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SOME ASPECTS OF LIVER DISEASE IN BLACK PATIENTS

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SOME ASPECTS OF LIVER DISEASE IN BLACK PATIENTS

BY

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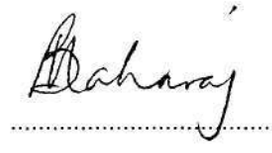
DECLARATION

I, **BREMINAND MAHARAJ**, DECLARE THAT THE WHOLE THESIS, UNLESS SPECIFICALLY INDICATED TO THE CONTRARY IN THE TEXT, IS MY OWN ORIGINAL WORK AND HAS NOT BEEN SUBMITTED FOR A DEGREE AT ANY OTHER UNIVERSITY.



B. MAHARAJ

To my parents, Mrs and (the late) Mr Hari Shanker Maharaj, my guardian Mr Juggernath Maharaj, Mothers Durga, Saraswathi and Kankali, and all parents.

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ABSTRACT

A study of the causes of liver enlargement amongst black patients at King Edward VIII Hospital, Durban, South Africa has revealed that congestive cardiac failure (36.7%), amoebic liver abscess (7.1%), hepatocellular carcinoma (5.8%) and cirrhosis (5.4%) are the most common causes in this population. Liver biopsy was needed to determine the cause in 28.7% of patients studied.

The diagnostic yield of percutaneous liver biopsy was increased by obtaining 2 or 3 consecutive specimens for histological examination by redirecting the biopsy needle through a single entry site. This benefit was achieved without an increase in morbidity or mortality.

Fatalities and complications associated with liver biopsy were more frequent at this hospital than in hospitals in Europe, The United Kingdom and North America. The complication rates after percutaneous or peritoneoscopic biopsy were 2.0% and 2.3% respectively. A total of 6 deaths was recorded. The morbidity and mortality rates were not increased when more than one specimen was taken during percutaneous biopsy. In the majority of patients in whom biopsy was carried out, after-care was either non-existent or inadequate.

The "Tru-Cut" needle was used for all percutanebus liver biopsies at King Edward VIII Hospital. Two techniques, including the method recommended by the manufacturer, have been found to be incorrect; the needle must be used correctly if an adequate biopsy specimen is to be obtained for histological examination and if serious complications are to be avoided.

Hepatic tuberculosis was diagnosed in 9% of patients with unexplained hepatomegaly who were subjected to liver biopsy. This disease did not yield any consistent clinical findings. In addition, liver function tests were of little diagnostic value and results of hepatic imaging

techniques were often normal. Accordingly, a high index of suspicion is needed and liver biopsy is essential in patients with unexplained hepatomegaly or hepatosplenomegaly, or pyrexia of unknown origin since biopsy provides the only means of diagnosing hepatic tuberculosis.

The accuracy of both ultrasonography and scintigraphy in distinguishing between normal and diseased livers was low (68% and 74% respectively). These techniques performed better at detecting focal than diffuse liver disease; the sensitivity of ultrasonography and scintigraphy in focal and diffuse disease were 88% and 92%, and 27% and 54% respectively. The specificity of both procedures was high for both types of liver disease (range 91-96%). Overlap between the ultrasonographic features of amoebic liver abscess, hepatocellular carcinoma and metastatic carcinoma resulted in a correct final diagnosis being made in only 81% of patients with amoebic liver abscess, 29% with hepatocellular carcinoma and 43% of patients with metastatic carcinoma who had an ultrasound scan. Neither technique was capable of determining the cause of diffuse liver disease. Therefore, when diffuse parenchymal liver disease is suspected, liver biopsy is needed to determine the presence and nature of the disease. In addition, liver biopsy or aspiration is usually required to determine the cause of focal disease in selected patients in whom space-occupying lesions are detected on hepatic imaging studies.

PREFACE

PREFACE

The work undertaken in this thesis was carried out in the Department of Medicine, University of Natal from February 1984 to December 1987.

While this work was in progress, the following papers which were relevant to this thesis were published.

1. Maharaj B, Cooppan RM, Maharaj RJ, Desai DK, Ranchod HA, Siddie-Ganie FM, Goqwana MB, Ganie AS, Gaffar MSA, Leary WP, Pudifin DJ. (1986).
   Causes of hepatomegaly at King Edward VIII Hospital, Durban. A prospective study of 240 black patients.
   South African Medical Journal 69: 183-184.

2. Maharaj B, Maharaj RJ, Leary WP, Naran AD, Cooppan RM, Pirie D, Pudifin DJ. (1986).
   Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver.
   Lancet i: 523-525.

3. Maharaj B, Maharaj RJ, Leary WP, Naran AD, Cooppan RM, Pirie D, Pudifin DJ. (1986).
   Sampling variability in percutaneous liver biopsy (letter).
   Lancet i: 975.

4. Maharaj B, Leary WP, Pudifin DJ. (1987).
   A prospective study of hepatic tuberculosis in 41 black patients.
   Quarterly Journal of Medicine 63: 517-522.

5. Maharaj B, Bhoora IG, Patel A, Maharajh J. (1989). Ultrasonography and scintigraphy in liver disease in developing countries. A retrospective survey.
Lancet ii: 853-856.

6. Maharaj B, Pillay S. (1990). "Tru-Cut" needle biopsy of the liver: importance of the correct technique.
Postgraduate Medical Journal (in press).

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CHAPTER 1

INTRODUCTION

Background To Proposed Studies

Until recently, medical practitioners and students in South Africa have had to obtain guidance in their work and study from text books that have been written in an environment very different from their own. This represented a significant limitation because the distribution and pattern of diseases is not uniform in different areas; certain diseases may be common in one geographical location, but be seldom seen elsewhere. Furthermore, the availability of resources for investigating and treating patients differs considerably between first and third world countries, and within developing countries.

This void is gradually being filled by text books written by health professionals with an intimate knowledge of medical practice in South Africa, a favourable development which must continue. The practice of medicine in South Africa, and indeed, in Africa and the rest of the world can and should be enriched and improved by the contributions of local academics and health care workers. Medical schools in South Africa have an obligation not only to train medical practitioners who are well-equipped to care for the populations they serve, but also to engage in research which is relevant to the needs of their local communities. The continual inflow of such scientific information from these institutions would lead to the accumulation of data that would supplement existing knowledge, lead to a revision of texts written by both African and non-African authors, favourably alter established practice and ultimately lead to an improvement in patient care in South Africa and throughout Africa.

Important contributions to various aspects of liver disease have been made by a number of workers in South Africa. These include major breakthroughs in the diagnosis (Powell et al., 1965), drug therapy (Powell and Elsdon-Dew, 1972; Wilmot et al., 1958) and other

aspects of the management of uncomplicated and complicated amoebic liver abscess (Adams and MacLeod, 1977a,b; MacLeod et al., 1966) which were made in Durban, clinical and laboratory investigations in Durban and Johannesburg which clarified many aspects of siderosis (Bothwell and Isaacson, 1962; Bothwell et al., 1965; Gillman et al., 1957; Isaacson et al., 1961; Wainwright, 1957), and research conducted in Johannesburg which has yielded important information on, inter alia, aetiological, clinical and diagnostic aspects of hepatocellular carcinoma (Kew, 1981; Kew and Geddes, 1982; Kew and Paterson, 1985; Kew et al., 1979) and hepatic tuberculosis (Essop et al., 1984; Hersch, 1964a,b).

This project was conducted at King Edward VIII Hospital, a teaching hospital attached to the University of Natal Medical School, Durban, South Africa, during the period 1984-1987. This hospital serves the Black community of Durban and surrounding areas. In common with other hospitals in developing countries, the tremendous pressure on hospital beds and cost are important considerations when planning patient management. Accordingly, a diagnosis has to be made without delay so that appropriate treatment can be instituted promptly. In order to achieve this goal, the pattern of disease must be known and the most effective methods of diagnosis must be utilised. These should preferably be non-invasive, safe and cheap; because of the risk of complications, invasive investigations should be reserved for those patients in whom non-invasive tests are unhelpful or are of limited value.

These studies were undertaken to delineate the pattern of liver disease and to determine the value and limitations of non-invasive and invasive investigations in detecting the presence and nature of liver disease in Black patients admitted to King Edward VIII Hospital. Radionuclide and ultrasound liver imaging and liver function tests are the non-invasive

tests that are generally available and widely used at King Edward VIII Hospital. Liver tissue is obtained for histological examination during percutaneous or peritoneoscopic liver biopsy, or at laparotomy.

This project was prompted by four observations. The first was that the only report on diseases of the liver encountered at King Edward VIII Hospital (Adams, 1979) had a number of limitations. This study was retrospective in nature and involved an analysis of summaries prepared by medical staff with varying levels of competence, including house officers, in one medical unit. All patients who had died were not included in the analysis because summaries were often not prepared. In addition, patients had not been investigated according to a predetermined protocol; histological confirmation of diagnoses would have been lacking in a number of cases. Furthermore, the lack of a protocol and the fact that the investigations currently utilized in clinical practice were not routinely available during the period under study (1955-1977) would make deductions on the possible role of special investigations in the diagnosis of focal and diffuse liver disease impossible. The second was that patients admitted to King Edward VIII Hospital frequently had incidental enlargement of the liver which was usually not investigated unless it produced symptoms. The third was that hepatic tuberculosis was very rarely considered as a possible cause of hepatomegaly in this hospital. The fourth was that patients with liver enlargement who consumed alcohol were not infrequently presumed to have alcoholic liver disease and no attempt was made to confirm the diagnosis. In some patients, an abnormal radionuclide or ultrasound liver scan, which demonstrated abnormalities consistent with diffuse liver disease, was accepted as proof of the diagnosis. This approach was at variance with that proposed by Hersch, who had stressed the need for liver biopsy in patients with unexplained hepatomegaly since hepatic tuberculosis often occurred without clinical or radiological evidence of extrahepatic involvement (Hersch, 1964a,b).

Historical perspectives on diagnostic procedures used in this project

Radionuclide Imaging

Radionuclide scintigraphy has been used to study the morphology and function of the liver and its related structures for more than a decade (Holder and Saenger, 1975). This diagnostic investigation requires the administration of a radioactive pharmaceutical followed by measurement of gamma radiation emitted from the body. It is simple for the patient and involves minimal risk. Recently, radioisotope procedures have been complemented by other imaging investigations such as ultrasound, computed tomography, and nuclear magnetic resonance. These mainly demonstrate hepatic structure and anatomical relationships, whereas radioisotopes give images of liver function. Function may be impaired by either focal or diffuse disease (Ackery and Smith, 1985).

Two types of radiopharmaceuticals are used for routine investigation: colloid preparations which are taken up by Kupffer cells of the hepatic sinusoids, or chemicals and dyes which are actively transported by hepatocytes. Liver concentration of these agents is related to hepatic blood flow and the capacity of the liver to extract the radiopharmaceutical from the circulation. To minimize the patient radiation dose, the physical half-life of the radioisotope label should be short (a few hours) and there should be no beta emission. Technetium-99m is ideal in these respects, with a 6h half-life, and no beta radiation. Technetium-99m sulfur colloid is by far the most widely used agent for routine liver scanning and, in the absence of severe liver disease, provides excellent images of the liver and spleen with very little uptake by other organs (Ackery and Smith, 1985).

Moore is credited with the first localisation study of patients using radiopharmaceuticals (Moore, 1948). In an attempt to assist in the diagnosis of brain disorders, Moore synthesised ^{131}I into diiodofluorescein, injected about 20 MBq (540 uCi) intravenously and monitored the radioactivity over regions of the head with a hand-held Geiger-Muller tube.

Many investigators were confined to the use of ^{131}I, as this radioisotope was readily available and had been used in the therapy of thyroid disorders during and since the 1930's. The development of the scintillation camera was a major contribution and influence on the progress of radionuclide imaging (Anger, 1958). During the 1960's there was continuing progress in the development of radiopharmaceuticals, rectilinear scanners and gamma cameras. Many different radioisotopes were evaluated in terms of imaging capabilities, radiation dose, availability and physiological measurement. The use of technetium-99m was another major land-mark in the development of radionuclide imaging. In the publication by Harper and co-workers images of the human brain, thyroid and liver were shown, and the advantages of using technetium-99m in terms of reduced radiation dose to the patient were discussed (Harper et al., 1964). The 1970's was a period of consolidation in radionuclide imaging. Many departments of nuclear medicine and radiopharmaceutical manufacturers were developing techniques and radiopharmaceuticals that were based upon technetium-99m. The ready availability, suitable half-life and optimum photon energy of technetium-99m made this radionuclide convenient to use and the trend towards low energy photon radionuclides helped gamma camera manufacturers to relax tolerances on imaging equipment. This, in turn, had the benefit of providing lighter equipment that became relatively more mobile, whilst reductions in the thickness of scintillators actually improved the performance of most equipment. In the early 1980's, many gamma cameras were capable of single photon emission computed tomography and/or whole body scans with either single or dual detectors. Such instruments are now routinely connected on line to data processors which can perform a vast array of tasks related to the acquisition and processing of image data. The gamma camera and computer system has become both a routine and research orientated diagnostic imaging device. Today, most centres rely on the gamma camera as the main radionuclide imaging device. The rectilinear scanner no longer serves the requirements of radiodiagnosis and the use of multidetector systems is beyond the financial scope of many hospitals (Jackson, 1986).

