THE RELATIVE IMPORTANCE OF VARIOUS CLINICAL FEATURES IN THE DIAGNOSIS OF CIRRHOSIS OF THE LIVER IN ZAMBIA

DR JAGDISH S. PATEL

BSc,MBChB

This dissertation was submitted for the Master of Medicine (M.Med) degree in Internal Medicine, University of Zambia.

November 1985.

CONTENTS

INTRODUCTION

Cirrhosis of the liver is best defined in morphological terms, but in spite of many attempts, discrepancies prevail between different authors. The standard nomenclature which is recommended by the International Association for the Study of Liver (1), outlines a rather lengthy explanation of what should be regarded as cirrhosis of the liver. A simple definition is adopted by the World Health Organisation (W.H.O.). It is defined as " a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules "(2).

Cirrhosis is a worldwide disease of increasing importance, and it is a common cause of morbidity and mortality. In the United Kingdom, it accounts for more than 1500 deaths each year, and in the United States, it has been found to be the third leading cause of death in urban males (3). In Africa, the exact incidence is not known, although it is believed to be common.

AETIOLOGY (Table A)

Hepatic cirrhosis is a chronic irreversible condition, the end result of many different causes.

Table A. CAUSES OF CIRRHOSIS

A. Infections

- Viral hepatitis
- Brucellosis
- Congenital syphillis

B. Drugs/Toxins

- Alcohol
- Methotrexate
- Oxyphenacitin
- Monoamine oxidase inhibitors
- Halothane
- Mycotoxins or plant poisons

C. Biliary obstruction

- Primary biliary cirrhosis
- Secondary biliary cirrhosis
  - a. stones
  - b. strictures
  - c. neoplasms
  - d. biliary atresia
  - e. choledochal cyst
  - f. Caroli's syndrome

D. Hepatic congestion

Budd-Chiari syndrome

Veno-occlusive disease

Cardiac failure

E. Metabolic disorders

Haemochromatosis : primary

: secondary

Wilson's disease

Alpha 1 -antitrysin deficiency

Fibrocystic disease

Galactosaemia

Glycogen storage disease

Tyrosinosis

Fructose intolerance

Abeta-lipoprotienaemia

Lipoatrophic diabetes

F. Nutritional

Intestinal bypass for obesity

G. Granulomatous disease

Sarcoidosis

H. Inflammation

Cryptogenic cirrhosis

Chronic active hepatitis

Indian childhood cirrhosis

I. Other

Hereditary haemorrhagic telangiectasia

Alcoholism is tne primary cause throughout Europe and the United States, and accounts for between half and two thirds of all cases of cirrhosis (4-7). Various epidemiological studies relate the incidence of cirrhosis to the per capita consumption of alcohol, and it has also been noted that countries with the greatest alcohol consumption also have the greatest incidence of cirrhosis. It is well documented that daily ethanol consumption exceeding 80 grams for ten years or more is associated with an increased incidence of cirrhosis (5). On the other hand, cirrhosis develops in only 10 to 30 per cent of chronic alcoholics (8). ; this is consistent with the notion that genetic, nutritional or other factors play a role in the pathogenesis of alcohol induced cirrhosis.

In contrast, it has been found that in tropical and subtropical countries, viral hepatitis has been implicated as the most common cause of cirrhosis (3,9,10,). Both hepatitis B, and the Non A Non B post transfusion hepatitis commonly progress to chronic liver disease. A useful serum marker of hepatitis B infection is the Hepatitis B surface antigen (HBsAg), which is commonly used to screen acute and chronic

Hepatitis B virus induced liver disease. The geographical variation in the incidence of HBsAg is however considerable, and it has also been demonstrated in seemingly healthy individuals. In the United States and other western countries, less than 1 per cent of the general population are HBsAg positive, whereas in Africa figures include 3.6% in Zimbabwe (11), 5.5% in Tanzania (12), 6.6% in Kenya (13), and 3.3% in Iraq (9). In Zambia, Gill (14), reports an incidence of 5% in the general population as compared to a frequency of 3.1% amongst health workers in Zambia (15). This may relate to the role of 'vertical transmission' (acquisition of hepatitis B virus from an infected mother to her newborn child), and 'horizontal transmission' (the transmission of hepatitis B virus infection among family members and other contacts) of the virus, which results in a high frequency of chronic hepatitis B virus infection states (16,17), and appears to contribute to the developement of cirrhosis (18,19).

In view of the high incidence of HBsAg in developing countries, it is not surprising that viral hepatitis is reported to be a common aetiological factor of cirrhosis in these areas. However, it must be noted

that most authors attribute the aetiology of cirrhosis in Africa to 'multiple factors'. Alcohol abuse, chronic viral infections, and various toxic dietery factors (including herbal remedies), may all be related to an immunocompromised state resulting in greater susceptibility towards the later developement of cirrhosis (20-24).

No cause is found in up to 30% of cases (Cryptogenic cirrhosis). Haemochromatosis accounts for about 5% of patients. Both Primary (Idiopathic) and Secondary (Acquired) haemochromatosis are established causes of cirrhosis. The latter is more important in Southern Africa, where "traditional alcohol", which is brewed in iron pots results in heavy daily iron consumption; this results in the known association between cirrhosis and siderosis in Black patients (25). Malnutrition is no longer considered to be primarily responsible for cirrhosis, although many patients with cirrhosis are malnourished. However, it is worthwhile to note that nutritional deficiencies may well be important in the 1-3% of patients who develop cirrhosis after an intestinal bypass operation for obesity (26,27). Other causes of hepatic cirrhosis which are rare in Africa, are outlined in Table A.

PATHOLOGY AND CLASSIFICATION

Previous classifications , based on a mixture of pathogenesis, morphological appearance, aetiology, and eponyms are confusing and undesirable. The lack of any relation between the cause of cirrhosis and its histological appearance, and the wide variety of histological appearances during the course of the disease limits both morphological and aetiological classifications. Currently, a simple anatomical classification (1), based on minimal criteria, and which lends itself to morphological statistical analysis, is recommended (28-30).

1. Micronodular cirrhosis is characterized by nodules of equal size, up to 3mm in diameter, asociated with septa up to 2mm in diameter, and of equal width. Many examples of cirrhosis associated with alcoholism, biliary obstruction, venous outflow obstruction, haemochromatosis, and Indian childhood cirrhosis, fall into this category.

2. Macronodular cirrhosis. Many nodules are more than 3mm in size, and some nodules up to 3cm in diameter are observed. The septa are irregular and vary in width and are often broad. Most cases of post necrotic and post hepatitic cirrhosis fall into this pattern.

PATHOLOGY AND CLASSIFICATION

Previous classifications , based on a mixture of pathogenesis, morphological appearance, aetiology, and eponyms are confusing and undesirable. The lack of any relation between the cause of cirrhosis and its histological appearance, and the wide variety of histological appearances during the course of the disease limits both morphological and aetiological classifications. Currently, a simple anatomical classification (1), based on minimal criteria, and which lends itself to morphological statistical analysis, is recommended (28-30).

1. Micronodular cirrhosis is characterized by nodules of equal size, up to 3mm in diameter, asociated with septa up to 2mm in diameter, and of equal width. Many examples of cirrhosis associated with alcoholism, biliary obstruction, venous outflow obstruction, haemochromatosis, and Indian childhood cirrhosis, fall into this category.

2. Macronodular cirrhosis. Many nodules are more than 3mm in size, and some nodules up to 3cm in diameter are observed. The septa are irregular and vary in width and are often broad. Most cases of post necrotic and post hepatitic cirrhosis fall into this pattern.

3. Mixed macronodular and micronodular cirrhosis

This term is applied to cases where micro and macronodules are present in approximately equal proportion.

This classification is simple, easily understood, and can be applied both at macroscopic and microscopic level. However, from the clinician's point of view, this classification is of little value, apart from epidemiological studies. Cirrhosis is more readily related to aetiology and the degree of functional disturbances; treatment and prognosis are related to clinical, biochemical, and immunological criteria.

Despite an extensive review by Popper H (8), on the pathogenesis of cirrhosis, many questions remain unanswered. While most cases of cirrhosis usually develop slowly and insidiously, occasionally the transition may be rapid, in some cases as short as five months (31). It is clear that the common initiating agent is liver cell necrosis. Hepatocellular injury, caused either directly by

toxins such as alcohol, or as a result of an inflammatory reaction mediated by an aetiological agent, leads to liver cell necrosis and death; this results in the collapse of the liver reticular framework. Regeneration of liver cells in the absence of an intact framework, results in the formation of nodules. Fibrogenesis, which occurs around damaged hepatocytes, causes further distortion of the normal liver architecture.

