymal failure. The patient has been untraced for several years.

Case No. A7.

Male, aged 34 years. Admitted to another hospital with haematemesis. Bleeding recurred repeatedly over 6 weeks. Transferred to Glasgow Royal Infirmary for opinion on suitability for porta-caval shunt. No history of dyspepsia. Hepatic and splenic enlargement had been noted 1 year previously when he had attended hospital with dermatitis. Alcohol consumption had been heavy in the past. Diet average. No history of jaundice.

Examination : Slight ankle oedema; petechiae on legs; early clubbing; minimal ascites; no naevi; no jaundice; liver and spleen both enlarged 5 inches. Veins visible in abdominal wall.

Radiology : Barium swallow failed to demonstrate varices.

Liver function tests : Serum albumin 3.7 g.%; serum globulin 5.2 g.%; colloidal gold 6; thymol turbidity ++; alkaline phosphatase 4.5 Bodansky units; serum bilirubin 0.4mg.%.

Progress : Because of recurrent bleeding and the finding of a persistent leucopaenia, splenectomy and porta-caval shunt advised. Three days after the operation he had a further haematemesis, went into coma and died.

Histology : Portal cirrhosis. Round cell infiltration of the band of fibrous tissue.

Case No. A8.

Male, aged 38. Seen at the out-patient clinic with complaint of aching pain in the left chest of 1 year's duration. Heavy alcohol consumption for 20 years. Appetite excellent and no dyspepsia. Diet average. No jaundice in the past.

Examination : The only positive finding was a palpable spleen 1 inch below the left costal margin.

Radiology : Barium swallow negative for varices.
X-ray chest: healed tubercle at right apex.

Liver function tests : Serum albumin 3.8 g.%; serum globulin 3.9 g.%; colloidal gold 1; thymol turbidity normal; serum bilirubin 0.7 mg.%.

Blood : Normal peripheral blood findings.

Progress : In the absence of any other cause of splenomegaly, presumed to have cirrhosis. Follow-up 6 months: no change in condition.

Case No. A9.

Male, aged 42 years. Admitted following a haematemesis. Upper abdominal discomfort for 6 months previously. Excessive alcohol consumption for many years and diet poor. No history of jaundice. Past history of pulmonary tuberculosis.

Examination : Thin man. No oedema, naevi, clubbing, or jaundice. Spleen enlarged 5 inches and liver 2 inches.

Radiology : Varices demonstrated by barium swallow. Pulmonary fibrosis on the left side.

Liver function tests : Serum albumin 4.6 g.%; serum globulin 2.1 g.%; colloidal gold 0; thymol turbidity mildly positive; alkaline phosphatase normal; serum bilirubin 0.4 mg.%.

Haematology : Leucopaenia and thrombocytopaenia.

Progress : Splenectomy and porta-caval shunt performed. Initial result excellent. Remained well for 2 years when haematemesis recurred and he developed ascites. Thereafter haematemeses were numerous and led to his death.

Post-mortem : Small granular liver : portal cirrhosis (Fig.1). Extensive varices in both oesophagus and stomach.

CASE A9

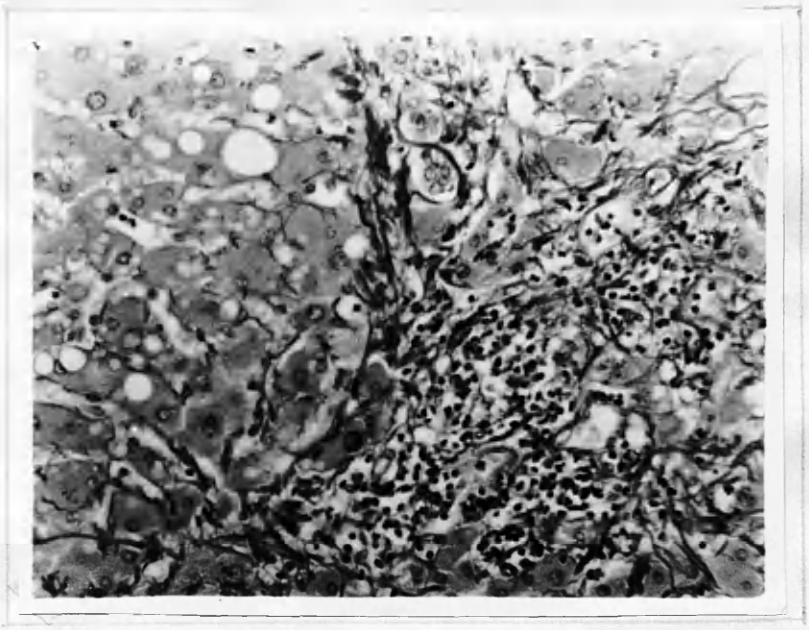

Fig. I.

ALCOHOLIC CIRRHOSIS

The liver is fatty with diffuse fibrosis. There is also some small round cell infiltration of the fibrous tissue. (x 180)

Case No. A10.

Male, aged 69 years. Admitted because of abdominal swelling of 10 weeks duration. Appetite had been poor for many months. Excessive alcohol consumption for the whole of his working life. Diet often below average.

Examination : Marked ascites; spider naevi present; no jaundice; neither liver nor spleen palpable.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 2.5 g.%; serum globulin 4.1 g.%; colloidal gold 2; thymol turbidity strongly positive; alkaline phosphatase 29 Bodansky units; serum bilirubin 1.5 mg.%.

Progress : Unco-operative patient who left hospital against advice. Survived for a further 6 months at home.

Post-hepatitis Cirrhosis

Case No. J1.

Male, aged 57 years. In 1950 jaundice developed 3 months after a T.A.B. innoculation. Illness mild and neither off work nor in bed. Jaundice recurred in 1953 and was accompanied by some gastro-intestinal symptoms. Although jaundice was of short duration he never felt well thereafter. He was admitted with a third attack of jaundice in 1954. Although not an alcoholic, alcohol consumption was above average. Cholecystectomy had been performed at the age of 40. Diet good.

Examination : Slight jaundice; small naevi on face; palms normal; no ascites; liver enlarged 1 inch and spleen 2 inches below respective costal margins.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 2.2 g.%; serum globulin 5.5 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase 4.4 Bodansky units; serum bilirubin 3.8 mg.%.

Progress : Further gall bladder exploration was performed. Coarse nodular cirrhosis noted at operation. No biliary calculi observed. Post-operative progress was initially good, but became drowsy 2 weeks after the operation, and lapsed into fatal coma.

Case No. J2.

Male, aged 71 years. In 1946 he had been jaundiced for 6 weeks but had received no treatment. In January 1952 he lost his appetite, felt nauseated and lost weight. These symptoms persisted for 3 months before jaundice was observed. Admitted in June 1952 by which time he felt well, although icterus was still present.

Examination : Slight jaundice; no naevi; no oedema; liver enlarged 3 inches; spleen not palpable.

Radiology : Barium swallow negative for varices.

Liver function tests : Serum albumin 4.0 g.%; serum globulin 3.3 g.%; colloidal gold 4; thymol turbidity positive; alkaline phosphatase normal; serum bilirubin 1.5 mg.%.

Progress : Icterus slowly cleared and the patient became asymptomatic. For 3 years the only positive clinical finding was hepatomegaly, affecting particularly the left lobe of the liver. In 1955 ascites developed and persisted until his death in 1956. Slight icterus was a terminal feature.

Case No. J3.

Female, aged 55. At the age of 17 she had contracted syphilis and had received intermittent treatment ever since. In 1952 jaundice developed 3 months after an injection and was accompanied by anorexia and upper abdominal discomfort. She remained jaundiced thereafter, and was admitted several months later. The dietary history was poor.

Examination : Jaundiced; oedema of legs; spider naevi present; visible veins in abdominal wall; liver enlarged 1 inch and spleen 2 inches.

Radiology : Barium swallow negative for varices.

Liver function tests : Serum albumin 2 g.%; serum globulin 3.5 g.%; colloidal gold 0; thymol turbidity positive; serum bilirubin 4.5 mg.%.

Progress : Continuous jaundice. Ascites developed 4 months later and the liver became impalpable. Died at home of liver failure 9 months after the onset of illness.

Case No. J4.

Female, aged 48 years. Admitted because of swelling of ankles and abdomen for 1 month. She had experienced poor appetite and intermittent diarrhoea for 4 months.

25 years previously she had been jaundiced for 1 week but had felt ill for 3 months.

12 years previously transient ascites had occurred after a normal pregnancy. Paracentesis had been performed and 12 pints removed. Ascites had not recurred and the patient had been well until the onset of symptoms which led to admission.

Examination : Pale; no jaundice; slight oedema of ankles; no naevi; liver enlarged 1 inch and spleen 3 inches. Doubtful ascites.

Radiology : No varices demonstrated by barium swallow. Gall stones present.

Liver function tests : Serum albumin 2.8 g.%; serum globulin 2.2 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase normal; serum bilirubin 1.0 mg.%.

Haematology : Iron deficiency anaemia.

Progress : Anaemia responded to oral iron and general improvement occurred. Cholecystectomy performed on the supposition that biliary disease might aggravate existing hepatic disease. Became comatose 3 days post-operatively and died 1 week later. The histology of the liver is shown in Fig. 2.

CASE J4

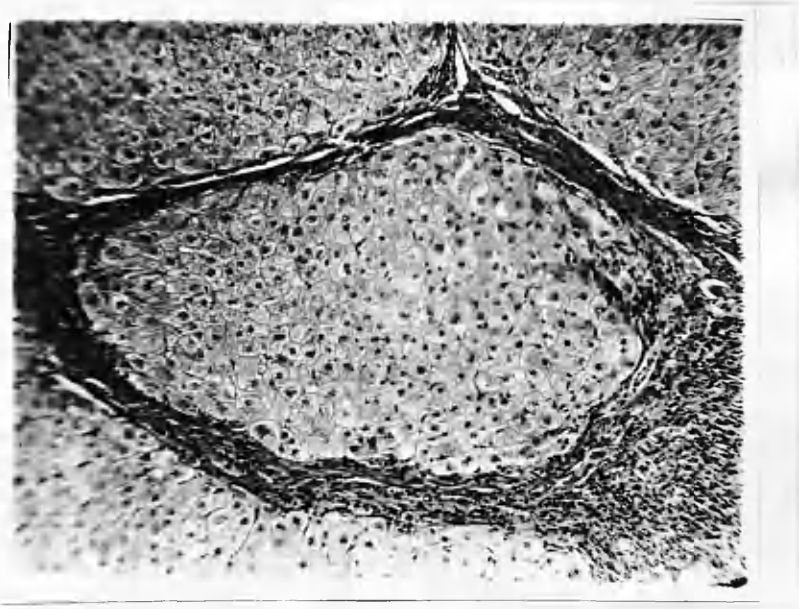

Fig. 2

Post hepatitis cirrhosis with nodular hyperplasia. (x 100)

CASE J 5

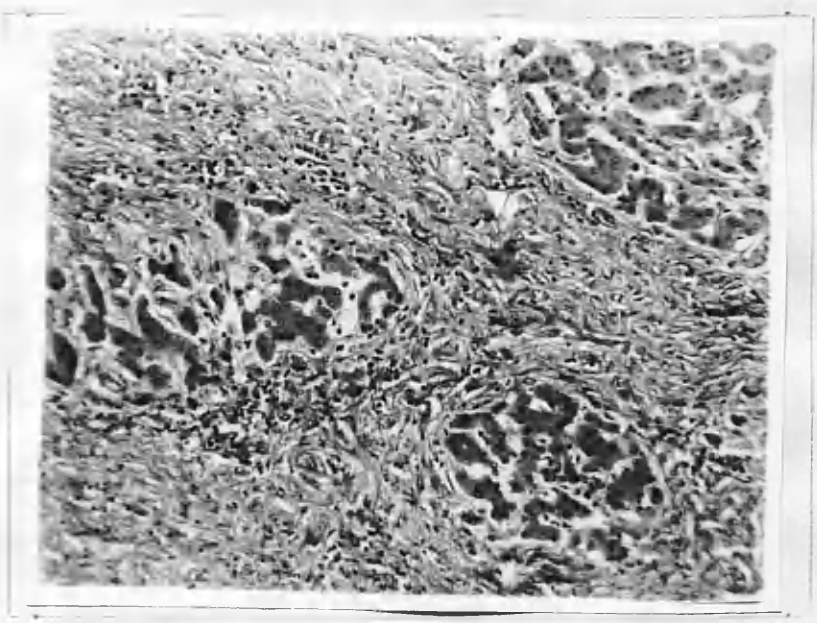

Fig. 3

Post hepatitis cirrhosis. Much of the parenchyma has been replaced by fibrous tissue and only "islands" of liver cells survive. (x 100)

Case No. J5.