Liver Imaging by Ultrasonography

Two major technological advances have resulted in ultrasonography becoming established as an essential and widely used imaging modality in the study of liver disease. The first was the development of grey-scale ultrasound in the early 1970's which resulted in the display of the normal liver parenchyma and, for the first time, made possible the demonstration of subtle focal defects as well as the recognition of diffuse parenchymal disease (Taylor et al., 1976). The second was the development of high-resolution, real-time (dynamic) ultrasound equipment (Taylor, 1982).

In 1880, the Curies discovered a means to produce and detect high-frequency sound waves (Shirley et al., 1978). Forty years later, in the face of the threat to the Allied Powers by submarines during the First World War, Langevin applied to submarine detection the ultrasonic techniques developed by the Curies in the laboratory (Shirley et al., 1978). During the Second World War this system evolved into the sophisticated Sound Navigation and Ranging (SONAR) systems. The Dussik brothers were the first to describe the use of ultrasound for imaging in 1937 (Shirley et al., 1978). They used a transmission technique, akin to x-radiography, to produce "hyperphonograms" of the head. In 1952 John J. Wild, using equipment designed to train US pilots in the use of radar, showed that it was possible to detect tumours of the breast and brain by comparing their echo patterns with those of normal tissue. In the same year, Howry and Bliss developed a machine to display the echoes from tissue boundaries, and published two-dimensional ultrasonic tomograms (Shirley et al., 1978). Close co-operation between a team led by Ian Donald, Regius Professor of Midwifery at Glasgow University, and an engineer, Tom Brown, led to the production of the first two-dimensional contact scanner in 1958 (Shirley et al., 1978).

In 1972, Kossoff described the grey-scale technique, which for the first time made it possible to image not only the large echoes from organ boundaries, but also the small ones from tissue infrastructure (Kossoff, 1972). This was a major technological advance. Also

in the early 1970's, a great deal of work was being done on finding solutions to the problems posed by moving structures in scans. Since it took five to ten seconds to build up a conventional ultrasound image, movement during the scan was a nuisance, and patterns of movement could not be studied. This led to the development of real-time systems which were designed to produce instantaneous moving images of moving structures. This proved to be another major technological advance. The pioneers in the field were Somer and Bom (Shirley et al., 1978).

After the advent of grey-scale ultrasonography, examination of the liver was performed with static-B scanners which obtained images at 1-cm intervals in both longitudinal and transverse planes. This procedure was time-consuming and required many adjustments of the scanner as well as expertise in scanning technique. In addition, certain areas of the liver and kidney were suboptimally visualised due to the anterior and lateral ribs. Initially, the resolution of real-time scanners was suboptimal compared with the images of static scanners, and real-time was used as an adjunct to static scanning. However, with the technological improvement of real-time sector scanners, resolution became either equal to, or better than that of the articulated arm scanners. The major drawback of real-time scanning was the small field-of-view and the small image size, which made orientation of the image difficult; however, this problem has been circumvented by the development of "wide" field-of-view scanners allowing larger images (Lewis, 1984). With ultrasonography, information about the entire abdomen may be obtained at one examination.

Liver Biopsy

Percutaneous needle biopsy of the liver is a useful diagnostic procedure for which a variety of techniques is employed. However, although it had first been used before the turn of the century, it did not become firmly established in clinical practice until the 1940's. Paul Erlich is credited with the first biopsy (Sherlock, 1985). This was carried out during a study of the glycogen content of the diabetic liver in 1883. This procedure was used again

by Lucatello in 1895 for the diagnosis of tropical liver abscess, and in 1907 by Schupfer for the diagnosis of cirrhosis and hepatic tumours (Sherlock, 1985). However, it gained acceptance only in the 1930's, and was used frequently during the Second World War to investigate military personnel suffering from viral hepatitis (Dible et al., 1943; Iversen and Roholm, 1939; Sherlock, 1985). The original needles consisted of a trocar and cannula with a bore of up to 3mm. Not long afterwards, it became evident that the incidence of haemorrhage could be reduced by decreasing the size of the bore (Knauer, 1978), and that safety was also adversely affected by the slow speed of the procedure. The introduction of the "one-second" method in 1958 was a major advance (Menghini, 1958). The Menghini needle permits the application of suction through a syringe attached to a needle hub. The tip of the needle is oblique and slightly convex towards the outside. This results in an excellent cut of the biopsy specimen without any need to rotate the needle. The other needle that is commonly used is the "Tru-Cut" needle, the disposable derivative of the Vim-Silverman needle. This needle uses a different principle - a trocar and cannula are introduced into the liver and a core of tissue is severed within the cannula without suction (Hegarty and Williams, 1984).

Peritoneoscopy is important in evaluating patients with liver disease because macroscopic and histological diagnosis of intra-abdominal disease can be made using this technique. During the procedure both the liver and peritoneum can be visualised and biopsied (under direct vision). The first attempts at visual examination of the peritoneal cavity without a large incision were reported in 1901 by Ott, who used a speculum and head mirror (Walker et al., 1943). Kelling was apparently the first to attempt such a procedure with an instrument which carried its own source of illumination, viz. the Nitze cystoscope, which was a new invention. He employed a pneumoperitoneum, but his work at that time (1901) was only experimental and was carried out on dogs. Nine years later, he described its use in two human patients, and again after the last war, he wrote favourably on the subject (Walker et al., 1943). Jacobaeus, the pioneer of thoracoscopy, was probably the first to

employ this type of instrument in the human patient, for he reported, in the same year as Kelling, three patients with ascites whom he examined in this manner (Walker et al., 1943). Kalk designed the instrument that formed the basis of the present day peritoneoscopes (Kalk, 1929). However, it was not until Ruddock devised a special instrument with a built-in biopsy facility that further progress was made and the safety of the procedure satisfactorily demonstrated (Ruddock, 1934, 1937). Nonetheless, the procedure remained unpopular in the English speaking countries until about 30 years ago.

Liver Function Tests

The term "liver function tests" is usually given to a group of biochemical investigations used by physicians in the identification and management of liver disease. Many tests have been proposed for this purpose, but in practice, not every test is done. The King Edward VIII Hospital laboratories measure serum bilirubin, aspartate transaminase, alkaline phosphatase, gamma glutamyltransferase, and serum albumin. Prothrombin time and partial thromboplastin time are usually measured in the haematology laboratory; they are useful markers of the severity of hepatocellular disease, but are not regarded as conventional liver function tests (McIntyre, 1983).

The observation of van den Bergh and Muller in 1916 that some of the bilirubin in serum from jaundiced patients reacted directly with Erlich's diazo reagent, whereas some required alcohol for the development of colour (indirect bilirubin) was a major advance in the clinical chemistry of jaundice (McIntyre, 1983). Malloy and Evelyn subsequently introduced a quantitative version of the van den Bergh test that allowed measurement of the direct and indirect bilirubin in the blood (Malloy and Evelyn, 1937). The work done by Roberts on serum alkaline phosphatase activity in patients with a variety of conditions in 1930 and in patients with jaundice in 1933 (Roberts, 1933), and King and Armstrong's description of their method of measurement of serum alkaline phosphatase a year later (King and Armstrong, 1934), were important contributions to the clinical chemistry of liver

disease. Another significant development was the observation made by De Ritis and co-workers in 1955 that elevations of aspartate transaminase occur in viral hepatitis (De Ritis et al., 1955). Wroblewski and LaDue, in the same year, considered an elevated aspartate transaminase to be an index of liver cell injury when they found increased levels of this enzyme in acute hepatitis and other hepatic disorders (Wroblewski and LaDue, 1955). Conventional liver function tests are currently widely used in the detection and assessment of liver disease.

CHAPTER 2

CAUSES OF HEPATOMEGALY AT KING EDWARD VIII HOSPITAL, DURBAN: A PROSPECTIVE STUDY OF 240 BLACK PATIENTS

Introduction

Patients admitted to the medical wards of King Edward VIII Hospital, Durban, frequently have enlargement of the liver which is incidental to the condition for which admission is required. This is usually not investigated unless it is the source of symptoms.

Hersch stressed the need for liver biopsy in patients with unexplained hepatomegaly since hepatic tuberculosis often occurred without clinical or radiological evidence of pulmonary or extrahepatic involvement (Hersch, 1964 a,b). Furthermore, he emphasised that hepatic tuberculosis may present as pyrexia of unknown origin, or clinically simulate cirrhosis, liver abscess or carcinoma of the liver.

Against this background a study was conducted to determine:

i. the causes of hepatomegaly in patients admitted to the medical wards of King Edward VIII Hosptial;

ii. the relative frequency of tuberculosis as a cause of hepatomegaly; and

iii. the efficacy of liver biopsy in detecting pathology in patients with unexplained hepatomegaly.

Patients and Methods

During this prospective study, which commenced in February 1984, every patient admitted to the medical wards of King Edward VIII Hospital, Durban was examined for liver enlargement. In all, 240 black patients with an enlarged liver, irrespective of the admission diagnosis, were included in this study.

The cause of the hepatic enlargement was determined by clinical and, in most cases, supplementary examination, including basic haematological and microbiological tests, ultrasound scans and liver biopsy using a "Tru-Cut" needle, as outlined below.

Patients were not subjected to percutaneous liver biopsy if a cause for the enlarged liver could be established:

i. on clinical grounds e.g. congestive cardiac failure;

ii. by simple haematological tests e.g. leukaemia;

iii. by ultrasonography e.g. amoebic liver abscess;

iv. by microbiological tests e.g. typhoid fever; or

v. by peritoneoscopy.

The results of haematological and biochemical tests and other specialised investigations, and the response to therapy, where applicable, were recorded in all patients.

Patients belonging to groups (i) - (v) above whose hepatomegaly did not respond as anticipated to appropriate therapy, and all other patients who did not fall into these groups, underwent percutaneous "Tru-Cut" needle biopsy of the liver provided that:

i. informed consent was obtained;

ii. their coagulation profile was normal; and

iii. no contraindication to biopsy was present.

Results

A cause for the hepatomegaly was found in 153 patients (63.8%) without recourse to biopsy. The remaining 87 patients (36.3%) with unexplained hepatomegaly required liver biopsy. This was achieved in 76 patients (31.7%) without encountering any complications. Liver biopsy was not performed in the remaining 11 patients (4.6%) either because consent was refused, a severe coagulation abnormality was present, or the clinician responsible for management considered the patient too ill or biopsy unnecessary.

A cause for hepatic enlargement was found in 69 (90.8%) patients in whom liver biopsy was carried out. The diagnoses made at liver biopsy are presented in Table 1a.

When 3 specimens were submitted for histological examination, the diagnostic yield of liver biopsy was increased. A solitary granuloma which was present in only one of the three biopsy specimens provided a diagnosis in 2 cases. In another 2 patients in whom the initial biopsy specimen was unhelpful, a repeat biopsy, during which two specimens were taken, provided a diagnosis. In the 7 patients in whom liver biopsy failed to provide a diagnosis, it was found that only one specimen had been sent for histological examination.

A cause for hepatomegaly was thus found in 92.5% of the 240 patients who were studied. The relative frequency of the various causes is presented in Table 2a.

Tuberculosis of the liver, which accounted for 9.2% of patients whose hepatomegaly was initially unexplained and 2.9% of all patients studied, did not present any consistent clinical findings. There was no age or sex preponderance in these 7 patients. In 3 patients, the disease had not been associated with loss of weight. Fever was absent in 2 cases. The liver varied in size and in consistency and was tender in 2 patients. Splenomegaly was present in 3 patients. The chest radiograph was normal in 3 patients and in another 3

showed soft nodular shadows. The remaining patient had a right lower lobe bronchopneumonia. The ranges for the various liver function tests were as follows: albumin levels: 18-33g/l (normal: 35-50g/l); globulin levels: 32-53g/l (normal: 25-30g/l); bilirubin levels: 5-23umol/l (normal: up to 17umol/l) and alkaline phosphatase levels: 136-737U/l (normal: up to 95U/l). Two patients had an elevation of the alkaline phosphatase level which was less than twice normal. The haemoglobin concentration was normal in 1 patient. Sputum was unobtainable in 5 patients and negative for acid-fast bacilli in the remaining 2 patients.