In cirrhosis of the liver it is important to note that the whole process is diffuse. Focal lesions do not constitute cirrhosis. The fibrosis is generalized, but variable in extent and distribution; this results in portal systemic vascular shunts, through involvement of the centrilobular areas linking portal tracts. The parenchymal nodules lack normal lobular organization, and are surrounded by fibrous tissue. Fibrosis is not synonymous with cirrhosis; similarly nodule formation without fibrosis is not cirrhosis.

CLINICAL FEATURES

The clinical presentation of cirrhosis of the liver has been extensively reviewed in western literature. Although many clinical abnormalities are noted in cirrhosis, it can present as an incidental finding at autopsy, or operation (7,32).

The age and sex distribution of cirrhosis is related to the cause. Primary biliary cirrhosis and chronic active hepatitis occurs more frequently in women. Alcoholism and haemochromatosis are more common in males. The majority of patients present between the ages of 40 and 70 years. Neonatal hepatitis and congenital causes are seen in infancy and childhood. Hepatomegaly is more common in the early stages of the disease; this later regresses in the face of hepatocyte destruction and continiuing fibrosis. Initially the general health and nutritional status is maintained. As the disease progresses, the patient may complain of weakness, weight loss, and fatigue. Non specific gastrointestinal symptoms, such as anorexia, nausea, vomiting, flatulence dyspepsia and upper abdominal discomfort may occur. Otherwise clinical features are related to the two main complications of cirrhosis: portal hypertension and hepatocellular insufficiency, or a combination of both.

A. Portal hypertension

a. Splenomegaly. This usually indicates portal hypertension. Enlargement of the spleen occurs in up to 50% of all cases of cirrhosis, but is seldom enlarged grossly in adults. This contrasts with cases of cirrhosis in Africa, where it lists as a major cause of gross splenomegaly (33,34).

b. Haematological changes. Moderate leucopenia and thrombocytopenia, secondary to hypersplenism is common. Factors such as haemodilution, hypersplenism, mild haemolysis, a depressed bone marrow, and nutritional deficiency all relate to the mild hypochromic, or normochromic anaemia, which occurs at some time in all cirrhotic patients (35).

c. Collateral circulation, secondary to portal hypertension, may result in gastro-oesophageal varices, haemorrhoids, and abdominal wall collaterals. Abdominal wall collaterals radiate from the umbilicus, and when prominent, they are referred to as "caput medusae". Bleeding from gastro-oesophageal varices is common, and in some patients haematemesis and/or malaena, may be the initial presenting symptoms.

d. Ascites. Cirrhosis is one of the commonest causes of ascites. Ascites, however is not due solely to portal hypertension. In cirrhosis, albumin

synthesis is diminished, resulting in hypoalbuminaemia, and a lowered colloid osmotic pressure. Retention of salt and water, secondary to diminished renal blood flow, and secondary aldosteronism, and portal hypertension plus lymphatic outflow obstruction in the cirrhotic liver, all attribute to the localization of fluid in the peritoneal cavity.

B. Hepatic insufficiency

a Jaundice. This is generally mild, and results from failure of bilirubin metabolism, and also partly due to intra hepatic cholestasis.

b Circulatory changes. Palmar erythema, finger clubbing, and vascular spiders, are all features of the peripheral and pulmonary vascular and haemodynamic changes which occurs in cirrhosis (36). Vascular spiders (spider naevi) are usually seen on the upper half of the body. These lesions comprise of a central spiral arteriole, with a variable number of radiating capillaries. Vascular spiders also occur during pregnancy, and are also seen in a few healthy individuals. All these features are rare in the African patient (37,38). Hypertension is unusual, but does occur with more frequency in cirrhosis (32). Hypoxia is common in cirrhosis, and may result in cyanosis.

c. Endocrine abnormalities. Gynaecomastia, due to hypertrophy of the glandular elements of the breast occurs commonly in alcohol related cirrhosis. It is the most striking feature of feminization, and together with hypogonadism, are the most frequently encountered endocrine abnormalities (39,40). Loss of libido occurs in both sexes, and there is impotence and testicular atrophy in the male. Women usually have amenorrhea and irregular menses, and are frequently infertile. Other features include reduction of body hair, and the lack of beard growth. The reason for hypogonadism has been extensively studied; no generally recognized mechanism has been established , and earlier reports citing the importance of serum oestrogen-progesterone imbalance, have been disputed (41).

d. Hepatic (portal-systemic) encephalopathy. The symptoms of hepatic encephalopathy are attributable to both hepatic failure and portal hypertension. Nitrogenous substances, which are absorbed from the gut, and normally detoxified in the liver, tend to reach the systemic circulation, thereby resulting in encephalopathy. Features of hepatic encephalopathy include changes in intellect, emotions, personality, and conciousness. Deterioration leads to drowsiness, stupor, and eventually coma. Examination usually reveals a flapping tremor(asterixis), sometimes

hyperreflexia, an extensor plantar response, and fetor hepaticus.

Other manifestations

1. Low grade fever in the absence of infection is seen in a third of cirrhotics.
2. Generalized hyperpigmentation, due to increased melanin deposition in the skin, is seen in all forms of cirrhosis, but most marked in haemochromatosis.
3. Dupuytren's contracture is associated with alcoholic cirrhosis, but it is also sometimes seen in the normal population.
4. Parotid enlargement occurs in some cases of alcohol related cirrhosis, but it is also seen in Sjogren's syndrome, diabetes mellitus, and malnutrition.
5. Haemorrhagic tendencies, secondary to decreased coagulation factors which are normally produced in the liver, can result in easy bruising and epistaxis.
6. Steatorrhea in the absence of pancreatitis, is more frequent.
7. Eye signs. Lid lag and lid retraction ~~is~~ may be seen in cases of cirrhosis (42).

Associated conditions

1. Diabetes mellitus. Impaired glucose tolerance is observed in up to three quarters of cirrhotic patients, and overt diabetes is two to four times more frequent than in the normal population (43).

2. Cholelithiasis. The frequency of gall stones is increased in cases of cirrhosis (44,45).

3. Abdominal hernias are more frequent in cirrhotics (46), and especially common in patients with ascites.

4. Peptic ulcers are said to be more common in association with cirrhosis, but this has been questioned (47,48).

5. Malnutrition is common in all forms of cirrhosis, and especially in alcoholic cirrhosis. This is attributed to inadequate food intake, malabsorption, and an impaired hepatic metabolic capacity (35).

6. Infections. Patients with cirrhosis of the liver are generally more susceptible to infections. There is an increased frequency of tuberculosis and spontaneous bacterial peritonitis in cirrhotics.

7. Multisystem disease. Chronic active hepatitis, cryptogenic cirrhosis, and primary biliary cirrhosis, are regarded as autoimmune diseases (49); they have certain immunological abnormalities, and can present as multisystem diseases. All three liver diseases can have high titres of autoantibodies, specifically the antinuclear antibody, smooth muscle antibody, antimitochondrial antibody, and the microsomal antibody (50).

INVESTIGATIONS

1. Liver function tests

None, any, or all routine liver function tests may be abnormal in cirrhosis. They only reflect the presence or extent of hepatocellular damage, rather than cirrhosis per se. Liver function tests can however act as pointers to the disease. They must be veiwed with caution, as the abnormalities are minimum, and in some cases, may be normal in spite of cirrhosis. Although increased serum transaminase activity is a sensitive index of liver damage, it has limited diagnostic or prognostic value. The serum glutamic pyruvic transaminase (SGPT) is more elevated than serum glutamic oxaloacetic transaminase (SGOT), although both enzymes can be mildly raised. A prolonged prothrombin time and a low serum albumin concentration are good indices of hepatic dysfunction, and relate well to prognosis. The serum alkaline phosphatase is moderately elevated, though very rarely more then 300 iu/l, this being noted in cholestatic liver disease and primary biliary cirrhosis.

2. IMAGING

Scintiscanning may show abnormal uptake of isotope by the liver, and an increased uptake by the bone marrow and the spleen. These changes are highly suggestive of advanced cirrhosis, although similar changes have been noted in liver tumours, cysts, or abscesses, as well as acute and chronic hepatitis, and hepatic congestion (51,52). Ultrasonography and Computed Tomography are not particularly useful in establishing a diagnosis of cirrhosis.

3. LIVER BIOPSY

Although cirrhosis may be strongly suspected on clinical grounds, the ultimate proof of diagnosis can only be obtained by a liver biopsy. The value of percutaneous liver biopsy remains controversial, and false negative results ranging from 4 to 80 per cent have been reported (53-55). Since the needle biopsy offers examination of perhaps a hundred thousanth of a rather large organ, sampling errors are inevitable. Some authors advocate the use of laparoscopy with guided biopsy to obtain more accurate results (56,57). The rare but possible complications of liver biopsy, such as haemorrhage and biliary peritonitis must also be borne in mind.

