Hepatic cirrhosis is a term applied to chronic diffuse liver disease of varied aetiology. All the different forms of cirrhosis have a common background of hepatic histology. All show disturbance of the essential lobular architecture of the liver, with proliferation of connective tissue and degeneration, death and regeneration of hepatic cells. Cellular infiltrations, usually with lymphocytes, and proliferation of bile ducts are nearly always present. This common hepatic histological picture may be produced in many different ways. The more important will be discussed.

Aetiology and Pathology of Cirrhosis

(1) Classic 'portal' or Laennec's cirrhosis:
   (a) Post-hepatitic.
   (b) Dietetic.
   (c) Alcoholic.
   (d) 'Banti's syndrome.'

(2) Cardiac cirrhosis, associated with congestive heart failure.

(3) Haemochromatosis, a cirrhosis associated with disordered iron metabolism.

(4) Biliary cirrhosis associated with extra-hepatic or intra-hepatic biliary tract obstruction.

(5) Bilharzial cirrhosis associated with bilharzial infection of the portal venous system.

(6) Hepatolenticular degeneration (Kinnier-Wilson's disease), a cirrhosis with associated degenerative disease of the central nervous system.

(7) Other postulated causes of cirrhosis such as chemical poisons, syphilis and malaria.

(a) Post-Hepatic Cirrhosis

Acute infective hepatitis is usually followed by complete restoration of the liver to normal. However, long-term sequelae are not unknown and, in many instances, hepatic cirrhosis can be directly related to a preceding acute infective hepatitis (Jones and Minot, 1923; Rennie, 1945). In these patients serial aspiration liver biopsies show a destruction of the normal reticulin framework of the liver lobule with nodular regeneration of surviving liver cells and the development of a true hepatic cirrhosis (Sherlock, 1948). (Figs. 1, 2, 3, 4.)

The exact importance of acute 'viral' hepatitis in the aetiology of cirrhosis remains uncertain. Ratnoff and Patek (1942) elicited a past history of jaundice in only 6.5 per cent. of 356 patients with cirrhosis. Howard and Watson (1947), however, obtained a history of previous infective hepatitis in 17 per cent. of patients with cirrhosis contrasted with 3 per cent. in a similar group without hepatic disease. The absence of a history of previous jaundice does not exclude acute hepatitis in the past, for mild attacks may well be passed over as intercurrent infections, quickly forgotten, and not related to the succeeding hepatic cirrhosis. Kelsall and his co-workers (1947) could find no difference between the clinical and pathological features of cirrhosis developing with no known cause and those of cirrhosis preceded by hepatitis. There seems no doubt that post-hepatitis cirrhosis and 'classical' Laennec's cirrhosis can present the same clinical picture. Future analysis of the effect of the great war-time epidemics of hepatitis on the incidence of cirrhosis will enable the aetiological importance of hepatitis to be better assessed.

(b) Dietetic Cirrhosis

Interest in the dietary production of liver lesions was initiated in 1924 by the observation of MacLeod and his group in Toronto that pancreatectomized dogs, although maintained on insulin, developed fatty change in the liver. This lesion could be prevented by choline. Later it was shown particularly by Himsworth and Glynn (1944) that dietetic deficiencies could result in two broad types of hepatic pathology. Deficiency of lipotrophic factors (e.g. choline) resulted in fatty infiltration of the liver and later cirrhosis, whereas deficiency of first-class protein led to massive hepatic necrosis and scarring, a condition perhaps analogous to post-hepatitis cirrhosis. The constituents of first-class protein which prevents massive hepatic necrosis were believed to be sulphydryl group containing amino acids (e.g. cystine). Methionine which contains both the lipotropic labile methyl and sulphydryl groups will prevent both fatty infiltration and post-necrotic scarring. The literature has been well reviewed by Witts (1947).

Application of these observations to disease in
man is more difficult. There seems no doubt that the high incidence of liver disease in underprivileged peoples can be related to dietetic deficiencies. This is true, for instance, of the fatty livers and pigment cirrhosis of South African babies (Gillman and Gillman, 1945), the malignant malnutrition (Kwashiorkor) of children in Uganda (Trowell, 1949), the fatty livers and cirrhosis of West Indian infants (Waterlow, 1947) and the cirrhosis of the liver common among the poor natives of the Punjab (Hughes, 1933). Certain diseases which interfere with the intake and metabolism of amino acids may be associated with dietetic liver lesions. For instance, a fatty liver is a practically constant association with chronic diarrhoea, particularly in ulcerative colitis, and this may progress to cirrhosis (Pollard and Block, 1948). Patients with amino acid loss in the urine, for instance the Fanconi syndrome, may show fatty change in the liver and cirrhosis. The relation of alcohol to hepatic cirrhosis will be discussed below. Apart from these considerations it seems unlikely that the dietary intake of protein in this country, even in the poorest groups, is so low as to result in liver injury and cirrhosis.