In all these patients, examination of liver biopsy specimens provided the only means of establishing a diagnosis of tuberculosis. Acid-fast bacilli were present in the liver in 4 cases. The liver and spleen decreased in size after treatment with anti-tuberculous drugs in all patients.

Table 1a LIVER BIOPSY FINDINGS IN 76 PATIENTS

			PATIENTS	
			Number	Percent
1.	Hepatocellular carcinoma		14	18.4
2.	Cirrhosis		13	17.1
3.	Tuberculosis		7	9.2
4.	Schistosomiasis		7	9.2
5.	Alcoholic hepatitis		7	9.2
6.	Fatty change		5	6.6
7.	Siderosis and septal fibrosis		5	6.6
8.	Metastatic adenocarcinoma		4	5.3
9.	Miscellaneous:		7	9.2
	a. Viral hepatitis	1		
	b. Intrahepatic cholestasis	1		
	c. Liver abscess (pyogenic)	2		
	d. Malignant histiocytoma	2		
	e. Capillaria hepatica	1		
10.	Normal liver tissue		7	9.2

Table 2a **CAUSES OF HEPATOMEGALY IN 240 PATIENTS IN KING EDWARD VIII HOSPITAL MEDICAL WARDS**

		PATIENTS	
		Number	Percent
1.	Congestive cardiac failure	88	36.7
2.	Amoebic liver abscess	17	7.1
3.	Hepatocellular carcinoma	14	5.8
4.	Cirrhosis	13	5.4
5.	Typhoid fever	11	4.6
6.	Lymphoma	11	4.6
7.	Leukaemia	11	4.6
8.	Tuberculosis	7	2.9
9.	Schistosomiasis	7	2.9
10.	Alcoholic hepatitis	7	2.9
11.	Metastatic carcinoma	6	2.5
12.	Other (causes with a frequency of <2.5%)	30	12.5
	a. Fatty change (2.1%)		
	b. Siderosis and septal fibrosis (2.1%)		
	c. Viral hepatitis (1.7%)		
	d. Pyogenic abscess (1.3%)		
	e. Polycystic disease (0.8%)		
13.	Undetermined	18	7.5

Discussion

Liver enlargement is a common finding in patients admitted to the medical wards of King Edward VIII Hospital, Durban. In this prospective study of 240 patients, a cause for the hepatomegaly was found in 153 (63.8%) of patients after clinical examination and the appropriate use of haematological and microbiological tests and the ultrasound scan. Liver biopsy was performed in 76 of the remaining 87 patients without encountering complications. Liver biopsy provided the diagnosis in 90.8% of these patients. Thus a cause for liver enlargement was found in 222 (92.5%) of patients studied.

The commonest cause was congestive cardiac failure (36.7%), followed by amoebic liver abscess (7.1%), hepatocellular carcinoma (5.8%), cirrhosis (5.4%), typhoid, lymphoma and leukaemia (4.6% each).

It should be noted that tuberculosis accounted for 2.9% of all patients with hepatomegaly (and 9.2% of patients with an initially unexplained hepatomegaly), a frequency similar to that of alcoholic hepatitis and schistosomiasis. It is important, therefore, to consider tuberculosis as a possible cause when confronted with a patient with unexplained hepatomegaly. There are no characteristic features in patients with hepatic tuberculosis. A high index of suspicion is therefore required, especially in areas where tuberculosis is endemic. Liver biopsy is mandatory in these circumstances since it provides the only means of establishing the diagnosis. Moreover, tuberculosis of the liver may simulate cirrhosis, hepatocellular carcinoma and liver abscess clinically (Hersch, 1964 a,b), and the serum alkaline phosphatase may be normal in these patients.

The results suggest that when liver biopsy is carried out, three specimens should be obtained for histological examination by using a single entry site and redirecting the biopsy needle; the diagnostic yield was improved without an associated increase in complications.

The relative frequency of the various causes of hepatomegaly in our hospital population differed from that reported from other parts of Africa. In a study of 82 patients (which excluded patients with congestive cardiac failure) conducted at the University Teaching Hospital, Lusaka, toxic hepatitis (19.5%), viral hepatitis (14.6%), hepatocellular carcinoma (14.6%), cirrhosis (13.4%) and schistosomiasis (12.2%) were the major causes of hepatomegaly (Bahl et al., 1975). There were no patients with hepatic tuberculosis in this study. At the Mulago Hospital in Kampala, Uganda, cirrhosis, hepatocellular carcinoma, viral hepatitis and schistosomiasis played a major part in producing liver disease (Patel and Lwanga, 1971). In a study of 49 cases of obscure hepatomegaly conducted at Ain-Shams University, Cairo, the pathological findings on examination of liver biopsy specimens were as follows: cirrhosis (15 patients), chronic non-specific liver infection (13 patients); infiltration, necrosis, degeneration (8 patients); normal liver (3 patients); malignancy (1 patient); undetermined (9 patients)(El Mehairy, et al., 1969). Only 1 patient in this study had hepatic tuberculosis.

CHAPTER 3

SAMPLING VARIABILITY AND ITS INFLUENCE ON THE DIAGNOSTIC YIELD OF PERCUTANEOUS NEEDLE BIOPSY OF THE LIVER

Introduction

Percutaneous needle biopsy of the liver is a useful device for detecting the presence and nature of hepatic pathology, but since only a very small portion of the liver is obtained, lesions that are not uniformly distributed throughout the organ may be missed. In order to improve the diagnostic accuracy of liver biopsy, more than one specimen may be taken when cirrhosis, chronic aggressive hepatitis, metastatic carcinoma, or granuloma is suspected (Abdi et al., 1979). Some investigators routinely perform two biopsies when liver metastases are suspected (Fernandez et al., 1963; Grossman et al., 1972). However, in a recent study, which excluded patients with suspected localised liver lesions, another group of investigators reported that a single liver biopsy was adequate for assessment of liver histology (Picciotto et al., 1984).

A prospective study conducted to determine the causes of hepatomegaly in patients admitted to the medical wards of our hospital indicated that the diagnostic yield of liver biopsy could be improved when three consecutive biopsy specimens were obtained by redirecting the biopsy needle through a single entry site ; morbidity was not increased, provided that standard precautions were taken (Maharaj et al., 1986a). These preliminary findings required confirmation because an improved diagnostic yield not associated with an increase in complications would have important implications for patient management. A study was therefore designed to determine sampling variability and its influence upon the diagnostic yield of percutaneous needle biopsy when 3 consecutive specimens are taken during the procedure, and the nature and frequency of complications associated with this procedure.

Patients and Methods

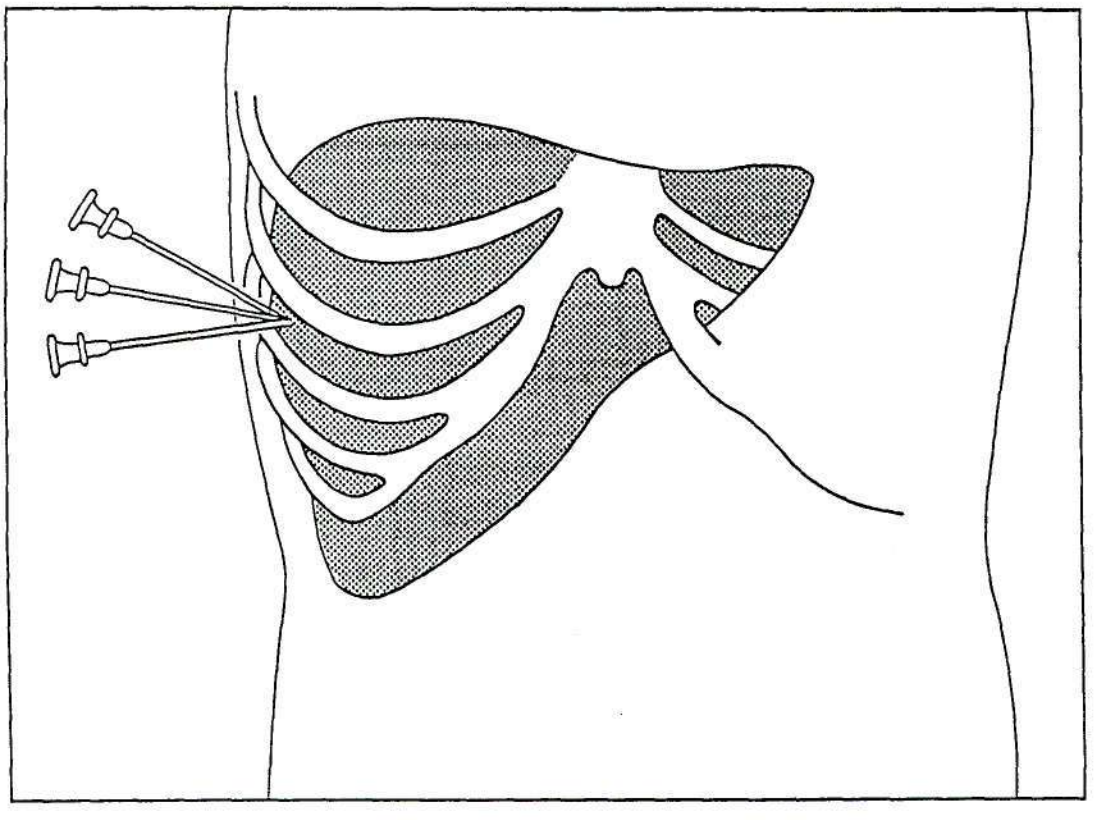
Biopsies were performed in the medical wards of King Edward VIII Hospital, Durban, by interns trained in the technique (Hegarty and Williams, 1984). Consent for the procedure was obtained in all cases after a full explanation of its implications.

Fifty-nine male and 16 female in-patients aged 12-70 years (mean 46.8 $\pm$ 17.0 years) in whom liver biopsy was indicated were included in the study. All had a platelet count greater than 100 x 10^9/l and prothrombin index greater than 75%. After infiltrating the skin and subcutaneous tissues with 2% lignocaine, 3 specimens were obtained using a "Tru-Cut" needle introduced through a single site and twice redirected by about 20^o to 30^o from the initial position (see figure). Thereafter, patients were monitored for complications (Hegarty and Williams, 1984); all were kept in hospital until a minimum of 24 hours had elapsed after the biopsy. Each specimen was placed in a separate bottle and coded so that their sampling order was unknown to the pathologists. After routine processing and staining, the 3 specimens were each examined by a different pathologist to eliminate any influence which findings on one biopsy specimen might have upon the interpretation of subsequent specimens from the same patient. The possibility of observer error between pathologists was reduced by submitting all biopsies to a single senior pathologist for review. All specimens were considered of adequate length for histological diagnosis (Sherlock, 1985).

Reports on the biopsy findings in each patient were then collated and any normal specimen was allocated the letter "N". If histological abnormalities were present in a single specimen, or the same abnormality was detected in more than one of 3 specimens collected from the same patient, the letter "A" was allocated to each such specimen. When pathological changes were present in more than one specimen but uniformity was lacking, "A" was used to indicate the specimen with least abnormalities and the letters "AA" and

"AAA" to denote specimens with pathology additional to that present in those coded "A" or "AA" respectively. Thus for each patient biopsied, the histological findings and symbol allocated to the first, the second and the third specimen, and the presence (and nature) of complications were known. Patients with similar distributions of symbols in the sequential biopsies were grouped together.

Schematic representation of the
liver biopsy technique used in this study



Results

The results obtained are presented in Table 1b. All specimens were normal in 11 patients (14.7%). In a further 27 patients (36%), the abnormalities present in all 3 specimens were similar. Thus, the findings were uniform in all 3 specimens in 50.7% of patients studied. In the remaining 49.3% (37 patients), sampling variability was found between the biopsy specimens.

The first specimen yielded maximum information in 70.7% of the 75 patients studied. The second specimen provided additional information in 13.3%, and the third in 16%. Had the order been reversed so that the third specimen became the first and vice versa, maximum information would have been obtained from the first specimen in 74.7% of patients. The second specimen would then have provided additional information in 9.3%, and the third would have given further information in 16%.

The influence of this sampling variability upon diagnoses that are frequently made by liver biopsy at our hospital (Maharaj et al., 1986a) is presented in Table 2b, which shows the distribution of lesions in 3 consecutive biopsy specimens. Hepatocellular carcinoma was present in all 3 specimens in 54.5% of cases, cirrhosis in 50%, metastatic carcinoma in 50%, and hepatic granulomas in 18.8% of cases. No sampling variability was found in the detection of alcoholic hepatitis (4 patients) and viral hepatitis (1 patient). The solitary case of angiosarcoma demonstrated this tumour in only the first specimen. Variability in the detection of fatty change and non-specific hepatitis was found in 1 patient.