Morbidity rates ranging from 0.12 -2.5 percent, and mortality rates as high as 0.6 per cent have been reported (58-60).

In view of all these factors, it must be considered whether a liver biopsy is justified in all cases; especially when a likely aetiological agent such as alcohol abuse, or the presence of the HBsAg in the blood, together with several clinical and biochemical features and a liver scan are compatible with the diagnosis of cirrhosis (61).

4. OTHER INVESTIGATIONS

These can help determine the cause of cirrhosis.

Of particular importance are :

a. Hepatitis B surface antigen

b. Detection of autoantibodies

c. Alpha1-antitrypsin

d. Serum and liver iron estimations

e. Serum copper and ceruloplasmin estimations

DIAGNOSIS

Cirrhosis of the liver is a histological diagnosis. There is no single presenting feature, or investigation which is diagnostic, apart from a liver biopsy. however, those cases which present with late (decompensated) features of cirrhosis (see Material and Methods, 1a), can be reliably diagnosed on clinical features and biochemical abnormalities alone, pending liver biopsy.

Classical features such as florid spider naevi, gynaecomastia, palmar erythema, and Dupuytrens contracture, are important diagnostic pointers, and are commonly seen in cases of alcohol related cirrhosis (32).

Also, in contrast to the western countries, where cirrhosis is the leading diagnosis in patients presenting with late features such as ascites and bleeding oesophagial varices, there are certain tropical diseases which mimic the clinical presentation of cirrhosis. These include chronic malaria, and schistosomal splenomegaly.

Tropical splenomegaly syndrome (T.S.S.) is characterized by splenomegaly associated with anaemia, and sometimes thrombocytopenia, a relative or absolute lymphocytosis, and sinusiodal lymphocytosis in the liver. It is postulated that these features are a consequence of an abnormal response to malaria. Lowenthal et al (34), in his article on 'Massive splenomegaly in Northern Zambia' noted that T.S.S. is a common cause in Zambia accounting for over 35% of cases. He also noted a similar pattern in other East and West African countries. In the same article he noted that cirrhosis of the liver was a common cause of massive splenomegaly, and accounted for 31/344 (9%) of all cases analysed.

Schistosomiasis is the major cause of liver disease and portal hypertension in the tropics (62). In comparision, alcohol related cirrhosis is the most common cause of portal hypertension in the western countries, accounting for up to 70% of cases (63). Although hepatic schistosomiasis is especially common in Egypt (64), and Brazil (65), this holds true for East and Central African countries also (33,66,67).

COMPLICATIONS AND PROGNOSIS

The main complications of cirrhosis of the liver; portal hypertension, hepatic failure, and hepatocellular carcinoma, are responsible for the gloomy figures for survival.

Portal hypertension

Cirrhosis of the liver is the major cause of intrahepatic portal hypertension (35); approximately 60% of patients with cirrhosis have varices (68). Upper gastrointestinal bleeding is a prominent presenting feature in these cases, and carries a high mortality rate. Approximately 30-40% of patients will die during the first episode of bleeding (69). However, the severity of underlying hepatocellular disease determines the prognosis in the patient, and it is well documented that survival figures are better in cases of cirrhosis with portal hypertension who have less advanced disease (70).

Hepatic failure

Hepatic failure as a result of cirrhosis carries a grave patient prognosis. Features of active (decompensated) liver disease relates well to the general overall survival. Outlook is poor if the patient has ascites, deepening jaundice, and features of hepatic encephalopathy. A rising serum bilirubin level, hypoalbuminaemia, and a prolonged prothrombin time which is uncorrectable by vitamin K, are biochemical indices of poor prognosis.

Hepatocellular carcinoma

The known associatin of hepatocellular carcinoma and liver cirrhosis has been documented worldwide; over 75% of cases arise as a result of long standing cirrhosis (71-74). Any cause of cirrhosis may be associated with malignant transformation. In western countries, alcoholic cirrhosis is most commonly associated (75,76), whereas in developing countries with high incidences of hepatocellular carcinoma, the related cirrhosis is almost always of the macronodular variety, related more frequently to chronic hepatitis B virus infection (77,78). Hepatocellular carcinoma is one of the more malignant tumours of the world and carries a grave prognosis. Survival time in patients is generally less than seven months (71,73); this period is often shorter in Africans (79).

Overall figures for survival in cirrhosis are gloomy. Stone et al (80) reports a 14% 5 year survival rate in cirrhosis. Twenty percent of patients presenting with ascites are alive after 5 years, while a similar proportion manage to survive only one year after variceal haemorrage (7). Powell et al (32), reports similar survival rates.

OBJECTIVES OF THE STUDY

1. TO EVALUATE THE SIGNIFICANCE OF CERTAIN CLINICAL AND BIOCHEMICAL ABNORMALITIES IN PREDICTING THE DIAGNOSIS OF CIRRHOSIS OF THE LIVER IN INDIGENOUS ZAMBIAN PATIENTS PRESENTING AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA.

2. TO DETERMINE THE INCIDENCE OF HEPATITIS B SURFACE ANTIGEN IN CASES OF CIRRHOSIS.

MATERIAL AND METHODS

1. Indegenous adult Zambian patients, aged sixteen years and above, who were admitted to the medical wards at the University Teaching Hospital, Lusaka, between 1st July 1984 and 30th June 1985, and who satisfied predefined selection criteria for cirrhosis of the liver, were initially admitted into the study.

a. Predefined selection criteria for liver cirrhosis

Cirrhosis of the liver is by definition a histopathological diagnosis. Predefined selection criteria were based on the clinical features of either latent (well compensated) or active (decompensated) cirrhosis (81).

Latent features:

mild pyrexia.

vascular spiders.

palmar erythema.

ankle oedema.

hepatomegaly and/or splenomegaly.

dyspeptic symptoms.

Decompensated features:

jaundice.

ascites.

abdominal wall collaterals.

gynaecomastia / gonadal atrophy.

fetor hepaticus / asterixis.

b. Exclusion of cases

Because none of the features mentioned above, are specific for cirrhosis, this selection criteria is also applicable to a large and varied range of different diseases. Therefore only those patients with one or more prominent features, and in whom a diagnosis of cirrhosis could not be excluded, were included in this study. Patients with features related to renal or cardiac disease were specifically excluded; as were cases of viral hepatitis, malaria, and other acute infections.

2. History. All cases were interviewed personally. A detailed history was taken, and the following parameters recorded:

-Age of the patient.

-Sex of the patient.

-Occupational history (past and present).

-Area of residence (detailing from childhood).

-Presenting complaints and duration.

-Associated symptoms and duration.

abdominal pain	jaundice
anorexia	oedema
nausea	pyrexia
vomiting	loss of libido
weight loss	encephalopathy
weakness	bleeding episodes
abdominal distension	others

-Past history of a, jaundice.

b, hepatitis.

c, blood transfusion.

d, scarifications.

-Past admissions and associated illnesses.

-Drug therapy.

-Dietary history.

-Alcohol history.

a. Alcohol consumption pattern

Every effort was made to obtain an accurate assessment of alcohol intake. Apart from the available commercial alcohol beverages, "traditional home made alcohol" has always proved to be popular amongst the local population. Two types of brews are available. The "local brew" which goes by the name of 'seven days', 'mowa', 'mbamba', etc, is brewed in iron pots. On the other hand, the "distilled brew", ('kachasu'), takes longer to prepare, and has a higher alcohol content. The local brew and the commercial "opaque beer" (kwown as 'chibuku'), are consumed in 2.5 or 5 litre tins, usually in group sittings.

The following types of alcoholic beverages are consumed in Zambia. The absolute alcohol contents are as estimated by Reily et al (82).

Type	Alcohol content %
Beer	4%
Spirits	40%
Wines	12%
Opaque beer	3%
Local home brews	3%
Distilled brews	20%

A reasonable estimate of the mean daily consumption of alcohol was obtained. Only alcohol intake for more than TEN years was considered significant. Alcohol consumption was verified by relatives whenever possible, and consumption patterns during times of other illnesses, drought, special occasion, etc, was taken into consideration.

Alcohol consumers were graded according to the daily intake of absolute ethanol (expressed in grams).

GRADE A: Moderate alcohol intake. (25-75 grams)

GRADE B: Heavy alcohol intake. (76-125 grams)

GRADE C: Very heavy alcohol intake. (more than 126 grams daily)

3.Physical examination.All the patients underwent a full physical examination; the following physical findings were recorded.

a. General examination.