(c) **Alcoholic cirrhosis**

Hepatic cirrhosis is 6.7 times as frequent in inebriates as in the temperate population (Jolliffe and Jellinek, 1941). However, alcohol poisoning alone will not lead to cirrhosis (Jolliffe and Jellinek, 1941; Best et al., 1949), and the relation between alcoholism and cirrhosis is probably indirect. Most alcoholics take a poor general diet which is particularly deficient in protein and lipotropic factors. At the same time their caloric intake in the form of alcohol is above normal. An imbalance between caloric intake and the supply of essential food factors results, and the consequent cirrhosis is dietetic and analogous to that described
above in animals on experimental diets (Best et al., 1949). This type of cirrhosis could probably be prevented by ensuring that alcoholics took not only adequate calories (alcohol) but also essential amino acids and lipotropes (first-class protein).

(d) 'Banti's Syndrome' (congestive splenomegaly, splenic anaemia)

In 1898 Banti described a primary splenic disease which was later followed by hepatic cirrhosis. Three stages were recognized, a pre-ascitic in which the disease was confined to the spleen with leukopenia and microcytic hypochromic anaemia, an intermediate with enlargement of the liver but with no hepatic symptoms and a third or ascitic stage with ascites, liver failure and gastrointestinal haemorrhage. However, this clinical history is very rare. In his wide experience Eppinger (1920) saw only one possible example. McNee (1932) states that he never encountered a case history really showing the sequence of events originally described. There are now grave doubts whether Banti's disease exists as a distinct entity. It seems probable that this syndrome will result from a wide variety of conditions, the common denominator of which is portal venous obstruction. The lesion may be in the splenic veins, in the portal veins (thrombosis, congenital occlusive bands, cystic dilatation, etc.) or in the liver itself (most varieties of cirrhosis). The leukopenia is not specific and occurs in practically all conditions where the spleen is hyperplastic. The anaemia can usually be related to gastrointestinal haemorrhage resulting from the portal hyper-tension. Overactivity of the splenic pulp (hypersplenism of Doan and Wright, 1946) may also contribute to the anaemia.

In clinical medicine there is little useful purpose served by retaining the term 'Banti's syndrome,' which should be replaced by 'portal venous obstruction' together with its cause.

2. Cardiac Cirrhosis

Cardiac failure, unless acute and of short duration, usually results in some centrilobular disappearance of liver cells with resultant collapse of the reticulin framework at the centre of the hepatic lobule. Reticulin proliferation may follow, spreading outwards from the central hepatic vein towards the periphery of the lobule. Eventually connective tissue from one central vein joins the connective tissue from adjoining lobules (Figs. 5 and 6). The portal tracts now apparently occupy a central position in the hepatic lobule surrounded by the connective tissue running between the hepatic veins. This is described as reversed lobulation. The lesion is a frank cardiac cirrhosis. This sequence of events occurs only when the cardiac failure relapses and is of long duration (Sherlock, 1950). It follows that although cardiac cirrhosis can occur with every type of chronic heart failure it is most frequently associated with mitral valvular stenosis.

3. Haemochromatosis

Increased iron in the liver is distributed both in the hepatic parenchyma and in the cells of the reticulo-endothelial system. If excessive, this

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**Fig. 5.** Cardiac cirrhosis. Congestion in the centrilobular zones from which bands of fibrous tissue pass to adjoining central areas. A portal tract occupies an apparently central position (reversed lobulation). H.E. × 90.

**Fig. 6.** Reticulin stains show the condensation and proliferation around the central veins from which bands pass to neighbouring central veins. Portal tracts normal. Modified Foot's stain × 80.
leads to liver cell disintegration and to portal tract fibrosis. Increased haemolysis and hence all forms of haemolytic anaemia are the commonest causes of hepatic siderosis. Multiple blood transfusions may also lead to increased iron in the liver (Schwartz and Blumenthal, 1948). However in none of these conditions is the iron deposition of sufficient extent to provoke such liver cell disintegration and fibrosis as to warrant the term cirrhosis. In true haemochromatosis there are not only coarse granules of iron in the liver and reticulo-endothelial cells, but also gross fibrosis, liver cell degeneration and disturbance of the lobular architecture (Fig. 7). Iron absorption from the intestines is normal (Fowler and Barer, 1937), and this condition is probably intracellular, interfering with the metabolism of the iron containing pigment cytochrome. An acquired form is described in infantile pellagra (Gillman and Gillman, 1945).

(4) BILIARY CIRRHOSIS

Obstruction to the common bile duct leads to centrilobular accumulation of bile pigment often with bile-stained focal necrosis of liver cells. The portal tracts show bile duct proliferation, fibrosis and scanty round-celled infiltration. As the biliary obstruction continues the fibrosis extends and increases, passing from portal tract to portal tract so that the lobule is surrounded by a band of connective tissue (Fig. 8). The essential lobular architecture, however, remains undisturbed and the lesion is not a true hepatic cirrhosis. Liver cell regeneration does not occur in the presence of biliary stasis (Mann, Fishbank, Gay and Green, 1931). If the biliary obstruction is incomplete, intermittent or surgical relief is possible, then nodular hyperplasia of liver cells occurs and a true hepatic biliary cirrhosis results (Fig. 9). Gallstones are the most frequent cause of intermittent biliary obstruction and of biliary cirrhosis.

