Current Practice

DISEASE OF THE DIGESTIVE SYSTEM

Cirrhosis of the Liver

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Hepatic cirrhosis is a chronic disease which is in many cases of unknown aetiology. Diagnosis must in the end depend on the finding of evidence of the disease in liver biopsy material, though its presence can be suggested by a variety of clinical, haematological, biochemical, and radiological abnormalities that can be associated with it.

Histology of the liver in cirrhosis shows the presence of three features.

Evidence of Liver Cell Damage.—Liver cells show a variety of degenerative changes leading up to frank necrosis. The severity of this lesion is variable and alters with phases of disease, and in particular it is likely to be accelerated following stresses such as intestinal haemorrhage or systemic infection.

Fibrosis.—This is an essential finding, though the presence of fibrous tissue itself is not synonymous with the diagnosis of cirrhosis, as fibrosis of the liver without an upset of basic hepatic architecture is a feature of diseases such as congenital hepatic fibrosis, schistosomiasis, etc.

The regeneration nodule is the diagnostic feature. This "hallmark" of the disease is an area of hyperplastic liver tissue encapsulated in fibrous tissue which develops from pockets of liver cells which survive diffuse hepatic damage. Such a nodule is functionally and anatomically abnormal. In particular, the thickness of liver cell plates and the relationship of hepatic veins to portal triads is disturbed, and there is therefore a departure from the normal regular arrangement of lobules and cells to their normal blood supply.

Types of Cirrhosis

It is convenient, though somewhat artificial, to recognize two major types of cirrhosis. In portal or "septal" cirrhosis the liver is uniformly and finely cirrhotic. Alcohol is a common cause of this disorder but is not its only cause. Regeneration nodules are small, 3–4 mm. in diameter, and the resulting "fine" granularity is characteristic.

"Multilobular," "coarse," or "post-collapse" cirrhosis is associated with a lesion showing large and variably sized nodularity. Broad bands of fibrous tissue transect the liver. Though called by many a "post-hepatic" type of cirrhosis multilobular cirrhosis does not always imply previous hepatitis, and may, for example, complicate some cases of alcoholism. The liver may on occasions be very small.

Causes of Cirrhosis

The following are the accepted causes of hepatic cirrhosis, though the precise aetiological precipitant of the hepatic disorder in each case is unknown. No acceptable cause is found

in many cases; this is commonly so in Britain, where 40% or so of cases are labelled as being of unknown cause—"cryptogenic."

Infectious Hepatitis.—A very small percentage of patients with infectious hepatitis and possibly a larger percentage with serum hepatitis develop cirrhosis. The evidence for this is based on serial histological studies.¹ The incidence after infectious hepatitis must be a small fraction of 1%, and some observers feel that infectious hepatitis never gives rise to chronic liver disease. Anicteric hepatitis—in that it causes less clinical upset to the patient—might be assumed to be less important, but recent studies of this type of disease in Korea and Formosa have shown a progression to cirrhosis in some patients.

Alcohol.²—This liver poison produces liver damage in a high percentage of patients who consume it in large quantities. The number who progress to cirrhosis is, however, small (about 10%). The cause for this progression is unknown and probably genetic in origin. Malnutrition is probably not an important factor.

Active Chronic Hepatitis ("Lupoid" Hepatitis).³—This disease of unknown aetiology is associated with chronic liver cell disease. Jaundice is a usual finding, and an attack of viral hepatitis may be an important precipitating event. The end result is a multilobular cirrhosis and the positive L.E. cell phenomenon found in some patients and the multiorgan involvement present (lesions such as ulcerative colitis, skin rashes, arthralgia, lung and renal disease) suggest that an autoimmune lesion plays at least a part in its progression. This disease may be chronic viral hepatitis, but until proof is available the precise aetiology remains uncertain.

Wilson's Disease.⁴—Cirrhosis, usually of a multilobular type, is an integral part of this disease, which is usually assumed to be due to an inherited deficiency of the copper-binding protein caeruloplasmin. The actual cause of the cirrhosis is unknown, but it may be related to copper deposition.

Haemachromatosis.⁵—Cirrhosis, usually of the portal type, is found in patients with this disease. There are probably two forms. One is inherited and the patient has an increased iron absorption from birth, and the other is probably acquired in patients with alcoholic liver disease. The increased iron absorption in this latter type is due either directly to the cirrhosis or perhaps due to deficiency of pancreatic secretion secondary to chronic (alcoholic) pancreatitis.

Primary Biliary Cirrhosis.⁶—This is a rare portal type of cirrhosis probably developing as the result of a hypersensitivity injury to small bile ducts. It is therefore accompanied by evidence of chronic obstructive jaundice. It is much commoner in females than in males. A further type of biliary cirrhosis is caused by infection and stasis above a stricture of the common bile duct—secondary biliary cirrhosis.