.pallor

.jaundice

.oedema

.pyrexia

.pigmentation

.finger clubbing

.Dupuytrens contracture

.spider naevi

.parotid enlargement

.palmar erythema

.white nails

.gynaecomastia

.testicular atrophy

.axillary hair

b. Systemic examination.

Gastro-intestinal tract. hepatomegaly

splenomegaly

ascites

abd wall collaterals

haemorrhoids

Abnormalities of:- Cardiovascular system.

- Respiratory system.

- Central nervous system.

4. Haematological studies. Routine haematological parameters were ~~obtained~~ done from the haematology laboratory (U.T.H.), which uses the coulter counter method (Coulter electronics Inc. U.S.A.). The erythrocyte sedimentation rate (ESR) was estimated using the Westergren method. Citrated blood was used to estimate the prothrombin time.

5.Biochemical studies. All biochemical parameters were analyzed using the Autoanalyzer (Coultronics France SA.).

6. Parasitological studies. Routine urinanalysis using the Multistix (Ames) method was carried out in all patients on admission. A microscopic examination was also undertaken in the ward laboratory. Stool examination was done routinely on admission using the KATO concentration technique. Fatients who had a prolonged stay in hospital had repeat stools examination weekly. A rectal snip was done on all patients, and examined for Schistosoma mansoni ova.

7.Radiological studies.A chest X ray and barium swallow ~~was~~ were undertaken in selected case.

8. Histological diagnosis. A blind needle liver biopsy, using the Menghini technique (83), was employed in those cases suitable for the procedure. The procedure was fully explained to the patient and a written consent obtained.

Contraindications to liver biopsy/exclusion of cases

a. Moderate ascites, not resolving with adequate therapy.

b. Patients with sepsis or fever.

c. Deep jaundice.

d. An absolute platelet count of less than 80,000/mm.

e. A one stage prothrombin time of less than 80%.

f. No consent.

The liver biopsy specimens were fixed in 10% formal saline, and processed in the Department of Pathology, University Teaching Hospital. All slides were reviewed personally, under supervision of the pathologist on call. A senior opinion was sought whenever there was any difficulty in interpretation of the biopsy specimen.

Did their pathologists change at any time

9. Presence of Hepatitis B surface antigen (HBsAg).

Sera was obtained from all cases and stored at minus 20 degrees Celcius, for the purpose of screening for HBsAg. In addition, samples of sera were obtained from healthy blood donors (with no previous history of jaundice, hepatitis, or previous blood transfusions), for the purpose of controls. All sera obtained was tested by the passive haemmaglutination technique using the Hepatest-3 screening kit for HBsAg(Wellcome Reagents Ltd).

10. THE FOLLOWING PARAMETERS WERE USED TO PREDICT A MORPHOLOGICAL DIAGNOSIS OF CIRRHOSIS OF THE LIVER:

1. Age of the patient
2. Sex of the patient
3. Presenting features
4. Grade of alcohol intake
5. The presence of ascites
6. The presence of hepatomegaly and/or splenomegaly
7. Haemoglobin and absolute platelet count estimation
8. Serum albumin and globulin (expressed in g/l)nd
9. Serum bilirubin (umol/l)
10. Serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase (Iu/l)
11. Prothrombin index (%)
12. The presence of Hepatitis B surface antigen

RESULTS

A total of 64 cases, aged between 19-70 years were initially included in the study. Of the twenty four patients who underwent a blind needle liver biopsy, only six were confirmed as cirrhosis of the liver on histology. Twenty eight cases were unsuitable for liver biopsy due to various reasons (low platelet count in 14 cases, tense ascites in 2 cases, no consent for procedure in 8 cases, 2 patients absconded, and liver biopsy was witheld in 2 cases due to their poor general condition). There were two cases of chronic myeloid leukaemia, diagnosed on peripheral blood smear and confirmatory bone marrow. The remaining ten cases, with ascites as the presenting feature, were diagnosed as cases of abdominal tuberculosis on further investigations. In view of the very small number of proven cases of cirrhosis of the liver, it was decided that a comparative study would be more useful.

The patients were grouped in different categories, based on histological diagnosis. It was also decided to include those patients with chronic leukaemia and abdominal tuberculosis for comparision, since they also satisfied the predefined selection criteria. A total of eight categories were defined (Table 1).

For the purpose of tabulation, the following abbreviations for each of the eight categories is outlined below.

1. Cirrhosis of the liver	: CIRRHOSIS
2. Tropical splenomegaly syndrome	: T.S.S.
3. Schistosomal splenomegaly	: SCHISTOSOMIASIS
4. Hepatocellular carcinoma	: HEPATOMA
5. Haemochromatosis	: SIDEROSIS
6. Normal liver biopsy	: NORMAL BIOPSY
7. Abdominal tuberculosis.	: TB ABDOMEN
8. Chronic myeloid leukaemia	: C.M.L.

Table 1. Age and sex distribution

	No of cases(%)	Males	Females	Mean age
CIRRHOSIS	6 (16.6)	6	0	52.3 (40-62)
T.S.S.	5 (13.9)	4	1	36 (19-60)
SCHISTOSOMIASIS	2 (5.6)	1	1	37 (35-39)
HEPATOMA	2 (5.6)	2	0	40.5 (30-47)
SIDEROSIS	3 (8.3)	3	0	65 (60-70)
NORMAL BIOPSY	6 (16.6)	4	2	40 (25-60)
TB ABDOMEN	10 (27.8)	7	3	35.7 (22-70)
C.M.L.	2 (5.6)	1	1	58.5 (50-70)

Age and sex distribution. (TABLE 1)

There were a total of twenty eight males and eight females, giving a male/female ratio of 3.5:1. The sex ratio for all cases initially included was 2.8:1. The high male ratio is apparent, and all cases of cirrhosis were males. The age range for all cases was 19-70 years. For cirrhosis alone, the age range was 40-62 years, with a mean age of 52.3 years.

Table 2. Presenting features

	Cirrhosis(6)	Non-cirrhotics(30)
Abdominal pain	5 (83.3%)	25 (83.3%)
Weight loss	4 (66.6%)	20 (66.6%)
Pedal oedema	4 (66.6%)	7 (23.3%)
Abdominal distension	3 (50%)	15 (50%)
Nausea/vomiting	1 (16.6%)	5 (16.6%)
Anorexia	1 (16.6%)	11 (36.6%)
General malaise	1 (16.6%)	15 (50%)
Fever	0	10 (33.3%)
Diarrhoea	0	7 (23.3%)
Jaundice	0	2 (6.6%)
Itching	0	2 (6.6%)

Presenting features. (Table 2)

Abdominal pain (83.3%), weight loss (66.6%), and abdominal distention (50%), featured most commonly in both groups. The abdominal pain was non-specific in most cases, only occasionaly related to the right hypochondrium. Abdominal distention was due to ascites in all 3 cases of cirrhosis; in comparision, 10 of the 15 cases of abdominal distention in the other categories were related to tuberculous abdomen. Of the remaining 5 cases, ascites was observed in patients with hepatocellular carcinoma, schistosomiasis and chronic myeloid leukaemia, (one

case each), and no clinical abnormality was noted in the other 2 cases. Pedal oedema was more common in cirrhotic cases (66.6%), as compared to 7 of the 30 cases (23.3%). Both fever and diarrhoea were more often seen in tuberculous abdomen (4 and 6 cases respectively). However only 3 cases in this group of patients presented with symptoms pertaining to the respiratory system. Non specific gastro-intestinal symptoms were uncommon presenting features in both comparitive groups.

None of the cirrhotic patients presented with features of hepatic encephalopathy or bleeding oesophagial varices. A past history of haematemesis was obtained in 2 cases, (hepatocellular carcinoma and schistosomiasis).

Table 3

Liver and spleen size and the finding of ascites

Category (cases)	liver size in cm (range)	spleen size in cm (range)	no (%)with ascites
CIRRHOSIS(6)	1.5 (1-2)	4.1 (0-15)	3 (50)
T.S.S.(5)	2.4 (0-8)	7.4 (3-10)	0
SCHISTOSOMIASIS (2)	2.5 (2-3)	7.5 (4-11)	1 (50)
HEPATOMA (2)	8 (6-10)	1 (0-2)	1 (50)
SIDEROSIS(3)	6.3 (5-8)	0	0
NORMAL BIOPSY(6)	4 (0-5)	0.18 (0-1)	0
TB ABDOMEN(10)	0.6 (0-3)	0	10 (100)
C.M.L.(2)	12 (4-20)	17.5 (11-24)	1 (50)

Liver and Spleen size. (Table 3)

Significant hepatomegaly was observed in cases of hepatocellular carcinoma and haemochromatosis only. The large liver size in both cases of chronic myeloid leukaemia was attributable to the blastic stage of the disease. Gross splenomegaly was observed in cases of tropical splenomegaly syndrome and chronic myeloid leukaemia. Only one case of abdominal tuberculosis had significant splenomegaly. No significant pattern of hepatosplenomegaly was observed in the cirrhotic group of patients.

