6

A Four-Year Study of Cirrhosis at Groote Schuur Hospital

Archie Cornelius Siyolo Solombela
MBChB (Natal) DTM&H (Wits) Dip For Med (SA)

A dissertation towards the degree of Master of Medicine (Medicine)

University of Cape Town

1999

DECLARATION OF AUTHORSHIP

I, Dr Siyolo Solombela, declare that:

- I am the author of the dissertation which follows
- the dissertation represents my own original work
- it has not been submitted to any other university
- it has not been submitted for publication elsewhere.

Signed by candidate

Cape Town

24 May 1999.

ACKNOWLEDGEMENTS

I wish to express my gratitude to the following people whose assistance and support has been invaluable:

Prof Richard Hift and *Prof Ralph Kirsch* for their support and encouragement, and for their assistance with the interpretation of the data and the preparation of the manuscript

Prof Solly Benatar and Prof Janet Seggie for encouraging me to proceed with my studies towards the degree of Master of Medicine

Dr Wendy Spearman for encouraging me in my interest in liver disease

Dr Tim Sole, *Dr Alan Gordon* and my colleagues at the Frere Hospital, for their help and support during my absences from East London for the purposes of this work

Dr Sedick Isaacs for his help with the statistics

The staff of Medical Informatics and of the Medical Accounting Process office, Groote Schuur Hospital, for providing me with vital information from the hospital information systems

Prof Jake Krige and *Prof Steve Beningfield* for providing me with information on costs

Dr Tim Tucker for providing me with data on the prevalence of the hepatitis viruses in Cape Town

Lavinia Petersen for assistance with the typing of the manuscript

Faiza Pearce for coordinating my visits to Cape Town

My wife and family for their love and support.

CONTENTS

CHAPTER 1: CIRRHOSIS: A REVIEW

INTRODUCTION

Cirrhosis is a common condition and results in severe morbidity and mortality. In South Africa, the mortality rate for cirrhosis in the white population was 6.9 per 100 000 in 1980, down from 11.7 per 100 000 in 1970 (Wyndham 1985). There are no figures for other population groups but a report from Durban (O'Keefe et al 1982) suggests that cirrhosis is common in the black population of Natal and cirrhosis is the eighth most common disease encountered in King Edward VIII Hospital.

Many studies have been done on survival or mortality rates for cirrhosis in both compensated and decompensated states in other countries (D'Amico et al 1986; Gines et al 1987). In the United States, cirrhosis has shown a decrease in mortality whilst there has been an increase in morbidity over the past two decades (Dufour et al 1993; Noble et al 1993).

Alcohol is the most common cause of cirrhosis in the United States and United Kingdom (Friedman et al 1992). The study of Saunders et al (1981) reported a high incidence of alcoholic cirrhosis in west Birmingham, UK, with a significant rise between 1969 and 1976. In the study of O'Keefe et al (1982) in Durban, the majority of their cirrhotic patients admitted to alcohol abuse and weekend bingeing. In the study of Seebaran et al (1988), also in Durban, alcohol was the major cause of cirrhosis in the Indian patients he studied.

In contrast to the importance of alcohol in western countries, it has been reported that chronic hepatitis B virus infection is responsible for most cases of cirrhosis in Africa and Asia (Sherlock and Dooley 1992; Dusheiko & Hoofnagle 1991). There appear however to be no reports directly comparing the prevalence of viral and alcoholic cirrhosis in South Africa.

DEFINITION OF CIRRHOSIS

The definition which we consider most appropriate is that of Anthony et al (1977), which defines cirrhosis as *a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules*. Whatever the aetiology of the liver injury, cirrhosis represents the end-stage histological pattern of the injury. Although the diagnosis of cirrhosis is ultimately histological, clinical and biochemical changes and the complications that arise from it allow a reasonably confident clinical diagnosis to be made.

However, a clinical diagnosis of cirrhosis made during life has a sensitivity of only 60%, suggesting that many cases of cirrhosis are missed during life (Dufour et al 1993). Stated differently, the true prevalence of cirrhosis is unknown because only 60% of patients with cirrhosis have signs or symptoms of liver disease. Some of the other 40% are discovered on routine examination, on examination for an unrelated complaint, or at autopsy (Dufour et al 1993, Conn & Attenbury 1993).

CLASSIFICATION

Currently two classifications, morphological and aetiological, are used for cirrhosis: The morphologic classification refers to the gross and microscopic appearances of the liver and is useful in studying patterns epidemiologically and, to some extent in correlating them, with the underlying aetiology.

1. Morphological classification

There are three morphologic forms: micronodular, macronodular and mixed cirrhosis.

a) Micronodular cirrhosis

The regularity of the nodules is an important feature of this form of cirrhosis. They are all or nearly all less than 3 mm in diameter. These micronodules are about one lobule in size, lack normal lobular organisation and are surrounded by fibrous tissue. This form of cirrhosis is characteristic of alcoholic cirrhosis (which is sometimes known as Laennec cirrhosis, after Laennec who described it in 1826). In micronodular cirrhosis, the liver itself is often normal-sized or enlarged, particularly when there is associated steatosis.

b) Macronodular cirrhosis

This is characterised by a variation in nodule size with most nodules more than 3 mm in diameter, and many as large as several centimetres. There may be normal lobules within some of the macronodules. The macronodules may be divided by slender and sometimes incomplete septa that link portal tracts, on the other hand large macronodules in a coarsely scarred liver may be surrounded by broad fibrous septa. This is characteristic of cirrhosis associated with viral hepatitis. In macronodular cirrhosis, the size of the liver may be normal but is often reduced.

c) Mixed cirrhosis

This form is characterised by the presence of both micro- and macronodules in approximately equal proportions.

The morphologic forms of cirrhosis may suggest possible aetiology but it is known that micronodular cirrhosis may progress to macronodular cirrhosis in the same patient (Fauerholdt et al 1983). Thus it may be impossible to link nodular size to a particular aetiological agent and in view of this, a direct aetiological classification would appear to be more appropriate.

2. Aetiological classification

The aetiological classification shown below (Table 1.1) has been adapted from two sources: Erlinger & Benhamou (1991) and Anthony et al (1977).

This classification divides the aetiology of cirrhosis into 3 broad groups:

1. Established aetiological agents of cirrhosis
2. Agents which have an association with cirrhosis but a causal relationship has not been proven
3. Cirrhosis for which the aetiology is not known.

1. Cirrhosis from established aetiological agents

a) Alcohol

b) Viral hepatitis including HBV, HDV and HCV

c) Metabolic disorders, e.g. iron overload, Wilson's disease, alpha-1 antitrypsin deficiency and rare inherited disorders, e.g. galactosaemia

d) Biliary disease
i) Intrahepatic biliary obstruction
ii) Extrahepatic biliary obstruction. Primary biliary cirrhosis and primary sclerosing cholangitis are included in this group.

e) Autoimmunity - autoantibodies are found in serum and other immune diseases may be present

f) Venous outflow obstruction including veno-occlusive disease, Budd-Chiari syndrome and cardiac failure.

g) Toxins and therapeutic drugs, e.g. certain pyrrolizidine alkaloids, methotrexate and alpha methyldopa.

h) Intestinal bypass operation for obesity.

i) Others - syphilis and sarcoidosis are included in this rare subdivision.

2. Unproven causes

a) Malnutrition - this is a doubtful cause of cirrhosis in man. Protein deficiency is known to cause gross fatty change but it does not lead to chronic liver disease.

b) Schistosomiasis is known to cause diffuse extensive hepatic fibrosis. Whether cirrhosis can result from schistosomiasis without other aetiological agent is not established.

3. Cirrhosis of unknown aetiology

a) With well-defined pattern - Indian childhood cirrhosis.

b) With no well-defined pattern - Cryptogenic cirrhosis.

Table 1.1. Aetiological classification of cirrhosis

CLINICAL FEATURES

The clinical features of cirrhosis have been well described and may differ in different races. There is some evidence that the classic features of cirrhosis seen in white patients differ from those seen in black patients (Wicks et al 1977; O'Keefe et al 1982), whereas those seen in coloured patients in Cape Town, particularly the cutaneous and endocrine features, are similar to those seen in white patients (Kirsch 1985). Clinical features that are commonly found in western patients with alcoholic cirrhosis but uncommonly in black patients are listed in Table 1.2 (Friedman et al 1992). Table 1.3 shows the symptoms and clinical findings respectively found in black patients (Kirsch 1985).

Patients with cirrhosis may be asymptomatic or they may present with non-specific symptoms such as lethargy, loss of weight and tiredness. Other patients may present with

Malaise, lethargy and dyspepsia	80%
Loss of libido	60%
Fever	3-10%
Pigmentation	25%
Spider naevi	50%
Dupuytren's contractures	10-30%
Gynaecomastia & testicular atrophy	20-30%

Table 1.2. Incidence of signs & symptoms of alcoholic cirrhosis in western patients (adapted from Friedman et al 1992).)

Symptoms			
Swelling of the body	60%	Weakness	20%
Abdominal pain	40%	Haematemesis	15%
Weight loss	30%	Jaundice	10%
Signs			
Hepatomegaly	70%	Clubbing	13%
Ascites and oedema	54%	Parotid swelling	12%
Emaciation	36%	White nails	8%
Splenomegaly	36%	Testicular atrophy	7%
Jaundice	35%	Gynaecomastia	1%
Abdominal veins	15%	Spider naevi	1%
Mental disturbance	14%	Palmar erythema	1%

Table 1.3. Incidence of symptoms and physical signs in black patients with cirrhosis (adapted from Kirsch 1985).

florid signs of chronic liver disease and/or one or more of the major complications of cirrhosis. The former are known as *compensated cirrhotics* as opposed to the *decompensated cirrhotics* who present with established complications.

LABORATORY FINDINGS

Biochemical and haematological findings differ according to whether the patient is compensated or not. In compensated cirrhotics, there may be no biochemical or haematological changes with the possible exception of a low serum albumin and increased globulin. There may be a high aspartate aminotransferase (AST) and alanine aminotransferase (ALT). One may find a mild normochromic anaemia which is often macrocytic. Both an AST/ALT ratio of more than two and a macrocytosis are commonly

found in alcoholic liver disease and may suggest alcohol as the cause of the illness. These findings are however of low specificity. Bilirubin, alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) are usually normal in compensated cirrhosis.

In decompensated cirrhosis, biochemical and haematological derangements are commonly found. A low albumin and raised globulin are present, resulting in a reversed albumin/globulin ratio. The AST, ALT, ALP and GGT are often elevated. The bilirubin is usually elevated and there may be clinical jaundice. The degree of these abnormalities in biochemistry may be related to the severity of the liver damage and also to the presence or absence of hepatitis at the time of investigation. The international normalised ration (INR) is often raised. Anaemia is frequent and is usually macrocytic. Leukopaenia and thrombocytopaenia may be found and may relate to hypersplenism. Electrolytes are usually normal but hyponatraemia is frequently found. (Conn & Attenbury 1993)

DIAGNOSIS

Decompensated cirrhosis can be suspected on clinical grounds; with typical laboratory findings and signs of complications, a diagnosis can be confidently made. However, compensated cirrhosis usually requires a liver biopsy for diagnosis as clinical findings may be confined to a small or large liver with or without an enlarged spleen. Imaging is used to evaluate a patient with cirrhosis but is not an accepted tool for diagnosis of cirrhosis although the finding of an irregular or shrunken liver is suggestive.

SPECIAL INVESTIGATIONS

Ultrasonography

Ultrasound examination is used in the complete evaluation of patients with cirrhosis for the following reasons:

1. *Assessment of liver size and shape*. This is useful when examination cannot accurately delineate liver size and shape, e.g. when the liver is displaced inferiorly by hyperinflated lungs, in the presence of ascites or in obese patients.
2. *Early detection of hepatocellular carcinoma*. Ultrasound can pick up early hepatocellular carcinoma, which will appear as a focal area of different echogenicity. It is however less sensitive than computerised tomographic scanning (CT) in tumour detection and staging (Redhead & Olliff 1995).
3. *Detection of small amounts of ascites*. Ultrasonography can detect volumes of ascites as small as 100 ml, and is far more sensitive than clinical assessment.
4. *Diagnosis of moderate-severe steatosis with cirrhosis*. Ultrasonography may suggest steatosis by demonstrating reduced echogenicity.
5. *Evaluation of portal hypertension*. Ultrasound allows the measurement of portal vein diameter; a diameter in excess of 15 mm is said to be diagnostic of portal hypertension. This has a specificity of 100% and sensitivity of about 50%. The presence of collateral veins can be detected by ultrasound in about 90% of patients with portal hypertension (Erlinger et al 1991). Splenomegaly, though not specific for portal hypertension, is also detected on ultrasound.
6. *Occlusion of portal or hepatic veins*. Ultrasound, particularly when combined with Doppler flow studies, may demonstrate the venous obstruction which may be associated with cirrhosis.

Computed tomography

A CT examination is not as useful as ultrasound in the evaluation of cirrhosis, except when hepatocellular carcinoma is suspected. It gives a better view of the extent of the tumour, especially if resection is planned. It is less sensitive and less specific than ultrasound in evaluation of portal hypertension (Erlinger et al 1991).

Endoscopy

Endoscopic examination is performed to diagnose oesophageal varices and to determine their size and extent. The varices can be graded, which may be of prognostic importance in assessing risk of rebleeding. Additionally it allows the recognition of portal hypertensive gastropathy and of peptic ulcer which are common in cirrhosis. Where biliary tract pathology is suspected, it may be coupled with endoscopic retrograde cholangiopancreatography (ERCP).

Liver biopsy

Liver biopsy is very important in the diagnosis of cirrhosis. It may suggest aetiology and allows assessment of inflammatory activity and of the extent of the disease. It is also important for the follow-up of most liver diseases. The biopsy may be performed by four routes: i) *percutaneous* liver biopsy, either blind or ultrasound-guided; ii) *transvenous* liver biopsy which is usually done via the transjugular approach; iii) *laparascopic* needle biopsy and iv) *wedge biopsy* at laparotomy or minilaparotomy.

The blind percutaneous liver biopsy is most commonly employed and is a safe procedure with a mortality rate of 0.01%. In the presence of minor coagulation problems, a plugged percutaneous liver biopsy can be done; in this technique, a Gelfoam plug is injected into the needle track to prevent bleeding. Additional coagulation support with fresh frozen plasma or platelets should however be given (Desmet & Fevery 1995). Ultrasound-guided biopsy is indicated for focal lesions. A transvenous liver biopsy is recommended in the presence of ascites or coagulopathy, in the assessment of hepatic vein obstruction and where portal pressure measurements are desired.

The diagnostic usefulness of the biopsy is maximised if there is close co-operation between the clinician and the pathologist. The clinician needs to supply all the relevant clinical and biochemical data as well as an adequate specimen to enable the pathologist to plan the processing and staining of the specimen. The biopsy specimen is stained with haematoxylin and eosin for conventional histopathological assessment. In specific cases, special stains are essential to the correct assessment (Desmet & Fevery 1995). These include:

1. *Stains for reticulin and collagen* which are important for accurate assessment of architectural changes and excessive matrix formation. These include the silver stain, Sirius red, chromotrope aniline blue, Masson's trichrome and Von Giesen stains.
2. *Perl's stain* for iron.
3. Shikata's *orcein stain* for hepatitis B surface antigen in hepatocytes.
4. *Immunohistochemical stains* for alpha-1 antitrypsin and viral antigens including HBsAg, HBcAg, HBeAg, hepatitis C, hepatitis D, herpes and cytomegalovirus (CMV) and an ever-increasing range of other applications.
5. *Special stains* and techniques may be applied to visualise specific features, e.g. amyloid is demonstrated with Congo Red under polarised light for amyloid; porphyrin crystals in erythropoietic protoporphyria may be viewed under polarised light or ultraviolet light.