The histological picture of biliary cirrhosis is sometimes encountered in patients in whom the bile ducts are patent or even dilated (Dible, McMichael and Sherlock, 1947). The clinical features and laboratory findings are usually identical to those found in association with obstruction to the extrahepatic bile ducts. This condition in the past has received many names, amongst them Hanot's cirrhosis, primary biliary cirrhosis, cholangiolitic biliary cirrhosis, or, where there are conspicuous cholesterol deposits in the skin, xanthomatous biliary cirrhosis. The lesion is an obliteration of the intrahepatic bile ducts and an infective aetiology seems most likely.

(5) BILHARZIAL CIRRHOSIS

This condition is due to invasion of the liver by the eggs of Bilharzia mansoni. The ova embolize in the portal vein from the intestines and are trapped in the portal tracts of the liver lobules (Fig. 10). A reaction is excited which includes fibrosis and inflammatory cell infiltration with necrosis of adjoining liver cells. The lesion is a true hepatic cirrhosis. Bilharzial cirrhosis is found particularly in Egypt, Central and West Africa and South America.

(6) HEPATO-LENTICULAR DEGENERATION (KINNIER-WILSON'S DISEASE)

In 1913 Kinnier-Wilson drew attention to the association of liver cirrhosis and degeneration of the central nervous system and, in particular, of the basal ganglia. The hepatic lesion corres-
ponds to the general pattern of cirrhosis and histologically cannot be distinguished from the usual 'portal' variety. The aetiology of the condition is uncertain. In erythroblastosis foetalis there is a liver lesion and also bile staining of the basal ganglia (kermiterus) and rhesus blood group incompatibility has been cited as the cause of Wilson's disease, particularly as the condition is familial. Studies on a large group of patients, however, have failed to show any relationship between the two diseases (Yannet and Lieberman, 1946). More interesting is the recent report of the association of persistent aminoaciduria and Wilson's disease (Uzman and Denny-Brown, 1948). This would provide a link between Wilson's disease and the dietetic cirrhoses.

(7) Other Postulated Causes of Cirrhosis

Chemical poisons

Acute carbon tetrachloride poisoning in man and experimental animals produces fatty infiltration of the liver. In rats and dogs repeated administration of carbon tetrachloride over long periods is needed to result in hepatic cirrhosis (Bollman and Mann, 1931; Cameron and Karunaratne, 1936). It might be thought that in man, also, prolonged exposure to the substance would lead to cirrhosis. However, this does not seem to be the case and prolonged industrial exposure to carbon tetrachloride appears to promote resistance rather than susceptibility. Investigation of a large series of workers using carbon tetrachloride failed to show a single case of cirrhosis due to the vapour (Smyth and Smyth, 1936). It appears that carbon tetrachloride is not an important aetiological factor in cirrhosis. This applies also to the related substances, chloroform and tetrachlorethene.

Arsenical poisoning has been reported with cirrhosis in man but is a rarity and arsenic intoxication is not an important cause of cirrhosis. The association of cirrhosis in syphilitics having had previous organic arsenical therapy is probably through a preceding serum hepatitis resulting from contaminated syringes.

Syphilis

Syphilis was formerly considered an important factor in the production of hepatic cirrhosis. This is apparently not so in adults, although in congenital syphilitic infants, invasion of the liver by the spirochaetes does result in pericellular fibrosis and cirrhosis. In adults the only lesion clearly related to syphilis is the gumma, which on healing leaves a scar. These scars may result in a coarsely nodular liver (hepar lobatum) but are never so widespread as to merit the term cirrhosis. It seems more likely that cirrhosis discovered in previously treated syphilitics is in fact related to a previous serum hepatitis. The opportunities for syringe transmission of hepatitis in patients attending venereal disease clinics is well known.

Malaria

Malarial parasites cause a reaction in the reticulo-endothelial system generally and hence proliferations both of the Kupffer cells of the hepatic
sinusoids and the large macrophages of the portal tracts. The destruction of red blood cells leads to release of bilirubin which further stimulates reticulo-endothelial proliferation. If severe, the anaemia and fever are associated with centrilobular liver cell necrosis. These features, however, do not result in chronic diffuse liver disease with fibrosis and destruction of the hepatic lobular architecture and malaria is of no importance in the aetiology of cirrhosis. The frequent occurrence of malaria and cirrhosis in the same patient must be ascribed to malaria and conditions causing cirrhosis (e.g. bilharziasis, malnutrition) being simultaneously present in the community.