Male, aged 21 years. In June 1946 he became ill with nausea and upper abdominal pain. In September 1946 jaundice was observed, and the following month he went to bed. He was not admitted to hospital until February 1947.

Examination : Jaundiced; no oedema; no ascites; liver enlarged 4 inches and tender; spleen not palpable. Visible veins in abdominal wall.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 3.6 g.%; colloidal gold 5; serum bilirubin 6.5 mg.%; alkaline phosphatase normal.

Progress : Laparotomy performed because of severe attacks of upper abdominal pain. Found to have cirrhosis and no cause for pain detected. Remained icteric. Haematemesis occurred in 1948 and ascites developed. Died of massive haemorrhage in May 1948.

Post-mortem : Multilobular cirrhosis with hepatoma of left inferior surface (Fig. 3). Oesophageal varices with rupture of a varix.

Case No. J6.

Female, aged 38 years. For 1 year she had observed intermittent slight jaundice and complained of poor appetite. The gall bladder had been explored but no stones were found. Symptoms persisted.

Examination : Slight icterus; no oedema; liver enlarged 2 inches and spleen 1 inch; no ascites.

Radiology : Barium swallow negative for varices.

Liver function tests : Serum albumin 2.7 g.%; serum globulin 5.8 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase normal; serum bilirubin 1.8 mg.%.

Progress : Faint jaundice persisted with serum bilirubin levels varying from 0.6 to 2 mg.%. The liver became impalpable, and ascites developed. Haemoglobin fell and petechial haemorrhages were observed. Death occurred almost 3 years after the onset of jaundice. The patient had been admitted to a surgical unit for incision of an abscess. Oedema and ascites were present. She was given nitrous oxide and oxygen for the small operation. She became comatose the following day and died.

Case No. J7.

Male, aged 28 years. Admitted to hospital with acute glomerulo-nephritis. Several days later he became icteric and ascites was detected. Undue drowsiness was followed by coma, and he died 8 days after admission.

There was a past history of jaundice 5 years previously which had been treated by bed rest in a military hospital. Mild jaundice had recurred a few months later.

Examination : Jaundiced; oedema, and later ascites, present. Neither liver nor spleen palpable. Urine contained albumin, blood, bile and urobilinogen; granular and cellular casts observed.

Radiology : None done.

Liver function tests : Serum albumin 2.7 g.%; serum globulin 4.0 g.%.

Bacteriology : Widal and Leptospiral agglutinations negative.

Post-mortem : Nodular multilobular cirrhosis (Fig. 4). Varices present. Subacute nephritis.

CASE J 7

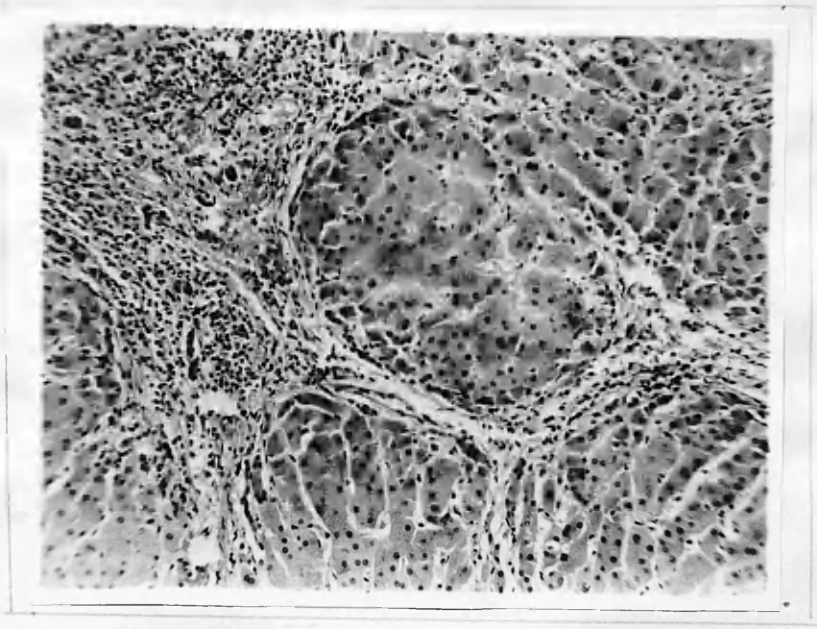

Fig. 4

Post-hepatitis cirrhosis.

There is nodular hyperplasia and round cell infiltration of the fibrous tissue. (X 100)

Case No. J8.

Male, aged 38 years. While in Nigeria in 1953 he became jaundiced with anorexia, loss of energy, and occasional vomiting. Off work for 14 weeks during which time he was periodically in bed. Returned to work without having made a recovery. Eight months after the onset of the illness he returned to Britain by aeroplane, and during the journey he observed swelling of feet and abdomen.

Examination : Slightly jaundiced; oedema and ascites present; spider naevi on face and arms; neither liver nor spleen palpable.

Radiology : Barium swallow not done.

Liver function : Serum albumin 1.8 g.%; serum globulin 4.0 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase normal; serum bilirubin 2.7 mg.%.

Progress : Despite treatment by diet, diuretics, intravenous Dextran, and finally cortisone, the course was progressive and he died in hepatic coma 13 months from the onset of jaundice.

Case No. J9.

Female, aged 37 years. In January 1954 a cholecystectomy was performed because of complaint of right upper abdominal pain. At operation multilobular cirrhosis was found and also evidence of chronic cholecystitis. Two months later she developed oedema and ascites and was admitted to the medical wards for treatment. Twelve years previously she had been jaundiced for 18 months, the first three of which were spent in bed.

Examination : No jaundice; no naevi, but well marked facial telangiectasis; ascites present; liver edge just palpable on inspiration; spleen not palpable.

Radiology : Varices demonstrated by barium swallow.

Liver function tests : Serum albumin 2.6 g.%; serum globulin 4.2 g.%; colloidal gold and thymol turbidity negative; alkaline phosphatase normal; serum bilirubin 0.2 mg.%.

Progress : Improved on a high protein diet. The patient could not be traced 6 months after discharge from hospital.

Case No. J10.

Male, aged 62 years. Anorexia, nausea and jaundice developed in May 1956, and because of persistent jaundice he was admitted to a surgical ward in June 1956 and a laparotomy was performed. The biliary system appeared normal and a liver biopsy showed subacute massive necrosis. He was transferred to the medical unit in July by which time jaundice was fading.

Examination : Apart from slight jaundice, clinical examination was negative.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 1.2 g.%; serum globulin 5.4 g.%; colloidal gold 5; thymol turbidity positive; alkaline phosphatase normal. Serum bilirubin 4 mg.%.

Progress : Jaundice disappeared and he was able to go home. Two months later he was seen as an out-patient. Oedema and ascites were noted but neither liver nor spleen were palpable and jaundice had not recurred. Untraced thereafter.

Case No. J11.

Male, aged 70 years. Seven years previously he had been in hospital with an apparently mild attack of hepatitis, jaundice persisting for only a few days. He was not followed up as recovery appeared to be complete. He remained well for over 6 years and then returned complaining of swelling of his legs and undue weight loss. For years he had had a chronic cough.

Examination : Oedema of legs; no naevi; palms normal; no ascites; liver enlarged 4 inches and spleen 2 inches. Crepitations at both lung bases.

Radiology : Barium swallow normal.
X-ray of chest suggested basal bronchiectasis.

Liver function tests : Serum albumin 3.7 g.%; serum globulin 2.6 g.%; colloidal gold and thymol turbidity normal.

Progress : No change in physical signs in the course of 15 months follow-up. Amyloid disease was not excluded. No albuminuria was detected.

Case No. J12.

Female, aged 52 years, admitted to hospital with a tuberculous right-sided pleural effusion. Jaundice had developed 2 years before and had been persistent. Laparotomy had been performed elsewhere and a diagnosis of subacute hepatitis was made.

Examination : Pale; jaundiced; no naevi; palms normal; finger clubbing; no ascites; liver palpable 2 inches and spleen 1 inch. Signs of right-sided pleural effusion.

Radiology : Barium swallow negative for varices.

Liver function tests : Serum albumin 4.2 g.%; serum globulin 4.1 g.%; colloidal gold 5; alkaline phosphatase 10.6 Bodansky units; serum bilirubin 2.5 mg.%.

Progress : Despite intensive treatment with diet and streptomycin very little change occurred. Death followed a haematemesis 3 years after the onset of jaundice.

Case No. J13.

Male, aged 57 years. Admitted to hospital with typical infective hepatitis. The diagnosis was confirmed by needle biopsy of liver. Slight jaundice persisted, and 3 months later ascites developed. A second needle biopsy revealed established hepatic fibrosis. Improvement occurred on dietary treatment, ascites subsided and jaundice faded.

One year later he was re-admitted with ascites and slight jaundice. Very grave deterioration had occurred and he died soon afterwards.

At post-mortem the liver was firm and fibrous. Both portal cirrhosis and secondary carcinoma were present. The primary tumour was in the head of the pancreas, but it was small and had not blocked the ampulla of Vater. Secondary deposits were present in the lungs and in bones.

Case No. J14.

Female, aged 34 years. Admitted to the Royal Infirmary following a haematemesis. Two years previously she had developed jaundice and had been investigated in another hospital. Liver biopsy had shown early cirrhotic changes. Jaundice had been persistent ever since.

Examination : Jaundice and oedema present, but no ascites. Liver enlarged 2 inches and spleen 3 inches.

Radiology : Varices demonstrated by barium swallow.

Liver function tests : Serum albumin 2.8 g.%; serum globulin 2.6 g.%; colloidal gold 1; thymol turbidity faintly positive; alkaline phosphatase normal.

Progress : Haematemeses recurred with great frequency and she died in hepatic coma following a large haematemesis 4 years after the onset of jaundice. Ascites and a left-sided pleural effusion were observed terminally.

Case No. J15.

Female, aged 17 years, was admitted to hospital with the complaint of undue tiredness and repeated epistaxis. Three years previously she had taken ill with nausea and vomiting. These symptoms had persisted for 3 months before jaundice was detected, and jaundice persisted for many months. Both the liver and spleen were said to be greatly enlarged.

Examination : The only positive feature on clinical examination was splenomegaly of 5 inches.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 1.6 g.%; colloidal gold 0; alkaline phosphatase normal.

Haematology : Anaemia, leucopaenia and variable thrombocytopaenia.

Progress : A needle liver biopsy showed no great abnormality: cellularity of the portal tracts was increased. Splenectomy was performed and at operation the liver was described as being 'hob-nailed', but no biopsy was taken. Death occurred 24 hours post operatively. The histology of the spleen was in keeping with a diagnosis of Banti's syndrome.

Case No. J16.

Female, aged 55 years, became ill in August 1955 with poor appetite and malaise. In September jaundice was noted, but she was not sufficiently ill to go to bed until October, when swelling of the legs was observed. She resumed activities after one month, although she still felt ill. Admitted to hospital in March 1956.

Examination : Slightly jaundiced; trace of ankle oedema; naevi on face; liver enlarged 3 inches; spleen not palpable.

Radiology : Varices not demonstrated.

Liver function tests : Serum albumin 1.6 g.%; serum globulin 4.5 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase 4.5 Bodansky units; serum bilirubin 3.4 mg.%.

Progress : Followed up for over 1 year and still alive. She now has the classical picture of advanced cirrhosis with mental confusion, naevi, flushed palms, slight jaundice, bruises on the limbs and hepatomegaly. No ascites has been detected.

Case No. J17.

Female, aged 59 years, was admitted to hospital because of severe anaemia and general ill-health. She had been jaundiced for 2 weeks 6 years previously but had not been in bed. The dietary history was very poor.

Examination : No jaundice; telangiectasis on face but no spider naevi; both liver and spleen enlarged 3 inches, and firm; no ascites.

Radiology : Refused to have X-rays.

Liver function tests : Serum albumin 3.3 g.%; serum globulin 4.1 g.%; colloidal gold 4; thymol turbidity negative; serum bilirubin 0.5 mg.%.

Haematology : Hypochromic anaemia with haemoglobin of 30%.

Progress : Irregular discharge from hospital.
No follow-up.

Case No. J18.