Ascites. (Table 3)

Ascites as a presenting feature was observed in all cases of abdominal tuberculosis. The ascitic fluid in all these cases was of an exudative nature. In comparision, only three of the six diagnosed cases of cirrhosis had presented with ascites.

Other clinical features.

Finger clubbing, palmar erythema, and parotid enlargement were seen in one case of cirrhosis who gave a positive history of very heavy alcohol intake. No cases of gynaecomastia or testicular atrophy were noted in any of the 28 male patients. So was the absence of Dupuytren's contracture and spider naevi.

Pyrexia was observed in 4 cases of tuberculosis of the abdomen, during hospitalization. Generalised hyperpigmentation was difficult to assess in all patients.

Table 4

		ALCOHOL INTAKE (GRADE)			
CASE	NO	(O)	(A)	(B)	(C)
CIRRHOSIS	(6)	1	1	2	2
T.S.S.	(5)	5	0	0	0
SCHISTOSOMIASIS	(2)	2	0	0	0
HEPATOMA	(2)	0	0	2	0
SIDEROSIS	(3)	0	0	0	3
NORMAL BIOPSY	(6)	3	2	1	0
TB ABDOMEN	(10)	8	0	1	1
C.M.L.	(2)	1	0	0	1

Grades of alcohol intake:

O : Mean ethanol intake of <25g/day

A : Mean ethanol intake (25-75)grams/day

B : Mean ethanol intake (76-125)grams/day

C : Mean ethanol intake (>126)grams/day

Alcohol consumption. (Table 4)

Heavy alcohol consumption related well to cases of cirrhosis, haemochromatosis, and hepatocellular carcinoma. Insignificant alcohol intake was recorded in all the other groups of patients, although one patient with abdominal tuberculosis, and also one patient with chronic myeloid leukaemia, admitted to very heavy alcohol intake.

LIVER HISTOLOGY.

1.*Cirrhosis of the liver*. The micronodular (3), macronodular (2), and mixed (1) variety were seen on histology in six cases. One case had associated schistosomiasis, as evidenced by periportal fibrosis; however no bilharzial ova or pigment was noted. Excess iron pigments featured prominently in all 3 cases of micronodular cirrhosis. Associated hepatocellular carcinoma was absent in all cases.

2.*Tropical splenomegaly syndrome*. Marked hepatic sinusoidal lymphocytic infiltration was the feature in 5 cases of T.S.S. The liver architecture was maintained, and malarial pigments within hepatocytes was observed in 2 cases. Relative lymphocytosis was also a feature in all 5 patients.

3.*Haemochromatosis*. Heavy siderosis was observed in all 3 cases, in the absence of histological features of cirrhosis. All three patients gave histories of heavy alcohol intake. (There was no clinical evidence of diabetes mellitus in the three cases of siderosis.)

4.*Schistosomiasis*. Features of hepatic schistosomiasis included marked pipestem fibrosis, and the presence of bilharzial granulomas. Both cases had a positive rectal snip.

5.*Hepatocellular carcinoma*. Both cases were of the trabecular type. There was no evidence of underlying cirrhosis on histology.

6.*Normal liver biopsy*. This group of patients (6 cases), did not show any specific pathology. No features of cirrhosis, tropical splenomegaly syndrome, haemochromatosis, tuberculosis, or malignancy was noted. Two cases featured a reactive liver (prominent kupffer cells and mononuclear sinusoidal infiltration).

OTHER CATEGORIES.

7.*Abdominal tuberculosis*. Although no liver biopsy was undertaken in this group of patients, there was sufficient clinical evidence to establish the cause of ascites in all cases. Two cases underwent a peritoneal biopsy to confirm diagnosis. Other diagnostic pointers included a high erythrocyte sedimentation rate (all cases), evidence of active disease on chest X ray as evidenced by positive sputum results (3 cases), and a positive Heaf test in 8 out of 10 cases. All cases showed an exudative fluid on ascitic tapping, but no tuberculous bacilli were cultured in any patient. All cases were treated with the appropriate drugs, and of the 5 cases followed up in the outpatients clinic, clinical evidence of response to treatment was remarkable.

8.*Chronic myeloid leukaemia*. A raised white cell count with a characteristic peripheral blood smear showing a complete spectrum of the granulocytic series, and a confirmatory bone marrow was noted in two cases.

Table 5

Mean haematological values

CASES	(NO)	HB	W.C.C.	APC	P.I.	ESR
CIRRHOSIS	(6)	11.3	5.58	152.6	84.3	44.5
T.S.S.	(5)	11.9	3.9	103.8	86.5	34.2
SCHISTOSOMIASIS	(2)	10.3	2.7	88.5	94	16
HEPATOMA	(2)	12.4	7.3	148	83	76
SIDEROSIS	(3)	14.3	7.5	136.6	87.3	60
NORMAL BIOPSY	(6)	13.4	6.1	142.8	90	64
TB ABDOMEN	(10)	10.3	6.5	247.5	86.7	107.3
C.M.L.	(2)	7.2	179	84	80	130

HB : Haemoglobin (grams/decilitre)

W.C.C. : Total white cell count (x10/9/litre)

APC : Absolute platelet count (x10/9/litre)

P.I. : Prothrombin Index (%)

ESR : Erythrocyte sedimentation rate (mm/hour)

Haematological features. (Table 5)

Haematological indices were similar in all categories other then cases of chronic myeloid leukaemia. A relative pancytopenia was observed in the two cases of schistosomiasis. The erythrocyte sedimentation rate (ESR) was significantly raised in cases of tuberculous abdomen. Relative lymphocytosis was a feature of T.S.S. As no positive diagnosis was confirmed in the initial 14 patients in whom liver biopsy was contraindicated due to a low platelet count, the value of thrombocytopenia as a haemaological parameter was not useful.

Table 6

Biochemical features. (expressed as mean values)

Category (cases)	Alb	A:G	Bil	Got	Gpt	Alk
CIRRHOSIS (6)	26.1	37.4	18.5	34.1	24.5	176.8
T.S.S. (5)	38.3	52.8	30.9	26.6	21.8	217.6
SCHISTOSOMIASIS (2)	34.5	46.1	20.6	66	44.5	274.5
HEPATOMA (2)	24.5	39.1	94.3	172	102	1312
SIDEROSIS (3)	33.6	44	17.4	80.3	37.6	158.6
NORMAL BIOPSY (6)	32	44.2	28	45.5	34.5	137
TB ABDOMEN (10)	26.7	40.6	24.1	31.1	17	139.5
C.M.L. (2)	-	-	17.8	30	12.5	459.5

Key to abbreviations:

Alb : Serum albumin (g/l)

A:G : Albumin/globulin ratio (%)

Bil : Serum bilirubin (umol/l)

Got : Serum glutamic-oxaloacetic transaminase (Iu/l)

Gpt : Serum glutamic-pyruvic transaminase (Iu/l)

Alk : Serum alkaline phosphatase (Iu/l)

Biochemical features. (Table 6)

Mean serum albumin and a lowered albumin:globulin ratio featured prominently in cases of cirrhosis, hepatocellular carcinoma, and abdominal tuberculosis. Mild hepatic dysfunction was seen in all the categories defined; however the two cases of hepatocellular carcinoma presented with deeper jaundice, and a grossly elevated serum alkaline phosphatase level.

Parasitological studies. Routine stool and urine examinations failed to reveal any bilharzial ova in any of the 36 cases. Repeat stool analysis in 20 cases were negative for S mansoni ova. A rectal snip was done in only 24 of the 36 cases included in the study. Both snips were positive for S mansoni ova in the schistsomiasis group; of the remainder cases, a further 3 snips were positive for ova (2 in TB Abdomen and 1 in T.S.S.).

Radiological studies.

Radiological investigations were done in selected cases only. This was due to lack of materials during the period of study. In 8 of the 10 cases of abdominal tuberculosis, 6 patients had evidence of active disease, and of these, 3 had positive sputum results. No oesophageal varices were observed in the 2 patients of cirrhosis, who underwent barium meal studies.