There are certain other causes of hepatic cirrhosis, most of which are rare. Prolonged right-sided heart failure may lead to cardiac cirrhosis, particularly if there is tricuspid incompetence

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or constrictive pericarditis present. In infancy galactosaemia and certain of the glycogen storage disorders may be responsible for cirrhosis, and congenital biliary atresia is accompanied by a chronic biliary cirrhosis. Ulcerative colitis is associated with an increased incidence of cirrhosis, and an interesting series of patients have been described in which cirrhosis is familial though there is no known aetiological factor.

In this country the bulk of the cirrhotics we see have either no acceptable aetiological cause (40%) or have had previous hepatitis (30%), or are alcoholic in origin (30%). The remainder are rare enough not to be considered in such a general breakdown of cases. The part played by malnutrition in the pathogenesis of cirrhosis remains unanswerable. Certainly in Britain it is not important, and even where severe protein malnutrition is present in childhood (kwashiorkor) follow-up studies have not usually demonstrated a persisting hepatic lesion. A newer approach has concerned the possibility of food contaminants in the pathogenesis of cirrhosis, and various moulds, particularly *Aspergillus flavus*, have been implicated. A derivative of this mould has been purified and named aflatoxin. It is hepatotoxic in some animals, possibly by interfering with protein synthesis in the liver.

Presentation

Cirrhosis of the liver is commonly diagnosed either by accident at a routine medical examination or as a result of an abnormality found in some special investigation done perhaps for another purpose; or following symptoms referable to chronic liver cell disease, such as dyspepsia, or anorexia, or more specifically a haematemesis, ascites, jaundice, or hepatic encephalopathy.

Physical Signs

The physical signs in a patient with liver cirrhosis are many, and a brief referral to Fig. 1 will remind the practitioner of the various places where he must look for physical signs. It is important to examine the whole of the patient, as in no other conditions are there so many areas to be searched. The

FIG. 1.—Physical signs of cirrhosis of the liver.

detection of, for example, increased numbers of spider angiomas would lead one to a systematic search for other clues. Remember, too, that at the end of the routine clinical examination there are two further clinical points to be elicited: evidence of a hepatic "flapping" tremor of the outstretched hands, and the presence of hepatic fetor. This latter physical sign is particularly important and on occasions may be the only physical sign of hepatic cirrhosis, though of course it is really a measure of an abnormal portal circulation rather than cirrhosis per se. The detection of these latter features would also lead the clinician to inquire more carefully for evidence of the neuropsychiatric pattern of hepatic encephalopathy.

Laboratory Tests

The laboratory tests which may be affected by liver disease so that an abnormal result is obtained are given below.

Haemoglobin, White Blood Count, and E.S.R.—A normochromic anaemia with a low white count and platelet count may be the result of chronic liver cell disease with secondary "congestive" splenomegaly. A raised E.S.R. results from abnormal serum proteins.

Serum proteins are often abnormal with a low serum albumin and raised globulin (particularly γ -globulin)—though hepatic disease is not the only cause of this abnormality.

The prothrombin index may be low and the prothrombin time prolonged.

L.E. cells may be found in the blood of patients with active chronic hepatitis.

A false positive W.R. and a positive test for rheumatoid factor may result from the abnormal serum proteins.

Of the specific "liver" function tests a raised serum bilirubin, even if only to 1 mg./100 ml., can be a valuable pointer, as are elevated enzyme levels—S.G.O.T. and S.G.P.T. and a raised serum alkaline phosphatase. A 5'-nucleotidase level in the blood may help in the distinction of elevation of the alkaline phosphatase of hepatic or osseous origin. For example, in primary biliary cirrhosis both sites may be implicated.

Radiological signs pointing to a possible diagnosis of cirrhosis include splenomegaly and varices on a barium swallow examination. Occasionally a patient thought to have a gastric carcinoma will in fact turn out to have gastric varices secondary to hepatic cirrhosis. Radiological signs of malabsorption may occasionally be seen on radiological examination of the small bowel.

Confirmation of the Diagnosis

In the presence of any of these physical signs, or if the patient has any suggestive abnormality of the tests described, admission to hospital is indicated to establish the diagnosis conclusively by liver biopsy and to determine the cause of the cirrhosis and find out whether any important complications, such as oesophageal varices, liver cell failure, or hepatic encephalopathy are present.

Provided that there is no bleeding tendency and that all tests of coagulation are normal, and if precautions have been taken, the diagnosis of hepatic cirrhosis should be established by needle biopsy of the liver. Unless this is done the diagnosis will be in doubt and management of the patient will be that much more difficult. A possible alternative is diagnosis by scintiscanning, or ultrasonic scanning. Diagnosis by these means can be fairly definite and avoids the slight risk to the patient of a biopsy. The techniques are not yet available in all centres.