Female, aged 35 years, became ill in January 1956 with upper abdominal pain after food. Several weeks later she lost her appetite and became jaundiced. She was in bed for 3 weeks and jaundice disappeared although poor appetite persisted. She was first examined at this time and no physical signs were observed, but shortly afterwards she again became jaundiced. Admitted to hospital in August 1956.

Examination : Slightly jaundiced; liver enlarged 2 inches; spleen not palpable; no naevi; no oedema; no ascites.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 2.7 g.%; serum globulin 3.7 g.%; colloidal gold 3; thymol turbidity positive; alkaline phosphatase 4.5 Bodansky units; serum bilirubin 2.4 mg.%.

Progress : Slight icterus has persisted. After some initial improvement she deteriorated with the development of mental confusion, oedema and ascites. The liver became impalpable. Still alive 1 year after admission to hospital, but gravely ill.

Case No. J19.

A man, aged 57 years, was admitted with the complaint of intermittent diarrhoea for 2 years. Three years previously he had been jaundiced for 6 months during which time his appetite had been impaired but he had not stayed off work.

Examination : Very thin; not jaundiced; palms flushed; no naevi; liver edge palpable at the costal margin; spleen not palpable.

Radiology : Highly suggestive of the presence of varices.

Liver function tests : Serum albumin 2.3 g.%; serum globulin 4.7 g.%; colloidal gold 6; thymol turbidity positive; serum bilirubin 0.5 mg.%.

Haematology : Megaloblastic anaemia.

Fat balance : 69% absorption of fat.

Progress : Improved following folic acid, yeast and oral iron. Died at home 5 years after the onset of jaundice. Emaciation and ascites were terminal features.

Case No. J20.

Male, aged 50 years, was admitted to hospital in 1950 with anorexia, nausea, upper abdominal discomfort and jaundice. Two years previously he had been jaundiced for 3 weeks but had not been off work.

Examination : Jaundice, hepatomegaly of 3 inches and a few visible veins in the abdominal wall were the only positive features.

Radiology : Barium swallow negative for varices. Opacity to the right of 3rd lumbar vertebra not thought to be a gall stone.

Liver function tests : Serum albumin 5.7 g.%; serum globulin 2.6 g.%; colloidal gold 1; alkaline phosphatase 5.8 Bodansky units; serum bilirubin 1.5 mg.%.

Progress : This patient was still alive in 1957. Although in fair health, slight jaundice has persisted, and from time to time he becomes ill for a few weeks with poor appetite and general malaise. The signs have not changed, but the left lobe of liver is much larger than the right. The possibility of a biliary cirrhosis was considered, and although not excluded, was thought to be unlikely.

Case No. J21.

Female, aged 45 years, was admitted in 1953 with persistent jaundice of 2 years duration. Between 1947 and 1950 she had been in ill-health complaining of undue tiredness, swelling of face and abdomen and pigmentation of the skin. Investigation in another hospital had revealed no significant abnormality.

In 1951 she became jaundiced and was re-admitted to hospital for a laparotomy. No obstructive lesion was found and the liver biopsy was reported as showing subacute hepatitis. Jaundice persisted, and she was admitted to the Royal Infirmary for assessment.

Examination : Well-nourished woman; slightly jaundiced; naevi present; palms flushed; left lobe of liver enlarged 3 inches.

Radiology : Barium swallow was negative for varices in 1953 but positive in 1955.

Liver function tests : Serum albumin 3.1 g.%; serum globulin 4.0 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 18.7 Bodansky units; serum bilirubin 3.2 mg.%.

Haematology : Hypochromic anaemia with haemoglobin of 44%.

Progress : Anaemia responded to iron and quite marked improvement took place. Urine became free of bile but urobilinogen persisted. The liver slowly became smaller. Death occurred at home 3 years later, said to be from pneumonia.

Case No. J22.

Female, aged 56 years, was admitted following a severe haematemesis. For 1 year she had observed intermittent jaundice and had felt unwell with poor appetite, nausea, and right upper abdominal pain after exercise. She had not been in bed.

Examination : Thin woman; jaundiced; slight ankle oedema; no naevi; liver enlarged 2 inches; spleen not palpable; no ascites.

Radiology : Not done.

Liver function tests : Serum albumin 1.7 g.%; serum globulin 3.2 g.%; colloidal gold 0; thymol turbidity normal.

Progress : Despite transfusion and oesophageal tamponade the bleeding continued and she died 3 days after admission.

Post-mortem : Finely granular liver, histologically compatible with post-hepatitis cirrhosis. Oesophageal and gastric varices present.

Case No. J23.

Male, aged 49 years, gave a history of excessively troublesome flatulent dyspepsia for 1 year. He was admitted to the surgical ward of the hospital because of poor appetite, upper abdominal discomfort and jaundice. Icterus lessened while under observation but did not clear. One month later he was admitted to the medical unit with ascites.

Examination : Deeply jaundiced; slight oedema; no naevi; marked ascites; liver and spleen not palpable.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 1.7 g.%; serum globulin 2.3 g.%; colloidal gold 2; thymol turbidity positive; serum bilirubin 4 mg.%.

Progress : Rapid deterioration with wasting, deepening jaundice and drowsiness. Terminal haematemesis and coma. Died 3 months after onset of jaundice.

Post-mortem : Small granular liver. Histology shown in fig. 5. Oesophageal varices present but small.

CASE J 23

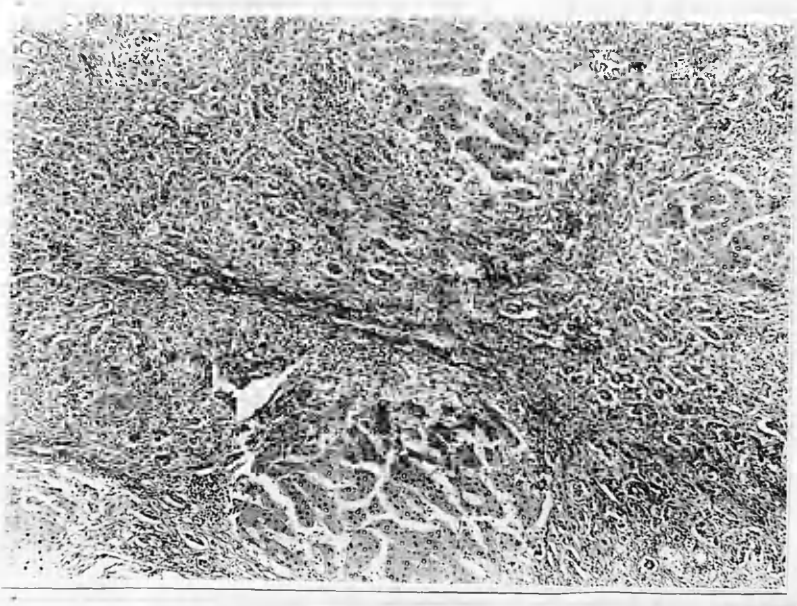

Fig. 5

Post-hepatitis cirrhosis.

There is very extensive destruction of the hepatic parenchyma with replacement fibrosis and proliferation of the bile ducts. (x 50)

Case No. J24.

Male, aged 38 years, was admitted following a haematemesis. In the 18 months preceding admission he had been jaundiced on 3 occasions, each lasting a few weeks and associated with anorexia. Alcohol consumption was grossly excessive but the diet was excellent.

Examination : Well-built man with slight jaundice; small naevi on arms; no oedema; liver enlarged 4 inches; spleen not palpable.

Radiology : Not done.

Liver function tests : Not done.

Progress : Shortly after admission the patient became manic, assaulting patients and staff. He was transferred to a mental observation ward where gradual recovery took place. Death occurred 18 months later following a massive haematemesis.

Case No. J25.

A female, aged 48 years, became ill in August 1955, complaining of anorexia and nausea. She did not go to bed. Three months later jaundice and swelling of the legs was observed. In January 1956 she was admitted to another hospital with ascites and between then and her admission to the Royal Infirmary in June 1956, paracentesis had been performed every few weeks.

Examination : An obese lady with oedema and ascites; liver and spleen were not palpable and there were no naevi.

Radiology : No varices.

Liver function tests : Serum albumin 1.8 g.%; serum globulin 2.8 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 5.7 Bodansky units.

Progress : Treated by ion-exchange resins with great benefit: maintained free of ascites for 1 year and able to do all household work. At the time of writing ascites is again returning. A surgical liver biopsy has recently been performed. The liver was nodular and the picture consistent with post-hepatitis cirrhosis.

Case No. J26.

Female, aged 44 years, admitted following a haematemesis. She had been ill at home for 9 months complaining of weakness, poor appetite, nausea, occasional vomiting, and of a "dirty colour" to the skin.

Examination : Doubtful icterus but urine contained bile. Hepatomegaly of 4 inches was the only other positive finding.

Radiology : Varices not demonstrated.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 3.5 g.%; colloidal gold 4; alkaline phosphatase 4.4 Bodansky units.

Progress : Numerous haematemeses over 2 years, with deterioration in liver function. She became more obviously icteric, and latterly developed ascites. Death followed pentothal anaesthesia, inadvertently given for the removal of a simple laryngeal papilloma, 3 years after first admission.

Post-mortem : Cirrhosis was confirmed. The histology of a biopsy is shown in fig. 6.

Note : The nature of this illness was not certainly infective hepatitis and I was doubtful whether to include this case here or with cryptogenic cirrhosis.

CASE J 26

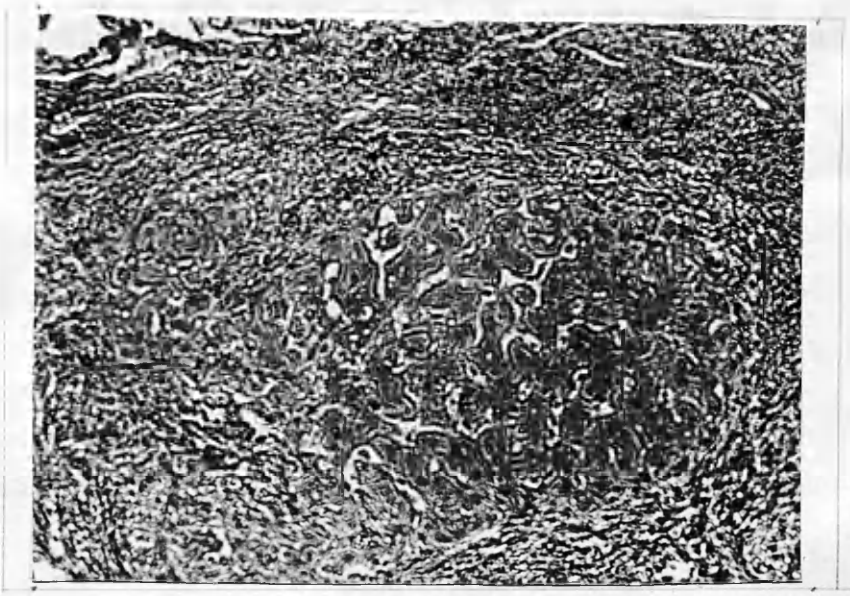

Fig. 6

Post-hepatitis cirrhosis

A needle biopsy specimen to show a hyperplastic nodule of parenchymal tissue surrounded by dense fibrosis. (x 80)

Case No. J27.

Male, aged 38 years, was admitted to hospital with the complaint of lassitude and swelling ankles. One year previously he had been in another hospital with slight jaundice, malaise and swelling of legs and abdomen. The spleen was palpable at that time and he was thought to have cirrhosis, but the illness may have been a subacute hepatitis.

Examination : Tall, thin man; slightly jaundiced; ankle oedema; spider naevi; flushed palms; liver not palpable; spleen palpable 1 inch.

Radiology : Varices demonstrated by barium swallow.

Liver function tests : Serum albumin 3.4 g.%; serum globulin 3.9g.%; colloidal gold 3; thymol turbidity positive; alkaline phosphatase normal. Bile in urine.

Haematology : Macrocytic anaemia.

Progress : Followed up until his death 3 years later. Icterus persisted but was never marked. There was little change in the signs, although ascites was present for several months before death. Increasing drowsiness was followed by a terminal small haematemesis and coma.

Case No. J28.

A male, aged 38 years, complained of flatulent dyspepsia for 18 months, and intermittent slight jaundice for 6 months, with right upper abdominal pain.

Examination : Slightly jaundiced; liver enlarged 4 inches; no other positive features.

Radiology : Not done.