6. *Electron microscopy* can be applied for further studies of biopsy specimens but is mainly *used for research purposes.*
7. *Biochemical measurements of iron and copper* are important in the assessment of haemochromatosis and Wilson's disease.

DIFFERENTIAL DIAGNOSIS

1. Differential diagnosis of compensated cirrhosis

One should consider conditions that cause abnormal liver function tests or portal hypertension such as:

i) *Chronic hepatitis* including hepatitis B and C virus, autoimmune hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency and drug-induced chronic hepatitis. Liver biopsy in these conditions may give the correct diagnosis.

ii) *Extrahepatic portal vein thrombosis* and *presinusoidal intrahepatic portal vein thrombosis.* Included amongst these are congenital hepatic fibrosis, hepatic schistosomiasis and regenerative nodular hyperplasia. Ultrasound examination may detect extrahepatic portal vein thrombosis and a biopsy is necessary for the intrahepatic causes.

2. Differential diagnosis of decompensated cirrhosis

There is a wide differential diagnosis in the patients with decompensated cirrhosis, who may present with one or more complications such as ascites, gastrointestinal bleeding and encephalopathy.

The differential diagnosis for ascites includes other chronic liver diseases, e.g. Budd-Chiari syndrome and veno-occlusive disease, as well as constrictive pericarditis. Ultrasound examination is useful in Budd-Chiari syndrome in which a markedly enlarged caudate lobe will be seen as well as abnormalities of the hepatic veins. Hepatic venography is often useful for chronic veno-occlusive disease, which has been seen following consumption of herbal teas containing pyrrolizidine alkaloids, chemotherapy for leukaemia and after hepatic irradiation. Liver biopsy is necessary for final diagnosis. Constrictive pericarditis characteristically causes gross ascites and hepatomegaly but no jaundice. The diagnosis can be made on clinical signs, by the recognition of pericardial calcification on radiographs, echocardiography, and if necessary, cardiac catheterisation.

Malignancy can also cause ascites. This may be a metastatic liver malignancy or a peritoneal malignancy, or occasionally, hepatocellular carcinoma. Ascitic fluid cytology, ultrasound and/or CT scan of the liver with guided liver biopsy is needed for diagnosis. Peritoneal biopsy may be necessary. Tuberculous peritonitis can present with ascites and the diagnosis is made on the basis of ascitic fluid analysis and peritoneal biopsy. Transudative ascites may be encountered in cardiac failure, renal failure, the nephrotic syndrome and with severe hypoalbuminaemia.

Gastrointestinal bleeding results from oesophageal varices and portal hypertensive gastropathy in cirrhosis as well as from peptic ulcer disease which is common in cirrhosis. In addition, bleeding can be from gastric erosions and occasionally from rectal varices. Endoscopy will determine the cause and the site of the bleeding.

Hepatic encephalopathy also has a wide differential diagnosis but the diagnosis can be narrowed down on history and other clinical findings. The differential diagnosis can be included in four groups of conditions – metabolic encephalopathies, toxic encephalopathies,

intracranial lesions and neuropsychiatric disorders (Riordan & Williams 1997). Metabolic encephalopathies include hypoglycaemia, electrolyte imbalance, hypoxia and uraemia. Blood biochemical analysis with clinical findings confirms the diagnosis. Toxic encephalopathies include alcohol intoxication, alcohol withdrawal and Wernicke-Korsakoff syndrome. Psychoactive drugs and certain toxins, e.g. heavy metals, may give a similar picture. Red blood cell transketolase, blood alcohol levels, therapeutic response to thiamine and toxicology will confirm the diagnosis. Intracranial lesions include subarachnoid, subdural and intracerebral haemorrhages, infarction, tumour abscess, meningitis and encephalitis. Lumbar puncture, CT scanning and/or angiography establish the diagnosis. Neuropsychiatric disorders may also present like hepatic encephalopathy and tests for organic brain syndromes are needed for diagnosis.

COMPLICATIONS

It is well known that once patients develop any of the major complications of cirrhosis, i.e. decompensation, the prognosis is poor. Indeed, they should be considered for liver transplantation. It has been estimated that the 5 year survival for patients who develop any of these complications is about 16% (Gines et al 1987). Decompensated patients present frequently to hospital for admission but studies of the frequency or reasons for admission in these patients and of the outcome of hospital treatment are lacking. The major complications of cirrhosis are ascites, spontaneous bacterial peritonitis, portal hypertensive variceal bleeding and hepatic encephalopathy, which are briefly discussed below.

Ascites

The formation of ascites in cirrhosis results from a combination of abnormalities in renal function as well as over-activity of the vasoconstrictor and anti-natriuretic systems which cause fluid retention and alter the haemodynamics of the portal and splanchnic circulation. These changes promote accumulation of the retained fluid in the peritoneal cavity (Gines et al 1997).

Sodium retention is the major factor in the pathogenesis of ascites formation and oedema as it causes extracellular volume expansion. The retention is secondary to increased sodium reabsorption from the renal tubules. Many factors are involved in the increased reabsorption but the most important are hyperaldosteronism and enhanced renal sympathetic activity.

Cirrhosis causes marked structural abnormalities in the liver which result in severe disturbance of hepatic and splanchnic circulation. Deposition of fibrous tissue and nodular formation alter normal vascular architecture and result in increased resistance to portal blood flow. The increased vascular resistance has effects both in the portal venous system and on the arterial side of the splanchnic circulation. In the venous side, there is development of portal hypertension and formation of collateral veins with portal systemic shunting of blood. On the arterial side there is marked arterial dilatation which increases portal venous inflow and contributes to increased pressure in the portal venous system. These changes predispose to ascites formation by increasing the filtration of fluid.

Theories of ascites formation

Two different mechanisms have been proposed for ascites formation, namely the overfill and the underfill theory.

1. The overfill theory

This theory suggests that there is a primary renal defect in sodium excretion which results in hypervolaemia. Reduction in systemic vascular resistance and increased cardiac output develop as a result of increased fluid retention. As the volume of the retained fluid increases, there is increased filtration of fluid into the interstitial space resulting in ascites and oedema.

2. Underfill theory

This theory proposes that sodium retention is a homeostatic response of the kidney to an underfilling of the arterial circulation secondary to arterial vasodilatation. The underfilling causes reduction in the effective arterial blood volume with a resultant increase in vasoconstrictive response and elevated anti-natriuretic factor secretion to compensate for the arterial underfilling. Since fluid is continuously leaking into the peritoneal cavity, the retained fluid cannot fill the intravascular compartment adequately and does not suppress sodium-retaining signals, thus creating a vicious cycle (Gines et al, 1997).

Treatment of ascites

Patients should be considered for transplantation. Those awaiting transplantation and those unsuitable for it are managed by dietary sodium restriction and diuretics. The diuretics used are a combination of furosemide and spironolactone and the dose can be increased to a maximum of 160 mg furosemide per day and 400 mg spironolactone per day, depending on the response. Dietary sodium restriction is the most important aspect as diuretics are essentially ineffective in the presence of a high sodium intake. This treatment is effective in controlling ascites or fluid overload in about 90% of patients (Runyon 1998).

Fewer than 10% of patients do not respond to this treatment and they should be considered for second-line therapy. These patients have refractory ascites which is defined as fluid overload unresponsive to sodium restricted diets and high-dose diuretic treatment. They have a poor prognosis with 50% of patients with refractory ascites dying within 6 months and 75% dying within 12 months.

Treatment options for refractory ascites include:

- Serial therapeutic paracentesis.
- Liver transplantation
- Peritoneal venous shunt
- Transjugular intrahepatic portal systemic stent shunt (TIPSS) (Runyon 1997).

These treatment options should be reserved for the patients who have failed adequate diuretic treatment.

Serial paracentesis should be performed as needed, which is usually every 2 weeks. Post-paracentesis albumin infusion may be unnecessary where a volume less than 5 litres is removed, albumin is expensive and has not been shown to decrease morbidity and mortality (Runyon 1997). However, where large volumes are withdrawn, albumin may be administered to maintain euvolaemia and to prevent renal decompensation.

Peritoneovenous shunting should be reserved for those patients who are not transplant candidates and are unsuitable for serial paracentesis because of previous abdominal surgery or inability to attend the hospital regularly.

TIPSS was initially recommended for treatment of variceal bleeding. It is now listed as one of the treatment modalities for refractory ascites. In uncontrolled trials, control in patients with diuretic-resistant ascites was achieved with this procedure (Runyon 1997).

Spontaneous bacterial peritonitis

A major complication of cirrhotic patients with ascites is spontaneous bacterial peritonitis (SBP). It is defined as bacterial infection of ascitic fluid in the absence of any intra-abdominal, surgically-remediable source of infection.

Several factors may predispose to SBP , including bacterial translocation across the gut wall promoted by a deficiency in local host immune defences, increased permeability of the intestinal mucosal barrier and intestinal bacterial overgrowth (Guarner & Soriano 1997). The deficient host immune defences described in cirrhotics include decreased reticulo-endothelial phagocytic activity, deficient opsonisation by the ascitic fluid and qualitative neutrophil dysfunction (Gomez et al 1994; Runyon 1998). Factors which facilitate the development of SBP are more severe liver disease, gastrointestinal haemorrhage, an ascitic fluid protein less than 10g/l and a previous episode of SBP.

A high index of suspicion is needed for the diagnosis of SBP. The diagnosis is confirmed by the determination of the ascitic fluid neutrophil count and on direct culture – fluid should be inoculated directly into blood-culture bottles. An ascitic fluid neutrophil count of more than 250 cells/ml is considered diagnostic of ascitic fluid infection. Cirrhotic patients with SBP frequently do not have typical signs of infection, and fluid should be aspirated and examined even when there is minimal suspicion of infection. It is suggested that an ascitic fluid analysis and culture should be performed in the following circumstances (Guarner & Soriano 1997):

- new onset ascites
- ascites present at the time of admission to hospital
- ascites accompanied by clinical signs and symptoms of infection
- ascites associated with a deterioration in clinical condition, including the development of impaired renal function

Third-generation cephalosporins and quinolones are the drugs of choice for treatment of SBP with a cure rate of more than 80%. Prophylactic selective intestinal decontamination with oral ofloxacin is useful in the prevention of SBP in high-risk patients, particularly those with repeated episodes (Guarner & Soriano 1997). It has been suggested that selective decontamination of the bowel with ofloxacin may predispose to the development of quinolone-resistant SBP in the future; practice has however shown this to be extremely uncommon (Llovet et al 1997).

The prognosis for patients with SBP is poor and 20-40% of patients die during that hospitalisation, usually from other complications of the underlying liver disease, such as gastrointestinal bleeding, renal failure or liver failure.

In the long term, 40-70% of survivors of an episode of SBP will develop another episode of SBP within one year. One-year survival after the first episode is 30-40% and is worse in patients with Child-Pugh Class C. In view of the poor prognosis, survivors of an episode of SBP should be considered for liver transplantation (Guarner & Soriano 1997).

Variceal bleeding

The most serious complication of portal hypertension is bleeding from ruptured oesophageal varices, which carries a mortality of 30-50%. In the presence of portal hypertension, collateral vessels open in the gastro-oesophageal, retroperitoneal, peri-anal and para-umbilical areas, as well as in the peritoneum and in areas of surgical anastamosis. Their effect is partially to decompress the portal system. Despite the presence of collaterals, a high portal pressure is maintained by increased splanchnic arterial flow. Distended gastro-oesophageal collaterals or varices are particularly hazardous in view of their propensity to rupture. The risk of bleeding from varices increases with severity of liver disease, variceal size and has been

correlated with the presence of so-called "cherry red spots", visible endoscopically, on the varices. It is also related to the pressure gradient between the portal vein and the inferior vena cava. Where less than 12 mm Hg, bleeding is unlikely, and the risk of bleeding is greatly reduced if a pressure reduction of 20% or more can be achieved in the portal system with therapy.

About 30% of patients with oesophageal varices will eventually bleed and the mortality is 50% with the first bleed. Patients who have bled once are likely to bleed again (Stanley & Hayes 1997). Not all gastrointestinal haemorrhage in the patient with varices is variceal in origin. Other causes include portal hypertensive gastropathy, also related to portal hypertension, or to causes such as peptic ulceration or gastritis; occasionally from varices in other sites such as the duodenum or rectum.

Management of variceal bleeding

Early resuscitation with colloid and blood is most important. Tracheal intubation may be required to protect the airway, particularly in the presence of a major haemorrhage or of encephalopathy.

Therapeutic endoscopy has been demonstrated to be the most efficacious form of therapy. It allows accurate identification of the source of bleeding followed by control of bleeding by injection sclerotherapy or variceal banding. Band ligation rather than sclerotherapy is now recommended, as, in comparison with sclerotherapy, it has been shown to reduce complications, speed the rate of variceal eradication, reduce bleeding rates and to reduce mortality (Stanley & Hayes 1997).

Pharmacological management with modern agents shows the same success rate as sclerotherapy in the immediate control of acute bleeding. Treatment can be initiated on admission to stabilise the patient prior to endoscopy. Vasopressin and its analogues are associated with significant side effects and are contraindicated in patients with known or suspected ischaemic cardiac disease. By comparison, somatostatin and its synthetic analogue octreotide are associated with a lower rate of complications and of side-effects. Octreotide is longer acting than somatostatin. Both are given as infusions. (Burroughs et al 1998). Pharmacological agents are useful when endoscopy is not available, but endoscopy should be arranged as soon as possible to confirm the source of the bleeding and to perform definitive treatment.

Balloon tamponade with the Sengstaken-Blakemore tube is life-saving in severe bleeding but placement by inexperienced people is associated with a 6-20% mortality rate from complications which include oesophageal perforation and pulmonary aspiration (Stanley & Hayes 1997).

TIPSS is the treatment of choice for the 10-20% of patients in whom endoscopic management fails. Failure may be defined as the occurrence of further variceal bleeding after two endoscopic treatments during a single hospital admission for an acute bleeding episode. TIPSS is however associated with hepatic encephalopathy which develops in about 20% of patients, and is frequently of temporary benefit only because of shunt occlusion.

Surgical portal systemic shunting is highly effective in the control of variceal haemorrhage, but is associated with a high rate of encephalopathy which has severely restricted its use. It has now largely been replaced by TIPSS but has a place in the management of severe, uncontrolled haemorrhage where TIPSS is unsuitable, as does oesophageal transection and devascularisation. Both represent major surgery in the decompensated patient and are associated with a high mortality.

Secondary prophylaxis

Rebleeding occurs in most patients, usually within a few weeks of the initial bleed. To prevent rebleeding, endoscopic variceal eradication by band ligation is recommended. Pharmacological agents are also used to prevent rebleeding. Beta-blockers are the drugs of choice, specifically non-cardioselective beta-blockers such as propranolol. They decrease portal pressure by reducing portal inflow as a result of a decrease in cardiac output caused by blockade of cardiac β-1 adrenoreceptors, as well as by causing splanchnic vasoconstriction secondary to blockade of vasodilatory β-2 adrenoreceptors in the splanchnic vasculature. For this reason, cardio-selective beta-blockers are less effective in reducing portal pressure than non-selective beta-blockers (Garcia-Pagan & Bosch 1997).