**Clinical and Laboratory Features of Cirrhosis**

Although the various types of cirrhosis have certain individual characteristics the effects of the lesion are common and can be divided into two main groups. Firstly there are those related to obstruction of the intrahepatic blood flow with consequent portal venous hypertension. The second group result from the functional inadequacy of the hepatic cells. The clinical investigation of a patient suffering from any type of cirrhosis involves an assessment of the part played by each of these major factors. The following account refers to classic ‘portal’ or Laennec’s cirrhosis which is used as a type example. The differential diagnostic features of the other varieties of cirrhosis will be described later.

**Assessment of Portal Venous Hypertension**

In hepatic cirrhosis the distortion of the hepatic lobular architecture and the fibrosis result in great diminution of the intrahepatic vascular bed (McIndoe, 1928). The portal venous blood flow is obstructed and the portal venous pressure rises (Whipple, 1945; Blakemore, 1948; Davidson, Gibbons and Faloon, 1950). The portal blood is deviated to channels anastomosing with the systemic system and the majority of the portal blood may be recovered from these collaterals rather than the hepatic vein (Dock, 1947). The clinical diagnosis of portal venous obstruction is presumptive and depends on the demonstration of dilated portal-systemic collaterals (Fig. 11). Attention should be paid in the clinical history to haematemesis which may come not only from oesophageal varicosities but also from dilated veins in the stomach wall. Bleeding from haemorrhoids must also be noted. The anterior abdominal wall should be carefully examined for distended veins. a frank ‘caput medusae’ is rare and usually only one or two veins are noted running from the umbilical region. The blood flow in these veins is radially away from the umbilicus (Fig. 12). This is in contra-distinction to collaterals occurring with inferior vena caval obstruction in which the blood flow is always upwards over the abdominal wall (Fig. 13). Tense ascites leads to functional obstruction of the inferior vena cava and may cause difficulty in the interpretation of anterior abdominal wall veins. The use of infra-red photography to show up the veins more clearly is to be recommended. As a further diagnostic aid a glucose drink may be given and 30 minutes later the glucose content of the blood in the anterior abdominal wall vein and in an antecubital vein estimated. A higher glucose content in the abdominal than in the antecubital vein confirms that the abdominal vein is a portal collateral (Sherlock and Walshe, 1946). Occasionally in cirrhosis the anastomotic umbilical vein may be so dilated that a venous hum can be heard above and to the right of the umbilicus (Cruveilhier-Baumgarten syndrome). The size of the spleen in cirrhosis is another good indication of the degree of portal hypertension. Portal obstruction is also one factor in the production of ascites and this will be discussed later. Oesophageal varicosities can often be demonstrated radiologically using a thick barium emulsion. Oesophagoscopy is rarely indicated. Proctoscopy is used to visualize haemorrhoids.
Assessment of Hepatic Cellular Function

Changes in Bile Pigment Metabolism

Jaundice in a cirrhotic patient means that the rate of destruction of liver cells has exceeded the capacity for regeneration and the lesion is a decompensated one. It is therefore of serious consequence and considerably worsens the prognosis. Icterus is rarely deep, serum bilirubin values being of the order of 2 to 5 mg./100 ml. In general the deeper the jaundice the greater the inadequacy of the liver cell function. Sometimes icterus is precipitated by an acute episode of liver damage such as an alcoholic bout or an intercurrent infection. In these patients jaundice is not so serious and may well disappear if the acute condition can be treated. An increase in the serum bilirubin value in cirrhosis is by no means constant and many patients with well compensated hepatic lesions have serum bilirubin values of less than 1.0 mg./100 ml.

The qualitative Van den Bergh reaction and the proportions of the serum bilirubin acting 'directly' and 'indirectly' with the diazo reagent are non-contributory in the clinical investigation of cirrhosis.

The bromsulphalein excretion test is a further sensitive method of estimating liver cell function (Helm and Machella, 1942). Bromsulphalein is probably metabolised very similarly to bilirubin and its retention in the blood stream after intravenous injection reflects an inability of the liver to excrete bile pigment. It is clearly of no value in patients with raised serum bilirubin concentrations in whom there is already a clear indication of inability to excrete naturally formed bilirubin.

Excess of urinary urobilinogen or its oxidation product, urobilin, further indicates failure of liver cell function. Urobilinogen is normally absorbed from the intestines and re-excreted by the liver into the bile. If liver cell function fails some of this urobilinogen is excreted by the kidneys into the urine (Fig. 14). Qualitative tests are simply performed either for urobilinogen by Ehrlich's aldehyde reaction or for urobilin by Schlesinger's alcoholic zinc acetate method. Daily urine testing for these substances often gives as good an evaluation of the state of the liver cells in cirrhosis as far more time-consuming laboratory procedures. Bilirubin appears in the urine only when the patient is frankly jaundiced.

Changes in Protein Metabolism

It is generally accepted that the liver plays a major role in the regeneration of the plasma proteins (Madden and Whipple, 1940). This is particularly true of the plasma albumin. Some plasma globulin may be formed elsewhere (Sabin, 1939). Chronic diffuse liver disease, therefore, results in a diminished plasma albumin level and this is partially compensated by an increase in the plasma globulin. In general, the lower the plasma albumin the greater the extent of hepatic cell necrosis and the worse the prognosis (Sherlock, 1946b).