Liver function tests : Serum albumin 2.9 g.%; serum globulin 3.1 g.%; colloidal gold 0; thymol turbidity positive; alkaline phosphatase 15 Bodansky units; serum bilirubin 0.9 mg.%.

Liver biopsy : Diffuse hepatic fibrosis.

Progress : Died at home 5 years later. Initially improved, jaundice faded, but the liver remained greatly enlarged. Jaundice recurred terminally.

Case No. J29.

Female, aged 21 years, was admitted to hospital with appendicitis. Ascites was noted at operation, and the liver was nodular. Post-operatively she remained in coma for several days.

One year before she had been in another hospital with 'subacute hepatitis'. Symptoms had been of general malaise, and the findings at that time were of splenomegaly, spider naevi, and slight jaundice. The patient took her own discharge from that hospital.

Examination : Thin young woman; slight icterus; no naevi; liver not enlarged; spleen palpable 3 inches; Ascites and right pleural effusion present.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 1.8 g.%; serum globulin 4.7 g.%; colloidal gold 6; thymol turbidity strongly positive; alkaline phosphatase normal; serum bilirubin 1.0 mg.%.

Progress : Ascites disappeared and great improvement occurred.
1 year later she developed what appeared to be a gastro-enteritis, became comatose and died.

Post-mortem : Liver shrunken, nodular, consistent with post-necrotic scarring.

Note : The history of hepatitis was quite atypical, and I had doubt whether to include this

patient with post-hepatitis cirrhosis or with cryptogenic cirrhosis. She is included here because of the finding of jaundice at the time of her original admission to hospital.

Case No. J30.

A female, aged 49 years, was admitted following a small haematemesis. For some months she had experienced right upper abdominal discomfort and had lacked energy. Appetite had been good. She had been jaundiced for 3 weeks 33 years before.

Examination : Not jaundiced; naevi present; palms flushed; liver enlarged 2-3 inches; spleen not palpable; no ascites.

Radiology : Barium swallow negative. Gall stones were thought to be present.

Liver function tests : Serum albumin 3.1 g.%; serum globulin 6.0 g.%; colloidal gold 3; thymol turbidity normal; alkaline phosphatase 12.7 Bodansky units; serum bilirubin 0.7 mg.%.

Progress : At laparotomy no gall stones were found. A liver biopsy was taken but the histology was difficult to interpret, some areas suggesting portal cirrhosis, others biliary cirrhosis. This patient was seen for the first time in 1957 and follow-up has been short. At present she is well.

Cryptogenic Cirrhosis

Case No. C1.

Female, aged 47 years, was first seen as an out-patient suffering from hypochromic anaemia. Diet had been poor for many years. The clinical findings were of pallor, splenomegaly of 2 inches, and rachitic deformity of the legs. There was an adequate response to oral iron therapy.

Admitted to hospital 2 years later following a sudden haematemesis.

Examination : Splenomegaly of 1 inch. Liver not palpable. No other signs.

Radiology : Oesophageal varices present.

Liver function tests : Serum albumin 3.6 g.%; serum globulin 3.9 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin 0.7 mg.%.

Progress : Splenectomy with spleno-renal anastomosis performed. Liver biopsy (Fig.7) showed only minimal changes but there was no apparent source of extrahepatic portal obstruction. Alive and well 1 year post-operatively.

CASE C I

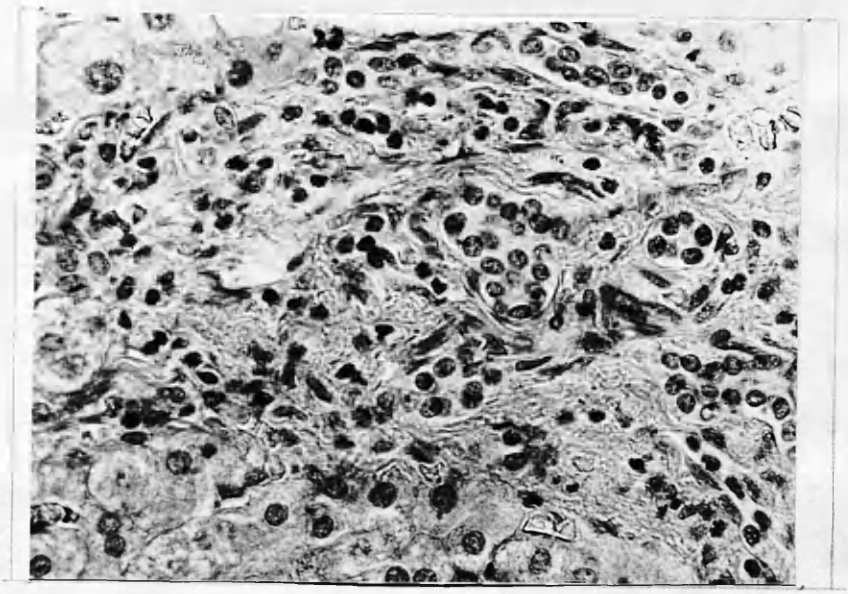

Fig. 7

Cryptogenic cirrhosis with portal hypertension.

Surgical biopsy specimen. Much of the liver appeared normal. The photomicrograph illustrates one of several areas of focal abnormality. (x 150)

Case No. C2.

Female, aged 57 years, was admitted on account of repeated haematemeses. She had previously been in the Royal Infirmary 11 years before suffering from splenomegaly and iron deficiency anaemia.

Examination : Liver enlarged 2 inches; spleen enlarged 4 inches. No other abnormality.

Radiology : Oesophageal varices present.

Liver function tests : Serum albumin 3.6 g.%; serum globulin 2.9 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin normal.

Progress : Splenectomy performed but shunt not carried out because of abnormal position of vessels. Varices excised. Liver biopsy - diffuse fibrosis. Follow-up for 3 years. Alive, well, and no recurrence of bleeding. Liver enlarged 1 inch. Rise in serum globulin, but other tests normal.

Case No. 63.

Female, aged 13 years, admitted because of swelling legs and purpura. Two years previously she had been investigated in a children's hospital because of a febrile illness associated with splenomegaly, hepatomegaly, leucopaenia and thrombocytopaenia. The spleen was removed and the histology was typical of 'Banti's disease.'

Examination : Hepatomegaly 2 inches; clubbing of fingers; scattered petechiae. Examination otherwise negative.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 2.2 g.%; serum globulin 3.8 g.%; colloidal gold 6; thymol turbidity positive; alkaline phosphatase 4.7 Bodansky units; serum bilirubin 0.7 mg.%.

Haematology : No abnormality.

Progress : Follow-up 6 years. Still alive and well. Liver no longer palpable. Serum albumin has risen to 3.5 g.%, but flocculation tests are still strongly positive. At present there are no physical signs of disease.

Case No. C4.

Male, aged 80 years, admitted to hospital for investigation of a macrocytic anaemia. Ill-health for 6 months with pallor, tiredness and dyspnoea.

Examination : Slightly jaundiced; pale; oedema of ankles; liver enlarged 3 inches; spleen tip palpable.

Radiology : Not done.

Liver function tests : Serum albumin 4.2 g.%; serum globulin 2.6 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin 0.6 mg.%.

Haematology : Macrocytic anaemia : macro-normoblastic erythropoiesis in bone marrow.

Progress : Anaemia proved to be haemolytic. No response to any haematinic. Follow-up 2 years. Died of cardiac failure following blood transfusion.

Post-mortem : Finely granular liver, portal fibrosis, and excessive quantities of iron present. Oesophageal varices present.

Case No. 05.

Male, aged 58 years, admitted with the complaint of recurrent right upper abdominal pain and vomiting for 6 months. Above average alcohol consumption when a younger man, but not in the amounts generally associated with cirrhosis.

Examination : Slightly jaundiced; trace of oedema; liver enlarged 1 inch; spleen enlarged 3 inches. Tenderness over gall bladder.

Radiology : Barium swallow negative for varices. Gall stones present.

Liver function tests : Serum albumin 4.2 g.%; serum globulin 2.7 g.%; colloidal gold 3; alkaline phosphatase normal; serum bilirubin 0.4 mg.%.

Progress : Gall stones removed. Grave deterioration followed operation with lassitude, icterus, anaemia, and fall in plasma albumin to 1.4 g.%. Spleen enlarged to 5 inches and he developed leucopaenia. Follow-up 2 years. Terminal ascites. Died in hepatic coma.

Post-mortem : Slight but definite hepatic fibrosis (Fig. 8). No varices. Congestive splenomegaly.

CASE C 5

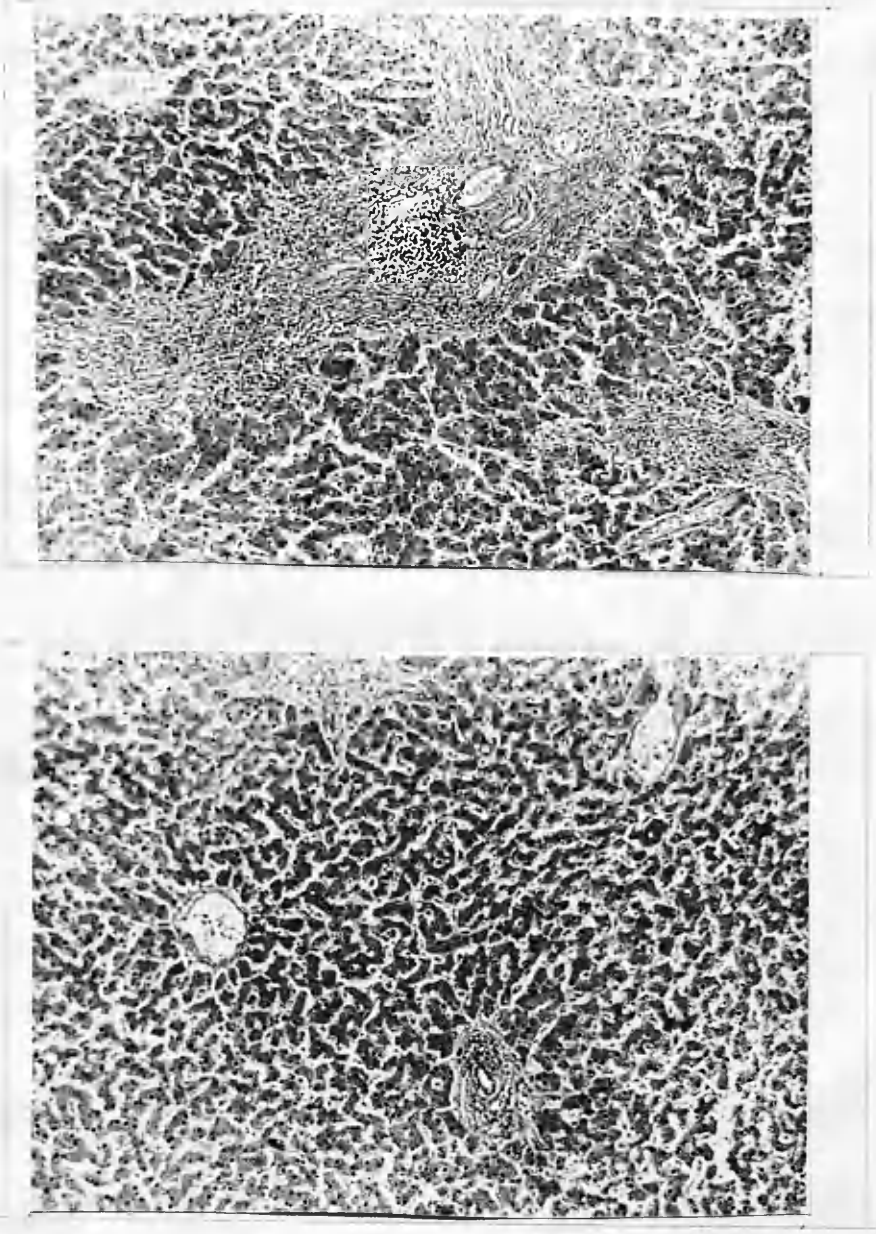

Fig. 8

Cryptogenic Cirrhosis

Progressive illness over two years. The upper photomicrograph shows a scarred area within the liver, while the lower picture is devoid of fibrous tissue. (x 80)

Case No. C6.

Female, aged 78 years, admitted with a 5-day history of upper abdominal pain, vomiting, breathlessness, and swelling of her legs. Long history of chronic bronchitis.

Examination : Very ill elderly lady with auricular fibrillation and oedema of legs and abdominal wall. Clinical diagnosis of cardiac failure.

Radiology : Barium swallow not done.
X-ray of chest: cardiac enlargement and congested lung fields.