Beta-blockers appear to lower the risk of bleeding by about 40% and mortality rates by 20%. It has been suggested that beta-blockers and sclerotherapy have similar effects on the rate of rebleeding and that there is no benefit in combining the two, compared to the use of one alone; further studies are in progress to provide more information on this. (Stanley & Hayes 1997, Garcia & Bosch 1997) Addition of nitrates to beta-blockers has been reported to provide additional benefit.

Primary prophylaxis of variceal bleeding

Patients known to have varices may be candidates for primary prophylaxis, and possibly all cirrhotic patients should be endoscoped biennially to detect their presence. Beta-blockers are the drugs of choice and it has been claimed that the risk of bleeding is reduced by 45%. Nitrates may be used as alternatives to beta-blockers in patients who do not tolerate them and there are reports that a combination of beta-blockers and nitrates are superior to beta-blockers alone. Endoscopy with sclerotherapy is not recommended in primary prophylaxis since many patients will never bleed and sclerotherapy is associated with complications.

Gastric varices and portal hypertensive gastropathy

Gastric varices may also bleed and are more difficult to control endoscopically than those in the oesophagus. Endoscopic treatment should be attempted if the varices are in a hiatus hernia, or in the proximal part of the lesser curvature in combination with oesophageal varices. For other gastric varices, pharmacological treatment is used; if unsuccessful, early TIPSS or shunt surgery is recommended.

Portal hypertensive gastropathy is the term used to describe the intensely hyperaemic gastric mucosa which may be encountered in portal hypertension, and which may give rise to severe non-variceal haemorrhage. It accounts for bleeding in about 5-8% of cirrhotics. The bleeding is diffuse and may be slow, presenting with anaemia or severe. Pharmacological treatment or if necessary TIPSS or surgery are indicated for control of bleeding.

Orthotopic liver transplantation should be considered in any patients with cirrhosis and variceal bleeding. Should prior shunt surgery be necessary for control of bleeding, TIPSS should be employed rather than a surgical portal systemic shunt as the latter, by disturbing the venous anatomy and by causing adhesions and tissue distortion, render later transplantation hazardous.

Hepatic encephalopathy

In cirrhosis, acute encephalopathy is usually associated with one or more precipitating

Secondary prophylaxis

Rebleeding occurs in most patients, usually within a few weeks of the initial bleed. To prevent rebleeding, endoscopic variceal eradication by band ligation is recommended. Pharmacological agents are also used to prevent rebleeding. Beta-blockers are the drugs of choice, specifically non-cardioselective beta-blockers such as propranolol. They decrease portal pressure by reducing portal inflow as a result of a decrease in cardiac output caused by blockade of cardiac β-1 adrenoreceptors, as well as by causing splanchnic vasoconstriction secondary to blockade of vasodilatory β-2 adrenoreceptors in the splanchnic vasculature. For this reason, cardio-selective beta-blockers are less effective in reducing portal pressure than non-selective beta-blockers (Garcia-Pagan & Bosch 1997).

Beta-blockers appear to lower the risk of bleeding by about 40% and mortality rates by 20%. It has been suggested that beta-blockers and sclerotherapy have similar effects on the rate of rebleeding and that there is no benefit in combining the two, compared to the use of one alone; further studies are in progress to provide more information on this. (Stanley & Hayes 1997, Garcia & Bosch 1997) Addition of nitrates to beta-blockers has been reported to provide additional benefit.

Primary prophylaxis of variceal bleeding

Patients known to have varices may be candidates for primary prophylaxis, and possibly all cirrhotic patients should be endoscoped biennially to detect their presence. Beta-blockers are the drugs of choice and it has been claimed that the risk of bleeding is reduced by 45%. Nitrates may be used as alternatives to beta-blockers in patients who do not tolerate them and there are reports that a combination of beta-blockers and nitrates are superior to beta-blockers alone. Endoscopy with sclerotherapy is not recommended in primary prophylaxis since many patients will never bleed and sclerotherapy is associated with complications.

Gastric varices and portal hypertensive gastropathy

Gastric varices may also bleed and are more difficult to control endoscopically than those in the oesophagus. Endoscopic treatment should be attempted if the varices are in a hiatus hernia, or in the proximal part of the lesser curvature in combination with oesophageal varices. For other gastric varices, pharmacological treatment is used; if unsuccessful, early TIPSS or shunt surgery is recommended.

Portal hypertensive gastropathy is the term used to describe the intensely hyperaemic gastric mucosa which may be encountered in portal hypertension, and which may give rise to severe non-variceal haemorrhage. It accounts for bleeding in about 5-8% of cirrhotics. The bleeding is diffuse and may be slow, presenting with anaemia, or severe and fatal. Pharmacological treatment or if necessary TIPSS or surgery are indicated for control of bleeding.

Orthotopic liver transplantation should be considered in any patients with cirrhosis and variceal bleeding. Should prior shunt surgery be necessary for control of bleeding, TIPSS should be employed rather than a surgical portal systemic shunt as the latter, by disturbing the venous anatomy and by causing adhesions and tissue distortion, render later transplantation hazardous.

Hepatic encephalopathy

In cirrhosis, acute encephalopathy is usually associated with one or more precipitating

factors such as. gastrointestinal bleeding, infection, over-diuresis, inappropriate sedation, a high-protein meal, renal failure, hypokalaemia, severe alkalosis, an alcohol binge, portal systemic shunting, worsening hepatic damage and the development of hepatoma. However, patients may have recurrent episodes of hepatic encephalopathy without any precipitating factors; this is termed *chronic recurrent encephalopathy*. Patients may also develop irreversible neurological deficits, known as *chronic persistent encephalopathy* or *hepatocerebral degeneration* (Cordoba & Blei 1997).

The most frequent neurological disturbance in cirrhosis is a mild cognitive impairment which may only be detected on psychometric testing. This is termed *subclinical encephalopathy* and may be present in 50-70% of all patients with cirrhosis.

Different mechanisms have been proposed for the development of hepatic encephalopathy. They include the following:

1. **Ammonia hypothesis**. There is accumulation of unmetabolised ammonia because of poor hepatic function and portal systemic shunting.

2. **False neurotransmitter hypothesis**. Aromatic amino acids (phenylalanine, tyrosine and tryptophan) increase at the expense of branched-chain amino acids (leucine, isoleucine and valine) with a reversal of the normal ratio. This is postulated to lead to the production of false neurotransmitters that may promote hepatic encephalopathy.

3. **Gamma-amino butyric acid (GABA)** hypothesis. There is an increase in the concentration of benzodiazepine-like substances that bind to the benzodiazepine-binding site of the GABA receptor and enhance its inhibitory action.

4. **Other hypotheses** include a reduction in the concentration of enzymes required for the urea cycle owing to zinc deficiency, and deposition of manganese in the basal ganglia.

Treatment that is of proven efficacy for hepatic encephalopathy is based on the ammonia hypothesis; there are other experimental treatments based on some of the other hypotheses.

Treatment of encephalopathy

Acute encephalopathy

This is usually associated with a precipitating factor but occasionally may develop spontaneously in patients with advanced cirrhosis and large portal systemic shunts. Treatment is based on correction of the precipitating factor and dietary protein restriction. Protein must not however be restricted unnecessarily and must be reintroduced once the patient improves.

Lactulose (beta galactofructose), a non-absorbable disaccharide, is the treatment of choice. It works by removing dietary and endogenous ammonia-producing substances in the gastrointestinal tract by its osmotic cathartic action. In addition, lactulose lowers colonic pH by the production of organic acids through bacterial fermentation. The decreased pH reduces urease-producing intestinal bacteria and thus reduces the production of ammonia in the colon. If oral administration or nasogastric tube administration is impossible, lactulose enemas may be used. The aim is to produce 2-4 soft, acidic stools per day. In lactose-intolerant subjects, lactose is as effective as lactulose.

Neomycin is also effective but is rarely used initially because of its ototoxic and nephrotoxic potential. Metronidazole may also be used over short periods as it has activity against urease producing organisms but is again associated with significant side-effects.

Chronic encephalopathy

Treatment for chronic encephalopathy is with dietary protein restriction and lactulose. Patients with TIPSS, surgical or spontaneous portal systemic shunts are also treated by protein restriction and lactulose, but embolisation or surgical ligation of portal systemic shunts may be beneficial if encephalopathy is refractory. In TIPSS, refractory encephalopathy can sometimes be managed by implanting a reducing stent.

Most patients will respond to the above measures. Patients who, in spite of these treatments, do not improve or develop recurrent encephalopathy need evaluation to exclude other disorders resembling encephalopathy or other occult precipitating factors, such as zinc deficiency. If no precipitating factors are found, one should search for large, spontaneous portal systemic shunts by Doppler ultrasound. If present, one may embolise or surgically reduce them (Cordoba & Blei 1997).

Management of encephalopathy should include evaluation for transplantation in appropriate candidates but the decision is difficult in patients with chronic encephalopathy because of the possibility of hepatocerebral degeneration with permanent neurological deficits.

PROGNOSIS

In 1964, Child and Turcott developed a system which was used to assess the risk of surgery in patients with liver disease and which was modified by Pugh et al (1973). This is now known as the Child-Pugh classification. This classification has been used for many years in the assessment of prognosis in cirrhotic patients. In this classification, five parameters are each given 1,2 or 3 points depending on severity and the scores from each variable are added together. The patients are divided into 3 strata depending on the score, which will range from 5-15. Those who score 5-6 are assigned to Child-Pugh class A, those who score 7-9 to class B and those who score 10-15 to class C. The classification is reproduced in the Table 1.4. In patients with primary biliary cirrhosis, the level of bilirubin is usually out of proportion to other evidence of liver failure so the scoring for bilirubin is different. Hepatic encephalopathy in this score is based on the staging of Trey et al (1966) (Table 1.5).

This score discriminates well between survivors and non-survivors, and since it is simple, easily available and cheap to employ, it has been very useful for prognostication in patients with cirrhosis (Infant-Rivard et al 1987).

When orthotopic liver transplantation became available for the definitive treatment of cirrhosis, a number of studies were done to allow for more accurate prognostication and therefore timing of liver transplantation in patients with cirrhosis. In these studies, the effects of different variables on the prognosis of cirrhosis were studied. In a Spanish study, Gines et al found that 42% of patients with compensated cirrhosis remained well-compensated after 10 years. Female sex, lower age and the absence of stigmata of chronic liver disease, as well as lower level of serum gamma globulin and alkaline phosphatase at the time of diagnosis were independent predictors of survival in a multivariate analysis (Gines et al 1987).

In a study of compensated and decompensated cirrhosis, Italian workers found that in compensated patients significant predictors of death were male sex, hepatitis B surface antigen positivity, increasing age, prolongation of the prothrombin time and oesophageal varices. In decompensated patients, significant indicators of death were hepatocellular carcinoma, encephalopathy, haemorrhage, higher AST levels, oesophageal varices, higher gamma globulin levels, prolongation of the prothrombin time, continued abuse of alcohol, hepatitis B surface antigen positivity, elevated GGT and reduced cholinesterase levels (D'Amico et al 1986).

Other studies have used different models to predict survival and prognosis of cirrhosis but there is no proof that the newer models are better than the Child-Pugh score and they are not used in most centres. All studies showed that development of one or more complications indicates a substantially worse prognosis in cirrhosis and therefore a decision on transplantation should be made as soon as complications are noted.

	Points scored for increasing abnormality		
Clinical & biochemical measurements	**1**	**2**	**3**
Encephalopathy (Grade)	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/l)	>35	28-35	<28
Prothrombin (seconds prolonged)	1-4	4-6	>6
For primary biliary cirrhosis bilirubin (mg/dL	1-4	4-10	>10

Table 1.4. Child-Pugh grading of the severity of liver disease

Stage	Mental state	Tremor	EEG changes
Stage 1 Prodrome (often diagnosed in retrospect)	Euphoria, occasionally depression; fluctuant mild confusion; slowness of mentation and affect; untidy slurred speech; disorder in rhythm	Slight	Usually absent
Stage 2 Impending coma	Accentuation of stage 1; drowsiness; inappropriate behaviour; ability to maintain sphincter control	Present (easily elicited)	Abnormal; general slowing
Stage 3 Stupor	Sleeps most of time but rousable; speech incoherent; confusion marked	Usually present if patient co-operative	Always abnormal
Stage 4 Deep coma	May or may not respond to painful stimuli	Usually absent	Always abnormal

Table 1.5. The staging of hepatic coma

CHAPTER 2: DESIGN OF THE STUDY

INTRODUCTION

Groote Schuur Hospital (GSH) is a large academic hospital Cape Town. It serves a population of about 2 million, comprising three population groups, black people of African origin, coloured, who are people of Asian or mixed origin, and white – of European descent. The hospital serves as a secondary referral centre for the surrounding regions, as a tertiary referral centre for the Western Cape province and much of the Eastern Cape province, and as a quaternary super-specialist centre for certain services, including liver and cardiac transplantation, for much of South Africa.

A significant number of patients with cirrhosis present for the first time at Groote Schuur Hospital with decompensation and a diagnosis of cirrhosis is made on the basis of association of signs of liver failure, portal hypertension, radiological features consistent with cirrhosis with or without a proven cause of cirrhosis (personal observation). A study in Italy and another study done in Birmingham showed that a proportion of 63% and 65% respectively of patients have decompensated cirrhosis when first seen and in the English study the figure was unchanged in 18 years (Saunders et al 1981, D'Amico et al 1986).

Most patients with cirrhosis remain compensated for many years and have a relatively long life expectancy. Clinical decompensation, which is evidenced by the development of one or more complications, has a poor prognosis. The high rate of repeated consultations in patients with cirrhosis confirmed the high morbidity associated with this condition (Dufour et al 1993). In the United States between 1973 and 1983, cirrhosis mortality declined by one third to 10.2/100 000 deaths and the decline continued through to 1987 when the death rate reduced to 9.2/100 000 deaths. Furthermore, an increase in morbidity was observed with this decreasing mortality rate (Noble et al 1993).

AIM OF THE STUDY

Accordingly, this study was intended to delineate the demographic and clinical profile of patients with cirrhosis admitted to our hospital, to assess the relative importance of the various underlying causes of cirrhosis, to assess the frequency of complications of cirrhosis and describe their presentation and management, to assess the outcome of treatment and to estimate its cost.

METHODS

Patients

All patients admitted to Groote Schuur Hospital have their diagnoses coded according to the International Classification of Diseases No. 9 (ICD-9); these are captured on computer. A sample of those patients with a computer-coded diagnosis of cirrhosis, which is under code 571, were retrospectively studied. Names of patients with the codes indicated in Table 2.1 were retrieved from the hospital computer system. Patients with the code for chronic hepatitis (code 571,4) were not eligible for this study and were not retrieved.

571	*Chronic liver disease and cirrhosis*
571.0	Alcoholic fatty liver
571.1	Acute alcoholic hepatitis
571.2	Alcoholic cirrhosis of liver
571.3	Alcoholic liver damage, unspecified
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.8	Other chronic non-alcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol

Table2.1. ICD-9 classification categories used for preliminary search for eligible subjects.

Inclusion criteria

Patients were eligible for study if they fulfilled the following criteria:

- Review of the hospital folder confirmed that the diagnosis of cirrhosis was correct
- They had been admitted for a period exceeding 24 hours on at least one occasion during the period 1/1/1993 and 31/12/1996.

Exclusion criteria

Patients were excluded for the following reasons:

- They carried a diagnosis of alcoholic fatty liver, acute alcoholic liver disease, alcoholic hepatitis, cholangitis, portal hypertension, or congenital hepatic fibrosis with no evidence of cirrhosis.
- The period of admission was less than 24 hours
- The hospital records were incomplete
- Patients admitted solely for the purpose of immediate transplantation were excluded as they represent a highly selected group.