In active cirrhosis, not only are the plasma proteins quantitatively abnormal but there is a change in their constitution as shown by electrophoretic analysis (Gray and Barron, 1943). This results in positive findings for various flocculation and precipitation tests. The most useful procedures are the thymol turbidity and the colloidal gold tests. A positive thymol turbidity (Maclagan, 1944) probably indicates continuing inflammatory cell change in the liver. A positive colloidal gold reaction (Gray, 1940) may represent continuing liver cell degeneration, especially with fatty change. It follows that the thymol turbidity test should be more often positive in post-hepatitis cirrhosis, whereas a positive colloidal gold reaction is usually associated with nutritional alcoholic cirrhosis. In practice, results for the two tests in cirrhosis usually run in parallel.
ascites in cirrhosis. There is also evidence that the peritoneum in patients with cirrhosis and ascites is unduly permeable to albumin (Patek et al., 1948). Additional factors may be involved. The urine of cirrhotics with ascites may contain an antidiuretic factor perhaps originating from the posterior lobe of the pituitary and not inactivated by a damaged liver (Ralli, et al., 1945). Sodium and water retention by the kidney may be another factor in the maintenance of ascites in cirrhosis (Farnsworth, 1948). Moreover, once ascites is present the diminished renal blood flow resulting from the increased intra-abdominal pressure (Bradley and Bradley, 1947) further tends to retain fluid in the tissues.

The aetiology of ascites in cirrhosis is therefore complex. Its presence implies that factors additional to portal hypertension are operating and, in general, is indicative of liver cell inadequacy.

**Changes in Carbohydrate Metabolism**

The liver is the keystone of carbohydrate metabolism. Ingested glucose reaches the liver by the portal vein and is there stored to be released to the bloodstream as required for the maintenance of the blood glucose concentration. The liver also converts the monosaccharides fructose and galactose to glucose. Abnormalities in the glucose, laevulose and galactose tolerance tests might be expected in patients with cirrhosis. However the reserve power of the liver with respect to carbohydrate metabolism is so great that very severe liver cell damage is necessary before these tests become positive and carbohydrate tolerance tests are of little practical importance in the study of cirrhosis. Similarly the cirrhotic liver might not be able to maintain a normal blood glucose value. Hypoglycaemic episodes do occur in the cirrhotic patient but are infrequent.

**Changes in Cholesterol Metabolism**

The liver excretes cholesterol in the bile and obstructive lesions of the biliary passages may be associated with a raised total serum cholesterol concentration. The hepatic parenchyma also esterifies cholesterol with fatty acids. The sera of active cirrhotics show a diminished proportion of esterified to free cholesterol and this ratio is an excellent index of hepatic cellular function. Unfortunately the use of this procedure is usually impracticable because of the tedious nature of the chemical estimation. The serum lipids in liver disease have recently been discussed by Man and her co-workers (1945).

**Haematological Changes**

Most textbooks describe a macrocytic anaemia
associated with cirrhosis. This is related to failure of the liver to synthesize and store the antipernicious anaemia principle. However, recent bone marrow studies do not support this concept as erythropoiesis is usually macronormoblastic and not megaloblastic (Berman et al., 1949). The anaemia is probably relative and is due to a marked increase in total blood volume with a relatively greater increase in plasma than circulating red cell mass; this suggests a more severe anaemia than actually exists (Bateman, Shorr and Elgvin, 1949). Anaemia in cirrhosis also results from alimentary tract blood loss related to portal venous hypertension, iron deficiency from poor dietary habits and disturbed haemoglobin metabolism from failure of proper protein synthesis in the liver.

The bleeding tendency in cirrhosis is usually attributed to inadequate prothrombin manufacture by the diseased liver and in general a prolonged prothrombin time in cirrhosis as a good reflection of severe liver cell damage. Thrombocytopenia may contribute to the bleeding tendency (Morlock and Hall, 1943).

**Detoxication Changes**

Poisons enter the body through the gastrointestinal tract and pass via the portal system to the liver. A cirrhotic liver detoxicates poisons less well than normal and this leads among other things to poor tolerance for morphia and barbiturate drugs which should be exhibited cautiously. This applies particularly to the short-acting barbiturate anaesthetics which are safe only in small doses and should only be used for inducing anaesthesia.

Some liver function tests are based on the detoxicating power of the liver. The most popular utilizes the conjugation by the liver of benzoic acid with glycine to form hippuric acid. Patients with active cirrhosis usually show an impaired hippuric acid synthesis test but this test has proved of little practical value as it is so often positive in non-hepatic conditions and bears little relation to underlying changes in the liver (Sherlock, 1945).