Liver function tests : Not done.

Progress : Died 5th day after admission.

Post-mortem : Perforated duodenal ulcer.
Cor pulmonale.
Multilobular cirrhosis.
Gall stones.

Case No. C7.

Male, aged 34 years. Sudden haematemesis in 1948 and again in 1949, followed by transient ascites on the latter occasion. Hospitalised in Singapore and returned home for shunt operation. Gross dietary deficiency, recurrent malaria, but no jaundice while a prisoner of the Japanese. Alcohol consumption greater than normal 1945-1948.

Examination : Slightly jaundiced; spider naevi; no oedema; no ascites; spleen enlarged 5 inches; liver not palpable.

Radiology : Oesophageal varices demonstrated.

Liver function tests : Serum albumin 2.9 g.%; serum globulin 2.1 g.%; colloidal gold 5; alkaline phosphatase 7.7 Bodansky units; serum bilirubin 4.8 mg.%.

Progress : Porta-caval shunt performed. Died 24 hours later of haemorrhage.

Post-mortem : Shrunken, nodular cirrhotic liver.

Case No. C8.

Male, aged 39 years. Sudden haematemesis in 1945 led to admission to another hospital, where splenomegaly was detected and cirrhosis diagnosed. Because of repeated haematemeses splenectomy was performed in 1947. (Histology - Banti's disease). Admitted to the Royal Infirmary in 1948 with a further haematemesis.

Examination : No abnormal physical signs.

Radiology : No varices seen.

Gastroscopy : Gastric varices present.

Liver function tests : Serum albumin 3.3 g.%; serum globulin 2.2 g.%; colloidal gold 2; alkaline phosphatase normal.

Progress : Porta-caval shunt performed.

Liver biopsy - typical multilobular cirrhosis (Fig. 9).

Follow-up 1 year. Died at home, cause unknown.

CASE C 8

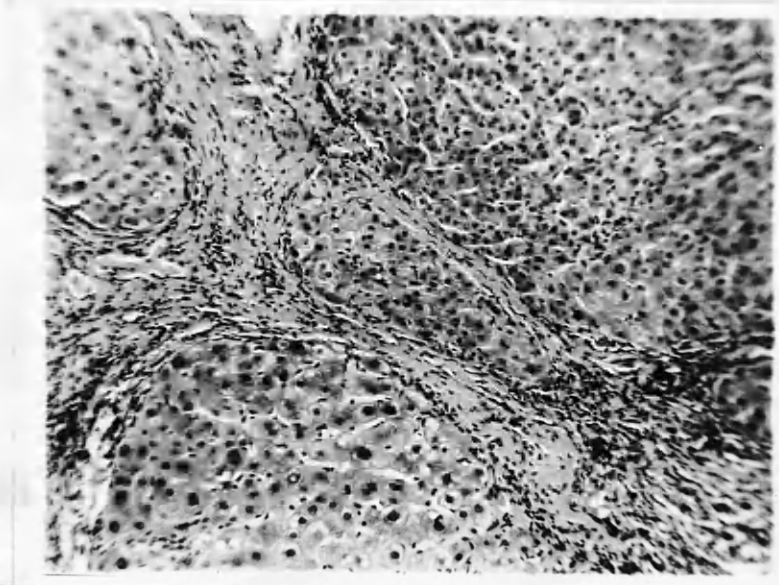

Fig. 9

Cryptogenic Cirrhosis with Portal hypertension
The liver is grossly scarred and the histological picture is indistinguishable from post-hepatitis cirrhosis. (x 100)

Case No. C9.

Female, aged 37 years. For 12 years she had been in ill-health with weakness, tiredness, and undue pallor. Appetite had been poor and the diet deficient. In 1951 she had been admitted to another hospital where hepatic and splenic enlargement had been noted, and anaemia treated with iron. Admitted to Royal Infirmary in 1953 because of anaemia.

Examination : Pallor; splenomegaly of 3 inches; liver edge just palpable. No other signs.

Radiology : Oesophageal varices not demonstrated.

Liver function tests : Serum albumin 3 g.%; serum globulin 3.4 g.%; colloidal gold 6; thymol turbidity positive; alkaline phosphatase and serum bilirubin normal.

Haematology : Hypochromic anaemia; leucopaenia and thrombocytopaenia.

Progress : Anaemia responded to iron. Splenectomy performed. No evidence of generalised portal hypertension at operation. Died in coma 14 days post-operatively.

Post-mortem : Thrombosis of portal vein; infarcts of liver. Mild early diffuse hepatic fibrosis.

Case No. C10.

Male, aged 55 years, admitted with severe haematemesis. No past history of dyspepsia or of jaundice.

Examination : Pale. Liver edge just palpable.
Examination otherwise negative.

Radiology : Not done.

Liver function tests : Not done.

Progress : Continued bleeding. Died 2 days after admission.

Post-mortem : Multilobular cirrhosis.
Ruptured oesophageal varix.
Syphilitic aortitis.

Case No. C11.

A male, aged 32 years, was admitted following a sudden severe haematemesis. Two years previously there had been a similar occurrence, but investigation in another hospital had revealed no abnormality.

Examination : Clinical evidence of severe blood loss. No other abnormal features. Liver and spleen not palpable.

Radiology : Not done.

Liver function tests : (Performed several days after admission). Serum albumin 2.9 g.%; serum globulin 1.9 g.%; colloidal gold 0; thymol turbidity normal.

Progress : Bleeding continued despite liberal transfusion. Transferred to surgical ward for emergency gastrectomy. At operation the liver was noted to be cirrhotic and bleeding to come from a ruptured oesophageal varix. Balloon tamponade applied. Ascites developed post-operatively. Died from further haematemesis 5 weeks later.

Post-mortem : Fine diffuse cirrhosis (Fig. 10).
Spleen enlarged.
Ruptured oesophageal varix.

CASE C II

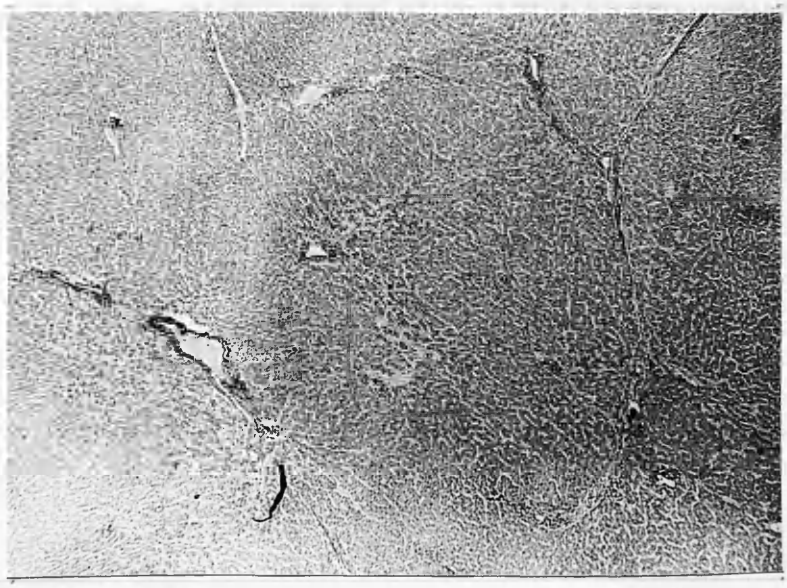

Fig. 10

Cryptogenic Cirrhosis with Portal hypertension.

Recurrent haematemesis caused death. Hepatic fibrosis is surprisingly slight. (X 50)

Case No. C12.

Female, aged 73 years, was admitted with an acute respiratory infection. She had been a diabetic for 14 years, and had rheumatic heart disease.

Examination : Signs of broncho-pneumonia and mitral valve disease.

Radiology : Not done.

Liver function tests : Not done.

Progress : Died 3 days after admission.

Post-mortem : Empyema : pulmonary collapse.
Mitral stenosis.
Fine multilobular cirrhosis.
Gall stones.

Case No. C13.

A female, aged 34 years, was first admitted to the Royal Infirmary in 1947 complaining of weakness, pallor, and swelling of her legs. She also had severe menorrhagia. In 1943 she had been in another hospital for investigation of albuminuria, and hepatic and splenic enlargement had been noted at that time.

Examination : Pale. Hypertension - 180/100 mmHg.
Albuminuria. Liver enlarged 3 inches.
Spleen enlarged 2 inches.

Radiology : Varices not demonstrated.

Liver function tests : Serum albumin 5.3 g.%; serum globulin 1.3 g.%; colloidal gold 3; alkaline phosphatase 10 Bodansky units.

Haematology : Severe hypochromic anaemia.

Progress : Improved following transfusion and iron therapy. Admitted 1 year later in uraemic coma and died.

Post-mortem : Multilobular cirrhosis (Fig. 11).
Chronic glomerulo-nephritis.

CASE C 13

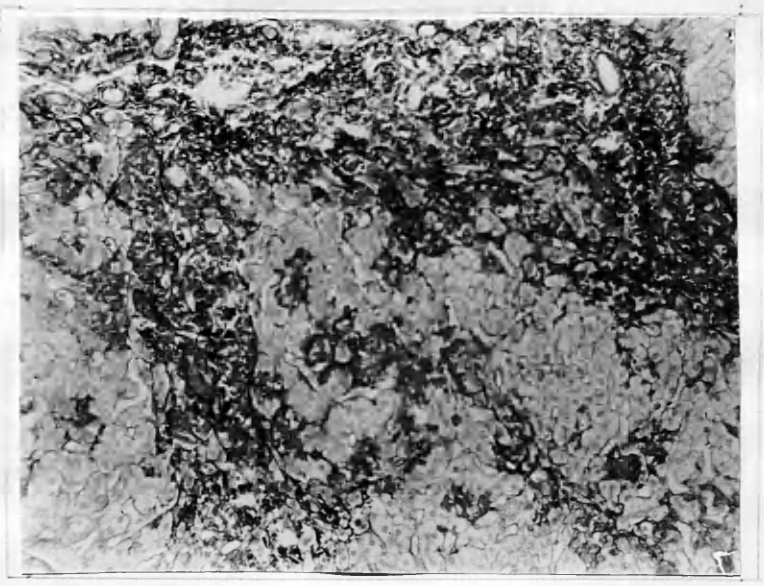

Fig. 11

Cryptogenic Cirrhosis and chronic Glomerulo nephritis.

Needle biopsy specimen to show extensive diffuse hepatic fibrosis.

(x 120)

Case No. C14.

A female, aged 64 years, gave a history of the loss of 7 stones in weight over a period of 2 years. Appetite was normal and there were no other symptoms.

Examination : Thin but not wasted. Liver enlarged 4 inches. Bruit audible below Xiphisternum. Spleen tip palpable. No oedema, ascites or naevi.

Radiology : X-ray chest, barium swallow, meal and enema normal.

Liver function tests : Serum albumin 4.5 g.%; serum globulin 4.2 g.% colloidal gold 0; thymol turbidity and alkaline phosphatase normal; serum bilirubin 1 mg.%.

Liver biopsy : Hepatic cirrhosis.

Progress : Progressive deterioration to death 3 months later.

Case No. C15.

Female, aged 71 years, was admitted following a large haematemesis. For 2 months she had been vaguely unwell with impaired appetite and slight weight loss.

Examination : Signs of severe blood loss. Neither liver nor spleen palpable and no stigmata of cirrhosis.

Radiology : Not done.

Liver function tests : Serum albumin 1.8 g.%.
Serum globulin 2.3 g.%.

Progress : Laparotomy performed because of continued bleeding: hepatic cirrhosis observed. Died post-operatively.

Post-mortem : Multilobular cirrhosis with coarsely granular liver. Ruptured oesophageal varix. Spleen appeared normal.

Case No. C16.

A female, aged 47 years, had had repeated haematemeses over a period of 7 years. She was admitted to the Royal Infirmary for opinion as to suitability for a porta-caval shunt. No past history of rheumatic fever or chorea.

Examination : Trace of ankle oedema.
Spleen enlarged 5 inches; liver not palpable.
Mitral stenosis.

Radiology : Oesophageal varices demonstrated.

Liver function tests : Serum albumin 4.5 g.%; serum globulin 2.7 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 1.3 Bodansky units; serum bilirubin 1 mg.%.

Haematology : Hypochromic anaemia and leucopaenia.

Progress : Thought to be suitable for porta-caval shunt but refused operation. Died at home 6 months later after a further haematemesis.

Case No. C17.