Subjects

413 candidates carrying the ICD-9 tags listed above were returned by the hospital computer system in random order. Of these, the first 98 folders were drawn and inspected further. The diagnosis of cirrhosis was confirmed by review of clinical and laboratory data, and all admissions between 1 January 1993 and 31 December 1996 were studied. Of the 98 folders drawn, 13 were excluded for the following reasons:

- The folders of 2 patients with apparent cirrhosis contained no data for the period of their admissions
- 11 patients were excluded because a diagnosis of cirrhosis was not substantiated; the contributory diagnoses were congenital hepatic fibrosis (2), portal fibrosis (2), tuberculous peritonitis, chronic suppurative lung disease, porphyria cutanea tarda, Korsakoff amnestic syndrome, severe cardiac failure, myelodysplastic syndrome and acute hepatitis B.

Thus, 85 of 98 folders (87%) surveyed fulfilled the inclusion criteria. Assuming, as seems reasonable, that the 98 folders were representative of the entire 413 patients returned by the hospital computer, we may deduce that the total population of patients with cirrhosis who were admitted to GSH during the study period would be approximately 358 patients (87% of 413 records).

These 85 folders, as a pilot sample of all those admitted, were then studied in detail.

RECORDING AND ANALYSIS OF DATA

The study set out to record all relevant data in terms of demography, diagnosis, how the diagnosis was made, severity, biochemical and haematological profiles, the presence of complications, utilisation of investigations and specific interventions such as surgery or endoscopy, and outcome. The following data were extracted from the folders by the author of this dissertation and recorded on a proforma sheet. The data were then captured on a personal computer in a custom-designed dBaseIV database (Borland International Inc, Scotts Valley, USA).

Data were analysed on a personal computer using Microsoft Access and Microsoft Excel (Microsoft Corporation, Seattle, USA); statistical calculations were made with the Statistica 98 edition software package (StatSoft Inc, Tulsa, USA). The graphs which appear below were prepared using Statistica or Microsoft Ecel 97 as appropriate.

Nature of the data recorded

Demography:

a) Name of patient and folder number
b) Age, sex and race.

Basis on which diagnosis was established:

More than one answer is possible

a) Biopsy-proven
b) Radiological
c) Clinical

Cause of cirrhosis:

More than one answer is possible

a) Alcohol
b) Iron overload
c) Hepatitis C virus
d) Hepatitis B virus
e) Primary biliary cirrhosis
f) Primary sclerosing cholangitis
g) Congenital
h) Cryptogenic
i) Other

Principal reasons for admission:

More than one answer is possible

a) Investigation/diagnosis
b) Transplant assessment
c) Ascites

d) Encephalopathy
e) Gastrointestinal haemorrhage
f) Other haemorrhage
g) Spontaneous bacterial peritonitis
h) Other infection
i) Renal failure
j) Hepatoma
k) Other problems

Investigations:

a) Liver function tests: total protein, albumin, globulin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT)
b) Electrolytes: - sodium, potassium, urea and creatinine
c) Alpha fetoprotein (AFP)
d) Haematological parameters: - haemoglobin (Hb), white cell count (WCC), platelet count, mean corpuscular volume (MCV) and international normalised ratio (INR)
e) Microbiological results: - blood culture, ascitic white cell count, , ascitic fluid culture,

Other investigations and procedures:

a) Chest x-rays
b) Ultrasound scans
c) Computerised tomography (CT) scans
d) Magnetic resonance imaging (MRI)
e) Endoscopic retrograde cholangiopancreatography (ERCP)
f) Endoscopy
g) Variceal injections
h) Paracentesis
i) Laparotomy
j) Any other procedures

Problems arising during hospital stay:

a) Ascites
b) Encephalopathy
c) Gastrointestinal haemorrhage
d) Other bleeding
e) Spontaneous bacterial peritonitis (SBP)
f) Other infection
g) Renal failure
h) Hepatoma
i) Alcohol withdrawal
j) Confusion not due to encephalopathy
k) Temperature
l) Other problems

Course and outcome

a) Number of admissions between 1 January 1993 and 31 December 1996
b) Number of days in hospital and number of days in intensive care unit (ICU)
c) Whether died during the admission or discharged
d) Whether known to have died subsequent to the admission and discharge.

CHAPTER 3: RESULTS

PATIENT COMPOSITION

85 patients were reviewed. There were 57 coloured patients, 14 black patients and 14 white patients, comprising 67.1%, 16.5% and 16.5% respectively. The percentage contribution of each group is shown in Table 3.1 and is compared with percentages of the hospital as a whole and for the Western Cape. The hospital figures are derived from hospital records for 1995, kept by the Medical Informatics Unit of Groote Schuur Hospital, and the population figures for the Western Cape from the 1996 census.

	This study	GSH profile	W Cape profile
Black	16.5	28	20.9
Coloured	67.1	62	54.2
White	16.5	10	20.8

Table 3.1. Distribution of patients by population group, compared with the distributions in the GSH patient population and in the Western Cape.

Gender and age

49 patients were male (57.6%) and 36 were female (42.4%) with a male-to-female ratio of 1.36:1. There is no significant difference in the mean age according to sex but the distribution of age at admission is different for male and female patients as shown in Table 3.2 and Figure 3.1. Male admissions peak between 40 and 70 years but are more evenly distributed between the ages of 30 and 90 years in female patients. The mean ages according to race are shown in Table 3.3. The mean age of white patients is significantly higher than that of coloured patients (p=0.009 student t test); the difference between white and black patients did not reach statistical significance, probably because of the small sample size.

	Mean age ±SD	Range
All patients	55.5±14.5	15 - 87
Females	57.0±18.5	15 - 87
Males	54.4±10.8	25 - 78

Table 3.2. Age in years on admission by sex.

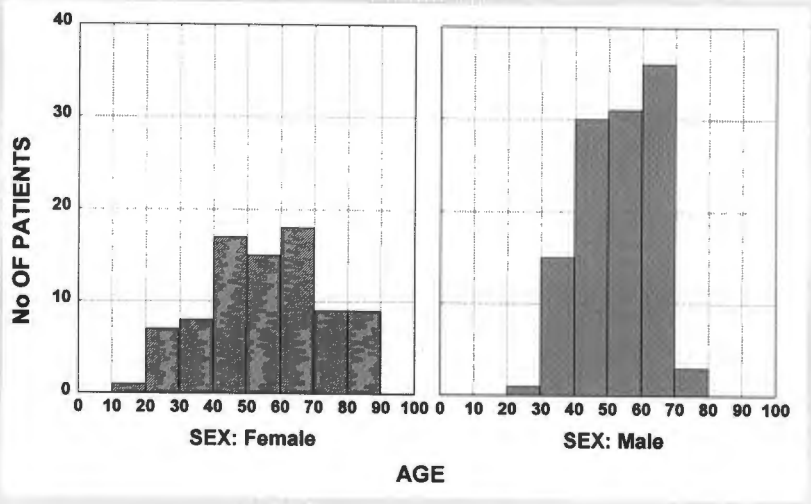

Figure 3.1. Age on admission by sex

	n	Age
Black	14	58.5±11.8 (39-79)
Coloured	57	53.2±14.6 (15-86)
White	14	60.5±15.3 (25-87)

Table 3.3 Age distribution by race.

DIAGNOSIS OF CIRRHOSIS

A diagnosis of cirrhosis was confirmed histologically on liver biopsy in 30 of the 85 patients (35%). In the remainder, the diagnosis was presumed on the basis of a typical clinical appearance; in some cases, ultrasound or CT scanning had been suggestive. Of the 68 patients with alcoholic cirrhosis, 19 or 27.9% had had liver biopsies performed whereas of 17 patients with no history of alcohol, 11 (65%) had had liver biopsies. Of the 12 patients with both alcoholic cirrhosis and viral infection, only 1 patient (8%) had had a liver biopsy performed.

AETIOLOGY OF CIRRHOSIS

Cirrhosis was classified as viral if hepatitis B surface antigen was positive and/or hepatitis C virus antibodies were positive. Only 3 patients had hepatitis C viral PCR for RNA done, of which 1 was negative whilst the antibodies were positive. This patient was counted as hepatitis C virus negative. The presumed causes of cirrhosis are shown in Table 3.4 below. Table 3.5 shows the aetiology of cirrhosis according to gender and race. Table 3.6 shows the proportion of patients according to race in whom viral infection played a role in the aetiology of cirrhosis.

71.4% of males had alcoholic cirrhosis compared to 58.3% of females; the difference is significant (p=0.002, based on Pearson's χ^2). The male-to-female ratio for alcoholic cirrhosis is 1.7:1; for viral cirrhosis it is 2:1, whilst for other causes of cirrhosis it is 1:4.5. Viruses co-existed with alcohol in 20.4% of the males.

Four males (8.2%) with no history of alcohol had the following causes of cirrhosis: hepatitis B virus, hepatitis C virus, congenital and cryptogenic cirrhosis.

Cause	Male	Female	Total
Alcohol alone	35	21	56
Alcohol with HBV	3	0	3
Alcohol with HCV	5	1	6
Alcohol with HBV and HCV	2	1	3
All alcohol (with or without viral infection)	**45**	**23**	**68**
HBV alone	1	1	2
HCV alone	1	3	4
HBV with HCV	0	0	0
All HBV or HCV (with or without alcohol)	**12**	**6**	**18**
Iron overload	0	1	1
Cryptogenic	1	3	4
Autoimmune	0	1	1
Biliary stricture	0	1	1
PBC	0	2	2
Congenital	1	1	2
Neither viral nor alcohol	**2**	**9**	**11**

Table 3.4. Aetiology of cirrhosis in 85 patients.

	Black			Coloured			White		
Sex	**M**	**F**	**Total**	**M**	**F**	**Total**	**M**	**F**	**Total**
Alcohol	6	3	9 (64%)	24	13	37 (63%)	4	5	9 (64%)
Alcohol+virus	3	0	3 (21%)	5	2	7 (12%)	1	0	1 (7%)
Virus alone	1	0	1 (7%)	1	3	4 (7%)	0	1	1 (7%)
Other	1	0	1 (7%)	3	6	9 (16%)	2	1	3 (21%)
Total	11	3	14	33	24	57	7	7	14

Table 3.5. Aetiology of cirrhosis according to gender and race. M: Male; F: female.

	Black	Coloured	White
HBV alone	2 (14.3%)	1 (1.8%)	0 (0%)
HCV alone	1 (7.2%)	7 (12.3%)	1 (7.2%)
Both HBV and HCV	3 (21.4%)	3 (5.3%)	0 (0%)
Total	**6 (42.9%)**	**11 (19.3%)**	**1 (7.2%)**

Table 3.6. Distribution of viral infection.

Figure 3.2 suggests that patients with a combination of alcoholic and viral liver disease present at a younger age than those with alcohol alone who in turn present younger than those with viral infection alone; Fig 3.2b however shows that this is in fact to the rather slower onset of hepatitis C-associated cirrhosis; hepatitis b-associated cirrhosis as an earlier onset..

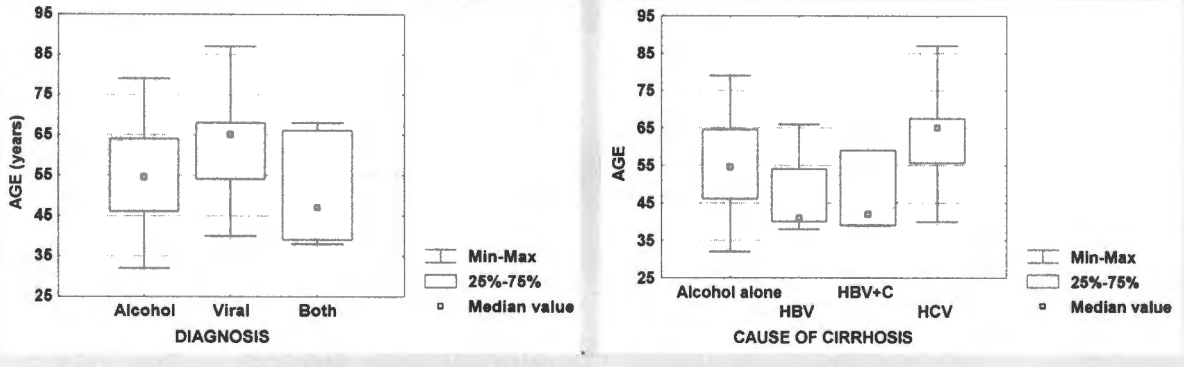

Figure 3.2. The median age on admission is dependent on the diagnosis; and is lower in alcohol-associated cirrhosis than in viral cirrhosis, and is earlier still where both are present (2a). However, subgroup analysis suggests that HBV-associated cirrhosis (with or without associated alcohol) presents earlier than alcoholic cirrhosis alone; HCV-associated cirrhosis (with or without alcohol) presents later than alcoholic cirrhosis alone (2b).

Thirteen females (36.1%) had no history of alcohol, and the causes of cirrhosis listed were hepatitis B virus, hepatitis C virus (3 patients), iron overload, autoimmune, cryptogenic (3 patients), primary biliary cirrhosis (2 patients), biliary stricture and congenital cirrhosis.

For the whole group of 85 patients, alcohol alone accounts for 56 cases of cirrhosis (65.8%). Viruses account for 18 patients with cirrhosis (21.2%) including 12 in whom there is alcohol involvement as well. Viruses are thus involved in 21.2% of patients with cirrhosis. Viral infection played a role in 43% of black patients, 19% of coloured patients and 7% of white patients.

PRINCIPAL REASONS FOR ADMISSION

Patients with cirrhosis are commonly admitted to hospital because of decompensation with evidence of one or more major complications of cirrhosis. Occasionally they are admitted electively for investigation only or assessment for liver transplantation and sometimes for an

unrelated problem. The number of admissions over the 4-year period is shown in Table 3.7. There is no significant difference in the number of admissions by gender or by race. Table 3.8 shows the principal reasons for admission ranked in the order of frequency. The five most frequent reasons for admission are GIT haemorrhage (31.5%), encephalopathy (27.6%), ascites (24.6%), infections (16.3%) and for investigation (14.8%). Figure 3.3 indicates that patients who suffered gastrointestinal haemorrhage were more likely to require repeated admissions than those who did not.

No. admissions	Mean ± standard deviation	Range
All patients	3.6±2.0	1 - 8
Female	3.9±2.4	1 - 8
Male	3.3±1.7	1 - 7
Black	3.4±1.5	1 - 5
Coloured	3.5±2	1 - 7
White	4±2.3	1 - 8

Table 3.7. Number of admissions by gender and race over the four-year period.

GIT haemorrhage	64 (31.5%)	Dehydration	6 (3.0%)
Encephalopathy	56 (27.6%)	Hernia repair	6 (3.0%)
Ascites	50 (24.6%)	Other haemorrhage	6 (3.0%)
Infections other than SBP	33 (16.3%)	Heart failure	5 (2.5%)
For investigation	30 (14.8%)	Stroke	4 (2.0%)
Acute alcoholic hepatitis	11 (5.4%)	Transplant assessment	2 (1.0%)
SBP	8 (3.9%)	Hepatoma	2 (1.0%)
Renal failure	7 (3.4%)		
Subtotals			
All haemorrhage	70 (34.5%)	All infections	41 (20.2%)

Table 3.8. Principal reasons for admission.