Apart from establishing the diagnosis it is vitally important to determine the presence of any treatable associated disease. Alcoholism is the most important, and a careful history from

the patient's relatives is a worth-while precaution. In young cirrhotics Wilson's disease must always be considered (estimation of serum caeruloplasmin and urinary or liver copper), not forgetting a careful clinical examination of the cornea for Kayser-Fleischer rings. Haemochromatosis must never be forgotten, as important cardiac complications and diabetes may occur and patients will improve in health with venesection. An estimation of the serum iron and iron binding capacity, studies of iron absorption, and estimation of liver and bone marrow iron are useful, and a differential desferrioxamine test may be particularly helpful. Primary biliary cirrhosis may be differentiated from secondary biliary cirrhosis by transhepatic

There are a number of other associated diseases in patients with cirrhosis. Peptic ulceration is thought by most observers to be increased in those with alcoholic cirrhosis and primary biliary cirrhosis. It is common, too, in those who have undergone a shunt operation, whatever the aetiology of the cirrhosis. Pulmonary tuberculosis is particularly important in the alcoholic, and failure to send ascitic fluid routinely for culture will sometimes prevent recognition of tuberculosis infection of the peritoneum. Diabetes mellitus is also important, at least, because it is common rather than difficult to control. The association of diabetes and cirrhosis must alert one to the possibility of haemochromatosis, but in fact it is not usual. Post-

FIG. 2.—Stages of development of hepatoma.

cholangiography, hepatic biopsy, and by the finding in primary cases of mitochondrial antibodies in the patient's serum. In young children galactosaemia, fibrocystic disease, and Fanconi syndrome need exclusion, as does the liver disease associated with ulcerative colitis. If no cause for the cirrhosis can be found, attention is next drawn to the presence of complications.

Complications

Portal Hypertension.—The presence of splenomegaly is suggestive and the presence of oesophageal varices is confirmatory evidence of portal hypertension. The degree of portal hypertension is not important, so that splenic pulp manometry or hepatic vein wedge catheterization is not routinely required. In patients with varices, however, portal venography is essential, as in the case of variceal haemorrhage knowledge of the patency or otherwise of the portal vein is an essential prerequisite of shunt surgery.

Liver Cell Function.—Jaundice, oedema, and ascites, and evidence of hepatic encephalopathy, all mean that a severe degree of liver failure is present. Without evidence of these one can assess liver function only by ancillary tests. A low serum albumin is still the best simple test of the state of liver cell function, but is not a specific test. An E.E.G. after protein loading may help to detect subclinical hepatic encephalopathy. In patients with well-compensated hepatic cirrhosis the diagnosis may rest on biopsy alone, and sensitive tests such as those of bromsulphalein metabolism may then be needed to detect a slight degree of impaired liver cell function. Activity of the hepatic lesion is suggested by the existence of pyrexia, the presence of jaundice, and elevated S.G.O.T. or S.G.P.T. (>100 units) levels in the serum. Biopsy evidence of activity is suggested by evidence of liver cell destruction and a heavy mononuclear cellular infiltrate in the portal tracts.

shunt diabetes is a disorder which has been recorded, and, though rare, it is important to remember that after a shunt operation the cirrhotic can present in diabetic rather than hepatic coma. Strong intravenous glucose solutions with neomycin are then inappropriate.

The last disorder on which I wish to comment is hepatoma. Though it is often multifocal and thus not amenable to surgery, a constant suspicion of its possible presence and early diagnosis are vital if treatment is ever to be feasible. The ways in which it does present are shown in Fig. 2. If a patient with a known cirrhosis deteriorates or develops abdominal pain the cause is a hepatoma until proved otherwise. About 20% of cirrhotic patients in this country will develop this complication.

Treatment of Cirrhosis

Treatment of Liver Cell Disease

The conventional treatment for uncomplicated cirrhosis is a high calorie, high protein diet, and the beneficial results originally obtained by Patek⁷ and his colleagues are often quoted in this context. Though it is probably impossible to improve liver function significantly by dietary means this is more likely to be successful in the alcoholic, particularly if one is able to stop the patient drinking as well. Severe liver cell dysfunction as seen in patients with chronic active hepatitis responds to steroid therapy, though there has been considerable discussion whether this is really a beneficial effect on the sick liver cell itself or merely a non-specific effect on bilirubin metabolism. It seems likely from studies of bromsulphalein metabolism that a real improvement results from steroid therapy, but there is no evidence to suggest that other types of liver disease are benefited. There seems in fact to be no long-term therapy that will improve liver function, though claims have been made for testosterone, corticosteroids,

and tolbutamide. In primary biliary cirrhosis, and possibly in some patients with chronic active hepatitis, there may be an indication for the use of immunosuppressive drugs, but great care must be taken in supervision of this type of therapy.