Male, aged 49 years, was admitted following a haematemesis. For 2 months he had experienced vague indigestion which bore no relationship to food. Alcohol consumption was at times above average.

Examination : No abnormal finding.

Radiology : Barium meal normal.

Liver function tests : Not done.

Progress : Thought to have a peptic ulcer, and discharged on peptic ulcer regime. Re-admitted 6 months later complaining of abdominal distension. On examination he was found to have oedema and ascites. Liver and spleen not palpable. Barium swallow demonstrated oesophageal varices, and a needle liver biopsy firmly established the diagnosis of cirrhosis. A further haematemesis occurred while in hospital, following which he became comatose and died.

Case No. C18.

A male, aged 59 years, complained of poor appetite and weight loss for 1 month. 1 week before admission abdominal swelling had occurred. There was a history of moderate alcohol consumption at week-ends, about £1 being spent.

Examination : Oedema and ascites.
Flushed palms but no naevi.
Clubbing of finger nails.
Liver and spleen not palpable.
Testicles small and unduly soft.

Radiology : No varices demonstrated.
Carcinoma of stomach.

Liver function tests : Serum albumin 2.7 g.%; serum globulin 4.1 g.%; colloidal gold 0; thymol turbidity normal.

Progress : Died 2 months later of cachexia.

Post-mortem : Carcinoma of stomach with metastases in liver.
Multilobular cirrhosis. (Fig. 12.).

CASE C 18

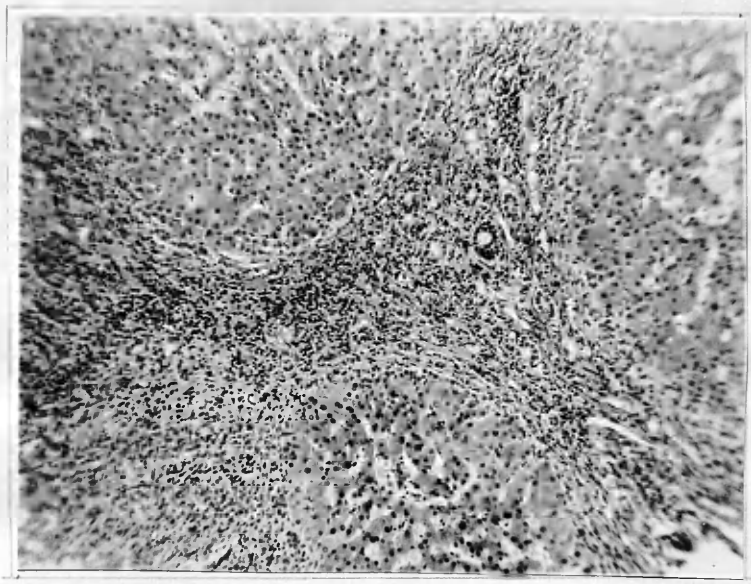

Fig. 12 a

Cryptogenic Cirrhosis

(x 100)

CASE C 18

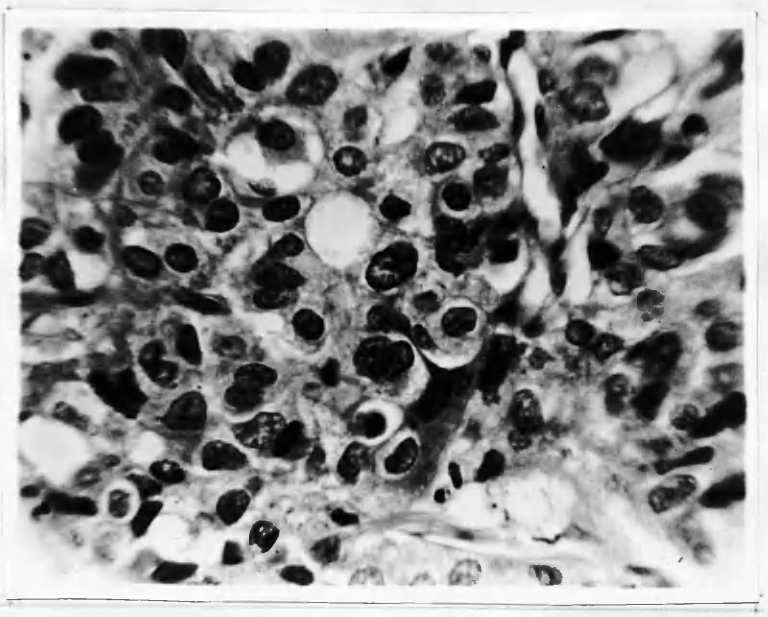

Fig. 12 b (x 500)

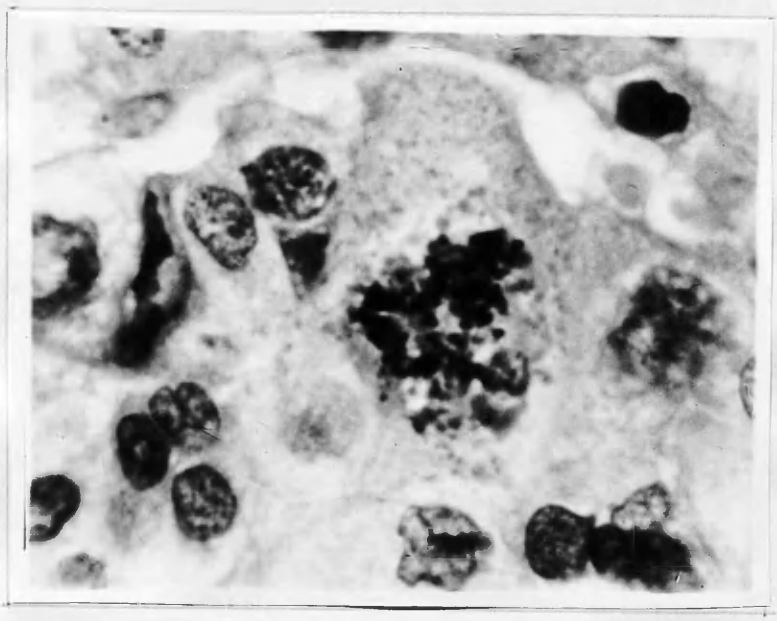

Fig. 12 c (x 700)

Cryptogenic cirrhosis with metastases from a carcinoma of stomach within the cirrhotic liver.

Case No. C19.

Male, aged 28 years, was admitted to a fever hospital with pneumonia. He had been troubled by a cough and spit since childhood. While in hospital it was noted that blood was being lost in the stools. Oesophageal varices were demonstrated by oesophagoscopy, and he was referred for a general medical opinion. The dietary history was below average.

Family history : Brother had splenomegaly and died from haematemesis.

Examination : Spider naevi on chest.
Liver enlarged 1 inch and spleen 5 inches.
Chest negative at time of examination.

Radiology : Barium meal normal.

Liver function tests : Serum albumin 4.4 g.%; serum globulin 2.6 g.%; colloidal gold 1; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin 0.3 mg.%.

Progress : Follow-up less than 1 year. No change in condition.

Case No. C20.

Female, aged 45 years. Ill-health for 10 months with poor appetite, weight loss, lassitude and breathlessness. No history of rheumatic fever.

Examination : Auscultatory findings of mitral stenosis and aortic incompetence. Spleen enlarged 1-2 inches. Not in cardiac failure.

Radiology : No varices seen. Left auricle enlarged.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 5.0 g.%; colloidal gold 5; thymol turbidity positive.

Haematology : E.S.R. 35-50 mm in 1 hour.

Progress : Initially presumed to have subacute bacterial endocarditis and received penicillin for 4 weeks. No change in condition at the end of that period - spleen remained enlarged and the E.S.R. elevated. Liver function tests then found to be abnormal. Follow-up 6 months. Has required digitalis because of auricular fibrillation and early cardiac failure.

Case No. C21.

Male, aged 67 years, complained of poor health for 2 years with loss of appetite and energy. Splenomegaly had been detected in another hospital a short time after the onset of this illness (aged 65) but no definite diagnosis had been made. Admitted to Royal Infirmary because of swelling of legs, and weight loss of 2 stones in 1 year.

Examination : Small glands in neck and axillae.
Oedema of ankles.
Spleen enlarged 3 inches. Liver edge just palpable. Veins visible beneath skin of abdominal wall.
Benign prostatic hypertrophy.

Radiology : Barium swallow and meal normal.

Liver function tests : Serum albumin 2.2 g.%; serum globulin 2.9 g.%; colloidal gold 0; thymol turbidity normal; acid phosphatase normal; serum bilirubin 0.6 mg.%.

Haematology : Mild hypochromic anaemia with haemoglobin of 73%. Sternal marrow normal.

Progress : Considerable benefit from high protein diet.
No follow-up.

Case No. C22.

A female, aged 69 years, was admitted in 1953 with severe gastro-intestinal bleeding. An emergency gastrectomy was performed. At operation the duodenum was scarred but no ulcer was seen. The liver and spleen were thought to be normal. She was re-admitted in 1956 following a further haematemesis. Dietary history was extremely poor.

Examination : Jaundiced; pale; tongue smooth; liver enlarged 3 inches and spleen tip palpable.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 4.5 g.%; thymol turbidity normal; serum bilirubin 2.4 mg.%.

Progress : Still alive in 1957. Jaundice has not subsided, and she has recurrent hypochromic anaemia, the result of bleeding haemorrhoids which have not yielded to surgical treatment. Liver function is less good, and there is continuous drowsiness.

Case No. C23.

A female, aged 47 years, had been in ill-health since the menopause at age of 42 years. She had always been subject to bronchitis and had been unduly breathless on exertion for some time. In 1955, at the age of 46 she had been in another hospital because of haematemesis. Haematemesis recurred one month later. She gave no history of dyspepsia.

Examination : Small woman with bronchitis.
Slight ankle oedema.
Spleen enlarged 4 inches; liver not palpable.
No clubbing of fingers. No naevi.

Radiology : Oesophageal varices present.

Liver function tests : Serum albumin 3.3 g.%; serum globulin 4.5 g.%; colloidal gold 1; thymol turbidity normal.

Progress : Follow-up short of 1 year. No change in condition.

Case No. C24.

A female, aged 55 years, was admitted in severe congestive cardiac failure and died shortly after admission. She had been known to have anaemia and splenomegaly 5 years previously, and hypertensive cardiac failure for 1 year.

Examination : Oedema; ascites; pleural effusions; jugular venous congestion; cardiac enlargement; B.P. 180/110 mmHg. Telangiectasis of face. Firm splenomegaly of 5 inches and liver enlarged 3 inches.

Radiology : Not done.

Liver function tests : Serum albumin 2.5 g.%; serum globulin 3.1 g.%; colloidal gold 0; thymol turbidity normal.

Haematology : No abnormality.

Comment : Presumptive diagnosis of cirrhosis based on history of splenomegaly for several years, the low serum albumin, and the very generalised fluid retention. The spleen was much too large and firm to be accounted for by cardiac failure. No post-mortem performed.

Case No. C25.

Female, aged 60 years. History of poor appetite and weight loss for 1 year. Occasional diarrhoea and abdominal pain for 2 months before admission. Intermittent joint pains for some years, thought to be in nature of rheumatoid arthritis. Admitted to a surgical unit where laparotomy was performed and hepatic cirrhosis observed.

Examination : Slight oedema; clubbing of finger nails; no naevi; liver enlarged 4 inches and spleen 3 inches; no ascites.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 2.9 g.%; serum globulin 3.7 g.%; colloidal gold 6; thymol turbidity positive; serum bilirubin 2.2 mg.%.

Progress : Patient untraced 1 year later.

Case No. C26.

Female, aged 48 years. Ill-health for 1 year with anorexia and weight loss. Admitted because of intermittent diarrhoea for 6 weeks. Diet poor.

Examination : Liver edge and spleen tip palpable. Veins visible beneath skin of the abdominal wall. No oedema and no jaundice.

Radiology : Oesophageal varices present. Barium enema negative.

Liver function tests : Serum albumin 5.3 g.%; serum globulin 2.9 g.%; colloidal gold 2; alkaline phosphatase 6.6 Bodansky units; serum bilirubin 0.2 mg.%.

Liver biopsy : Hepatic cirrhosis.

Progress : Progressive course. Oedema and ascites developed 4 months later, and she died at home 1 year after original admission.

Case No. C27.

A man, aged 48 years, was admitted to another hospital for investigation of hypertension. He complained of undue fatigue of several months duration, and had occasional morning vomiting. He did not admit to excessive alcohol consumption although his occupation was that of a barman. He was transferred to the Royal Infirmary for further investigation.