LABORATORY VALUES

Biochemical results

Tables 3.9 and 3.10 show the biochemical results encountered in these patients. Table 3.9 reflects the average, minimum and maximum values measured across all admissions; Table 3.10 indicates the proportion of our total study population who fell outside the normal range,

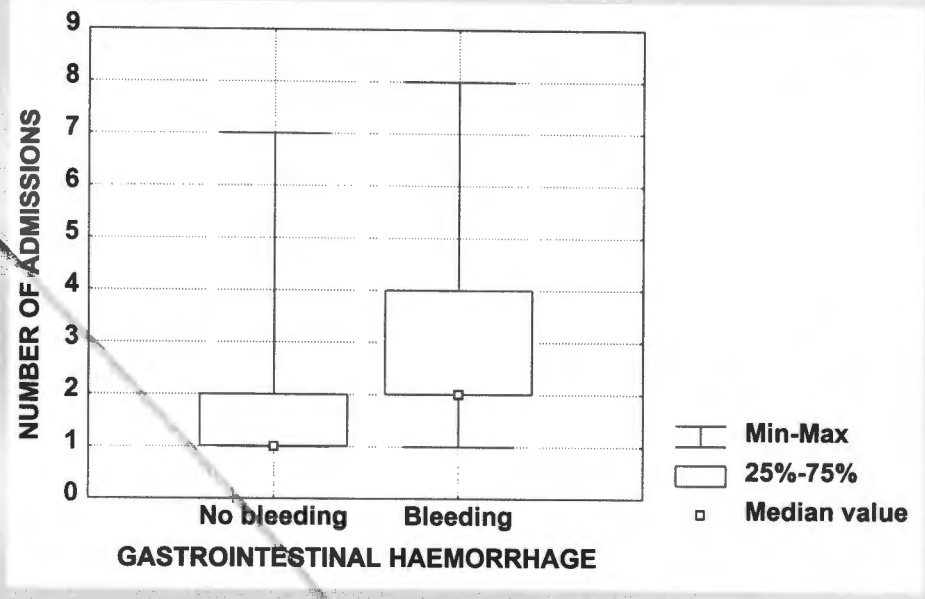

Fig 3.3. Number of admissions per patient during the period of the study categorised by the presence of gastrointestinal haemorrhage at any stage of the study.

or outside the significant values indicated, at any stage during the period of the study.

87.1% of the patients had an albumin less than 35 and in 70.6% it was less than 30. 90.6% had bilirubin more than 17 and in 62.4% it was more than 40, suggesting clinical jaundice. AST was raised in 90.6% of patients and was raised to twice normal value in 70.6% compared to ALT, which was raised in 62.4% and raised to twice normal value in only 30.6%. More than 50% of patients had alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) more than twice normal. Table 3.11 shows the AST/ALT ratio in different causes of cirrhosis. There is a significant difference in the AST/ALT ratio in patients with alcoholic cirrhosis with or without viral infection and patients with viral cirrhosis without alcohol. It is significantly higher in alcoholic cirrhosis (p=0.018 by ANOVA).

Variable	n	Mean±standard deviation	Min	Max
Total protein	164	72.2±11.8	32	124
Albumin	166	28.0±6.7	13.0	48
Globulin	163	44.3±12.0	11.0	97.0
Bilirubin	166	95.9±125.1	4.0	818.0
AST	164	100.8±209.7	14.0	2160.0
ALT	164	39.9±58.4	5.0	510.0
AST/ALT				
ALP	162	162.9±115.0	51	722.0
GGT	73	232.2±285.7	12.0	1434.0

Table 3.9. Biochemical values averaged over all admissions.

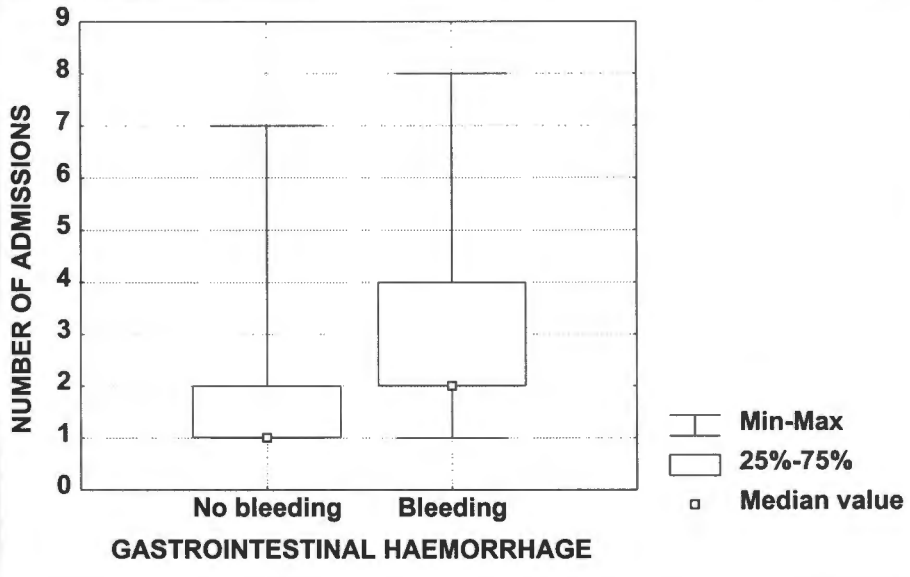

Fig 3.3. Number of admissions per patient during the period of the study categorised by the presence of gastrointestinal haemorrhage at any stage of the study.

or outside the significant values indicated, at any stage during the period of the study.

87.1% of the patients had an albumin less than 35 and in 70.6% it was less than 30. 90.6% had bilirubin more than 17 and in 62.4% it was more than 40, suggesting clinical jaundice. AST was raised in 90.6% of patients and was raised to twice normal value in 70.6% compared to ALT, which was raised in 62.4% and raised to twice normal value in only 30.6%. More than 50% of patients had alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) more than twice normal. Table 3.11 shows the AST/ALT ratio in different causes of cirrhosis. There is a significant difference in the AST/ALT ratio in patients with alcoholic cirrhosis with or without viral infection and patients with viral cirrhosis without alcohol. It is significantly higher in alcoholic cirrhosis (p=0.018 by ANOVA).

Variable	n	Mean±standard deviation	Min	Max
Total protein	164	72.2±11.8	32	124
Albumin	166	28.0±6.7	13.0	48
Globulin	163	44.3±12.0	11.0	97.0
Bilirubin	166	95.9±125.1	4.0	818.0
AST	164	100.8±209.7	14.0	2160.0
ALT	164	39.9±58.4	5.0	510.0
AST/ALT		2.6±1.4	0.3	10.1
ALP	162	162.9±115.0	51	722.0
GGT	73	232.2±285.7	12.0	1434.0

Table 3.9. Biochemical values averaged over all admissions.

Variable	Cut-off value	n	Cut-off exceeded	Cut-off exceeded %
Total protein	>80	85	26	22.1
	<60	85	17	14.5
Albumin	<35	85	74	87.1
	<30	85	60	70.6
Bilirubin	>17	85	77	90.6
	>40	85	53	62.4
AST	>25	85	77	90.6
	>50	85	60	70.6
ALT	>25	85	53	62.4
	>50	85	26	30.6
AST/ALT	>2	85	57	67.0
ALP	>70	83	79	95.2
	>140	83	43	51.8
GGT	>50	47	36	76.6
	>100	47	31	66

Table 3.10. Proportion of patients showing biochemical values outside the normal range or beyond some significant levels at any stage of the study.

Alcohol	2.71
Alcohol+HBV or HCV	2.49
HBV or HCV	1.63
Other	2.50

Table 3.11. AST/ALT ratios

Electrolytes

These are shown in Table 3.12 and 3.13 below. The mean sodium was significantly lower in males than in females ($p=0.014$ Mann-Whitney U test) (Fig 3.4.). There was a trend to a lower sodium in alcoholic rather than viral cirrhosis ($p=0.08$; Mann-Whitney U test) with median values of 136 and 139 mmol/l. A correlation of sodium with Child-Pugh score showed a highly significant correlation ($p<0.001$, Pearson Product-Moment correlation), and a significant association between hyponatraemia and ascites ($p=0.003$, Student's t test). These results are discussed further in the following chapter.

Variable	n	Mean (S.D.)	Min	Max
Sodium	187	136±5.7	106	146
Potassium	187	4.1±0.8	2.1	8.2
Urea	185	7.7±8.2	0.4	74
Creatinine	187	115±104	44	1019

Table 3.12. Electrolyte values averaged over all admissions.

Variable	Cut-off	n	Exceeded	% Exceeded %
Sodium	<135	84	39	46.4
Potassium				
Urea	>6.7	84	38	45.2
Creatinine	>115	84	29	34.5

Table 3.13. Proportion of patients showing electrolyte values outside the normal range or beyond some significant levels at any stage of the study.

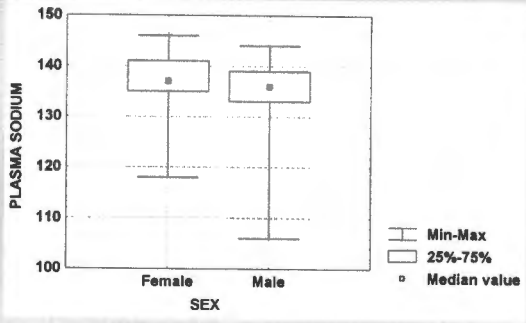

Figure 3.4. Hyponatraemia is correlated with sex.

Haematological results

The mean haematological values are shown in Table 3.14; Table 3.15 indicates the proportion of our total study population who fell outside the normal range, or outside the significant values indicated, at any stage during the period of the study. INR was abnormal in 74.4% of patients and was more than 2 in 28.8% of patients. Anaemia was present in 78.3% of the patients and in 53% of the patients, the haemoglobin was less than 10. 22.9% had leucopenia and 56% had a thrombocytopenia of less than 100. The mean cell volume (MCV) was raised in 66.3% of patients.

Table 3.16 shows the white cell count in infected and non-infected patients. Infected patients are defined as those in whom the presence of infection as a significant factor was recorded in the notes. Figure 3.4a shows the white cell count according to the presence or absence of

infection, while Figure 3.4b shows the white cell count categorised by the cause of the cirrhosis and suggests that the white cell count is lower in viral cirrhosis than in alcohol-associated cirrhosis. Figure 3.5 shows the MCV in alcohol and viral cirrhosis and shows that this correlates poorly with cause.

Variable	n	Mean (SD)	Min	Max
INR	152	1.7 ± 0.7	0.9	4.5
HB	117	10.4 ± 2.8	1.9	17.0
White cell count	166	8.6 ± 5.6	0.9	31.2
Platelets	166	133 ± 88	13	568
MCV	158	96.9 ± 10.8	66	113

Table 3.14. Haematological values averaged over all admissions.

Variable	Cut-off	n	Cut-off exceeded	Cut-off exceeded %
INR	>1.3	78	58	74.4
	>=2	78	25	25.6
HB	<12	83	65	78.3
	<10	83	44	53
White cell count	>11	83	33	39.8
	<4	83	19	22.9
Platelets	<150	82	61	74.4
	<100	82	46	56
MCV	>94	80	53	66.3
	>=100	80	41	51.2

Table 3.15. Proportion of patients showing haematological values outside the normal range or beyond some significant levels at any stage of the study.

Infection	n	Mean (S.D.)	Median	Minimum	Maximum
Infection present	44	10.2 (7.0)	8.1	0.9	31.2
No infection	122	8.1 (7.5)	7.0	2.1	30.1

Table 3.16. White cell count in patients with and without infection.

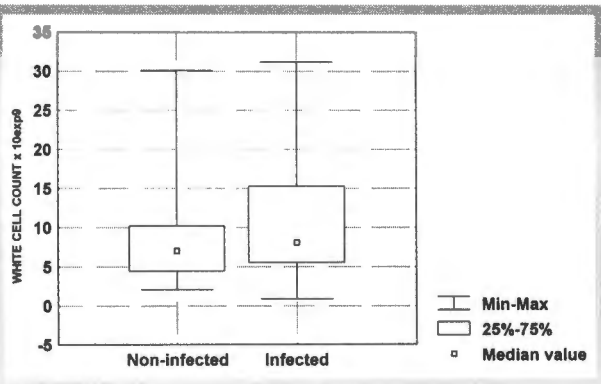

Figure 3.4a. Correlation between WCC and presence or absence of infection.

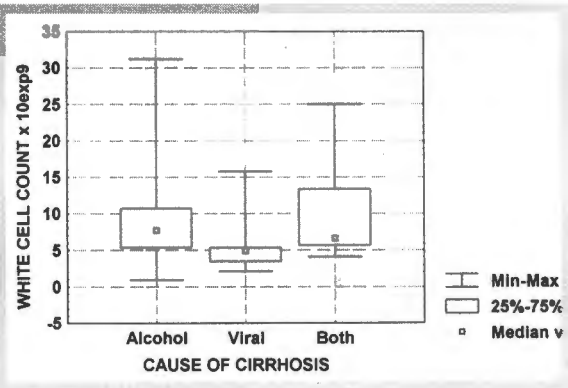

Figure 3.4b. Correlation between WCC and cause of cirrhosis.

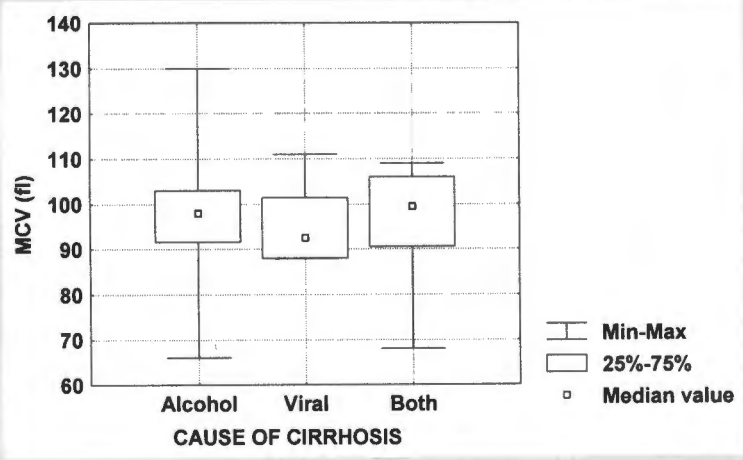

Figure 3.5. Influence of the cause of cirrhosis on MCV.

COMPLICATIONS OF CIRRHOSIS

Figure 3.6 shows the incidence of complications of cirrhosis present both at the time of admission and as an aggregate of those present when admitted as well as those which developed subsequently. Only one patient is recorded as having developed SBP subsequent to admission; encephalopathy, ascites and renal failure, frequently present when first admitted, also developed subsequently in a significnat proprtion of the remainder during the course of hospitalisation.

Temperature

The mean temperature on admission was 36.6 ± 0.8 with a minimum of 35 and a maximum of 39.9. There was, as expected, a significant difference in temperature on admission between those patients with infection and those without (p=0.009 ANOVA). There was however a large overlap. This is shown in Figure 3.7.