There were no complications in any of the 75 patients studied; none required narcotic analgesics, intravenous fluids, blood transfusion, or developed an acute abdomen.

Table 1b. **REPRESENTATION OF LIVER BIOPSY FINDINGS WHEN THREE SPECIMENS WERE TAKEN (75 PATIENTS)**

			PATIENTS	
FIRST SPECIMEN	SECOND SPECIMEN	THIRD SPECIMEN	No.	%
N	N	N	11	14.7
A	A	A	27	36.0
N	A	A	3	4.0
N	A	AA	1	1.3
A	N	A	2	2.7
A	N	N	2	2.7
A	AA	A	4	5.3
A	AA	AA	3	4.0
A	A	N	1	1.3
A	A	AA	9	12.0
AA	AA	A	2	2.7
AA	A	A	6	8.0
AA	A	N	2	2.7
AA	A	AAA	1	1.3
AAA	A	AA	1	1.3

N = normal; A = abnormal; AA = abnormalities >A; AAA = abnormalities >AA

Table 2b. **SAMPLING VARIABILITY IN THE DETECTION OF IMPORTANT LIVER PATHOLOGY WHEN THREE BIOPSY SPECIMENS WERE TAKEN.**

DIAGNOSIS	SPECIMEN			PATIENTS	
	1st	2nd	3rd	No.	%
Hepatocellular carcinoma	+	+	+	6	54.5
	-	+	+	2	18.2
	+	+	-	1	9.0
	+	-	-	2	18.2
Cirrhosis	+	+	+	7	50.0
	+	+	-	2	14.3
	-	+	+	1	7.1
	-	-	+	4	28.6
Metastatic carcinoma	+	+	+	2	50.0
	-	-	+	1	25.0
	+	-	-	1	25.0
Caseating tuberculoid granuloma	+	+	+	2	66.6
	-	+	-	1	33.3
Schistosomal granuloma	+	-	+	1	25.0
	+	+	-	1	25.0
	-	-	+	1	25.0
	+	-	-	1	25.0
Non-caseating tuberculoid granuloma	-	-	+	3	33.3
	-	+	-	1	11.1
	+	-	-	4	44.4
	+	+	+	1	11.1

+ = present; - = not present

Discussion

Sampling variability of considerable magnitude was present in the detection of cirrhosis, hepatocellular carcinoma, metastatic carcinoma and hepatic granulomas. In many of these cases the diagnosis would not have been made if only one biopsy specimen had been submitted for histological examination.

Variability in the diagnosis of cirrhosis has been reported by other workers, (Abdi et al., 1979; Baunsgaard et al., 1979; Soloway et al., 1971; Vido and Wildhirt, 1969; Waldstein and Szanto, 1950). With the use of a biopsy technique similar to that used in this study, Soloway and colleagues diagnosed cirrhosis in all 3 biopsy specimens in only 2 of 8 patients with this disease and reported that when 3 sequential liver biopsies were obtained in the conventional manner over a 1-3 year period in patients with cirrhosis, histological evidence of the disease was not always found (Soloway et al., 1971). These authors concluded that the failure to demonstrate cirrhosis on a single needle biopsy specimen in patients with chronic active liver disease offered no assurance that the lesion was not present (Soloway et al., 1971). Abdi and co-workers reported that cirrhosis was confirmed on the first biopsy specimen in 16 of their 20 autopsy-proven cases; diagnostic accuracy was increased to 100% after examining 3 specimens (Abdi et al., 1979). Vido and Wildhirt found that a single blind liver biopsy failed to demonstrate cirrhosis in 51% of 254 patients in whom the diagnosis had been made at peritoneoscopy (Vido and Wildhirt, 1969). In contrast, Braunstein, who performed multiple liver biopsies at autopsy, reported that a single needle biopsy was accurate in the recognition of cirrhosis. However, analysis of his findings reveals that the degree and distribution of fibrosis was consistent in only 6 of 30 patients. Furthermore, in 5 patients who fulfilled the criteria for "far-advanced" cirrhosis, at least 1 specimen was found to be normal (Braunstein, 1956). A more recent report stated that a highly significant correlation existed between the findings at percutaneous liver

biopsy and those obtained after examination of both the percutaneous biopsy specimen and 2 specimens taken during peritoneoscopy (Picciotto et al., 1984). However, the number of patients in whom cirrhosis was detected in all 3 biopsies is not mentioned. These authors appeared to prefer laparoscopy as a means of confirming this diagnosis; the reason for this was not stated. In another study a highly significant correlation was found between 2 percutaneous specimens in the detection of cirrhosis, although the diagnosis was made in both specimens in only 8 of 12 patients (Baunsgaard et al., 1979).

Hepatocellular carcinoma was detected in all 3 specimens in 54.5% of patients with this diagnosis in our study. No other data on sampling variability in the diagnosis of this tumour are available for comparison. However, an autopsy-proven case of hepatocellular carcinoma involving the right lobe of the liver was missed by 3 sequential right costal liver biopsies in one study (Abdi et al., 1979).

Metastatic carcinoma was uniformly represented in all three biopsy specimens in 50% of patients with this diagnosis. In a study conducted by Grossman and co-workers metastatic carcinoma was diagnosed by the first biopsy in 41% of cases; diagnostic accuracy increased to 54% with 2 biopsies (Grossman et al., 1972). These workers now routinely perform two biopsies when trying to demonstrate liver metastases. Similar figures were obtained in other studies (Abdi et al., 1979; Conn and Yesner, 1963).

Granulomas were found in all 3 specimens in only 18.8% of our patients with this lesion; this did not occur in schistosomiasis. A lack of uniformity in the presence of caseating tuberculoid granulomas was noted in 1 of 3 patients with this diagnosis. The detection of a solitary non-caseating tuberculoid granuloma (in only 1 of 3 specimens) influenced the management of 6 of 8 patients with this lesion. Because of the clinical suspicion of hepatic tuberculosis, appropriate therapy was commenced; 3 patients responded to treatment, and 3 were lost to follow-up. The seventh patient was subsequently found to have typhoid

fever and the significance of the granuloma in the remaining patient was uncertain. Liver biopsy is commonly carried out in patients with hepatomegaly or hepatosplenomegaly of uncertain aetiology and in patients with pyrexia of unknown origin in the hope of finding a treatable cause, such as tuberculosis. The magnitude of sampling variability found in the detection of hepatic granulomas in this study has important therapeutic implications. Sampling variablity (of lesser magnitude) has been reported in other studies (Abdi et al., 1979; Klatskin and Yesner, 1950; Wagoner et al., 1951).

There is a paucity of data on the frequency and nature of complications that occur when 2 or more consecutive biopsy specimens are taken because studies on sampling variability have been conducted mainly in cadavers (Abdi et al., 1979; Braunstein, 1956; Grossman et al., 1972; Wagoner et al., 1951; Waldstein and Szanto, 1950), while most of those that have been performed in vivo make no mention of complications (Baunsgaard et al., 1979; Picciotto et al., 1984; Soloway et al., 1971). An increased incidence of minor complications has been found after 4 consecutive biopsies in a study in which 344 patients required between 2 and 11 biopsies (Perrault et al., 1978). We encountered no complications in our study.

These findings demonstrate that important pathological abnormalities can be overlooked in patients with hepatic disease when liver biopsy is performed in the conventional manner. Furthermore, the method used in this study, during which 3 specimens are obtained by using a single intercostal entry site and twice redirecting the biopsy needle about 20° to 30° from the original direction, can be used by relatively inexperienced clinical staff (interns) without an increase in complications. The improved diagnostic yield achieved by using this method has important implications for patient management; its greatest impact will be in developing countries where cirrhosis, hepatocellular carcinoma, liver metastases,

and granulomatous liver disease, including tuberculosis and schistosomiasis, are important and frequent causes of liver pathology (Bahl et al., 1975; El Mehairy et al., 1969; Maharaj et al., 1986a; Patel and Lwanga, 1971).

CHAPTER 4

A PROSPECTIVE STUDY OF HEPATIC TUBERCULOSIS IN 41 BLACK PATIENTS

Introduction

Many textbooks of clinical medicine fail to stress the importance of tuberculosis of the liver as a possible cause of hepatomegaly in areas where tuberculosis is endemic. In a prospective study conducted at King Edward VIII Hospital, Durban, hepatic tuberculosis was diagnosed in 9% of patients with an initially unexplained hepatomegaly (Maharaj et al., 1986a). Inconsistency in the clinical findings in this small group of seven patients with hepatic tuberculosis suggested that a high index of suspicion was required to avoid overlooking this diagnosis and an expanded study was instituted to assess the accuracy of these preliminary findings.

Patients and Methods

This study was conducted at King Edward VIII Hospital, which serves the black community of Durban and surrounding areas. During a 22-month period, patients in whom liver biopsy was carried out as part of the investigation of unexplained hepatomegaly, hepatosplenomegaly of uncertain cause or pyrexia of unknown origin were considered for inclusion in the study. Of the 48 patients entered initially, 41 with granuloma(s) in the liver were included in the final analysis because one of the following criteria for the diagnosis of hepatic tuberculosis was present: caseation or acid-fast bacilli in the liver; evidence of tuberculosis elsewhere; response to antituberculous treatment.

The patients were aged between 21 and 75 years. In each case, the history, findings on physical examination, and results of haematological and biochemical tests and special investigations were recorded. The response to antituberculous treatment was also noted when possible.

Results

Hepatic tuberculosis was diagnosed in 41 black inpatients (24 male and 17 female). Their mean age was 44.5 $\pm$ 15.8 years.

Forty-six per cent of patients had abdominal symptoms (usually pain in the right upper quadrant and distension), 61% had lost weight and 78% had respiratory symptoms (cough; dyspnoea; chest pain). The reasons for hospital admission in five patients were alcohol intoxication, confusion, seizures, recurrent pelvic inflammatory disease and urinary tract infection. Hepatic tuberculosis was an incidental finding.

The physical findings are present in Table 1c. Pyrexia was noted in 63% of patients; in one patient the temperature settled within three days of starting co-trimoxazole for presumed bronchopneumonia.

Jaundice, unrelated to antituberculous drugs, was present in 6(15%) patients; two developed hepatic encephalopathy which responded to appropriate treatment. Liver enlargement ranged from 1 to 7 cm (mean 3.9 $\pm$ 3.4cm) in the right midclavicular line and from 1 to 11cm (mean 3.8 $\pm$ 2.2cm) in the mid-thoracic line. In no case was splenomegaly greater than 4cm.

The results of haematological and biochemical tests are presented in Table 2c. Anaemia (Hb<13g/dl in males and <12g/dl in females) (Report of a WHO Scientific Group, 1968) was detected in 73% of patients; the haemoglobin concentration was lower than 10g/dl in 17% of patients. The white cell count was below $4x10^9$/l in 4% of patients and elevated in 17%. Thrombocytopenia (<$100x10^9$/l) was noted in 7% of patients and thrombocytosis (>$450x10^9$/l) in 12%. Pancytopenia was not observed. The prothrombin index was greater than 75% in 93% of patients; in the remaining three patients, the prothrombin index rose after the administration of vitamin K.

Hypoalbuminaemia (<35g/l) was present in 95% of patients and was severe (<20g/l) in 38%. Hyperglobulinaemia (>35g/l) was noted in 78%, with levels greater than 50g/l in 20% of patients. In 43% of patients the serum bilirubin concentration was raised; levels were greater than 40umol/l in 20%.

Serum alkaline phosphatase levels were normal in 13% of patients; elevations equal to almost twice the normal value were noted in 20% of patients, while another 20% had elevations nearly three times the normal value. The mean serum sodium level was129.5 $\pm$ 6.6mmol/l. Hyponatraemia was present in 66% of patients. The ascitic protein concentration was measured in eight patients; a transudate was present in three and an exudate in five patients (Bastani et al., 1985).

Ultrasonography was normal in 17 of 18 (94%) patients who underwent this procedure. In the remaining patient, increased echogenicity of liver tissue was noted. Tc-99m sulphur colloid liver scans were obtained in 17 patients and were normal in eight (47%) patients. Decreased uptake of the radiocolloid by the liver with shunting to the spleen or bone marrow was noted in seven patients. An increased extrahepatic uptake was the only abnormality in two patients.

Chest radiographs were normal in 22% of patients. One patient had apical scarring. Two had ill-defined opacities in their upper lobes. Soft, nodular opacities were the most frequent finding in the other patients.

Percutaneous liver biopsy was carried out in 88% of patients and peritoneoscopic biopsy in the others. In addition to granuloma(s), caseation with acid-fast bacilli, caseation without acid-fast bacilli and acid-fast bacilli without caseation were detected in 37, 15 and 22% of patients respectively. Thus, acid-fast bacilli were seen in 59% of patients.