Table 7. Hepatitis B surface antigen screening test

	NO OF CASES	HBSAG+ve (%)
CONTROL GROUP	140	25 (17.9)
ALL CATEGORIES	36	10 (27.7)
CIRRHOSIS	6	3 (50)
HEPATOMA	2	2 (100)

Hepatitis B surface antigen (HBsAg). (Table 7)

A total of 25 out of 140 (17.9%) sera obtained from healthy blood donors (control group), were reactive. Of the 36 cases included in this study, there were 10 reactive sera (27.7%). Both cases of hepatoma were positive (100%), as were 3 of the 6 cases of cirrhosis (50%). In the case of one patient who had a past history of hepatitis, but in whom the liver histology was essentially normal, the serum was reactive. The remaining reactive sera was obtained in haemochromatosis (one case), tropical splenomegaly syndrome (one case), and abdominal tuberculosis (two cases).

DISCUSSION

This study was undertaken to evaluate some of the clinical features and biochemical abnormalities associated with cirrhosis in the indigenous Zambian patient. Cirrhosis of the liver is a common condition in adult Zambian patients. Over the past ten years, a number of articles have featured various clinical presentations of cirrhosis in Zambia (Table 8). In all these articles, the patient selection criteria varies, and a review of the literature has not documented the typical clinical features in Zambian cirrhotics.

The predefined criteria of patient selection for this study was based on the typical presenting features of cirrhosis (81). Only patients with one or more selection features, in whom a diagnosis of cirrhosis was probable, were included in the study.

Table 8

Article (ref)	Year	Total cases	Cases of cirrhosis(%)
Massive splenomegaly (34)	1974	44	11 (25)
Massive splenomegaly (67)	1980	344	31 (9)
Hepatomegaly (85)	1975	82	11 (13.4)
Jaundice (86)	1975	50	8 (16)
Hepatocellular carcinoma (87)*	1976	166	97 (58.4)
Hepatocellular carcinoma (88)*	1980	86	26 (30)
Upper gastro-intestinal bleeding (89)	1980	78	11 (14)

*= cirrhosis associated primary liver cancer

Initially the aim was to include only confirmed cases of cirrhosis into the study. However, of the 24 patients who underwent liver biopsy, only 6 were diagnosed as cases of cirrhosis on histology.

The incidence of HBsAg in the normal Zambian population has been well documented (14). The present study has also aimed to determine the incidence of HBsAg in cases of cirrhosis. One hundred and forty healthy adult Zambians were used as controls.

A histological diagnosis of cirrhosis was established in 6 (16.6%) patients. All were males with a mean age of 52.3 years, and 3 (50%) were positive for hepatitis B surface antigen (HBsAg). A history of heavy alcohol intake was obtained in 5 patients. Classical pointers of cirrhosis, such as spider naevi, Dupuytren's contracture, gynaecomastia, and testicular atrophy were absent in all cases.

The interaction of various factors is important in the aetiology of cirrhosis in the tropics (20-24), and the role of viral hepatitis is still considered as the main causative agent in these areas (9,10,23). While alcohol accounts for up to 80% of cirrhosis in western countries (4-7), alcohol is increasingly becoming a major health issue in Zambia and other African countries (90). In rural areas of the continent, the overall picture is one of a high consumption of illicit "alcohol" brews.

In this study, the majority of cirrhotic patients (5/6) volunteered a history of heavy alcohol intake (Table 4). In 3 (50%) patients, the liver histology conformed to a micronodular variety, with excess iron stores. O'Keefe's retrospective study on cirrhosis in the South African black population showed that a majority (73%) of biopsy specimens had evidence of micronodular cirrhosis, with frequent additional findings of siderosis and fat deposits (37).He attributes alcohol as a major factor in the causation of cirrhosis in that country. This also seems to be the pattern in Zambia.

While only 3 cases of cirrhosis were HBsAg positive (Table 7), all of them gave a history of alcohol intake. Two patients had macronodular cirrhosis, whereas the remaining HBsAg positive case had micronodular cirrhosis. The high incidence of HBsAg in normal healthy African populations may well be related to horizontal transmission of the infection (18); Vertical transmission does not appear to be common in Zambia (91). As compared to previous studies in Zambia (14,15), the carrier rate of HBsAg was significantly higher (17.9%). A high incidence (20%) was also noted in a recent study by Msiska R et

al 1985 (92). This variation may only be a reflection of the sensivity of the method used. A larger study is neccesary to verify these observations. One case of micronodular cirrhosis with Grade C alcohol intake, was also HBsAg positive. The association between HBsAg and alcohol consumption in cirrhotics is well established (93,94).

The male predominence in cirrhosis is well documented, and this was also the case in this series (Table 1). However there were no cases under the age of 40 years. This contrasts with cases in South Africa and Zimbabwe (37,95), where cirrhosis is seen in a younger age group, some cases presenting even below the age of 20 years. Abdominal pain, weight loss, pedal oedema, and abdominal distension were the main presenting complaints in cirrhotic patients (Table 2). None were specifically related to cirrhosis in comparision with other categories., although pedal oedema featured more commonly in the former.

Mild hepatomegaly in the absence of significant parenchymal damage, is common in most tropical countries (23). In all patients with cirrhosis, liver enlargement was insignificant (Table 3). Splenomegaly was noted in 3 (50%) cases of cirrhosis, and in one case, it was grossly enlarged (15cm). Gross splenomegaly as a presenting feature is not unusual in Africa (34).

Hypoalbuminaemia is a well established feature of cirrhosis. This proved to be so in all 6 cases; however this biochemical feature was also notable in the 2 patients with hepatocellular carcinoma as well as all 10 cases of abdominal tuberculosis. Other biochemical parameters of liver function were only slightly deranged, and proved to be unhelpful. Similarly a mild normochromic anaemia which featured in all patients with cirrhosis, was noted in other comparative cases. A raised erythrocyte sedimentation rate also featured prominently in all categories compared.

Classical pointers of cirrhosis are rare in Africa (37,38). This was also true in the cases analyzed. Only one patient presented with finger clubbing, palmar erythyma, and parotid enlargement. The inclusion of these features in the initial case selection criteia proved to be of no value.

Hepatocellular carcinoma is the most common malignant tumour of men in Zambia (91); and is associated with a very high incidence of HBsAg. Both male patients in this study were HBsAg positive, with evidence of underlying cirrhosis on histology.

S mansoni is important in Zambia, where the overall prevailence of infection is close to 2% (101). Only 2 (5.6%) cases of hepatic schistosomiasis were encountered in this study. Lowenthal (34) states that multiple pathology is a rule rather than an exception in African patients. In all cases analyzed, only one case of cirrhosis was associated with schistosomiasis.

SUMMARY

1. Cirrhosis of the liver is not uncommon in Zambia; however certain tropical diseases, which are prevailent in Zambia, should always be considered in the differential diagnosis of cirrhosis.

2. A male predominence is a prominent feature of cirrhosis in Zambia.

3. Alcohol is an important factor in the developement of cirrhosis in the indigenous Zambian.

4. Cirrhosis is associated with a high incidence of Hepatitis B surface antigen (HBsAg) in Zambia.

5. Hypoalbuminaemia is common in patients with cirrhosis.

6. Classical pointers of cirrhosis, such as spider naevi, Dupuytren's contracture, palmar erythema, gynaecomastia, and testicular atrophy, are rare in patients with cirrhosis in Zambia.

REFERENCES

1. Leevy C M, Popper H, Sherlock S (criteria committee) Diseases of the Liver and Biliary Tract: Standardization of Nomenclature, Diagnostic Criteria, and Diagnostic Methodology, Fogarty International Center Proceedings, No 22, DHEW Publication No (NIH) 76-725. Washington, DC, US Government Printing Office 1976.
2. Bulletin of the World Health Organization, 55'4; 521-540, 1977.
3. Thomson A D, (1981). Cirrhosis of the liver. The Practitioner. 225: 449-459.
4. Brunt P, and Petrie M. (1974). Chronic liver disease in North East Scotland. (Unpublished data).
5. Lelbach W K. (1975). Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. Annals of the New York Acedemy of Science. 252, 85
6. Hodgson H J F, and Thompson R P H. (1976). Cirrhosis in Souh London. Lancet. 2. 118.
7. Saunders J B, Walters J R F, Davies P, and Paton A. (1981). A 20 year prospective study of cirrhosis. British Medical Journal. 282, 263.
8. Popper H. (1977). Pathological aspects of cirrhosis. A review. American Journal of Pathology. 7. 228-258.

9. Boxall E H, Flewett T H, Paton A, and Passam S W. (1976). Hepatitis B surface antigen and cirrhosis in Iraq. Gut. 15. 52-58.