Oedema

Though little can be done for the sick liver cell, the resultant effects of fluid retention can be controlled in the vast majority of cases by modern diuretic therapy. There is no doubt that the introduction of potent oral diuretics was the turning-point, and it is now rare to see patients attending for repeated tapping of ascites. One might imagine as a result of this that the outlook for the patient with ascites has improved. This is far less certain, and it seems that control of ascites is merely one facet of liver failure and control is unlikely to be of lasting benefit. It is, however, equally noticeable that the removal of fluid by a successful diuretic regimen brings about a dramatic improvement in the patient's well-being, a return of strength, and disappearance of cachexia. It must be remembered that the cirrhotic patient with chronic ascites developing without a precipitating factor needs stringent sodium restriction, dietary potassium supplements, and the use of various types of diuretics, often in combination, in order to achieve a diuresis. Cirrhotics retain fluid more avidly than other groups of patients with oedema, and initial treatment in hospital is usually desirable. Most patients with chronic fluid retention need a low sodium diet, a potent oral diuretic such as chlorothiazide or frusemide, often with an aldosterone antagonist. Potassium supplements are vital; the patient with chronic liver cell disease is particularly prone to potassium depletion, which in turn often presents clinically as hepatic precoma or coma.

Infusions of human salt-free albumin may have a temporary beneficial effect, but there is no value in their long-term use.

Haemorrhage from Varices⁸

The cause of variceal rupture is unknown. Bleeding may follow the taking of aspirin or a respiratory infection or have no apparent cause. Not uncommonly it may occur for the first time in a patient being treated in hospital for liver-cell failure such as ascites. Often it has no apparent precipitant, but it is a serious complication, carrying a mortality for the first bleed of about 25%. Treatment is directed at replacing the blood volume, the stoppage of bleeding from the ruptured varix, and the prevention of dangerous complications—particularly hepatic encephalopathy.⁸

Unfortunately, it is quite usual for bleeding to occur in bouts, and though bleeding may cease it commonly recommences, particularly in patients with poor liver cell function. Confronted with such a case it is important to confirm that bleeding is from varices and also to decide if the patient needs or is fit enough for surgery. If bleeding ceases, most surgeons favour an elective portacaval anastomosis, provided the patient has reasonable liver function and is not too elderly. The reason for caution is related to the high postoperative incidence of liver failure, and in particular of hepatic encephalopathy. If bleeding does not cease and the patient is fit for surgery, then most would favour a direct surgical attack on the varices (oesophageal transection) rather than an emergency portacaval anastomosis, which carries a high mortality. The operation of oesophageal transection and varix ligation may succeed in controlling haemorrhage, or it may be necessary if liver function improves to perform an elective portacaval anastomosis at a later date. Injection of sclerosing solutions into and around oesophageal varices is a possible alternative as a "holding" procedure, and, of course, it carries a much lower mortality than formal surgery. It is, however, a less certain method for guaranteeing a cessation of bleeding.

Hepatic Encephalopathy

Signs and symptoms suggestive of hepatic encephalopathy (hepatic flap and fetor, confusion, drowsiness, and stupor) are likely to follow the use of diuretic and sedative drugs, alimentary bleeding, a high protein intake, or infection. They are a signal for the cessation of all oral protein and the administration of a broad spectrum nonabsorbable antibiotic such as neomycin. They are a signal, too, for an energetic search for a cause of the condition, and serum electrolyte estimations (hypokalaemia), blood cultures, chest x-ray, and urine cultures (infection) are all required. In chronic cases of encephalopathy, found particularly in patients who have survived a portacaval anastomosis, other therapeutic measures have been used with variable success, and in particular surgical colonic bypass has been suggested as an alternative to chronic protein restriction and long-term neomycin.

Prognosis

The outlook for the patient with cirrhosis is reasonable, provided liver cell function is adequate and bleeding from oesophageal varices does not occur. Hepatoma is, of course, an ever-present threat. Once evidence of hepatic decompensation has appeared the prognosis is poor. In a recent study of our own cases the two-year mortality after the onset of hepatic failure was over 50%. Though new methods of treating liver cell failure are constantly being suggested, there is little doubt that the basis of the disease is a sick liver, and only replacement of the sick liver cell by a healthy one is likely to have a long-lasting effect. Whether hepatic transplant will be the answer is difficult to know. The patient with decompensated cirrhosis is a bad surgical risk, particularly for the major procedure of organ transplant. Further, unlike chronic renal failure, there is no way of bringing about an improvement in the patient's condition before operation, there being no equivalent of chronic dialysis treatment as for the uraemic subject. It will require very fine judgement to say who is fit enough for organ transplant yet bad enough to justify it.

Further studies to elucidate the cause of the disease are urgently required, too, so that adequate preventive measures can be taken.

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