Response to antituberculous treatment and evidence of tuberculosis elsewhere confirmed the diagnosis of hepatic tuberculosis in 27% of patients. Co-existing liver disease was present in 15 (37%) patients; two had alcoholic hepatitis, one had micronodular cirrhosis with alcoholic hepatitis, eight had siderosis plus septal fibrosis, and four had fatty change. Tuberculous peritonitis was diagnosed in one patient.

It was not possible to monitor the response to antituberculous drugs (streptomycin, isoniazid, pyrazinamide and rifampicin) in all patients because they were often transferred to other hospitals and peripheral clinics. In 20% of patients, transfer was delayed until improvement had occurred. Their temperature responded after 7 to 16 days (mean 11 days). However, improvement in appetite occurred earlier, and increase in weight and reduction in the size of the liver and spleen were also noted. Two deaths were recorded. One patient died three days after starting treatment; isolated hepatic tuberculosis was confirmed at autopsy. The other died on the day treatment was started; autopsy was not performed.

Table 1c. SYMPTOMS AND SIGNS IN 41 PATIENTS WITH HEPATIC TUBERCULOSIS

	PATIENTS	
	Number	Percent
Abdominal symptoms	19	46.3
Respiratory symptoms	32	78.0
Loss of weight	25	61.0
Pyrexia	26	63.4
Jaundice	6	14.6
Hepatomegaly	39	95.1
Soft	22	56.4
Firm	16	41.0
Hard	1	2.6
Irregular surface	4	10.2
Tender	17	43.6
Splenomegaly	13	31.7
Ascites	10	24.4

Table 2c. LABORATORY DATA IN 41 PATIENTS WITH HEPATIC TUBERCULOSIS

Parameter	Normal Range	Mean ± SD	Range
Haemoglobin (g/dl)			
Males	14 - 18	11.5 ± 1.9	5.6 - 13.8
Females	12 - 16	10.5 ± 3.2	5.2 - 16.3
White cell count ($x10^9$/l)	4 - 10	7.6 ± 3.4	3.8 - 20.0
Platelet count ($x10^9$/l)	150 - 400	284.5 ± 146.9	68.0 - 695.0
Albumin (g/l)	35 - 50	23.1 ± 8.4	9.0 - 62.0
Globulin (g/l)	25 - 30	42.9 ± 9.3	20.0 - 66.0
Bilirubin (umol/l)	0 - 17	24.0 ± 25.4	2.0 - 174.0
Alkaline phosphatase (umol/l)	30 - 95	394.4 ± 316.4	77.0 - 1304.0
Aspartate transaminase (umol/l)	10 - 42	924.0 ± 89.4	14.0 - 496.0
Sodium (mmol/l)	135 - 148	129.5 ± 6.6	110.0 - 142.0

Discussion

This study confirms that there are no consistent clinical findings in patients with tuberculosis of the liver. Abdominal symptoms, weight loss, pyrexia, hepatomegaly and splenomegaly were absent in 54, 39, 37, 5 and 68% of patients respectively. Analysis of the results of other studies, some of which include cases diagnosed at autopsy, confirms our finding that pyrexia and weight loss are not always present (Essop et al., 1984; Johri et al., 1970), jaundice is common (Alvarez and Carpio, 1983; Essop et al., 1984; Hersch, 1964a) and liver failure does not imply a poor prognosis (Alvarez and Carpio, 1983; Essop et al., 1984). The liver is not invariably enlarged (Alvarez and Carpio, 1983; Essop et al., 1984; Guckian and Perry, 1966; Ross et al., 1956) but, when it is, variation in size, consistency and degree of tenderness occur (Alvarez and Carpio, 1983; Essop et al., 1984; Hersch, 1964a); 44% of our patients had a tender hepatomegaly.

Biochemical abnormalities also lack consistency. Normal serum albumin and alkaline phosphatase levels were present in some of our patients, whereas severe hypoalbuminaemia and marked elevations of serum alkaline phosphatase levels were noted in others. None of the patients studied by Johri and his colleagues had abnormal alkaline phosphatase levels (Johri et al., 1970), whereas Alvarez and Carpio (Alvarez and Carpio, 1983) and Essop and co-workers (Essop et al., 1984) reported normal levels in 25 and 17% of their patients respectively. In the past, emphasis has been placed on the value of a disproportionate elevation of the serum alkaline phosphatase level when hepatic granulomas, including tuberculosis, are suspected (Essop et al., 1984; Ross et al., 1956); it is now clear that the presence of normal alkaline phosphatase levels does not rule out hepatic tuberculosis (Essop et al., 1984; Frank and Raffensperger, 1965; Hersch, 1964a). Furthermore, in 48% of our patients, levels could not be distinguished from those associated with cirrhosis of the liver in our hospital (O'Keefe et al., 1982). Thus, our findings agree with those of Guckian and Perry, viz. that liver function tests are not of diagnostic value (Guckian and Perry, 1966), and support Spiro's view that normal liver function tests should not deter the

clinician from performing liver biopsy when disseminated tuberculosis is suspected (Spiro, 1983). Our findings also support McIntyre's contention that there is a tendency to read more into the results of liver function tests than the confirmation of liver disease, even though these tests alone have limited capability for differential diagnosis (McIntyre, 1983). It is also important to note that transudative ascites does not exclude hepatic tuberculosis; transudates occurred in three of our patients, one of whom had concomitant tuberculous peritonitis.

The fact that ultrasound and Tc-99m sulphur colloid liver scans were normal in 94 and 47% of patients respectively confirms that hepatic imaging techniques are of little value in this condition (Essop et al., 1984). Chest radiographs were normal in 22% of our patients. Alvarez and Carpio reported that 35% of their patients had normal chest radiographs (Alvarez and Carpio, 1983). None of the patients studied by Johri and co-workers had abnormal radiographs (Johri et al., 1970). Thus, hepatic tuberculosis cannot be excluded by the absence of clinical or radiological evidence of pulmonary disease. Haematological abnormalities were also inconsistent. Anaemia was absent in 27% of patients. White cell and platelet counts were normal in the majority of patients, and both high and low counts were noted. Guckian and Perry reported that tuberculin skin testing was positive in only 41% of patients; one of their eight patients with sarcoidosis also had a positive test (Guckian and Perry, 1966).

In addition to hepatic tuberculosis, other forms of liver disease, including cirrhosis and alcoholic hepatitis, were also detected on histological examination of the biopsy specimens from some patients. Not only can hepatic tuberculosis co-exist with other forms of liver disease, but it may also simulate cirrhosis, liver abscess and carcinoma of the liver (Alvarez and Carpio, 1983; Atoba and Junaid, 1980; Essop et al., 1984; Hersch, 1964a).

Since the clinical picture of hepatic tuberculosis is so variable a high index of suspicion is necessary, especially in communities where tuberculosis is endemic. Support for this is provided by Essop and co-workers who reported that this disease was suspected clinically in only 47% of their patients (Essop et al., 1984). A liver biopsy should be performed in patients with unexplained hepatomegaly or hepatosplenomegaly or pyrexia of unknown origin as it provides the only means of making the diagnosis. Since sampling variability in the detection of hepatic granulomas occurs, two consecutive biopsy specimens should, if possible, be obtained by redirecting the biopsy needle through a single intercostal entry site (Maharaj et al., 1986b). Work done in some institutions has shown that when more biopsies are performed, more granulomas are detected (Frank and Raffensperger, 1965; Guckian and Perry, 1966; Hersch, 1964a).

Because caseation necrosis is not always found and acid-fast bacilli are difficult to detect, many workers accept the presence of a non-caseating granuloma as evidence of tuberculosis and accordingly begin antituberculous treatment (Alvarez and Carpio, 1983; Essop et al., 1984; Frank and Raffensperger, 1965; Hersch, 1964a; Johri et al., 1970; Spiro, 1983). Clinical response proves the diagnosis. It is noteworthy that acid-fast bacilli were seen in 59% of our patients, a frequency much higher than that reported previously (Alvarez and Carpio, 1983; Essop et al., 1984; Frank and Raffensperger, 1965; Guckian and Perry, 1966; Johri et al., 1970; Hersch, 1964a). In 38% of these patients, caseation was absent. We believe that acid-fast bacilli should be sought because their presence provides unequivocal evidence of the diagnosis, but it is important that adequate liver tissue be sent for histological examination (Guckian and Perry, 1966). One author recommends laparotomy to confirm the diagnosis if needle biopsy is negative (Hersch, 1964a).

Response to antituberculous treatment is monitored clinically. In keeping with previous reports, improvement in appetite occurred early. The temperature settled within two weeks (Johri et al., 1970; Terry and Gunnar, 1957), and regression of hepatomegaly and

splenomegaly, as well as weight gain were noted (Alvarez and Carpio, 1983; Johri et al., 1970; Terry and Gunnar, 1957). The value of short-course chemotherapy in patients with hepatic tuberculosis has not yet been established. However, a recent report by Dutt and co-workers (Dutt et al., 1986) that short-course chemotherapy was successful in 95% of patients with other forms of extrapulmonary tuberculosis suggests that a similar outcome can be expected in patients with hepatic tuberculosis.

This study illustrates that hepatic tuberculosis has no pathognomonic features. That a greater awareness of this condition is required is demonstrated by our study in which increased use of liver biopsy in patients with unexplained hepatomegaly or hepatosplenomegaly and pyrexia of unknown origin resulted in the diagnosis being made in 41 black patients during a period of 22 months, whereas the condition was considered rare in our hospital during the 22-year period between 1955 and 1977 (Adams, 1979).

CHAPTER 5

THE ROLE OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DETECTING FOCAL AND DIFFUSE LIVER DISEASE IN DEVELOPING COUNTRIES

Introduction

Radionuclide scintigraphy and ultrasonography are used in many countries to evaluate patients in whom liver disease is supected. However, these imaging modalities are not readily available in developing countries. In response to the growing desire of developing countries to acquire equipment for imaging, a group of experts, who were chosen by the World Health Organisation, recommended that equipment for ultrasonography be purchased (Palmer, 1985). They argued that even for those radionuclide scanning procedures that had not become obsolete as a result of newer methods of imaging such as ultrasonography, certain difficulties existed, including the supply of the required radioisotopes in developing countries. Furthermore, this imaging modality did not demonstrate the nature of the disease or give sufficiently accurate anatomical information when abnormalities were detected.

In the light of the fact that greater use of ultrasonography could result from this recommendation, and that most of the publications on hepatic imaging have emanated from developed countries where the pattern of liver disease is likely to differ from that encountered in developing countries (Atoba and Junaid, 1980; Bahl et al., 1975; El Mehairy et al., 1969; Maharaj et al., 1986a; Patel and Lwanga, 1971), a study was conducted to determine the role of ultrasonography and scintigraphy in the detection of focal and diffuse liver disease in developing countries.

Patients and Methods

Patient Population

This retrospective study was conducted at King Edward VIII Hospital, Durban. Ultrasound and scintigraphic liver scans can be requested by any member of the hospital staff, and are carried out by a radiologist or radiologist-in-training.

Patient Selection

A list of all patients in whom liver biopsy had been carried out during 1984-1987 (inclusive) was obtained from the Department of Anatomical Pathology. Their hospital records were reviewed to determine if an ultrasound and/or scintigraphic liver scan had been performed.

When either imaging procedure had been carried out, patients were considered for entry into the study and the following information was recorded: the temporal relationship of the scan(s) to the liver biopsy, the clinical history, findings on physical examination, the results of special investigations, including the liver biopsy and scan findings, final diagnosis and response to appropriate therapy (where applicable).

Liver biopsy had been carried out in patients suspected of having either focal or diffuse liver disease because they had either unexplained liver or splenic enlargement or both, deranged liver function tests, jaundice, fever of unknown origin, unexplained weight loss, lymphoma, or abnormalities detected during hepatic imaging studies, peritoneoscopy or laparotomy. Liver tissue had been obtained during either percutaneous liver biopsy, peritoneoscopy or laparotomy.

Because liver biopsy is normally not used in the management of patients with amoebic liver abscess, a common disease encountered at our hospital, a list of all patients in whom this diagnosis had been made during the study period was obtained from the hospital computer and their hospital records reviewed. Patients were considered for inclusion in the study when either imaging procedure had been performed and when the criteria for the diagnosis of amoebic liver abscess were fulfilled.

Histology

Liver tissue submitted for histological examination was processed and stained in a routine manner. Special staining procedures were also used when indicated. All specimens were examined by a senior pathologist.

Assignment of Final Diagnosis

Amoebic liver abscess was diagnosed when amoebic serology was positive, aspiration yielded "anchovy-sauce" pus or treatment with metronidazole produced a beneficial response.