10. Bagshawe A F. Parker A M, and Jindani A. (1971). Hepatitis associated Antigen in liver disease in Kenya. British Medical Journal. 1. 88-89.

11. Seggie J, and Gelfand M. (1974). Hepatitis B surface antigen (HBsAg) in Rhodesia. South African Medical Journal. 48. 1423.

12. Linqvist K J, and Nantulya V M, (1975). Hepatitis B antigen in the coastal region of Tanzania. East African Medical Journal. 2. 217.

13. Parker A M, Miruri K L, and Preston J K. (1971). Hepatitis associated antigen in blood donors in Kenya. East African Journal of Medicine. 48. 470.

14. Gill G V. (1979). Hepatitis B surface Antigenaemia: Incidence and significance in Zambian Blood Donors. Medical Journal of Zambia. 13.51.

15. Bhagwat G P, and Parmar S. (1983). Hepatitis B surface antigen (HBsAg): (A survey of hospital staff in Zambia). Medical Journal of Zambia. 17. 106.

16. Larouze B, London W T, Saimot G, Werner B G, Lusbadar E D, Payet M, and Blumberg B S. (1976). Host responses to hepatitis B infection in patients with Primary Hepatocellular Carcinoma and their families: A case control study in Senegal, West Africa. Lancet. 2. 534.

17. Beasley R P, Hwang L, Lin C, Steven C E, Wang K, Sun T, Hsich F, and Szumuness W. (1981). Hepatitis B immuneglobulin (HBIG) efficacy in the interruption of perinatal transmission of Hepatitis B virus carriers. state. Initial report of a randomized double blind placebo-controlled trial. Lancet. 2. 388.

18. Tabor E, Gerety R J, Vogel C L, Bayley A C, Anthony P P, Chan C H, and Barker L F. (1977). Hepatitis B virus infection and Primary Hepatocellular Carcinoma. Journal of the National Cancer Institute. 58. 1197.

19. Trichopoulos D, Tabor E, Gerety R J, Xirouchaki E, Sparios L, Munoz N, and Linsell C A. (1978). Hepatitis B and Primary Hepatocelular Carcinoma in a European population. Lancet. 2. 1217.

20. Conn H O, in Schiff L, ed. (1972). Diseases of the Liver. 4th edition, chapter 26. Philadelpia. J B Lippincott.

21. O'Keefe S J, El Zayadi A R, Carraher T E, et al. (1980). Lancet. 2. 615.

22. E B Adams. A Companion to Clinical Medicine in the Tropics and Subtropics. (1979). Oxford University Press.

23. G C Cook. Chronic hepatic injury in Tropical Gastroenterology. (1980). 1st edition. Oxford Medical Publications.

24. Neame P B, and Pillay V K G. (1964). Spontaneous hypoglycaemia, hepatic and renal necrosis following the intake of herbal medicines. South African Medical Journal. 38. 729.

25. Walker A R P, and Arvidsson V B. (1953). Transactions of the Royal Society of Tropical Medicine and Hygiene 47. 536.

26. Baker A L, Elson C O, Jaspau J, and Boyer J L. (1979) Liver failure with steatonecrosis after jejunoileal bypass. Recovery with parentral nutrition and reanastomosis. Archives of Internal Medicine. 139. 289.

27. Haines N W, Baker A L, Boyer J L, Glagov S, Schner H, Jaspan J, Ferguson O J. (1981). Prognostic indicators of hepatic injury following jejunoileal bypass performed for refractory obesity. A prospective study. Hepatology. 1. 169.

28. Meister H P, Szanto P B, and Schoolman H. (1963). Quantitative-morphologic evaluation of postnecrotic cirrhosis. Virchows Arch (Pathol Anat). 336. 447-464.

29. Ludwig J, and Elveback L R. (1972). Parenchyma weight changes in hepatic cirrhosis: A morphometric study and discussion of the method. Lab Invest. 26. 338-343.

30. Kaneda M, and Takahashi T. (1970). Histometrical analysis of hepatic parenchyma in normal and cirrhotic livers. Tohuku J Exp Med. 100. 201-225.

31. Krieg D, and Weigl E. (1969). Epidemiologische Untersuchungen zum Problem des post hepatitischen Leberzirrhose. Acta Hepatosplen. 16. 25-34.

32. Powell L W, Mortimer R, and Harris O D. (1971). Cirrhosis of the liver: a comparitive study of the four main aetiological groups. Medical Journal of Australia. 1. 941.

33. Wiles W A. (1980). The aetiology of gross splenomegaly in Rhodesia and the significance of bilharziasis. The Central African Journal of Medicine. 26. 3-5.

34. Lowenthal M N, Hutt M S R, Jones I G, Mohelsky V, and O'Riordon E C. (1980). Massive splenomegaly in Northern Zambia. 1. Analysis of 344 cases. Transactions of the Royal Society of Tropical Medicine and Hygiene. 74. 91-98.

35. Shearman David J C, and Finlayson Niall D C. (1982). Cirrhosis in Diseases of the Gastrointestinal tract and Liver. Churchill Livingstone Publication. First Edition.

36. Martini G A, Baltzer G, and Arndt H. (1972). Some aspects of circulatory disturbances in cirrhosis of the liver. In Popper H, Schaffner F (eds). Progress in liver disease. Grune and Stratton, New York. Vol 4. p231.

37. O'Keefe S J, Simjee A E, and Seedat Y K. (1982). Clinical presentation and biochemical abnormalities in Black (Zulu) patients with cirrhosis in Durban. South African Medical Journal. 61. 775.

38. G M Edington and H M Gilles. Cirrhosis in Pathology in the Tropics. (1976). 2nd edition. Edward Arnolds (Publishers) Ltd.

39. Baker H W G, Burger H G, deKretser D M, Dulmanis A, Hudson B, O'Connor S, paulsen C A, Purcell N, Rennie G C, Seah C S, Taft H P, and Wang C. (1976). A study of the endocrine manifestations of hepatic cirrhosis. Quaterly Journal of Medicine. 45. 145.

40. Green J R B. Mechanism of hypogonadism in cirrhotic males. Gut. 18. 843.

41. Galvao-Teles A, Anderson D C, Burke C W, Marshall J C, Corker C S, Bown R L, and Clark M L. (1973). Biologically active androgens and oestradiol in men with chronic liver disease. Lancet. 1. 173.

42. Summerskill W H J, and Molnar G D. (1962). Eye signs in hepatic cirrhosis. New England Journal of Medicine. 266. 1244.

43. Conn H O, Schreiber W, Elkington S G, Johnson T R. (1969). Cirrhosis and Diabetes.1. Increased incidence of diabetesin patients with Laennec's cirrhosis. American Journal of Digestive Diseases. 14. 837.

44. Bouchier I A D. (1969). Postmortem study of the frequency of gallstones in patients with cirrhosis of the liver. Gut. 10. 705.

45. Nicholas P, Rinaldi P A, and Conn H O. (1972). Increased incidence of cholelithiasis in Laennec's cirrhosis. A postmortem evaluation of pathogenesis. Gastroenterology. 63. 112.

46. O'Hara E T, Oliai A, Patek A J J, and Nasbeth D C. (1975). Management of umbilical hernias associated with hepatic cirhosis and ascites. Annals of Surgery. 181. 85.

47. Langman M J S. (1973). Changing patterns in the epidemiology of peptic ulcers. Clinics in Gastroenterology. 2. 219.

48. Phillips M M, Ramsey G R, and Conn H O. (1975). Portocaval anastomosis and peptic ulcers; a non association. Gastroenterology. 68. 121.

49 Golding P G, Smith M, and Williams R. (1973). Multisystem involvement in chronic liver disease. Studies on the incidence and pathogenesis. American Journal of Medicine. 55. 772.

50. Doniach D, and Walker J G. (1969). A unified concept of autoimmune hepatitis. Lancet. 1. 813.

51. Johnson R B, Castell D O, and Lukash W M. (1969). Liver scanning for detection of collateral circulation in liver disease. A survey of 567 hepatic scans. Journal of the American Medical Association. 207. 528.

52. Gould L, Collica C, and Comprecht R F. (1972). Scintiphotographing in Congestive Cardiac Failure. The disappearing flying bat pattern. Journal of the American Medical Association. 219. 1734.

53. Bruguera M, Borda J M, Mass P, and Rodes J. (1974). A comparision of accuracy of peritoneoscopy and liver biopsy in the diagnosis of cirrhosis. Gut. 15. 799.

54. Vido I, and Wildhert E. (1969). Korrelation des laperoskopischen und histologischen Befundes bei chronischer Hepatitis und Zirrhosis. Dtsch Med Wochenschr. 94. 1633.