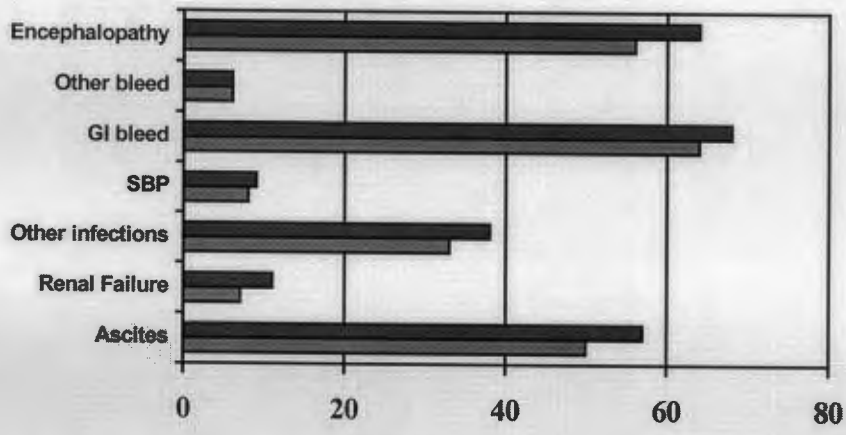

Figure 3.6. Frequency of complications; either at time of admission or, cumulatively, by end of admission. The lower, light bar represents the proportion of admissions in which the presence of the complication was already noted on admission; the upper, dark bar represents the proportion in whom the complication was noted at any stage on or during admission.

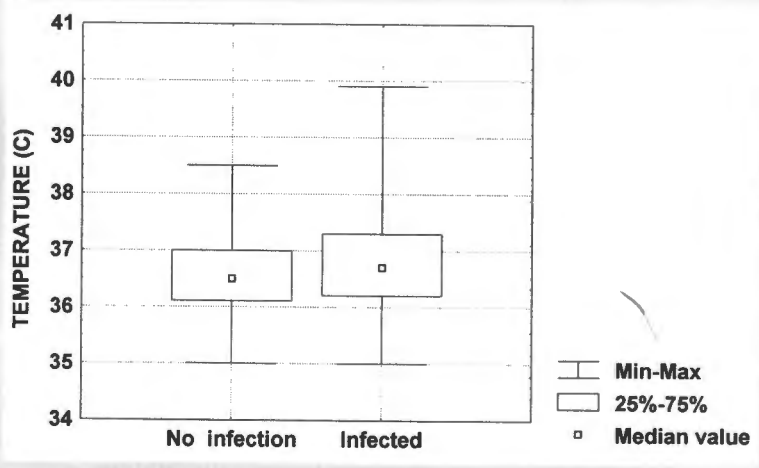

Figure 3.7. Influence of presence of infection on temperature.

Blood cultures

Blood cultures were performed in 72 of the 203 admissions of which 10 (13.9%) were positive. The organisms grown from the blood cultures are shown in Table 3.17.

Ascitic fluid white cell count

The results of ascitic fluid white cell count are shown in Table 3.18. 66 ascitic fluid cultures were performed. Four cultures yielded positive results, 1 of which grew *Staphylococcus epidermidis* which was probably a contaminant. The other 3 cultures representing 4.5% of the total submitted grew *Streptococcus pneumoniae, Eschericha coli* and corynebacteria species.

Proteus mirabilis	1
Strep. pneumonia	2
Klebsiella pneumoniae	1
E. coli	1
Staph. aureus	1
Enterobacter	1
Salmonella species	2
Staph epidermidis (? contaminant)	1

Table 3.17. Organisms recovered on blood culture.

Number submitted	35
Mean WCC (Range)	350 (40-2500)
Neutrophil count:	
Number reported adequately	19
Mean (S.D.)	151 (559)
Range	1-2460
Number>250	1

Table 3.18. Analysis of ascitic fluid for WBC count.

OUTCOME AND PROGNOSIS

28 patients died in hospital while the deaths of a further 13 patients were noted in the folders by the time they were reviewed in 1997 yielding 41 patients in total. This translates to a mortality of 48.2% over approximately 5 years. The Child-Pugh classification of those patients who could have their Child Pugh scores calculated is shown in Table 3.19 with the number of admission per patient and the overall mortality for each class. The probability of survival according to the Child-Pugh classification is shown in Figure 3.7.

There was no significant difference between the causes of cirrhosis and the Child-Pugh score. A higher Child-Pugh score was associated with a high number of admissions ($p=0.04$, Spearman rank order correlation coefficient).

PROCEDURES AND INVESTIGATIONS PERFORMED

The more common investigations and procedures performed during the course of admission are listed in Table 3.20 below. The columns reflect the number and percentage of all admissions in which at least one such investigation or procedure was performed.

	Class A	Class B	Class C
Patients	8	28	41
Admissions	18	55	67
Admissions/patient	1.6	2.1	2.8
Range	1-4	1-5	1-8
Average hospital stay	6.5	8.5	9.9
Range	2-13	2-36	1-33
Overall mortality	25%	39.3%	63.4%

Table3. 19.Mortality categorised by Child-Pugh class.

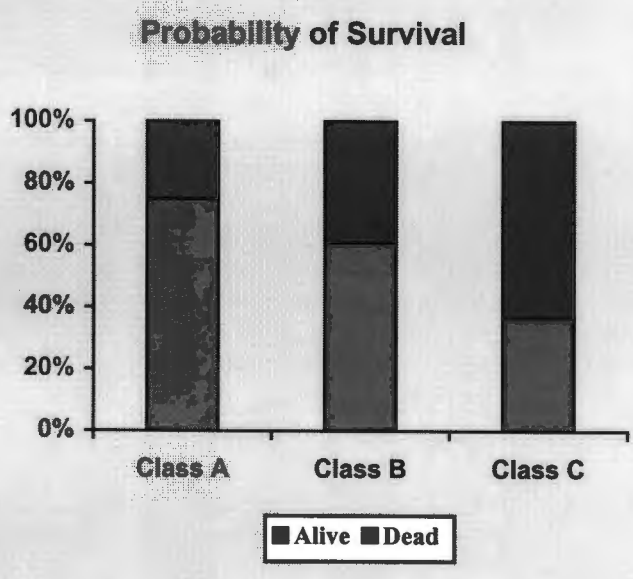

Figure 3.7. Probability of survival categorised by Child-Pugh class.

COSTS

Costs are worked out from figures compiled by the Medical Accounting Process (MAP) office at Groote Schuur Hospital, which calculates ward costs for the different units and sub-units at GSH. The ward costs include blood, nursing and medical salaries, telephone, transport, catering, stationery, medical consumables and pharmacy. Costs of procedures and theatre, e.g. endoscopy and variceal injections, and radiological investigations, e.g. X-rays, ultrasound and CT scans, are not included. The ward procedures such as abdominal paracentesis and lumbar punctures are not separately costed, as they are subsumed within the MAP figures applied to each admission. The figures shown represent an underestimation since laboratory investigations are separately costed, and some of the investigations listed in the table were performed not once, but serially.

Procedure	Number	%	Procedure	Number	%
Chest X-ray	110	54%	Other procedures	15	7%
Endoscopy	70	34.5%	Head CT scan	9	4.4%
Abdominal paracentesis	66	33%	Abdominal CT scan	8	3.9%
Variceal injections	42	21%	ERCP	7	3.4%
Abdominal X-ray	19	9.3%	Lumbar punctures	5	2%
Liver biopsies	18	9%	Laparotomies	2	1%
Ultrasound	16	7.9%			

Table 3.20. Investigations and other procedures performed during admission. The columns reflect the number and percentage of all admissions in which at least 1 such investigation or procedure was performed.

The mean length of admission for patients was 7.8 days, range 1-36. Figures compiled by the MAP office indicate that the average daily cost per patient in 1998 in a surgical ward was R353.00 and in a medical ward R340.00. Assuming that patients with gastrointestinal bleeding and hernia were admitted to the surgical area, (mean length of admission 7 days) and those with other problems to the medical area (mean length of admission 8.2 days), ward costs in 1998 terms may be estimated according to Table 3.21.

The estimated cost of the radiological procedures was supplied by Professor S Beningfield, Dept of Radiology, Groote Schuur Hospital and is derived from the South African Medical Association's scale of benefits whilst the estimated costs for surgical and endoscopic procedures was supplied by Professor J Krige, Dept of Surgery, Groote Schuur Hospital. Table 3.22 shows the cost of other investigations and procedures.

Adding these two figures together suggests a figure of R685 930 as a total estimated cost for the in-hospital care of these 85 patients over a period of four years; during these four years 41 of these 85 patients died. This equates with an estimated cost per patient per year for in-patient admissions of R2017, with a 12% mortality each year. Conversely, extrapolating to the figure of 358 eligible patients whose names were returned by the hospital computer system, the estimated cost over this period would be approximately R2.9 million.

	Admissions	Average stay	Total days	Total cost
Medical	130	8.2	1066	362 440
Surgical	73	7.0	511	180 383
Total	**203**		**1577**	**542 823**

Table 3.21. Estimated total cost for all admissions for cirrhosis in the subjects under study.

Procedure	Cost (Rand)	Total cost (Rand)
Abdominal CT scan	904.86	7239
Abdominal X-ray	59.20	1125
Chest X-ray	59.20	6512
Endoscopy and variceal injections	300.00	100800
ERCP	371.50	2600
Head CT scan	648.78	5839
Laparotomies	8000.00	16000
Ultrasound	187.00	2992
Total		143107

Table3. 22. Cost of investigations and other procedures performed during admission.

CHAPTER 4: DISCUSSION

DEMOGRAPHIC DATA

Race

Compared to their contribution to the patient population of GSH, white patients are over-represented in this study of cirrhosis (p=0.03, Pearson's χ^2; Table 3.1). There are two likely reasons for this discrepancy. Firstly, whereas most white patients in the Western Cape are able to afford and therefore attend private medical services, those with chronic disorders such as cirrhosis may attend the public sector for financial reasons. Secondly, the Groote Schuur Hospital Liver Clinic is a super-specialist unit, offering services, including transplantation, which are not available in the private sector. In contrast, black patients are under-represented among the cirrhotic population in comparison with their representation in the general hospital population (p=0.02 Pearson's χ^2,). The explanation for this is not immediately apparent. It is not generally believed that cirrhosis is any less common among black patients than among other patients, but only a population-based study would be able to determine whether the incidence of cirrhosis actually varies with race. The number of coloured patients with cirrhosis is in direct proportion to their representation amongst the general hospital population.

Of peripheral interest is the observation that, in comparison with their contribution to the population of the Western Cape, black patients are over-represented in the general hospital population (p=0.000, Pearson's χ^2); probably because a high proportion are indigent and entirely dependent on state health services. Additionally it is generally believed that a significant number of black patients domiciled in the Eastern Cape province attend Groote Schuur hospital for treatment because of perceived deficiencies within the Eastern Cape health care system.

Sex

It is apparent that the sex ratio for cirrhosis differs between black patients on the one hand, and coloured and white patients on the other (Table 3.5). The overall male-to-female ratio of this population is 1.36:1. The ratio for coloured and white patients are 1.3:1 and 1:1 respectively, which are similar to the 1.3:1 ratio in the study of Seebaran in Indian cirrhotic patients in Natal. By contrast, our observed ratio for black patients is 3.6:1. This is similar to the 3:1 male-to-female ratio found in two studies in black cirrhotic patients (Wicks et al 1977, O'Keefe et al 1982). By comparison, the male to female ratio described in western countries for cirrhosis is 2:1.

The sex-ratio differences between black patients and the coloured and white patients may relate to different patterns of drinking in these communities. Culturally, in the black community, alcohol intake, particularly of beer and spirits, is discouraged amongst females.. Even traditional beer is taken by young females only on special occasions, but is generally freely available to older women. However, as a personal observation, there has been an increase in ethanol intake in black females in the urban areas in the form of beer, wine, aperitifs and liqueurs. In contrast, in the coloured and white communities, it is accepted for females to take alcohol, especially wine on social occasions.

Gender and age

In this study, there was a strong clustering of admissions for cirrhosis in males between the fourth and seventh decades, with a pronounced peak in the fifth to seventh decades, while for females there was a wider spread over the third to the eighth decade (Fig 3.1). This may be related to the fact that most cirrhosis in our male patients was related to alcohol and might therefore be expected to develop after about 20 years of heavy ethanol abuse, followed by a further 5-10 years before they decompensate to the point of requiring admission. The causes of cirrhosis are more diverse in females and may present earlier, as with autoimmune hepatitis, or later, as with primary biliary cirrhosis.

One of the interesting and significant findings was that the mean age at admission was significantly lower for coloured patients than for the other two groups (Table 3.3). This cannot be accounted for by a difference in aetiology of the cirrhosis; alcohol accounted for about 64% in all three groups. A possible explanation for the older age in whites is that younger patients with cirrhosis may have less advanced disease, may still be economically active and therefore better able to afford private medical care, only requiring state assistance at an older age. We are unable however to account for the later presentation of black patients; as such a mechanism would not apply. A possibility we considered is that a higher prevalence of viral cirrhosis might predispose to variations in age; this is difficult to sustain since both black and white patients, with the highest and lowest incidence of viral cirrhosis, had a higher age than the coloured patients, with an intermediate level.

DIAGNOSIS OF CIRRHOSIS

Because of the importance of giving a patient a prognosis, as well as being able to assess the extent of liver disease, all patients presenting clinically with cirrhosis should as far as possible have a liver biopsy. This is additionally invaluable in monitoring the progress of liver disease and in assessing response to therapy. In alcoholic cirrhosis biopsy is important to confirm the diagnosis, to stage liver damage for prognosis and to exclude coexistent pathology, such as viral hepatitis or iron overload, as specific treatment may be essential for those with a second, potentially remediable cause. Certainly in non-alcoholic cirrhosis, such as autoimmune, viral or primary biliary cirrhosis, a biopsy is important to determine the cause, to assess the activity in the liver and the extent of the damage and to direct specific intervention such as steroid or antiviral therapy (Desmet & Fevery 1995).

Yet in this study, only 35% of patients had their cirrhosis confirmed histologically. Reports suggest that two thirds of cirrhotics are already in a decompensated state when seen for the first time and therefore likely to have coagulation problems, ascites and other complications which might contra-indicate biopsy (Saunders et al 1981, D'Amico et al 1986). This might be one reason for the low biopsy rate in our study. We note that only 2 of 203 admissions were electively for transplant assessment; the remainder were largely for crisis management such as haemorrhage and infection. Additionally, when clinical signs and radiological features suggesting cirrhosis are found with a strong history of ethanol abuse and negative tests for other causes of cirrhosis, a clinical diagnosis of alcoholic cirrhosis has often been regarded as acceptable.

The low rate of histologically-proven cirrhosis in our study suggests that biopsy is under-utilised as a diagnostic tool in our patients. In order to improve the biopsy rate in patients with cirrhosis, we would recommend that all patients, irrespective of how they first come to medical attention, should be evaluated at least once by a hepatologist or a physician with expertise in the management of liver disease, and that patients suspected of having cirrhosis should be assessed and biopsied early in their course, before they decompensate to the point where biopsy becomes dangerous. Where relative contraindications to percutaneous biopsy exist, consideration should be given to the use of transjugular biopsy or plugged percutaneous biopsy.

AETIOLOGY OF CIRRHOSIS

Alcohol

The major cause of cirrhosis in our patients is alcohol. In this series, alcoholic cirrhosis accounts for 56 patients (65,8%) (Tables 3.4, 3.5). This is similar to the incidence of alcoholic cirrhosis in West Birmingham of 66.4% (Saunders et al 1981). In our patients the male-to-female ratio of patients with alcoholic cirrhosis was 1,7:1, which is somewhat lower than the ratio found in western countries, quoted as 2:1 to 4:1 (Friedman et al 1992).