Examination : Well-built man. B.P. 260/140 mmHg. Liver enlarged 4 inches, firm, left lobe larger than right. Spleen tip palpable.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 3.5 g.%; serum globulin 3.4 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin 0.2 mg.%.

Progress : Follow-up just short of 2 years during which time there was little change in his condition. Latterly he had symptoms of left ventricular insufficiency and he was digitalised. Failed to report thereafter.

Case No. C28.

A male, aged 61 years, was admitted to a surgical unit with acute small bowel obstruction due to adhesions. Cirrhosis and ascites were noted at operation. He had been in ill-health since a haematemesis 1 year previously, complaining of weight loss, breathlessness, and latterly of swelling of legs and abdomen.

Examination : Oedema; ascites; hepatomegaly of 1 inch; spleen not palpable.

Radiology : Not done.

Liver function tests : Serum albumin 1.0 g.%; serum globulin 2.4 g.%; thymol turbidity positive; alkaline phosphatase normal; serum bilirubin 2.5 mg.%.

Progress : Further haematemesis while in the medical ward, after which he was comatose for 36 hours but eventually recovered. Died following a second haematemesis 1 month later.

Case No. C29.

A female, aged 43 years, was first admitted to the Royal Infirmary in 1946 with anaemia and ascites. In 1939 abdominal swelling had developed after the birth of a child, and "splenic anaemia" had been diagnosed in another city hospital. The dietary history was poorer than average.

Examination : Pale; ankle oedema; liver enlarged 2 inches; spleen enlarged 4 inches; ascites present.

Radiology : Barium swallow normal.

Liver function tests : Serum albumin 3.7 g.%; serum globulin 2.6 g.%; colloidal gold 5; alkaline phosphatase normal.

Haematology : Hypochromic anaemia (Hb = 50%) with leucopaenia.

Progress : Improved greatly under treatment and ascites disappeared. Not re-admitted until 1950 when she had the first of many haematemeses, and had re-developed ascites. Died in 1953 after a further haematemesis.

Case No. C30.

A female, aged 57 years, was admitted in 1953 with anorexia and upper abdominal pain after food. A gastric ulcer was demonstrated radiologically. The spleen and liver were palpable at this time, but liver function tests were entirely normal. The dietary history was below average in respect of proteins. A presumptive diagnosis of cirrhosis was made.

She remained well until 1955 when she began to lose appetite and weight, and developed ascites.

Examination : Naevi on face; spleen enlarged 5 inches; liver not palpable; ascites present; small left-sided pleural effusion.

Radiology : No varices demonstrated. Gastric ulcer again demonstrated.

Liver function tests : Serum albumin 3.3 g.%; serum globulin 2.4 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 6.7 Bodansky units; serum bilirubin 1 mg.%.

Progress : Survived until 1956. Diuretics and ion exchange resins not effective. Died in hepatic coma. Very cachectic terminally. The liver remained impalpable and the spleen very large.

Case No. C31

A female, aged 58, complained of ill-health for 5 years with undue fatigue, varicose ulceration of a leg, and iritis. In the months preceding admission appetite had been impaired and she had experienced nausea and flatulence.

Examination : Pale; spleen enlarged 4 inches; liver not palpable; no ascites.
Rheumatoid arthritis (old).

Radiology : Negative for varices.

Liver function tests : Colloidal gold 2; alkaline phosphatase and serum bilirubin normal.

Haematology : Hypochromic anaemia (Hb = 55%). Normal response to iron.

Progress : Patient unwilling to report to hospital. Follow-up for 6 years through letter to practitioner. Two years after discharge she was reported to be less well and that both liver and spleen were readily palpable. Thereafter she improved, but there has been no change in the physical signs.

Case No. 632.

A female, aged 67 years, was admitted for investigation of a hypochromic anaemia. She had felt unduly tired for several months.

Examination : Slight ankle oedema; liver enlarged 2 inches; spleen not palpable; hypertension - B.P. 240/100 mmHg. Bilateral extensor plantar responses.

Radiology : No varices demonstrated.
Osteo-arthritis of cervical spine.

Liver function tests : Serum albumin 3.8 g.%; serum globulin 3.8 g.%; colloidal gold 0; thymol turbidity normal.

Haematology : Hypochromic anaemia (Hb = 59%). Normal response to iron.

Progress : Follow-up for 6 months. Very well at the end of that period, and blood restored to normal. The size of the liver had increased, however, and the edge was palpable 5 inches below the costal margin. It felt quite soft. The neurological signs were attributed to cervical spondylosis.

Case No. 033

A man of 70 was admitted on account of an acute exacerbation of a chronic bronchitis. Alcohol consumption was moderate at week-ends.

Examination : Orthopnoeic, cyanosed. Slight ankle oedema; liver enlarged 2 inches and the spleen 1 inch. No ascites.
Signs of chronic bronchitis.

Radiology : No varices demonstrated.
Radiological findings of bronchitis, and emphysema.

Liver function tests : Serum albumin 3.7 g.%; serum globulin 4.0 g.%; colloidal gold 0; thymol turbidity and alkaline phosphatase normal; serum bilirubin 0.3 mg.%.

Progress : Rapidly improved with antibiotic therapy.
Liver and spleen remained palpable.
No follow-up after discharge.

Case No. C34

A man of 30 years was admitted following a haematemesis. He had felt unduly tired for 3 months but had not been off work. There was no past history of dyspepsia.

Examination : Splenomegaly of 1 inch was the only abnormal finding.

Radiology : Varices present.

Liver function tests : Colloidal gold 0; alkaline phosphatase normal; serum bilirubin 0.2 mg.%.

Progress : Advised to have operation to exclude extra-hepatic portal obstruction. Advice refused. Liver biopsy - normal tissue obtained. Admitted to another hospital 1 year later following a haematemesis. Ascites developed and required paracentesis on one occasion. Seen by request 8 years after original admission. Spleen still palpable; urobilinogen in urine; leucopaenia. Serum albumin reduced to 2.8 g.% and globulin increased to 3.8 g.%. Thymol turbidity positive but colloidal gold 0. Patient has been untraced for past 3 years.

Case No. C35.

A man of 52 years was seen at the out-patient department on account of chronic bronchitis present for 10 years. Diet possibly deficient in protein. He was said to have had an enlarged liver since the age of 7.

Examination : Small stout man with rachitic bowing of tibiae. Emphysematous chest. Liver enlarged 3 inches and spleen 7 inches.

Radiology : Large oesophageal varices present.

Liver function tests : Serum albumin 3.7 g.%; serum globulin 2.9 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin 1.0 mg.%.

Progress : Remained well for 2 years apart from symptoms of bronchitis.

Died following a haematemesis in 1957.

Case No. C36.

A man aged 59 years, was admitted on account of anorexia, weight loss, epigastric discomfort and pallor of 2 months duration.

Examination : Pale. Normal tongue. Liver enlarged 2 inches and firm. Examination otherwise normal.

Radiology : No varices. Duodenal ulcer.

Liver function tests : Not done.

Haematology : 1) Macrocytic anaemia - Hb = 33%
2) Megaloblastic erythropoiesis
3) Free hydrochloric acid in gastric juice
4) Response to vitamin B12
5) Fat balance 89% absorption

Progress : Follow-up for 4 years. He has remained well on regular vitamin B12 therapy but the liver remains enlarged 2-3 inches and liver function tests are positive. (1957: serum albumin 3.5 g.%; serum globulin 3.9 g.%; colloidal gold 4.).

Case No. C37.

A male, aged 67 years, complained of anorexia for 1 year. Six months prior to admission to the Royal Infirmary he had developed oedema and ascites. A laparotomy had been carried out elsewhere and the report was of a cirrhotic liver with no evidence of cancer. Paracentesis had been performed every 2 weeks since then.

Examination : Gross oedema; clubbing of fingers; spleen enlarged 1 inch; liver edge just palpable and firm; gross ascites; evidence of weight loss.

Urine : Massive albuminuria. Urobilinogen present.

Radiology : X-ray chest negative. Too ill for barium examination.

Liver function tests : Serum albumin 1.8 g.%; serum globulin 5.0 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin less than 1 mg.%.

Renal function : Blood urea 83 mg%.

Progress : Gum biopsy negative for amyloid. Given ion-exchange resins, but progressive rise in blood urea took place, and blood pressure fell to 90/60 mmHg. Became drowsy with flapping tremor of fingers, and died in coma.

Case No. 038.

A woman, aged 41, had been in good health until the birth of her 6th child, following which she became weak, tired, breathless and had swelling of her legs. She was admitted 1 year after childbirth on account of ascites.

Examination : Slight oedema; clubbing of finger nails; firm hepatic enlargement of 3 inches; spleen not palpable; ascites; small left basal effusion.

Radiology : Barium swall not done. X-ray of chest confirmed the presence of effusion.

Liver function tests : Serum albumin 3.0 g.%; serum globulin 4.5 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase normal; serum bilirubin 0.7 mg%.

Progress : Received ion-exchange resins for 1 month without appreciable effect. Discharged home on high protein diet and ascites slowly cleared. Seen 6 months later when she felt well but still had some intra-abdominal fluid, hepatomegaly of 3 inches and a palpable spleen 1 inch below the left costal margin.

Case No. 039.

A female, aged 50 years. At the age of 21 she had the right leg amputated because of chronic osteomyelitis. At the age of 49 she had recurrent haematuria and retrograde pyelography showed 'blunting of the calyces', possibly from chronic pyelonephritis. In the same year a laparotomy was performed because of abdominal pain and a mass in the left flank. An enlarged spleen was removed, the histology of which was consistent with Banti's syndrome. The surgeon did not comment on the liver.

Examination : Clubbing of fingers; no oedema; liver edge just palpable; splenectomy scar.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 1.7 g.%; serum globulin 2.5 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 8 Bodansky units; serum bilirubin normal.

Renal function : Albuminuria. Blood urea 35 mg.%.

Gum biopsy : Negative for amyloid.

Progress : Developed ascites a few months later, which was satisfactorily controlled by ion-exchange resins. Fair health for a further 3 months when the blood pressure and blood urea began to rise. Last seen 8 months after original admission when she was very drowsy with a blood urea of 160 mg.%.

Case No. C40.

A woman, aged 47, was first admitted in 1951 with anorexia and weight loss of 5 stones in 2 years.

Examination : Tongue rather smooth; liver edge just palpable spleen not palpable; no ascites.

Radiology : Barium examination of the alimentary tract negative, but the radiologist commented on splenic enlargement.

Liver function tests : Serum albumin 3.3 g.%; serum globulin 3.7 g.%; colloidal gold 0; thymol turbidity normal; alkaline phosphatase 8.5 Bodansky units; serum bilirubin 0.8 mg.%.

Haematology : E.S.R. 104 mms.

Liver biopsy : Early fibrosis with lymphocytic infiltration.

Progress : Slow improvement with weight gain. Basal metabolic rate normal. Not seen between 1952 and 1957. At the latter time she was very ill with gross ankle oedema (serum albumin 0.6 g.%; serum globulin 7.7 g.%; colloidal gold 5), flushed palms, and slight jaundice (serum bilirubin 3.8 mg.%). For 6 months she had been losing weight with poor appetite and persistent nausea.

Case No. C41.

A woman, aged 56, was admitted in 1956 with a haematemesis. Between 1953 and 1956 haematemesis had occurred 4 times. She gave no history of dyspepsia.

Examination : Slightly icteric; telangiectasis on face; tongue rather smooth; spleen enlarged 6 inches; liver not palpable.

Radiology : Oesophageal varices present.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 3.6 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin 1 mg.%.

Haematology : Leucopaenia and thrombocytopaenia.

Progress : Splenectomy performed with immediate and sustained rise in white cells and platelets. Liver stated to show a mild degree of fibrosis and the histology of the spleen was typical of Banti's syndrome.

Three months following operation she developed what appeared to be a typical infective hepatitis with positive flocculation tests. Slight jaundice persisted for several weeks, disappeared, and then recurred again a month later. At the time of writing she is in moderately good health but has slight ankle swelling (1957).

Case No. C42.

A female, aged 68 years, gave a history of anorexia, periodic vomiting, weakness and tiredness of 6 months duration. Dietary history was average and she had never been jaundiced. She was admitted with pain in right upper abdomen.

Examination : Pale and obese. Spider naevi on chest and arms. Liver palpable 2 inches below costal margin. Spleen not palpable. No oedema and no ascites.

Radiology : Chest negative. Not fit for barium examination.