In all other cases, the diagnosis was made by histological examination of liver tissue obtained during percutaneous liver biopsy, peritoneoscopy or laparotomy. Because sampling variability influences the diagnostic yield of liver biopsy, important pathology can be overlooked in patients with hepatic disease when liver biopsy is carried out in the conventional manner. Accordingly, careful consideration was given to the clinical findings, results of other investigations, and findings at laparotomy or autopsy in all cases.

In the event of dual pathology, the disease which was more likely to influence the prognosis of the patient was selected as the primary pathology.

A separate category of "Carcinoma - Primary or Secondary" was created because there were cases in which the pathologist was unable to decide whether the carcinoma was a primary hepatocellular carcinoma or a metastatic carcinoma. The clinical records and other investigations were unhelpful in distinguishing between the two diseases. An ultrasound diagnosis of either hepatocellular carcinoma or metastatic carcinoma was accepted as correct in cases that fell into this category.

No attempt was made to determine the source of metastases in patients with metastatic carcinoma of the liver.

Inclusion and Exclusion Criteria

Patients were entered into the study provided that none of the following exclusion criteria was present:

i. the interval between the imaging procedure and liver biopsy was greater than two weeks;

ii. liver tissue was considered inadequate for histological diagnosis;

iii. liver biopsy was deemed to have missed a lesion or if there was doubt about the final diagnosis;

iv. siderosis, septal fibrosis, or fatty change was considered to be of mild or moderate degree by the pathologist;

v. extrahepatic biliary obstruction was present;

vi. a liver scan was considered technically suboptimal by either radiologist.

Imaging Technique

Radionuclide liver scintigraphy was performed 20 minutes after the administration of 2 to 4 mCi of technetium-99m tin colloid. Scintigraphy was done with a large field of view gamma camera (Elscint Apex 415, Elscint, Haifa, Israel). A high resolution parallel hole collimator (APC - 3) was used. Anterior, posterior and right lateral views were obtained.

The ultrasound scans were obtained using commercially available real-time sector scanners with a 3-3.5 MHz transducer (ATL-Mark 100 and ATL-Ultramark 8, Advanced Technological Laboratories, Bellevue, USA). Routine transverse and longitudinal scans were carried out. When indicated, oblique and other planes were used. The diagnostic echo patterns were obtained at standard instrument settings, although higher gain settings were required for optimal results in some patients.

All scans were recorded on a "Cronex" daylight film which is clear-based.

Interpretation of Scans

Each scan was identified only by a code number and assessed without knowledge of the patient's clinical details, results of any investigations (including liver biopsy) or the final diagnosis. All scans were examined by two senior radiologists who worked independently of each other. Their observations and interpretations were recorded in a pre-arranged manner which is outlined below; in each case they were required to record their diagnostic impression (normal, diffuse parenchymal liver disease, focal liver disease).

The report of the person who initially performed the imaging study (radiologist-in-training or specialist radiologist) was also interpreted by the author in a similar fashion; when the report suggested that diffuse or focal liver disease was present, this was taken to represent a categoric judgement on the presence of the abnormality for the purpose of this study.

Each scintigraphic scan was read for homogeneity of uptake, presence or absence of extrahepatic uptake or space-occupying lesions ("cold areas"). Diffuse liver disease was taken to be present when any of the following was detected: decreased and/or irregular liver uptake, increased splenic uptake, increased bone marrow uptake. Splenic enlarge-

ment was not regarded as a sign of diffuse liver disease because there are many other causes of splenomegaly in our hospital. A focal area of decreased uptake was indicative of a space-occupying lesion.

For each ultrasound scan, a comment was made on the echogenicity of the liver parenchyma and on the diagnostic impression (normal, diffuse parenchymal liver disease, space-occupying lesion). Echogenicity of liver parenchyma was considered increased if the density of echoes in the liver was greater than that in the parenchyma of the right kidney.

A focal area of increased, decreased or mixed echogenicity was considered consistent with a space-occupying lesion. A final diagnosis was made whenever the features of the space-occupying lesion were characteristic of a particular disease. In all other cases a differential diagnosis was offered. Since hepatocellular carcinoma may affect the liver in a diffuse manner (Kamin et al., 1979), a diffusely coarse and disorganised echo pattern was accepted as indicating infiltration of the liver by neoplasia whenever the radiologist interpreted the ultrasound as such.

A diffuse increase in echogenicity was interpreted as diffuse parenchymal liver disease. Splenomegaly and ascites were not used as signs of liver disease in this study because causes of these abnormalities, other than portal hypertension, are frequently encountered in this hospital. Because there is no consensus on whether it is consistently possible to distinguish between the various causes of diffuse parenchymal liver disease at ultrasonography, and because there are many causes of diffuse liver disease at our hospital, it was decided that a comment on the possible cause of the diffuse abnormality would not be made.

Coding

After both radiologists had completed their assessment of the scans their reports were collated. Differences were resolved at a consensus meeting. The reports in which there was agreement between the two radiologists and their joint report from the consensus meeting (in those cases lacking uniformity) were used in the analysis of the accuracy of the liver scans, and of the interobserver differences between the radiologist who initially carried out the imaging procedure and the two senior radiologists. The results of each scan was compared with the final diagnosis and classified as true positive, false negative, true negative and false positive.

Analysis

Each technique was assessed sequentially for its accuracy in differentiating normal from abnormal liver, space-occupying lesions (focal liver disease) from diffuse liver disease and normal livers, and diffuse parenchymal liver disease from space-occupying lesions and normal livers, and its accuracy in detecting space-occupying lesions in patients with amoebic liver abscess, hepatocellular carcinoma, metastatic carcinoma and carcinoma-primary or secondary, and diffuse liver disease in patients with cirrhosis, severe siderosis and septal fibrosis, severe siderosis, alcoholic hepatitis, hepatitis due to other causes, fatty change, tuberculosis, schistosomiasis and granulomatous liver disease including tuberculosis and schistosomiasis.

In addition, the accuracy of ultrasonography in both detecting a space-occupying lesion in and making a correct diagnosis of amoebic liver abscess, hepatocellular carcinoma, metastatic carcinoma and carcinoma-primary or secondary, and the accuracy of each imaging procedure in detecting diffuse parenchymal liver disease in patients in whom cirrhosis co-existed with hepatocellular carcinoma was assessed.

This was done by calculating the sensitivity, specificity, accuracy, accuracy of a positive test and accuracy of a negative test for each technique from the test results. Sensitivity is the number of true positive studies divided by the sum of the true positive and false negative results and indicates the proportion of patients with the disease whose imaging study was correctly interpreted as positive. Specificity is the number of true negative studies divided by the sum of the true negative and false positive studies and refers to the proportion of patients with no disease whose imaging study was correctly interpreted as negative. Accuracy, which denotes the proportion of patients whose imaging studies were correctly interpreted as positive or negative, is calculated by dividing the sum of true positive and true negative results by the sum of true positive, false negative, true negative and false positive results. The accuracy of a positive test, which describes the probability that the patient actually has the disease given that the patient has a positive test, is the number of true positive studies divided by the sum of true positive and false positive studies. The accuracy of a negative test describes the probability that the patient is actually normal given that the patient has a negative test and is calculated by dividing the number of true negative studies by the sum of true negative and false negative studies. Since the accuracy of a positive test depends on the prevalence of the disease, this was calculated by dividing the number of patients with the disease (true positive plus false negative) by the total number of patients being imaged (the sum of true positive, false negative, true negative and false positive studies) (Ashare, 1980; McClees and Gedgaudas-McClees, 1984; McNeil and Adelstein, 1976; Powell-Jackson et al., 1987).

The interobserver variability between the two senior radiologists for each technique, as well as the interobserver variation between the person who initially performed the procedure and the two senior radiologists was determined. This step was taken because it is the initial report that influences the further management of patients.

No attempt was made to determine the cause of false positive scintigraphic or ultrasound examinations as these have been extensively studied by other workers and adequate explanations have been given, nor was an attempt made to determine the size of space-occupying lesions in this study.

Results

There were 599 patients who fulfilled the inclusion criteria; nine patients had been excluded because their scans were considered technically suboptimal and uninterpretable.

Table 1d shows the final diagnosis of the patients studied and the number of ultrasound and scintigraphic scans examined; ultrasonography was more frequently utilised than scintigraphy in all 3 patient categories. Both procedures were carried out in 131 patients, 71 with focal liver disease, 44 with diffuse liver disease and 16 normal patients.

The comparative accuracy of ultrasonography and scintigraphy in distinguishing between normal and liver disease is shown in Table 2d. Ultrasound scanning had a lower sensitivity, higher specificity, lower accuracy, similar accuracy of a positive test and a lower accuracy of a negative test than scintigraphic scanning. The sensitivity, accuracy, and the accuracy of a negative test was low for both imaging techniques.

In the detection of focal liver disease (space-occupying lesions), ultrasonography was noted to have a lower sensitivity, a higher specificity, a similar overall accuracy, a higher accuracy of a positive test and a lower accuracy of a negative test than scintigraphy (Table 3d). However, with the exception of the sensitivity of ultrasonography which remained lower than that of scintigraphy, the trend in the detection of diffuse liver disease was different (Table 3d). Ultrasound scanning had a similar specificity, a lower accuracy, a lower accuracy of a positive test, and a similar accuracy of a negative test. The sensitivity of both procedures in diffuse disease was low. Both imaging modalities proved superior in

detecting space-occupying lesions; the sensitivity, accuracy, and accuracy of a negative test of both investigations and the accuracy of a positive ultrasound scan were higher in focal disease, while the specificity of both procedures and the accuracy of a positive scintigraphic scan was similar in both focal and diffuse liver disease (Table 3d).

The accuracy of ultrasonography and scintigraphy in detecting space-occupying lesions in patients with amoebic liver abscess, hepatocellular carcinoma, metastatic carcinoma and carcinoma-primary or secondary is shown in Tables 4d and 5d respectively. The sensitivity of ultrasonography and scintigraphy ranged from 62 to 100% and 82 to 100% respectively, specificity of ultrasonography for all diseases was 98% and of scintigraphy ranged from 93-94%, accuracy of ultrasonography and scintigraphy ranged from 96-98% and 92-94% respectively, the accuracy of a positive test from 62-90% and 39 to 76% respectively, and accuracy of a negative test from 97 to 100% for both procedures.

The accuracy of ultrasonography and scintigraphy in detecting diffuse liver disease in patients with cirrhosis, severe siderosis and fibrosis, severe siderosis, alcoholic hepatitis, hepatitis due to other causes, fatty change, tuberculosis and schistosomiasis is shown in Tables 6d and 7d. The sensitivity of ultrasonography and scintigraphy ranged from 0 to 60% and 20 to 80% respectively, the specificity of ultrasonography for all diseases was 97% and of scintigraphy ranged from 95 to 96%, accuracy of ultrasonography and scintigraphy ranged from 88 to 96% and 90 to 95% respectively, the accuracy of a positive test from 0 to 52% and 8 to 72%, and the accuracy of a negative test from 90 to 99% and 93 to 99% respectively.

In the detection of diffuse liver disease in all patients with granulomatous liver disease (including tuberculosis and schistosomiasis), the sensitivity and accuracy of a positive test was lower for ultrasonography than scintigraphy (Table 8d). However, the sensitivity and accuracy of a positive test was low for both procedures. The specificity, accuracy and accuracy of a negative test of the two imaging techniques were similar.

When evaluating the ability of ultrasonography to both detect a space-occupying lesion in, and make a correct diagnosis of, amoebic liver abscess, hepatocellular carcinoma, metastatic carcinoma and carcinoma (primary or secondary), scans of patients with the appropriate disease were classified as false negative if a space-occupying lesion was not detected, or if a space-occupying lesion was detected and a final diagnosis was either not made (i.e. a differential diagnosis was given), or was incorrect. The results are presented in Table 9d. The sensitivity ranged from 29 to 81%, specificity from 94 to 99%, accuracy from 86 to 96%, accuracy of a positive test from 26 to 93% and the accuracy of a negative test from 87 to 97%.

When the accuracy of the two imaging modalities in distinguishing between normal and liver disease in those patients (n=131) who had both investigations (Table 10d) is compared to that observed in all patients studied (Table 2d), the trend is similar, although the figures differ.