The liver is the essential organ for the inactivation of oestrogens and other steroids and this may be the explanation of certain endocrine changes in cirrhosis. These are well reviewed by Lloyd and Williams (1948). In males loss of body hair,
gynaecomastia and testicular atrophy may occur. In females changes in the menstrual pattern, in body hair and atrophy of breasts and uterus occur. Certain cutaneous lesions which occur both in cirrhotics and in pregnant women are attributed to excess of circulatory oestrogens. These include vascular spiders and palmar erythema. Cutaneous arterial spiders are found only in the vascular territory of the superior vena cava. They consist of a central point, which may be raised, and in which pulsation is sometimes seen. Branching vessels radiate from the centre. Pressure of the centre with a pin head leads to blanching of the entire lesion (Bean, 1945). The palmar erythema is seen over the pads of the fingers and over the thenar and hypothenar eminences. The surface is red and mottled, with increased temperature. The soles of the feet may be similarly affected. All these evidences of endocrine imbalance indicate inadequacy of liver cell function.

**Aspiration Liver Biopsy in Cirrhosis**

The patient presenting the full picture of decompensated liver disease does not require an aspiration liver biopsy to confirm the diagnosis. However a high proportion of patients with cirrhosis remain compensated and have equivocal clinical features and normal biochemical tests. Scrutiny of the last 50 case histories of patients with cirrhosis seen at the Postgraduate Medical School shows that in 25 there was doubt in the clinical diagnosis. In all these patients liver function tests were non-contributory but in 24 a correct diagnosis could be made with the aid of the aspiration liver biopsy sections. There are certain drawbacks to the use of this technique in the cirrhotic subject. If ascites is present the liver may be ‘ballottable’ and difficult to fix; paracentesis should be performed before the puncture is attempted. Failure may also result if the liver is very tough and difficult to pierce; a few liver cells may then be extracted leaving the fibrous framework behind (Sherlock, 1946a). Particular care should also be taken if it is suspected that the liver has greatly contracted as there is chance of the biopsy trocar missing the liver and perforating a hollow viscus such as the gall bladder. However, suspected cirrhosis still remains one of the important indications for aspiration liver biopsy and in the great proportion of cases gives an accurate diagnosis and enables the activity of the lesion to be assessed. Serial aspiration hepatic biopsies may be used to follow progress and to evaluate therapy instituted.

**Diagnosis of the Type of Cirrhosis**

As has already been indicated the investigation of all patients suspected of suffering from cirrhosis involves an evaluation of the liver cellular function and the degree of portal venous hypertension. The cirrhosis associated with different aetiological factors may present more diagnostic features.

Classic ‘portal’ or Laennec’s cirrhosis has been used as the type example and has been discussed fully above. The importance of alcoholism and of infective hepatitis in the preceding history may again be emphasized. A suggested outline of the minimum investigation of a suspected case of portal cirrhosis is shown in Table 1.

Wilson’s disease or hepato-lenticular degeneration is recognized by its familial nature and by the associated neurological signs of basal ganglia degeneration. Slit lamp studies may show the characteristic golden yellow pigment rings in the cornea (Kayser Fleischer rings). Liver cell failure or portal hypertension are rare.

**Table 1**

**Outline of the Investigation of a Patient with Hepatic (Portal) Cirrhosis**

**Occupation, Age and Sex:**

**Clinical History:**

- Digestive disturbance — anorexia and flatulent dyspepsia.
- Abdominal pain.
- Jaundice. Colour of urine and faeces.
- Swelling of abdomen and legs.
- Haemorrhage — nose, skin, alimentary tract.
- Weight loss.

**Past Health:**

- Jaundice.

**Social:**

- Heredity, alcohol consumption, Forces service in hepatitis epidemics.

**Examination:**

- Nutrition and evidences of vitamin deficiencies.
- Jaundice.
- Vascular spiders, palmar erythema, gynaecomastia.
- Finger clubbing. Distribution of body hair.
- Abdomen: Ascites, abdominal wall veins, liver, spleen.
- Oedema.

**Investigations:**

- Proctoscopy for piles.
- Barium swallow X-ray for oesophageal varices.
- Infra-red photograph of anterior abdominal wall for superficial veins.

**Biochemical :**

- Serum bilirubin concentration.
- Bromsulphalein excretion test (if serum bilirubin value less than 1 mg./100 ml.).
- Urinary urobilin (ogen) daily (qualitative test).
- Serum alkaline phosphatase concentration.
- Serum albumin. Concentratim.
- Serum globulin. Concentratim.
- Serum thymol turbidity test.
- Serum colloidal gold test.

**Aspiration Liver Biopsy if diagnosis is still uncertain.**
Patients with haemochromatosis may have skin pigmentation and endocrine disturbances, particularly gonadal atrophy and diabetes. Exact diagnosis involves the demonstration of excess iron in the tissues. In the skin it is shown by biopsy or the ferricyanide intradermal test (Beardwood and Rouse, 1944), in the liver by aspiration biopsy (Fig. 7) or in the urine by iron staining of the centrifuged deposit. The liver lesion in haemochromatosis is usually compensated and portal hypertension, jaundice and ascites are rare.