55. Hollund B, Poulsen H, and Schilichting P. (1980). Reproducibility of liver biopsy diagnosis in relation to the size of the specimen. Scandinavian Journal of Gastroenterology. 15. 329.

56. Zotti S, Papaleo E, Marin Gn Patella M, Bergaura S, Cardironi M W, Cecchetto A, and Dagnini Gm (1981). Laparoscopy and liver biopsy in the morphological diagnosis of cirrhosis: Concordance and diagnostic validity. Italian Journal of Gastroenterology. 13.14.

57. Pagliaro L, Rinaldi F, Craxi A,Piazza S, Filippazzo G, Gatto G, Genova G, Magrin S, Maringhini A, Orsini S, Palazzo U, Spinello M, and Vinci M. (1983). Percutaneous blind biopsy verses Laparoscopy with guided biopsy in the diagnosis of cirrhosis. Digestive Diseases and Sciences. 28. 39.

58. Terry R. (1952). Risks of needle biopsy of the liver. British Medical Journal. 1. 1102.

59. Bowden L, and Kravitz S. (1953). Needle biopsy of the liver. Adiagnostic aid in the treatment of cancer. Cancer. 6. 1010.

60. Parker J G, Simon M, Zimetbaum M, et al. (1962). Needle liver biopsy in benign and malignant disease: comparision of the Menghini and Vim Silverman technics. American Journal of Digestive Diseases. 26. 507.

61. Blackwell J N, Lean A C B, Macleod I B, Sumerling M D, Finlayson N D c. (1981). Laparoscopy and Radioisotope imaging in the investigation of suspected liver disease. Digestive Diseases and Sciences. 26. 507.

62. Warren K S, and Mahmoud A A f. (1975). Algorithms in the diagnosis and management of exotic diseases. 1. Schistosomiasis. Journal of Infectious Disease. 131. 614.

63. Obeid F, Smith R F, Elliot J P,et al. (1983). Bilharzial portal hypertension. Archives of Surgery. 118.702.

64. Hassab M A. (1967). Gastroesophageal decongestion and Splenectomy in the treatment of esophageal varices in Bilharzial cirrhosis: Further studies with a report on 355 cases. Surgery. 61.169.

65. Abdalla P. (1965). Surgical treatment of portal hypertension due to Schistosomiasis. Surgery. 57.680.

66. De Cock K M, Awadh S, Raga R c, Wankya B M, and Lucas B. (1982). Esophagial varices in Kenya. American Journal of Tropical Medicine and Hygiene. 31. 579.

67. Levitt D, Desai M, and Bhagwandeen S B. (1974). An investigation into a series of massive splenomegaly at the University Teaching Hospital, Lusaka, Zambia. East African Medical Journal. 51. 928.

68. Olsson R. (1972). The natural history of esophageal varices. A retrospective study of 224 cases with liver cirrhosis. Digestion. 6. 65.

69. Resnick R H, Chalmers T C, Isihara A M, Garcaeu A J, Callow A M, Schimmel E M, O Hara E J, and the Boston Inter-Hospital Liver Group. (1969). A controlled study of prophylactic portocaval shunt. Annals of Internal Medicine. 70. 675.

70. Baker L A, Smith C, and Lieberman G. (1959). The natural history of esophageal varices. A study of 115 cirrhotic patients in whom varices were diagnosed prior to bleeding. American Journal Of Medicine. 26. 228.

71. Kew M C, Dos Santos H A, and Sherlock S. (1971). Diagnosis of Primary Cancer of the Liver. British Medical Journal. 4. 408.

72. Al-Sarraf M, Go T S, Kithier K, and Vaitkevicious V K. (1974). Primary liver cancer: A review of clinical features, blood groups, serum enzymes, therapy, and survival, in 65 cases. Cancer. 33. 574.

73. Inde D C, Sherlock P, Winawer S J, Fortner J G. (1974). Clinical manifestations of Hepatoma. A review of 6 years experience at a cancer hospital. The American Journal of Medicine. 56. 83.

74. Johnson P J, Krasner N, Portmann B, Eddleston A L W F, and Williams R. (1978)m Hepatocellular carcinoma in Great Britain; influence of age, sex, HBsAg status, and aetiology of underlying cirrhosis. Gut. 19. 1022.

75. Lee F I. (1976). Cirrhosis and Hepatoma in Alcoholics. Gut. 7. 77.

76. Omata M, Aschavai M, Liew C T, and Peters R L. (1979). Hepatocellular carcinoma in the U.S.A.: Aetiological considerations. Gastroenterology. 76. 280.

77. Prince A M. (1981). Hepatitis B virus and hepatocellular carcinoma: molecular biology provides further evidence for an etiological association. Hepatology. 1. 73.

78. Blumberg B S, and London W T. (1981). Hepatitis B virus and the prevention of primary Hepatocellular Carcinoma. New England Journal of Medicine. 304. 782.

79. Kew M C, and Gedder E W. (1982). Hepatocellular Carcinoma in rural Southern African Blacks. Medicine. 61. 98.

80. Stone W D, Islam N R K, and Paton A. (1968). The natural history of cirrhosis. Experience with an unselected group of patients. Quarterly Journal of Medicine. 37. 118.

81. Sherlock Sheila. Hepatic Cirrhosis in Diseases of the Liver and Biliary System. Fifth edition. (1975). Blackwell Scientific Publications.

82. Reily C, Ngwebai M, and Okafor B. (1974). The Methanol, Ethanol, and Fusel oil contents of some Zambian alcoholic drinks. Medical Journal of Zambia. 8.13.

83. Menghini G. (1958). One second needle biopsy of the liver. Gastroenterology. 35. 190.

84. T D V Swinscow. Statistics at square one. (1980). British Medical Association Publication.

85. Bahl V. Mistry C M, and Obineche C N. (1975). Hepatomegaly in Lusaka. Medical Journal of Zambia. 9. 5. 135.

86. Bhagwandeen S B, Obineche E N, Mistry C M, and Mistry R R. (1975). Jaundice in Adult Zambians. A Clinico-Pathological correlation. Medical Journal of Zambia. 9. 1. 14.

87. Naik K G. (1976). Primary Carcinoma of the Liver in Zambia. Medical Journal of Zambia. 10. 6. 146.

88. Krishnamurthy K R, and Patil B S. (1980). A Retrospective Study of 86 Cases of Hepatocellular Carcinoma. (unpublished data).

89. Tuakli J, and Worsornu L. (1977). Aetiology of Acute Upper Gastro-Intestinal Bleeding at the University Teaching Hospital, Lusaka, Zambia. Medical Journal of Zambia. 11. 3. 63.

90. Ribson E B. (1985). Community response to alcohol-related problems. W.H.O. Public Health. Paper 81.

91. Cairns J M, Tabor E, and Gerety R J. (1978). Hepatitis B carriers in pregnancy: A preliminary report. Proceedings of The Association of Surgeons of East Africa. 1. 80.

92. Msiska R M. (1985). The incidence of HBsAg in viral hepatitis. (unpublished data).

93. Chevillote G, Durbec J P, Gerolami P, Berthezene P, Bidart J M, and Camatte R. (1983). Interaction between Hepatitis B virus and Alcohol consumption in Liver Cirrhosis. Gastoenterology. 85. 141.

94. Ohnishi K, Iida S, Iwama S,Goto N, Nomura F, Takashi M, Mishima A, et al. (1982). The effect of chronic habitual alcohol intake on the developement of Liver Cirrhosis and Hepatocellular Carcinoma. Relation to Hepatitis B surface antigen carriage. Cancer. 49. 672

95. Gelfand M. (1955). Transactions of the Royal Society of Tropical Medicine and Hygiene. 49. 370.

96. Francis T I. (1972). Abdominal Tuberculosis in Nigerians. A clinico-pathological study. Trop Geogr Med. 24.232.

97. Das P, and Shukla H S. (1976). Clinical diagnosis of Abdominal Tubercuosis. British Journal of Surgery. 63. 941.

98. El-Hassan A M, Tag El-Deen M H. (1982). Primary intestinal tuberculosis in Sudan. Ann Trop Med Parasit. 76. 317.

99. University Teaching Hospital. Medical records/statistics department. Tuberculosis statistics (1975 to 1984).

100. Barry M. (1973). Iron and Chronic Liver Disease. Journal of the Royal College of Physicians. London. 8. 52.

101. Fine J. (1975). Prevailence of Bilharzia in Zambia. Medical Journal of Zambia. 8. 3. 56.

ACKNOWLEDGEMENTS

1. Dr B Bisseru FRCP - Department of Medicine

2. Dr W Kaunda MRCP - Department of Medicine

3. Cooper (Zambia) Limited - Lusaka