The accuracy of ultrasound and radionuclide scintigraphic scanning in detecting focal and diffuse disease in the patients who had both investigations is shown in Table 11d. In both types of liver disease, ultrasonography was noted to have a lower sensitivity, a similar specificity, a lower accuracy, a similar accuracy of a positive test, and a lower accuracy of a negative test than scintigraphy. In this group of patients, the specificity, accuracy and accuracy of a positive test in focal disease of scintigraphy, accuracy of a positive test of both procedures in diffuse disease, and accuracy of a negative scintigraphic test in diffuse

disease were higher than that noted in the whole study (Table 3d) and would account for the discrepancies noted in the performance of the two procedures in all patients studied compared to the smaller subset who had both investigations. It is noteworthy that in both types of liver disease, the sensitivity of ultrasonography was lower than that of scintigraphy, in keeping with the observations in all patients studied. Also in this group of patients, the sensitivity of both procedures in diffuse disease was low (Table 11d).

Agreement between the findings at ultrasonography and scintigraphy was present in 58 of 71 patients with focal liver disease, 22 of 44 patients with diffuse disease and 15 of 16 patients with a normal liver who had both procedures (Table 12d). The results were correct (true positive) in all, except one, of the patients with focal disease in whom the findings of both techniques concurred. In contrast, in the majority of patients with diffuse liver disease, the results were false negative.

The scintigraphic findings were correct in 12 of 13 patients with focal disease and 16 of 22 patients with diffuse liver disease in whom agreement between the results of the two imaging modalities was lacking (Table 12d).

The sensitivity of ultrasound and scintigraphic scanning in detecting cirrhosis (diffuse liver disease) in patients who had both cirrhosis and hepatocellular carcinoma was 41 and 67% respectively (Table 13d); the other calculations were not done, because it was not possible to determine whether the remaining patients with hepatocellular carcinoma had cirrhosis since the specimens that were submitted for histological examination consisted entirely of tumour tissue.

Of the 41 false negative ultrasound scans in cirrhosis, 23(56%) occurred in patients with micronodular cirrhosis, 2 (4.9%) in macronodular cirrhosis and 16 (39%) in the mixed type of cirrhosis. Five (27.7%) false negative scintigraphic scans belonged to the first group, 3

(16.7%) to the second group and 10 (55.6%) to the third group. There were 12 scintigraphic scans of patients with cirrhosis which were false positive for space-occupying lesions. They were distributed among the three groups as follows : 3(25%), 5(41.6%) and 4(33.3%) respectively. An ultrasound scan of a patient with micronodular cirrhosis and 2 ultrasound scans of patients with the mixed type of cirrhosis were incorrectly interpreted as having space-occupying lesions.

Interobserver differences in the detection of focal liver disease, diffuse disease and normal liver were frequent with both imaging modalities (Table 14d). The two senior radiologists differed on 25.5% of ultrasound scans and 11% of scintigraphic scans of patients with diffuse liver disease; the magnitude of the differences between the initial observer who carried out the procedure and the two senior radiologists was greater - 30.3% and 20.5% respectively. With the exception of the interobserver differences between the two senior radiologists for scintigraphic scans in normal individuals, which occurred in 14.5% of scans, the frequency of interobserver differences in focal disease and normal liver were much lower than in diffuse liver disease. Overall, interobserver differences were more frequent for ultrasound scans.

It was also noted that the two senior radiologists differed in their interpretation of 72 of the 217 (33.2%) ultrasound scans of patients with focal liver disease in whom they had both correctly detected the presence of space-occupying lesions. In some instances, one offered a differential diagnosis while the other made a final diagnosis. In other instances, one made a final diagnosis which was correct, while the other did not.

Table 1d. **FINAL DIAGNOSIS IN THE 599 PATIENTS STUDIED.**

	Number of patients	Number of ultrasound scans	Number of scintigraphic scans
FOCAL DISEASE	268	217	122
Amoebic liver abscess	76	69	11
Hepatocellular carcinoma	94	75	56
Metastatic carcinoma	72	49	39
Carcinoma primary/secondary	23	21	14
Miscellaneous	3	3	2
a. Hydatid disease			
b. Tuberculosis			
c. Lymphoma			
DIFFUSE DISEASE	229	145	127
Cirrhosis	86	54	49
Severe siderosis + fibrosis	13	8	7
Severe siderosis	16	7	11
Alcoholic hepatitis	23	18	10
Hepatitis - other	11	8	5
Fatty change	14	10	6
Tuberculosis	27	17	16
Schistosomiasis	28	15	16
Granulomatous disease-other	6	5	3
Lymphoma	4	2	3
Amyloidosis	1	1	1
NORMAL	102	63	55
TOTAL	599	425	304

Table 2d. ACCURACY OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DISTINGUISHING BETWEEN NORMAL LIVER AND LIVER DISEASE IN PATIENTS WITHOUT AND WITH LIVER DISEASE.

	Ultrasound scans	Scintigraphic scans
Liver disease	362	249
Normal	63	55
True Positive	229	180
False Negative	133	69
False Positive	4	10
True Negative	59	45
Sensitivity	0.63	0.72
Specificity	0.94	0.82
Accuracy	0.68	0.74
Accuracy of Positive Test	0.98	0.95
Accuracy of Negative Test	0.31	0.39
Prevalence	0.85	0.82

Table 3d. ACCURACY OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DETECTING FOCAL OR DIFFUSE LIVER DISEASE.

	FOCAL DISEASE		DIFFUSE DISEASE	
	Ultrasound scans	Scintigraphic scans	Ultrasound scans	Scintigraphic scans
Scans of patient with the disease	217	122	145	127
Scans of patients without the disease	208	182	280	177
True Positive	190	112	39	68
False Negative	27	10	106	59
False Positive	8	17	12	12
True Negative	200	165	268	165
Sensitivity	0.88	0.92	0.27	0.54
Specificity	0.96	0.91	0.96	0.93
Accuracy	0.92	0.91	0.72	0.77
Accuracy of Positive Test	0.96	0.87	0.76	0.85
Accuracy of Negative Test	0.88	0.94	0.72	0.74
Prevalence	0.51	0.40	0.34	0.42

Table 4d. ACCURACY OF ULTRASONOGRAPHY IN DETECTING SPACE-OCCUPYING LESIONS IN PATIENTS WITH CERTAIN FINAL DIAGNOSES FALLING INTO THE CATEGORY OF FOCAL LIVER DISEASE.

	Amoebic Liver Abscess	Hepatocellular Carcinoma	Metastatic Carcinoma	Carcinoma Primary / Secondary
Scans of patients with the disease	69	75	49	21
Scans of patients without the disease	356	350	376	404
True Positive	69	65	40	13
False Negative	0	10	9	8
False Positive	8	8	8	8
True Negative	348	342	368	396
Sensitivity	1.00	0.87	0.82	0.62
Specificity	0.98	0.98	0.98	0.98
Accuracy	0.98	0.96	0.96	0.96
Accuracy of Positive Test	0.90	0.89	0.83	0.62
Accuracy of Negative Test	1.00	0.97	0.98	0.98
Prevalence	0.16	0.18	0.12	0.05

Table 5d. **ACCURACY OF SCINTIGRAPHY IN DETECTING SPACE-OCCUPYING LESIONS IN PATIENTS WITH CERTAIN FINAL DIAGNOSES FALLING INTO THE CATEGORY OF FOCAL LIVER DISEASE.**

	Amoebic Liver Abscess	Hepatocellular Carcinoma	Metastatic Carcinoma	Carcinoma Primary / Secondary
Scans of patients with the disease	11	56	39	14
Scans of patients without the disease	293	248	265	290
True Positive	11	54	32	13
False Negative	0	2	7	1
False Positive	17	17	17	17
True Negative	276	231	248	273
Sensitivity	1.00	0.96	0.82	0.93
Specificity	0.94	0.93	0.94	0.94
Accuracy	0.94	0.94	0.92	0.94
Accuracy of Positive Test	0.39	0.76	0.65	0.43
Accuracy of Negative Test	1.00	0.99	0.97	0.99
Prevalence	0.04	0.18	0.12	0.05

Table 6d. **ACCURACY OF ULTRASONOGRAPHY IN DETECTING DIFFUSE LIVER DISEASE IN PATIENTS WITH CERTAIN FINAL DIAGNOSES FALLING INTO THE CATEGORY OF DIFFUSE LIVER DISEASE.**

	Cirr-hosis	Severe sider-osis + fib-rosis	Severe sider-osis	Alcoh-olic hepat-itis	Hepat-itis-other	Fatty change	Tuber-culosis	Schisto-somiasis
Scans of patients with the disease	54	8	7	18	8	10	17	15
Scans of patients without the disease	371	417	418	407	417	415	408	410
True Positive	13	0	1	10	1	6	3	3
False Negative	41	7	6	8	7	4	14	12
False Positive	12	12	12	12	12	12	12	12
True Negative	359	405	406	395	405	403	396	398
Sensitivity	0.24	0	0.14	0.56	0.13	0.60	0.18	0.20
Specificity	0.97	0.97	0.97	0.97	0.97	0.97	0.97	0.97
Accuracy	0.88	0.95	0.96	0.95	0.96	0.96	0.94	0.94
Accuracy of Positive Test	0.52	0	0.08	0.45	0.08	0.33	0.20	0.02
Accuracy of Negative Test	0.90	0.98	0.99	0.98	0.98	0.99	0.97	0.97
Prevalence	0.13	0.02	0.02	0.04	0.02	0.03	0.04	0.04

Table 7d. ACCURACY OF SCINTIGRAPHY IN DETECTING DIFFUSE LIVER DISEASE IN PATIENTS WITH CERTAIN FINAL DIAGNOSES FALLING INTO THE CATEGORY OF DIFFUSE LIVER DISEASE.

	Cirrhosis	Severe siderosis + fibrosis	Severe siderosis	Alcoholic hepatitis	Hepatitis-other	Fatty change	Tuberculosis	Schistosomiasis
Scans of patients with the disease	49	7	11	10	5	6	16	16
Scans of patients without the disease	255	297	293	294	299	298	288	288
True Positive	31	2	5	8	1	2	8	8
False Negative	18	5	6	2	4	4	8	8
False Positive	12	12	12	12	12	12	12	12
True Negative	243	285	281	282	287	286	276	276
Sensitivity	0.63	0.29	0.45	0.80	0.20	0.33	0.50	0.50
Specificity	0.95	0.96	0.96	0.96	0.96	0.96	0.96	0.96
Accuracy	0.90	0.94	0.94	0.95	0.95	0.95	0.93	0.93
Accuracy of Positive Test	0.72	0.14	0.29	0.40	0.08	0.14	0.40	0.40
Accuracy of Negative Test	0.93	0.98	0.98	0.99	0.99	0.99	0.97	0.97
Prevalence	0.16	0.02	0.04	0.03	0.02	0.02	0.05	0.05

Table 8d. ACCURACY OF HEPATIC IMAGING IN DETECTING DIFFUSE LIVER DISEASE IN ALL PATIENTS WITH GRANULOMATOUS LIVER DISEASE (INCLUDING TUBERCULOSIS AND SCHISTOSOMIASIS).

	Ultrasound scans	Scintigraphic scans
Granulomatous liver disease	37	35
No granulomatous liver disease	388	269
True Positive	6	17
False Negative	31	18
False Positive	12	12
True Negative	376	257
Sensitivity	0.16	0.49
Specificity	0.97	0.96
Accuracy	0.90	0.90
Accuracy of Positive Test	0.33	0.59
Accuracy of Negative Test	0.92	0.93
Prevalence	0.03	0.12

Table 9d. DIAGNOSTIC ACCURACY OF ULTRASONOGRAPHY IN BOTH DETECTING A SPACE-OCCUPYING LESION AND MAKING A CORRECT FINAL DIAGNOSIS.

	Amoebic Liver Abscess	Hepatocellular Carcinoma	Metastatic Carcinoma	Carcinoma Primary/ Secondary
Scans of patients with the disease	69	75	42	21
Scans of patients without the disease	356	350	376	404
True Positive	56	22	21	9
False Negative	13	53	28	12
False Positive	4	7	19	26
True Negative	352	343	357	378
Sensitivity	0.81	0.29	0.43	0.43
Specificity	0.99	0.98	0.95	0.94
Accuracy	0.96	0.86	0.89	0.91
Accuracy of Positive Test	0.93	0.76	0.53	0.26
Accuracy of Negative Test	0.96	0.87	0.93	0.97
Prevalence	0.16	0.18	0.12	0.05

Table 10d. ACCURACY OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DISTINGUISHING BETWEEN NORMAL LIVER AND LIVER DISEASE IN PATIENTS WHO HAD BOTH PROCEDURES.

	Ultrasound scans	Scintigraphic scans
Liver disease	115	115
Normal	16	16
True Positive	73	94
False Negative	42	21
False Positive	2	3
True Negative	14	13
Sensitivity	0.63	0.82
Specificity	0.88	0.81
Accuracy	0.66	0.82
Accuracy of Positive Test	0.97	0.97
Accuracy of Negative Test	0.25	0.38
Prevalence	0.88	0.88

Table 11d. ACCURACY OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DETECTING DIFFUSE OR FOCAL LIVER DISEASE IN PATIENTS WHO HAD BOTH INVESTIGATIONS.