Cardiac cirrhosis usually has no specific clinical or biochemical associations. It does not produce portal venous hypertension, and jaundice in patients with heart failure does not necessarily indicate cardiac cirrhosis (Sherlock, 1950). Cardiac cirrhosis can occur with all the aetiological forms of heart failure, but is most frequent in patients with mitral stenosis and tricuspid valvular incompetence in whom congestive failure is intermittent and prolonged.

Bilharzial cirrhosis is recognized by its geographical distribution. It results in portal hypertension without much hepatic parenchymal dysfunction. Aspiration liver biopsy may demonstrate the ova of the parasite in the portal tracts (Fig. 10).

Biliary cirrhosis is usually associated with clinical manifestations of the causative lesion. This is frequently gallstones and there is usually some systemic infection with mild fever, leucocytosis and raised erythrocyte sedimentation rate. Jaundice is fluctuant. Ascites and portal hypertension are terminal. The biochemical findings are those of obstructive jaundice with an increased serum alkaline phosphatase and cholesterol and normal plasma proteins and flocculation tests. Aspiration liver biopsy may be diagnostic, but in a phase where jaundice is minimal and intrahepatic bile pigment retention slight, the histological appearances can be very difficult to distinguish from those of 'portal' cirrhosis.

**Treatment of Cirrhosis**

The treatment of cirrhosis with liver cell failure is very disappointing. The best results occur when the failure has a very clear precipitating cause. Thus an acute infection may respond to antibiotics, and the anaemia of a gastrointestinal haemorrhage be relieved by blood transfusion, with consequent liver cell regeneration and a return to a compensated state. If the liver cell failure is related to an acute alcoholic episode, recovery of function may follow abstinence and, in general, all patients with cirrhosis should become total abstainers. Where there is no apparent cause for the failure or when the cause has been treated, the management of the patient must be on more general lines.

Bed rest is essential, and should be continued while improvement continues. The work of Patek and his group (1941) showing the advantages of a nutritious diet in the treatment of cirrhosis was a landmark in this field. Their present regime includes a 3,500 calorie diet containing 140 gm. protein, 175 gm. fat and 365 gm. carbohydrate with 50 gm. powdered brewer's yeast (Patek et al., 1948). It may be difficult to persuade the patient to take such a liberal diet, moreover this may not be necessary. Good results are recorded with a basic caloric and protein intake, provided bed rest is emphasized and alcohol forbidden (Buck, 1948; Klatskin and Yesner, 1949). The addition of methionine and choline is said to be of value (Franklin, Salk, Steigmann and Popper, 1948; Kinsell et al., 1948) as is intravenous 'crude' liver extract (Ralli et al., 1949). These reports usually have either inadequate control groups or the controls are taken from a time when therapeutic measures such as chemotherapy and blood transfusion were not so generally available as they are at present. Moreover, excess amino acids given to a patient with active liver disease may further strain hepatic metabolism and be injurious. It is therefore difficult to assess the value of these various therapeutic agents. A reasonable regime seems to be a diet containing about 2,500 calories with 100 gm. protein. Fat need not be restricted within the caloric total. Fresh brewer's yeast, if tolerated, can be given in one dessertspoon doses stirred in milk three times a day. This provides additional first-class protein and also the vitamin B complex. Further dietetic supplements are not necessary.

Ascites modifies the treatment. Paracentesis abdominis is only palliative and results in great loss of body protein. Measures must be taken to prevent the fluid reaccumulating and of these the most helpful is the restriction of sodium chloride intake (Eisenmenger et al., 1949). A cirrhotic patient who is accumulating ascites can, by both renal and extrarenal channels, excrete only 1.5 g. sodium chloride daily. Every gram of sodium chloride taken above this amount means that 100 ml. water will be retained in the tissues. Sodium chloride intake should therefore not exceed 1 gram daily. It may be difficult to maintain the protein content of such a diet without the use of low salt content bread and low sodium milk powder. Mercurial diuretics may also be useful in the prevention of further ascites. Human salt-poor albumin infusions have been used to raise the serum colloidal osmotic pressure but are of only transitory value and untoward reactions to them have been reported (Faloon et al., 1949).

The treatment of portal venous hypertension is largely surgical and is chiefly concerned with
anastomosis of the portal and systemic venous systems. In cirrhosis there is already intrahepatic obstruction to the portal vascular bed and further diversion of portal blood into the systemic veins is not attended by any serious effects on the liver cells. Most patients with alcoholic cirrhosis have disturbed liver cell function and candidates for porto-caval anastomoses are usually found in the group of younger subjects with posthepatitis cirrhosis. In these patients normal liver cell function may exist with gross portal venous hypertension.