Liver function tests : Serum albumin 2.5 g.%; serum globulin 4.0 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin 0.5 mg.%.

Haematology : 1) Macrocytic anaemia (Hb = 50%). E.S.R. 130 mm in 1 hour.
2) Megaloblastic erythropoiesis.
3) Free hydrochloric acid in gastric juice.
4) No response to parenteral vitamin B12.
5) Response to folic acid orally.
6) Fat balance unsuccessful as patient could not take diet.

Progress : Remained in ill-health despite response to folic acid. Deceloped severe peripheral neuritis and a recto-vaginal fistula. Colostomy performed, but became drowsy and finally comatose.

Post-mortem : Fine hepatic cirrhosis mainly affecting the left lobe of liver. No varices. Spleen normal.

Case No. C43.

A female, aged 43 years, complained of malaise and tiredness following a miscarriage in June 1952. In August 1953 she thought her abdomen was swollen. She was admitted in October 1953 with jaundice and ascites.

Examination : Jaundiced. Oedema, ascites, and spider naevi present. Liver and spleen both enlarged 3 inches.

Radiology : Oesophagus normal. Doubtful presence of varices in cardiac end of stomach.

Liver function tests : Serum albumin 2.2 g.%; serum globulin 2.2 g.%; colloidal gold 3; thymol turbidity normal; alkaline phosphatase 2.2 Bodansky units; serum bilirubin 4 mg.%.

Haematology : Haemoglobin 140%; red blood cells 7.14 million per cu.mm; white blood cells 30,000 per cu.mm; platelets 250,000 per cu.mm. Marrow: hypercellular.

Progress : Received a single dose of 5 millicuries radioactive phosphorus. Anorexia, jaundice and ascites persisted for 6 months. Gradual recovery. Follow-up until June 1957. No change in hepatic and splenic enlargement and liver function remains severely impaired. Blood values have remained normal for 3 years.

Case No. 044.

In 1951 a female, aged 54 years, was diagnosed as having polycythaemia vera and was treated with deep X-ray therapy. For about 6 years preceding treatment she had been aware of discomfort in the left upper abdomen. Further X-ray therapy was given in 1953. In 1954 she became jaundiced with anorexia, occasional diarrhoea, and intermittent epistaxis.

Examination : Telangiectasis on face; spontaneous bruising; liver enlarged 3 inches; spleen enlarged 4 inches.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 2.8 g.%; serum globulin 2.9 g.%; colloidal gold 3; thymol turbidity positive; alkaline phosphatase 10.6 Bodansky units; serum bilirubin 4.3 gm.%.

Haematology : Hypochromic anaemia (Hb = 57%). Platelets 450,000 per cu.mm.

Progress : Slight jaundice persisted for 9 months and finally cleared. The spleen enlarged to fill the whole left side of the abdomen and caused considerable discomfort. The spleen was removed in 1956, following which the white cell count rose to 100,000 per cu.mm. and the marrow showed marked myeloid hyperplasia. Myleran was given with good effect. A liver biopsy during the operation confirmed the presence of hepatic fibrosis. The patient is still alive, and although liver function is impaired she is in fair health.

Case No. 045.

A female, aged 61 years, was admitted with redness and swelling of her legs. Nine years previously polycythaemia vera had been diagnosed and she had received X-ray therapy. Symptoms returned 5 years later and she was treated with radio-active phosphorus.

Examination : Oedema; spider naevi; telangiectasis; flushed palms; liver and spleen both enlarged 4 inches. Hypertension - B.P. 174/115 mmHg.

Radiology : Barium swallow normal.

Liver function tests : Serum albumin 3.2 g.%; serum globulin 4.1 g.%; colloidal gold 5; thymol turbidity strongly positive; serum bilirubin 0.2 mg.%.

Haematology : Haemoglobin 97%; red blood cells 5.3 million per cu.mm; white blood cells 47,000 per cu.mm; platelets 132,000 per cu.mm.

Progress : Follow-up for 1 year. Progressive deterioration with falling haemoglobin and troublesome pain in the legs. Ultimate fate of this patient is unknown.

Case No. 046.

A female, aged 41 years, complained of undue tiredness for 3 years. The diet was below average. Periods had been heavy for 1 year.

Examination : Pale; slight ankle oedema; spleen palpable 1 inch; liver edge felt at costal margin.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 3.9 g.%; serum globulin 4.1 g.%; colloidal gold 2; thymol turbidity normal.

Haematology : Hypochromic anaemia (Hb = 30%).

Progress : Complete return of blood to normal with oral iron therapy. Spleen remains palpable but follow-up is only 6 months. The diagnosis of cirrhosis is presumptive and based on the persistence of splenomegaly and a high serum globulin.

Case No. C47.

A female, aged 60 years, was admitted with auricular fibrillation and congestive cardiac failure. For 1 year she had been losing weight despite a good appetite, and had been unduly nervous.

Examination : Small nodule on isthmus of thyroid. Clinical signs of thyrotoxicosis (tremor, warm skin, tachycardia). Hypertension - B.P. 270/120 mmHg. Liver enlarged 3 inches and spleen 2 inches.

Radiology : Barium swallow not done.

Liver function tests : Serum albumin 4.8 g.%; serum globulin 3.4 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin normal.

Haematology : Hypochromic anaemia (Hb = 73%).

Progress : Treated with thiouracil and digoxin. Follow-up for 1 year. Now judged to be euthyroid, and there is no longer evidence of cardiac failure, but the spleen is still enlarged 3 inches and the liver 5 inches. There is no glandular enlargement and the patient is in good health.

Case No. C48.

A man of 32 years was admitted in 1952 with a history of anorexia, periodic diarrhoea and upper abdominal discomfort for 2 weeks. In the past he had occasionally drunk to excess but was not a habitual alcoholic.

Examination : Drowsy, not icteric but bile present in urine. Liver enlarged 1 inch and spleen tip palpable.

Radiology : No varices demonstrated.

Liver function tests : Serum albumin 2.7 g.%; serum globulin 3.0 g.%; colloidal gold 0; thymol turbidity normal; serum bilirubin 0.8 mg.%.

Progress : Recovered in course of 2 weeks. Follow-up for 5 years, until 1957. Spleen became definitely palpable, and from time to time he has developed anorexia and malaise. In 1956 he developed an inguinal hernia, and the sac was noted to contain ascitic fluid. A porta-caval anastomosis was done (1957) following which portal-systemic encephalopathy developed with mental confusion and periods of coma. Mental symptoms are fairly well controlled when dietary protein is restricted to 40 g. per day. The appearance of a liver biopsy is shown in fig. 13.

CASE C 48

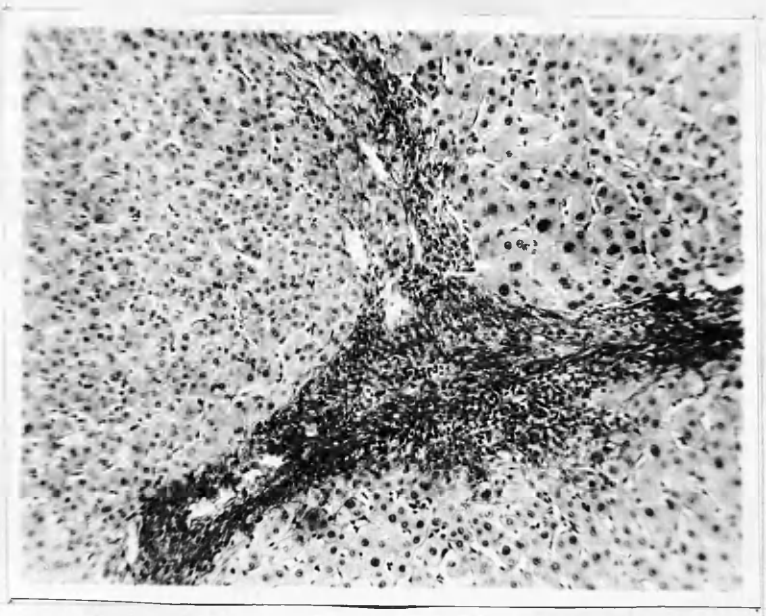

Fig. 13
Cryptogenic Cirrhosis

Possibly excessive alcohol in the past; and possibly a subclinical infective hepatitis in 1952. Surgical biopsy in 1957. The liver is coarsely scarred and there is considerable round cell infiltration of the fibrous tissue. x 100

Case No. 049.

A female, aged 55 years, was admitted to another hospital in 1954 complaining of malaise, weakness and breathlessness. She was observed to be slightly jaundiced and the spleen was palpable. In 1956 she developed oedema and ascites, and was admitted to the Royal Infirmary.

Examination : Jaundiced; telangiectasis on cheeks; oedema and ascites; spleen enlarged 8 inches; liver edge just palpable.

Radiology : Barium examination not performed.

Liver function tests : Serum albumin 2.4 g.%; serum globulin 3.6 g.%; colloidal gold 4; alkaline phosphatase 13 Bodansky units; serum bilirubin 32 mg.%.

Haematology : Haemoglobin 66%; reticulocytes 6-10%; platelets 97,000 per cu.mm. E.S.R. 63 mms in 1 hour. Coomb's test positive to titre 1/640. Fragility of red cells normal. Wassermann Reaction positive.

Progress : Treated with penicillin and cortisone (Prednisolone). Platelets rose to normal, bilirubin fell to 3.2 mg.%. Obvious clinical improvement, but faecal urobilinogen remained very high. The patient left hospital against advice and has not been traced since. This patient was thought to have decompensated cirrhosis and a symptomatic haemolytic anaemia.

Chapter 8.

CASE No. 3

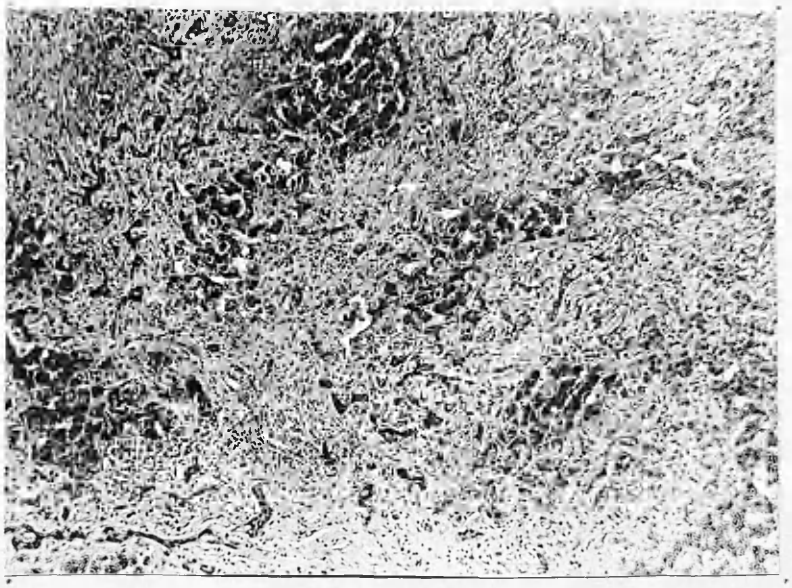

Fig. 14
Biliary Cirrhosis

Post mortem specimen. The patient had a primary carcinoma of a hepatic duct and had been jaundiced for 18 months. The photomicrograph illustrates the very extensive parenchymal damage which has resulted. (x 80)

UNIVERSITY OF GLASGOW

Faculty of Medicine,
GLASGOW, W.2.

Professor D.F. Cappell.

8th October, 1958.

Dear Sir,

Degrees of M.D. and Ch.M.

I would remind you that a Clinical Examination has been abolished as a compulsory requirement for the Higher Degrees of M.D. and Ch.M. In its place the Faculty has resolved 'that a candidate may be required to present himself before the examiners for interview or for further examination on the subject-matter of his thesis and related subjects. When a candidate is required to undergo further examination, this examination may be a written, or oral, or practical test, or any combination of these, as the examiners think fit.'

It is the Faculty's intention to restrict, in general, the imposition of an examination to those cases in which there may be doubt about

(a) the originality of the work, or,

(b) the title of the Thesis to receive the highest award of Honours.

but apart from these, there may be special cases in which the Reader may think that further examination would be desirable.

I am therefore desired to ask you in returning your report to give your opinion whether the candidate should be required to appear for:-

(a) interview or examination at all;
(b) an interview only;
(c) a written examination;
(d) an oral examination;
(e) a practical or clinical examination;
(f) a combination of (c), (d), and (e).

Yours faithfully,