How reliably were our patients correctly identified as having alcoholic cirrhosis, particularly as the biopsy rate was low? Patients labelled as alcoholic cirrhosis in this study are those in whom there was a history of heavy alcohol use and in whom no other cause was demonstrated; where both a history of alcohol use and evidence of viral infection were present, these were recorded separately. However, this diagnostic categorisation was by no means rigorous. There was no quantitation of the alcohol intake, the duration of alcohol intake, nor of the pattern of exposure – continual versus binge drinking – all of which are known to influence the rate of development of cirrhosis in drinkers. The descriptive terms used in the hospital notes suggestive of excessive alcohol intake were "history of alcohol abuse" or "alcohol bingeing over weekends" and similar non-specific terms. This may have resulted in an overestimation of alcoholic cirrhosis in our study. It is also possible that other causes of cirrhosis were underestimated as a result of incomplete diagnostic workup, such as failure to request and record ferritin estimations, auto-antibodies, hepatitis C viral markers and, indeed, biopsies in every patient; especially where the admitting doctor believed that alcohol to be the most probable cause. This was due in part to the high proportion of patients who presented with major complications for the first time; a considered diagnostic protocol may be lost in the urgent necessity to control the acute complications; frequently a surgeon rather than a physician was caring for the patient.

Viral hepatitis

Viral infections frequently co-existed with excessive alcohol use (Tables 3.4, 3.5). 2.6% of our patients are classified as both alcohol and hepatitis B, 5.2% as alcohol and hepatitis C and 2.6% as alcohol and both hepatitis B and C. The figures in males were twice that at 6,1%, 10,2% and 4,1% respectively.

Viral infection was overwhelmingly more common in black than in white patients, with an intermediate prevalence in coloured patients. Indeed, hepatitis B infection was present in 35.7% of our black patients, compared with 7.1% and 0% of the coloured and white patients. The prevalence of seropositivity for hepatitis B surface antigen is estimated at 4-5% in healthy black blood donors in South Africa and less than 0.1% in white blood donors ((Bird & Gibbs 1994); a population survey in black people living in the Western and Eastern Cape suggested an HBs antigen carrier rate of 4.3% (Tucker et al 1996). A figure of 4% for the coloured population of the Western Cape has been suggested (Tucker T, personal communication). It is unclear why hepatitis B is represented at seven times the frequency amongst black patients with cirrhosis compared with coloured patients ($p=0.004$, by means of Fisher's χ^2), despite an equivalent rate of carriage of hepatitis B in their populations and an equivalent rate of alcohol use. It is possible that the difference is artefactual; were alcoholic cirrhosis more common in coloured than in black patients, a correspondingly smaller percentage would be reflected as due to viral infection. Ethnic-dependent differences in viral pathogenicity would also offer an explanation, but have not been shown. Though vertical transmission of HBV is known to correlate with a more rapid progression to cirrhosis, the evidence suggests that transmission in South Africa is largely horizontal, and does not differ with race. Nor are the figures biased by a presentation with early hepatoma, as only two hepatomas, were recorded in patients with cirrhosis; both were related to hepatitis C viral infection - not hepatitis B; the patients were a black and a coloured male respectively. During

the study period, other patients were assuredly admitted with hepatoma, yet were obviously not classified as having cirrhosis as they are not reflected in this study. This in fact is in accordance with our clinical experience; though we occasionally see hepatomas develop in patients known to have hepatitis C, most hepatomas in association with HBV develop so rapidly that they are diagnosed in patients who have not previously been recognised to be either cirrhotic or indeed HBV positive.

Local figures for the prevalence of HCV are 1,8% in the black population (Tucker et al 1996) and less than 1% in the coloured and white populations (Tucker T, personal communication). A strong correlation with cirrhosis is shown in this study, as also a suggestion that co-infection and concurrent alcohol use are present in many patients. Though hepatitis C appears more common in black and coloured cirrhotics than in whites, despite a similar background rate in the population, the difference is not significant ($p=0.3$, by means of Fisher's χ^2).

Our results suggest that patients with viral cirrhosis present later than those with alcoholic cirrhosis (Figure 3.2a). However, on closer inspection, we find that patients with hepatitis B present younger than those with alcohol, hepatitis C at an older age (Figure 3.2b). This is as expected: hepatitis C viral infection is known to be an indolent process with a slow progression to cirrhosis; the progression is more rapid with hepatitis B. Though numbers are small, our results suggest, as seems reasonable, that the combination of both viruses, or either virus with alcohol, is associated with a more rapid progression.

Other causes of cirrhosis

There were too few patients with causes of cirrhosis other than alcohol or viral to perform any further analysis.

Recommendations

In order to improve the certainty of the diagnosis in patients with cirrhosis, we would, recommend the following steps. All patients should be subjected to a screening programme for those aetiological factors which are prevalent in a particular area or population, as is outlined below.

In our patients, the minimum screening would include:

For alcoholic liver disease

- An accurate history of alcohol intake, including qualitative and quantitative description should be formally recorded on every patient

For drug-related liver disease

- An accurate history of drug therapy

For viral cirrhosis

- Hepatitis B viral markers
- Hepatitis C antibodies, followed by polymerase chain reaction (PCR) for viral RNA detection in those who test positive, in order to eliminate false positives

For autoimmune disease, including primary biliary cirrhosis

- Autoimmune markers: particularly anti-nuclear antibodies (ANA), anti-smooth muscle, anti-liver-kidney-microsome (LKM1) and antimitochondrial antibodies

For haemochromatosis

- Ferritin levels and transferrin saturation

Where appropriate, the following should be performed:

For biliary tract disease
- ultrasound
- cholangiography

For Wilson's disease
- Caeruloplasmin, urinary and serum copper estimations and corneal slit-lamp examination for Kayser-Fleischer rings

For alpha-1 antitrypsin deficiency
- Alpha-1 antitrypsin estimation

For non-alcoholic steatohepatitis
- Serum lipid profile and plasma glucose or oral glucose tolerance test
- must be used to confirm the presence of hepatitis C in those patients with positive antibodies

For other, rarer diseases
- The appropriate tests.

And, whenever possible

- Ultrasound
- Liver biopsy with an expert opinion

In every case it is essential that the information is not only sought and tests requested, but that the results are adequately recorded.

REASONS FOR ADMISSION

There were overlapping reasons for admission and some patients were admitted with two or more complications, such as gastrointestinal bleeding and encephalopathy or encephalopathy, ascites and infection (Table 3.8). Although ascites is the commonest of the major complications of cirrhosis (Runyon 1997), it was not the most frequent reason for admission in our patients, probably because ascites can often be controlled on an outpatient basis, as is the policy of the Liver Clinic at Groote Schuur Hospital.

Gastrointestinal haemorrhage

The most common reason for admission in our patients was gastrointestinal haemorrhage, the most serious complication of cirrhosis with a high mortality rate (Stanley & Hayes 1997). There are a number of reasons why haemorrhage should be the most common reason for admission. Firstly, gastrointestinal bleeding is said to be more frequent in alcoholic than in other forms of cirrhosis 55% of our patients were alcoholic and therefore at particular risk of haemorrhage. Secondly, patients who have had one haemorrhage are at higher risk of bleeding in the future (Stanley & Hayes 1997), and thus more likely to be readmitted, a finding confirmed in our study (Fig 3.3). Not reflected in this graph are most of those patients who returned for elective sclerotherapy only, or for minor haemorrhage. They are admitted overnight only and are not captured in this study, which excluded patients staying in hospital for less than 24 hours. It is therefore likely that most of the repeated readmissions reflected in Fig 3.3 would have been for further acute complications.

It is unlikely that any of the patients in our study received either primary or secondary pharmacoprophylaxis with beta-blockers or isosorbide for variceal bleeding as these forms of treatment were not implemented at Groote Schuur Hospital until later. Primary prophylaxis reduces the risk of bleeding by 45%; applied to our study population, admissions for GIT bleeding might have been significantly reduced.

Encephalopathy

Since most patients with low-grade encephalopathy can be treated as out-patients with lactulose and protein restriction, they are seldom admitted for this reason alone, as indicated in this study, where only one of 56 patients with encephalopathy on admission was not recorded as having an additional problem necessitating admission; Severe hepatic encephalopathy is usually precipitated by one or more factors which may themselves be indications for admission. In our study, encephalopathy on admission was almost always part of a more severe spectrum of presenting problems; alone or in combination, we recorded ascites (15) gastrointestinal bleeding (8), infections including SBP (14), other problems (10) and renal failure (6) in association with encephalopathy. It therefore appears that encephalopathy is but rarely a reason for admission itself, but is usually a consequence of another adverse factor or indeed, serves as a marker of severe decompensation.

Ascites

Uncomplicated ascites may be controlled by salt restriction and diuretics on an outpatient basis, and treatment is successful in about 90% of patients. Patients with refractory ascites or ascites complicated by spontaneous bacterial peritonitis, or ascites in association with other complications of cirrhosis need in-patient management.

Patients with significant ascites should undergo paracentesis for ascitic fluid analysis at their first presentation. In general, however, admission will be required for resistant ascites requiring multiple paracenteses, for ascites complicated by infection, encephalopathy or renal failure, and where ascites is merely one aspect of a decompensating cirrhosis. Of the fifty admissions in this study in which ascites was felt to be a significant reason for the admission, 17 were admitted for control of ascites only; most of these were recorded as having received paracentesis. The other 33 all had other problems necessitating admission in addition; including 11 complicated by SBP or other infections. Ascites however frequently coexisted with encephalopathy; 15 admissions were necessitated by the combination.

Infections, including SBP

Infection, including SBP, accounted wholly or partly for 20.2% of all admissions, confirming that infection is a major hazard in patients with cirrhosis. The problem of infection in cirrhosis is discussed in more detail later. Only 8 admissions were recorded as having SBP as a major reason for admission; the literature suggests a figure of 7-23% (Navasa 1997), and we suspect that SBP may have been missed in a significant number of our cases. This is discussed later.

Renal failure

Renal failure was in fact an uncommon cause for admission, being present in seven admissions. Only one of these was recorded as having "problematic" ascites on admission despite a known association between ascites (and its treatment) and hepatorenal syndrome. It is possible that renal failure may have developed as a result of over-vigorous and too successful diuresis with consequent dehydration in these patients; however, all were very ill – five had evidence of infection, six were encephalopathic – suggesting that renal failure may have resulted from intercurrent acute illness or end-stage disease. Indeed, three of these patients died during the same admission, and one died subsequently.

LABORATORY FINDINGS

Albumin, bilirubin and aminotransferases

A low albumin reflects decreased liver synthetic function (and is a marker of poor hepatic function); the decrease is also related to malnutrition associated with cirrhosis, and contributes to oedema and ascites formation. In this study, 87% of patients had a reduced serum albumin, and in 70.6% it was less than 30, confirming the self-evident fact that it is largely patients with advanced cirrhosis who require hospitalisation (Table 3.10). The mean globulin concentration exceeded the albumin, demonstrating the classic reversed albumin-globulin ratio which is secondary to increased antibody production resulting from bypassing of the liver as a result of portal systemic shunting, poor hepatic synthetic function, loss of Kupffer cells and other mechanisms.

Typically, patients with compensated cirrhosis may demonstrate normal bilirubin and aminotransferases. The high proportion of patients in this study with abnormal values - over 90% had hyperbilirubinaemia and an elevated AST - reflects the high proportion of severe and decompensated cirrhosis seen in this in-patient population.

AST/ALT ratio

An AST/ALT ratio exceeding 2 is said to be a sensitive indicator of alcohol-associated liver disease. The disproportionately raised AST in alcoholic liver diseases may be due to the preferential release of mitochondrial AST or may reflect the zonal distribution of these enzymes within the liver acinus. AST is a mitochondrial and cytosolic enzyme which is distributed throughout the liver acinus whilst ALT is a cytosolic enzyme located predominantly within the periportal zone. With alcohol, it is predominately the mitochondria, and the centriacinar zone (zone 3) which are affected. In other forms of liver disease associated with hepatocellular damage, ALT is usually raised proportionately more than AST. However, values of more than 2 are also seen in other forms of cirrhosis. A rising AST/ALT ratio in patients with viral hepatitis and primary biliary cirrhosis suggests the onset of cirrhosis.

An AST/ALT ratio greater than 2 was seen in 67% of our patients, which correlates well with an estimated incidence of 64% of alcoholic cirrhosis amongst our cirrhotic patients (Table 3.11). However, use of the AST/ALT ratio as a predictor of alcoholic cirrhosis in our patients had a sensitivity of 77.3%, specificity of 68.4%, positive predictive value (PPV) of 89.5% and negative predictive value (NPV) of 46.4%, in keeping with the rather poor discriminatory ability of this test in advanced cirrhosis of any sort.

Sodium

The plasma sodium was significantly lower in males than in females (Fig 3.4), and there was a trend to a lower sodium in alcoholic versus non-alcoholic disease. This may account in part for the sex difference since alcoholic cirrhosis was more common in males. Factors which may have contributed to a lower sodium in alcoholic liver disease include a greater severity of cirrhosis or more severe secondary hyperaldosteronism in association with ascites. However in this study we were unable to show a higher rate of ascites in alcoholics than in viral cirrhosis (34% vs 46%). Therefore the difference in sodium cannot relate to the presence or absence of ascites alone. Certainly, in this study, there was a strong correlation between hyponatraemia and severity of cirrhosis as measured by the Child-Pugh score, as well as between hyponatraemia and ascites. This may be due to secondary hyperaldosteronism, the effects of diuretics and salt restriction, and, again, increasing severity of cirrhosis.

Macrocytosis

A macrocytosis is often associated with alcohol abuse and may relate both to folate deficiency and to a direct effect of alcohol on the bone marrow. It is however also a feature of liver disease *per se*. The MCV exceeded 94 in 66.3% of our patients and exceeded 100 in 51.2% (Table 3.15 , Fig 3.5). This is consistent with alcohol intake as well as chronic liver disease. There was no difference in alcoholic and non-alcoholic cirrhosis in MCV, and macrocytosis serves as a very poor predictor of alcoholic disease with advanced cirrhosis. Using a cut-off value of 94fl, the sensitivity for alcoholic disease was 71.4%, the specificity 52.9%, the PPV 84.9% and the NPV, 33.3%. Using a cut-off of 100fl, the values were 57.1%, 70.6%, 87.8% and 30.8%. This is insufficiently accurate for any meaningful place in diagnosis.

White cell count

In cirrhotics a low white cell count is not infrequently found in the presence of infection, presumably the result of immunoparesis and of hypersplenism. Although the white cell count was higher in patients with infection than those without, there was a large overlap (Fig 3.4a) and, in infected subjects, the median value was only 8.1, which is within the normal range. Indeed, using a white cell count of 11 as a predictor of infection yields a sensitivity of 31.8%, specificity of 78.7%, PPV of only 35.0% and NPV of only 76.2%. Thus an elevated white cell count in cirrhosis is poorly predictive of infection, while a normal white cell count may be associated with infection in 25% of cases.

Coagulopathy

The platelet count was reduced in most of our patients, and the INR was elevated in 75% (Table 3.15). In cirrhosis, a low platelet count is related to hypersplenism and to the direct effects of alcohol on platelets. The raised INR reflects impaired liver synthetic function. All coagulation factors are synthesised by the liver except Factor VIII which originates from extrahepatic sites as well (Conn & Attenbury 1993). These results are compatible with an advanced degree of cirrhosis in our study population. Neither the INR nor the platelet count predicted the occurrence of GIT bleeding in this study, suggesting that this complication is more dependent on non-haematological factors such as portal pressure (Nevens et al,1998).

Comparison with some previous studies

The biochemical and haematological results in our patients are similar to the results of the patients of O'Keefe et al (1981) and Seebaran et al (1988), except that our patients have higher bilirubin, aminotransferase and alkaline phosphatase levels. Furthermore, our patients were more anaemic and had more severe thrombocytopaenia than the patients studied in Durban. This suggests that our patients were more ill than those studied in Durban; it may also reflect a rising threshold for admission with shrinking resources over the ten years between the studies in Durban and the present. A partial factor may however be our exclusion of admissions lasting less than 24 hours, which would exclude the least severe illness; this alone is however unlikely to account for the difference.