The treatment of bleeding oesophageal varices depends on the severity of the haemorrhage. A small oozing may stop spontaneously with or without blood transfusion. Severe haemorrhage can sometimes be checked by the introduction of a balloon into the stomach which, after inflation, is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached (Rowntree et al., 1947). Porto-caval anastomoses performed as a surgical emergency to relieve portal pressure and stop haemorrhage are fraught with considerable hazard (Linton, 1949). The injection of oesophageal varicosities through an oesophagoscope is rarely attempted nowadays. The danger of full doses of morphine to cirrhotic patients with bleeding oesophageal varicosities must again be emphasized.

I am indebted to Mr. E. V. Willmott for the microphotographs and to Miss Patricia Burrows for the diagrams.

BIBLIOGRAPHY


BEAN, W. B. (1945), Medicine, 24, 243.

BEARDWOOD, J. T., JUN., and ROUSE, G. P., JUN. (1944), Clinics, 3, 421.


DIBLE, J. H., MICHEALSON, J., and SHERLOCK, S. (1947), Gastroenterology, 9, 736.


GRAY, S. J. (1940), Arch. intern. Med., 68, 524.


MCINDOE, A. H. (1928), Arch. Path., 5, 23.


RATNOFF, O. D., and PATEK, A. J., JUN. (1942), Medicine, 21, 207.


VOLKLER, W., GRINDLAY, J. H., and BOLLMAN, J. L. (1920), Gastroenterology, 14, 40.


WILSON, S. A. K. (1923), Brain, 34, 205.

WILLS, L. J. (1947), Lancet, 2, 45.

certainly possible to improve the results of medical treatment in our present state of knowledge. First the diagnosis of ulcer should be established as early as possible after symptoms begin and thorough treatment with bed rest should be given at the onset; how rarely does one see a patient in a hospital bed with an ulcer history of less than a year? It is in this respect that our professional colleagues so often have the advantage over the hospital patient.

Secondly, the diet prescribed should be palatable; in spite of dietitians how many hospitals can be said to provide this? Moreover, some attempt should be made to instruct not only the patients themselves but also their wives in the methods of preparation of such a diet.

Finally, the social circumstances of the patient must be considered and every help given to enable him to adjust himself to the difficulties and responsibilities of his daily life.

The Editor much regrets the omission of the full caption to Fig. 11 in Dr. Sherlock's important article on 'Cirrhosis of the Liver' in our September issue. The illustration is reproduced in full on page 595 in the present issue.

ANNOTATION

The Milk Drip

Since Winkelstein (1932) first introduced the continuous alkalinized milk drip for the treatment of peptic ulcer, this method of therapy, with certain modifications, has enjoyed increasing popularity. Not only has it been widely adopted in the management of the dyspepsias, but also as a means of feeding in certain cases of injury or disease of the mouth or pharynx. In a number of conditions of nervous origin as well as in certain forms of renal disease it has proved a life-saving measure.

The basis for Winkelstein's introduction of the milk drip in the treatment of peptic ulcer rested upon his observation that night sampling of the resting gastric contents in cases of gastric and duodenal ulcer showed abnormally high curves for both free and total acid. In duodenal ulcer, especially, a high continuous curve was obtained. He subsequently showed the absence of free hydrochloric acid in such cases during milk drip treatment and concluded that the method is a logical and practical means of producing constant achlorhydria.

Subsequent experience has proved the value of Winkelstein's method of treatment, but in recent years more concentrated modified milk mixtures fulfilling calorie, vitamin and electrolyte requirements have been devised. Details of five such diets will be found elsewhere in this issue. The main advantage of these fortified milk mixtures is that a completely balanced diet can be administered in a volume of 3 or 4 pints and that patients may be fed by continuous intragastric drip for an indefinite period.

The original alkalinized milk drip had certain disadvantages, namely that it was difficult to achieve a gain in the weight without giving huge quantities; that a vitamin deficiency—especially of ascorbic acid, so important in the healing of ulcers—and an anaemia were prone to develop; and, finally, that the large intake of alkali was not without risk.

The apparatus consists of a suitable container with rubber tubing, an adjustable clip and a blood transfusion drip chamber. The clip is adjusted to deliver about 30 drops a minute. A Ryle's tube is
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Fig. 11.—The effects of obstruction to the portal venous system.

<table>
<thead>
<tr>
<th>Site of Obstruction</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Splenomegaly.</td>
</tr>
<tr>
<td>B</td>
<td>Splenomegaly, haemorrhoids.</td>
</tr>
<tr>
<td>C</td>
<td>Splenomegaly, haemorrhoids, flatulent dyspepsia, delayed water absorption from the intestines.</td>
</tr>
<tr>
<td>D</td>
<td>Splenomegaly, haemorrhoids, flatulent dyspepsia, delayed water absorption, gastric and oesophageal varices.</td>
</tr>
<tr>
<td>E</td>
<td>Splenomegaly, haemorrhoids, flatulent dyspepsia, delayed water absorption, gastric and oesophageal varices, engorgement of the anterior abdominal wall veins around the umbilicus.</td>
</tr>
</tbody>
</table>