COMPLICATIONS OF CIRRHOSIS

In addition to those major complications of cirrhosis present on and indeed necessitating admission, further complications developed in many of our patients during their hospital stay, as reflected in Fig 3.6. There was no correlation between the cause of the cirrhosis and the overall prevalence of encephalopathy, ascites, infection, SBP or renal failure.

Gastrointestinal haemorrhage

This was significantly more frequent in alcohol-associated cirrhosis than in patients with another cause ($p=0.005$, by χ^2). Patients with both alcohol and viral infection behave like those with alcohol alone with a high rate of haemorrhage whilst bleeding was significantly less frequent in those with viral cirrhosis alone.

Infection

Fever is an extremely poor predictor of infection on admission as shown in Fig 3.7, despite a significant difference in medians; because of the large degree of overlap. The organisms grown on blood culture are known to be common organisms causing infection or bacteraemia in cirrhosis. In particular, *E. coli* is the commonest organism causing bacteraemia and SBP in cirrhotics; *Streptococcus pneumoniae* and *Klebsiella* are also commonly found (Caly & Strauss 1993). Only one patient had both a positive blood culture and an ascitic fluid culture; surprisingly, the organisms were not the same - *Enterobacter* from the blood and *E. coli* from the ascites.

Spontaneous bacterial peritonitis

Despite current recommendations that a quantitative neutrophil count on ascitic fluid should be performed in any decompensated cirrhotic with ascites since it is the most sensitive test for SBP, an ascitic fluid white cell count was performed in only 35 admissions, or 53% of all those in whom diagnostic or therapeutic paracentesis was done (Table 3.18). Some of these may in fact be regarded as inadequately investigated since a differential white cell count was not done; it is a neutrophil count greater than 250/ml which offers the most sensitive test for SBP (Gaurner & Soriano 1997). Somewhat more (66, or 83%) had fluid submitted for culture. It is recommended that ascitic fluid be inoculated directly into blood-culture bottles, which increases the positive yield from 50% to about 80% in SBP (Gaurner & Soriano 1997). We suspect that this was performed in few of our patients; and is consistent with the observation that of the 9 patients in the study recorded as having SBP, only 3 positive cultures (33%) were reported. Even this figure is likely to represent an overestimate because the inadequate diagnostic protocol for SBP employed in these patients almost certainly underestimated the true incidence of SBP. Indeed, only one of the nine labeled as having SBP was correctly proven to have SBP with the demonstration of an elevated ascitic fluid neutrophil count. SBP was recognised in only 4.4% of our admissions, which is considerably fewer than the 8-27% reported in the literature during a single hospital admission (Gaurner & Soriano 1997).

Other infections

The total incidence of infection, including SBP, reflected in our patients' folders was 23.2%. This is lower than the 30-50% of admissions with infection during hospitalisation in cirrhotics quoted in the literature (Navasa et al 1997), again suggesting that a proportion of patients with infection were missed. This may be in part due to the poor negative predictive value of a normal temperature and white cell count as described above, failure to perform the appropriate tests for SBP and a low index of suspicion for infection in cirrhotic subjects.

PROCEDURES AND INVESTIGATIONS

The most common procedure performed is a chest radiograph, followed by endoscopy, abdominal paracentesis and variceal injections (Table 3.19). The high frequency of endoscopy and variceal injection is obviously related to the frequency of gastrointestinal haemorrhage in these patients.

OUTCOME AND PROGNOSIS

Of the patients admitted during the years 1993 to 1996, 48.2% had died by early 1997 (Table 3.20, Fig 3.7) when the folders were reviewed; this may be an underestimate as further patients may have died at home or elsewhere, the fact not being recorded in the folder. Historically the 4-year survival for decompensated alcoholic cirrhosis, following the development of ascites, has been estimated at 30% (D'Amico et al 1986) and 25% (Saunders et al 1981), when the observation was made that there had been little change in the mortality of cirrhosis over the previous two decades. It is unlikely that there has been any major improvement since, though improvements in the recognition and management of SBP and gastro-intestinal haemorrhage may have improved the 4-year survival to some degree. However, the single factor most likely to have significantly improved survival over the past decade has been an exponential increase in transplantation coupled with greatly improved graft survival. Significantly, none of the patients in this study was transplanted though two were admitted for assessment for transplantation. The unsuitability of these patients for transplantation probably relates to their advanced disease, as well as to a shortage of donors and the poor social and educational background of many of our patients.

COSTS

The costs we have calculated for these patients amount to approximately R2017 per year (Table 3.21, 3.22). This is a conservative estimate; same-day or overnight admissions for endoscopy, sclerotherapy, paracentesis and biopsy were not included; procedures were costed once though in many cases they would have been repeated serially or repetitively, and the costs associated with out-patient therapy and with transplantation have not been included. Even so, a figure of R2.9 million for the in-hospital treatment of cirrhosis over a 4 year period is not unimpressive, especially when the true figure may be double that or more.

IN CONCLUSION

Prevention of cirrhosis

In view of the poor prognosis, measures are needed to improve the outcome and to prevent the progression of disease in patients with cirrhosis. In our study and those in other countries, the cirrhosis in most patients is due to alcohol, second is infection with the hepatitis viruses. Alcoholic cirrhosis is by definition preventable; increasingly, viral cirrhosis can be avoided by public health measures, by vaccination and potentially by specific antiviral therapy.

Alcohol

The fight against alcohol abuse in South Afric has not been well organised. Alcohol misuse is related to many factors which include easy availability, heavy advertising and societal pressure, socio-economic issues such as social class, employment, housing, availability of recreation facilities and education, and historical issues such as the "dop" system on farms in the Western Cape. A multidisciplinary approach is needed, with tight co-ordination of public and private agencies. There is a role for doctors, psychologists, social workers and legislators in:

- improving education and living standards
- discouraging the glamourisation and advertising of alcohol
- reducing its easy availability
- educating the public, and particularly children, about the dangers of its misuse

- improving access to healthier recreational activities
- improving access to facilities for the care and rehabilitation of those addicted to alcohol.

This is a long-term project. Success with anti-smoking campaigns in some countries has suggested that sensible, sustained programmes can modify public behaviour; till this point there has not been the same will to tackle alcohol misuse as there has with smoking.

In reviewing the folders of the patients we studied, we observed with concern that there was no formal record of any counselling of the patient with regard to cessation of alcohol. Presumably some advice or injunction was given, but there was additionally no record of even a single patient having been referred to any agency such as a psychiatrist, alcohol treatment centre, social worker or Alcoholics Anonymous despite many of the patients having several admissions over the 4 years. This may reflect a resigned and fatalistic attitude on the part of the doctors, coupled with an undue pre-occupation with the biological, rather than psychosocial dimensions of their patients. Doctors should play a more significant role in the early identification of patients with alcoholic liver disease, in treating, counselling and referring them to appropriate agencies such as psychologists and social workers for treatment. Support groups should be created in communities for people who have problems with alcohol abuse as well as making this alcohol abuse a public health problem so that employers are able to refer these patients for help.

Viral hepatitis

The introduction of a national hepatitis B vaccination programme for children is an important step towards reduction of hepatitis B viral cirrhosis, and will greatly add to the modest benefits already achieved by the introduction of adult vaccination of high-risk groups, of secondary prophylaxis and of screening of blood donations. The benefits of universal immunisation will take time to manifest.

Health education with regard to hepatitis B and hepatitis C viral infection and spread will also be helpful. "Safe-sex" campaigns for the prevention of the human immunodeficiency virus (HIV), may contribute to a reduction in the sexual spread of hepatitis B and, perhaps, C. Because hepatitis B and C viral infection usually present clinically long after the initial infection, there is a tendency to underestimate the poor prognosis associated with them.

Management of cirrhosis

From this study, it is clear that in many instances there were insufficient recorded data to substantiate the aetiological diagnosis assigned to the patient, e.g. lack of information on the degree and duration of alcohol exposure, and a low rate of histological diagnosis in patients with cirrhosis. In the interests of a better understanding of patients and therefore of better management, as well as for the improvement of data collection for further studies and quality-assurance assessments of the quality of care, data collection and recording on every patient needs to be more systematically undertaken.

The management of patients with complications of cirrhosis can be improved by conforming to modern recommendations. Increasingly evidence-based guidelines are becoming available for the prevention and treatment of ascites, encephalopathy, variceal haemorrhage and SBP; examples include protocols for primary and secondary prevention of variceal bleeding, for the diagnosis of SBP and for prophylactic antibiotic use to prevent it in those prone to frequent recurrence. As suggested above, the institution of primary and secondary prophylaxis for variceal bleeding might reduce our admission rate. The need to refer suitable patients for possible liver transplantation must be widely understood.

Continuing education of all doctors and health-care workers caring for patients with cirrhosis, either in hospitals or in the community, is vital; indeed, the patients themselves should not be forgotten, but included as equal partners in their own care.

REFERENCES

Anthony PP, Ishak KG, Nayak MC, Paulsen HE, Scheuer PJ, Sobin LH. The morphology of cirrhosis: Definition, nomenclature and classification. *WHO Bulletin* 1977; 55: 521-231.

Bird AR, Gibbs BJ. Blood transfusion and hepatitis viruses. *S Afr Med J* 1994; 84: 570-2.

Burroughs AK, Planas P, Svodoba P. Optimising emergency care of upper gastrointestinal bleeding in cirrhotic patients. *Scand J Gastroenterol* (Suppl) 1998; 33: 226: 14-24.

Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatology* 1993; 18: 353-358.

Conn OH, Attenbury CE. Cirrhosis. In: Schiff L, Schiff ER (eds). Diseases of the Liver, 7th Ed. JB Lippincot: Philadelphia, 1993; pp 875-934.

Cordoba J, Blei AT. Treatment of hepatic encephalopathy. *Am J Gastroenterol* 1997; 92:1429-39.

D' Amico G, Morabito A, Pagliaro L, Marubini E, and The Liver Study Group of "V. Cervello" Hospital. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sciences* 1986; 31: 486-475.

Desmet V, Fevery J. Liver biopsy . *Balliere's Clinical Gastroenterology* 1995; 9: 811-828.

Dufour MC, Stinson FS, Fe Caces M. Trends in cirrhosis, morbidity and mortality: United States, 1979-1988. *Sem Liv Dis* 1993; 13: 109-125.

Dusheiko G, Hoofnagle JH. Hepatitis B. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J (eds). Oxford Textbook of Clinical Hepatology, Vol. 1. Oxford University Press: New York, 1991; pp 571-592.

Erlinger S, Benhamou JP. Cirrhosis: clinical aspects. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J (eds). Oxford Textbook of Clinical Hepatology, Vol.1. Oxford University Press: New York, 1991; pp 380-390.

Fauerholdt L, Schlichting P, Christensen E, Poulsen H, Tygstrup N, Juhl E and The Copenhagen Study Group for Liver Diseases. Conversion of micronodular cirrhosis into macronodular cirrhosis. *Hepatology* 1983; 3: 928-931.

Friedman C, Millward-Sadler GH, Arthur MJP. Liver fibrosis and cirrhosis. In: Millward-Sadler GH, Wright R, Arthur MJP (eds). Wright's Liver and Biliary Disease. 3rd Edition. W.B Saunders: London,1992; pp 821-881.

Garcia-Pagan JC, Bosch J. Pharmalogical prevention of variceal bleeding. New developments. *Balliere's Clinical Gastroenterology* 1997; 11: 271-287.

Gines P, Fernandes-Esparrach G, Arroyo V. Ascites and renal functional abnormalities in cirrhosis: Pathogenesis and treatment. *Balliere's Clinical Gastroenterology* 1997; 11: 365-385.

Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, Caballeria J, Rodes J, Rozman C. Compensated cirrhosis: Natural history and prognostic factors. *Hepatology* 1987; 7:122-128.

Gomez F, Ruiz P, Schreiber AD. Impaired function of macrophage Fc-gamma receptors and bacterial infection in alcoholic cirrhosis. *N Engl J Med* 1994; 331: 1122-8.

Guarner C, Soriano G. Spontaneous bacterial peritonitis. *Sem Liv Dis* 1997; 17: 203-216.

Infant-Rivard C, Esmeoli S, Villeneuve JB. Clinical and statistical validity of conventional prognostic factors in predicting short term survival among cirrhotics. *Hepatology* 1987; 7: 660-664.

Kirsch R. Evidence of alcoholic liver disease in South Africa. In: Hall P (ed). Alcoholic Liver Disease. Edward Arnold: London, 1985; pp 184-192.

Llovet JM, Rodriguez-Iglesias P, Moitinho E, et al. Spontaneous bacterial peritonitis in patients with cirrhosis undergoing selective intestinal decontamination. J *Hepatology* 1997; 26: 88-95.

Navasa M, Rimola A, Rodes J. Bacterial infections in liver disease. *Sem Liv Dis* 1992; 17: 323-333.

Nevens F, Bustami R, Scheys I, et al. Variceal pressure is a factor predicting the risk of a first variceal bleeding. A prospective cohort study in cirrhotic patients. *Hepatology* 1992; 27: 15-19.

Noble JA, Fe Caces M, Steffens RA, Stinson FS. Cirrhosis hospitalisation and mortality trends, 1970-1987. *Public Health Reports* 1993; 108: 192-197.

O'Keefe SJ, Simjee AI, Seedat YK. Clinical presentation and biochemical abnormalities in black (Zulu) patients with cirrhosis in Durban. *S Afr Med J*. 1982; 61: 775-778.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646-9.

Redhead DN, Olliff SP. Imaging: Focus on hepatocellular carcinoma and liver transplantation. *Balliere's Clinical Gastroenterology* 1995; 9: 771-790.

Riordan SM, Williams R. Treatment of hepatic encephalopathy. *N Engl J Med* 1997; 337: 473-9

Runyon BA. Bacterial infections in patients with cirrhosis. *J Hepatology* 1993; 18: 271-272.

Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology* 198; 27: 264-272.

Runyon BA. Treatment of patients with cirrhosis and ascites. *Sem Liv Dis* 1997; 17: 249-260.

Saunders JB, Walters JRF, Davies P, Paton A. A 20 year prospective study of cirrhosis. *Br Med J.* 1981; 282: 263-266.

Seeberan AR, O'Keefe SJD, Ackerman BS. Patterns of cirrhosis in Natal Indians. *S Afr Med J* 1988; 74: 622-624.

Sherlock S, Dooley J. Diseases of the liver and biliary tract. 10th Ed. Blackwell Series: London 1992; pp 371-384.

Stanley AJ, Hayes PC. Portal hypertension and variceal haemorrhage. *Lancet* 1997; 350: 1235-1239.

Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusions. *Ne Engl J Med* 1966; 274: 473-81.

Tucker TJ, Kirsch RE, Louw SJ, Isaacs S, Kannemeyer J, Robson SC. Hepatitis E in South Africa: evidence for sporadic spread and increased seroprevalence in rural areas. *J Med Virol* 1996; 50: 117-9.

Wicks ACB, Thomas GE, Clain DJ, Loon E, Seggie J, Bramston B. Cirrhosis of the liver in Rhodesian blacks. *S Afr Med J* 1977; 51: 911-914.

Wyndham CH. Deaths and mortality rates from largely preventable causes of death in Whites in RSA. Comparisons of the situations in 1970 and 1980. *S Afr Med J* 1985; 67: 975-976.