	FOCAL DISEASE		DIFFUSE DISEASE	
	Ultrasound scans	Scintigraphic scans	Ultrasound scans	Scintigraphic scans
Scans of patients with the disease	71	71	44	44
Scans of patients without the disease	60	60	87	87
True Positive	58	69	15	25
False Negative	13	2	29	19
False Positive	2	3	2	3
True Negative	58	57	85	84
Sensitivity	0.82	0.97	0.34	0.57
Specificity	0.97	0.95	0.98	0.97
Accuracy	0.89	0.96	0.76	0.83
Accuracy of Positive Test	0.97	0.96	0.88	0.89
Accuracy of Negative Test	0.82	0.97	0.75	0.85
Prevalence	0.54	0.54	0.34	0.34

Table 12d. DEGREE OF AGREEMENT BETWEEN FINDINGS AT ULTRASONOGRAPHY AND SCINTIGRAPHY IN PATIENTS HAVING BOTH PROCEDURES. (N = 130)

	Focal disease		Diffuse disease		Normal
Agreement		58		22	15
True Positive	57		9		
False Negative	1		13		
True Negative				13	
False Positive				2	
Disagreement		13		21	1
Ultrasound correct	1		6	1	
Scintigraphy correct	12		15	0	
Total		71		43	16

Table 13d. ACCURACY OF ULTRASONOGRAPHY AND SCINTIGRAPHY IN DETECTING CIRRHOSIS (DIFFUSE LIVER DISEASE) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND CIRRHOSIS.

	Ultrasound scans	Scintigraphic scans
Hepatocellular carcinoma plus cirrhosis (n = 28)	22	18
True Positive	9	12
False Negative	13	6
Sensitivity	0.41	0.67

Table 14d. INTEROBSERVER DIFFERENCES BETWEEN THE TWO SENIOR RADIOLOGISTS (OBSERVER 1 AND 2) AND BETWEEN THE INITIAL OBSERVER (OBSERVER 3) AND THE TWO SENIOR RADIOLOGISTS IN DETECTING NORMAL, DIFFUSE AND FOCAL LIVER DISEASE ON ULTRASONOGRAPHY AND SCINTIGRAPHY.

	Observer 1 vs Observer 2		Observer 3 vs Observer 1 & 2	
	Ultrasound scans	Scintigraphic scans	Ultrasound scans	Scintigraphic scans
DIFFUSE DISEASE				
Total no. of scans	145	127	145	127
No. of differences	37	14	44	26
% of differences	25.5	11.0	30.3	20.5
FOCAL DISEASE				
Total no. of scans	217	122	217	122
No. of differences	19	7	17	7
% of differences	8.8	5.7	7.8	5.7
NORMAL				
Total no. of scans	63	55	63	55
No. of differences	5	8	6	6
% of differences	7.9	14.5	9.5	10.9
TOTAL				
Total no. of scans	425	304	425	304
No. of differences	61	29	67	39
% of differences	14.4	9.5	15.8	12.8

Discussion

A hepatic imaging procedure is usually requested to determine if liver disease is present. The two most important parameters when assessing the accuracy of an examination performed in screening for disease are the sensitivity and accuracy of a negative test (McClees and Gedgaudas- McClees, 1984). Patients with positive screening examinations are more likely to be subjected to further studies to delineate the nature of a detected lesion better. It is important that a screening examination should not miss disease which is present, even at the risk of obtaining a few false positive results. Therefore, high sensitivity is of paramount importance in this situation. It is also important for the physician to have confidence in a negative screening examination if further investigations are to be avoided. The accuracy of a negative test is as important as sensitivity (McClees and Gedgaudas-McClees, 1984). In the present study, which includes patients with a wide spectrum of diseases, the sensitivity of both ultrasonography and scintigraphy in detecting liver disease was low (63% and 72% respectively), and the accuracy of a negative test was even lower (31% and 39% respectively), indicating that the role of these procedures in screening for liver disease in this environment is limited. In contrast, in a review of all published reports on studies in which ultrasonography and scintigraphy had been used to screen for the presence of liver disease, it was found that the sensitivity (75% and 86% respectively) and accuracy of a negative test (76% and 83% respectively) of both techniques were higher (McClees and Gedgaudes-McClees, 1984). These workers also reported that the sensitivity of scintigraphy and accuracy of a negative scintigraphic test in diffuse liver disease were 87% and 91% respectively; figures for ultrasonography were not given (McClees and Gedguadas-McClees, 1984). These results are dissimilar to ours. The sensitivity of scintigraphy was 54%. The sensitivity in the diseases which were included in this category ranged from 20-80%. This study confirms previous reports that the abnormalities detected during hepatic scintigraphy occur in many conditions which disturb normal architecture and function, and are not characteristic of any of these (Ackery and Smith, 1985), that dif-

fuse parenchymal liver disease is frequently inseparable from normal and will continue to be difficult to detect with this technique (Nishiyama et al., 1975), and that scintigraphy is of little diagnostic value in hepatic tuberculosis (Essop et al., 1984; Maharaj et al., 1987a). Thus, despite the fact that its sensitivity was twice that of ultrasonography, this imaging modality is of little value in screening for diffuse liver disease. It is noteworthy that in patients in whom the findings of the two imaging techniques disagreed, scintigraphy was more often correct.

The performance of ultrasonography in the detection of diffuse liver disease in the present study was poor; the sensitivity was 27% and the accuracy of a negative test was 74%; alcoholic hepatitis and fatty change were the only diseases in which the sensitivity exceeded 50%. In the other diffuse diseases, it ranged from 0% to 24%. The sensitivity of ultrasonography in detecting diffuse disease in patients with cirrhosis plus hepatocellular carcinoma was also low (41%). This study indicated that severe siderosis plus fibrosis does not produce any ultrasonographic abnormalities and will always be missed by this imaging modality. The sensitivity in hepatic tuberculosis was extremely low and confirms an earlier report that ultrasonography is of no diagnostic value when this treatable disease is suspected (Maharaj et al., 1987a). In another investigation, it was reported that increased echogenicity was noted in 7 patients; the number of patients who underwent this procedure is not stated (Essop et al., 1984). It is also evident that only a minority of patients with hepatic schistosomiasis, a granulomatous liver disease which has recently been noted to occur with a frequency similar to that of hepatic tuberculosis at this institution (Maharaj et al., 1986a), will be detected by ultrasonography. It has been stated that, due to their small dimensions, the granulomas are usually not detected by ultrasound studies (Cerri et al., 1984). These workers have described the ultrasonographic features of hepatosplenic schistosomiasis and indicated that this condition can easily be distinguished from cirrhosis (Cerri et al., 1984). It is possible that if the criteria they described were used in the present study, more patients could have been detected. The findings in

the present study also support the conclusion that ultrasonography does not provide information useful in the diagnosis of viral hepatitis (Giorgio et al., 1986). Abnormal ultrasound examinations were present in only 24% of patients with cirrhosis. Of the false negative scans, 56% occurred in patients with micronodular cirrhosis. It has been previously recognised that ultrasonography fails to detect macronodular cirrhosis more often than micronodular cirrhosis (Dewbury and Clark, 1979). It could be argued that the sensitivity of ultrasonography would have been improved had ancillary signs of cirrhosis been included in the present study. The rationale for not using the ancillary signs was that their presence did not imply that cirrhosis was the diagnosis; in this environment there are a number of causes of portal hypertension, including schistosomiasis and portal vein thrombosis, and of ascites, including peritoneal tuberculosis. The sensitivity of ultrasonography in alcoholic hepatitis and fatty change was 56% and 60% respectively. However, this figure is not high enough to make this a satisfactory screening procedure. The accuracy of a positive ultrasonographic test in all forms of diffuse liver disease was low. In addition, interobserver differences between the two senior radiologists were present in 25% of ultrasound scans of patients with diffuse liver disease.

The present study indicates that diffuse liver disease can frequently not be distinguished from normality by ultrasonography, and that liver biopsy will continue to play an important role in detecting the presence and nature of diffuse liver disease. Our deductions are supported by the work of others. In a recent study, only 11% of patients with cirrhosis showed an increase in reflectivity, while this abnormality was detected in 50% of patients with fatty livers, 42% of patients with minimal change livers and 33% of normal livers (The Clinical NMR Group, 1987). In another recent investigation, the sensitivity of ultrasonography in cirrhosis, fatty change, chronic active hepatitis and chronic persistent hepatitis was 68%, 55%, 41% and 31%. It should be noted that ancillary signs of portal hypertension were used to support a diagnosis of cirrhosis (Celle et al., 1988).

Some workers have indicated that it is possible to distinguish between hepatic fibrosis and fatty change on ultrasonography (Saverymuttu et al., 1986). This has not been the experience of other workers (Celle et al., 1988; Sandford et al., 1985; The Clinical NMR Group, 1987), who have also expressed the view that ultrasonography is not a useful screening investigation for parenchymal liver disease. Our approach, which was to determine only if evidence of diffuse disease was present, is supported by these findings. It was argued that if an abnormal scan was encountered during screening, the patient could be evaluated further by liver biopsy because ultrasonography would not enable us to determine which of the various causes of diffuse liver disease encountered in this institution was present.

In contrast, the sensitivity of both ultrasonography and scintigraphy in the detection of focal liver disease was much higher (88% and 92% respectively); the corresponding values for accuracy of a negative test were also higher (88% and 94% respectively). In the analysis of published reports, the sensitivity of the 2 procedures was 72% and 87% respectively, and the accuracy of a negative 67% and 86% respectively. The specificity of both tests in our study were high, 96% and 91% respectively. This data indicates that both imaging modalities are useful in screening for focal liver disease. However, ultrasonography is capable of providing information on morphology and, as such, can aid in establishing a cause of the focal disease.

However, although ultrasonography was found to have a high accuracy in the detection of space-occupying lesions in the present study, overlap between the ultrasonographic features of amoebic liver abscess, hepatocellular carcinoma and metastatic carcinoma resulted in a correct final diagnosis being made in only 81% of patients with amoebic liver abscess, 29% with hepatocellular carcinoma and 43% of patients with metastatic carcinoma who had undergone ultrasonography. The observation that the 2 senior radiologists differed in their interpretation of 72 (33%) of the 217 ultrasound scans of

patients with focal liver disease in whom they had both correctly detected the presence of space-occupying lesions, lends support to the fact that the amount of overlap between the ultrasonographic features of amoebic liver abscess, hepatocellular carcinoma and metastatic carcinoma, which are common causes of liver disease in this environment (Maharaj et al., 1986a), is fairly substantial. This contention is further supported by data arising from analysis of published reports which describe the ultrasonographic appearances of these diseases. Studies on the ultrasonographic morphology of hepatocellular carcinoma and amoebic liver abscess in patients at this institution indicated that lesions may be multiple (43% and 25% respectively), echogenic (67% and 1% respectively), occur in the left lobe (43% and 17% respectively) and have a smooth (10% and 68% respectively) or irregular edge (90% and 32% respectively) in both diseases (Boultbee, 1979; Boultbee et al., 1979). In a subsequent investigation, 13% of amoebic liver abscesses were noted to be echogenic (Simjee et al., 1985). Hypoechoic lesions may also occur in both conditions; this abnormality was detected in 84% of patients with amoebic liver abscess (Boultbee et al., 1979) and 23% of patients with hepatocellular carcinoma (Maringhini et al., 1988). Thus, it is possible that each disease may mimic the other in certain patients. This has been found to be the case; in the paper on amoebic liver abscess (Boultbee et al., 1979) it was reported that in 3 patients, amoebic liver abscess was incorrectly diagnosed as a hepatic tumour and that in 2 patients, the latter disease was wrongly diagnosed as amoebic liver abscess during ultrasonography. In addition, Boultbee recorded that one patient with hepatocellular carcinoma, which had a smooth edge on ultrasonography, was aspirated and 400 ml of "pus" obtained (Boultbee, 1979), while Barnes and co-workers encountered a patient with amoebic liver abscess in whom the ultrasound scan was misinterpreted as demonstrating a hepatic tumour (Barnes et al, 1987). Greater awareness of this diagnostic problem among both radiologists who perform ultrasonography and doctors who are responsible for the care of patients is needed, especially since the clinical presentation of these 2 diseases is often similar viz. right upper quadrant pain and tender hepatomegaly. In contrast, it is generally accepted that the ultrasonographic appearance

of pyogenic liver abscess, an uncommon condition in this environment, is non-specific and varies from anechoic to high echogenic lesions, and that, although some ultrasonographic features of pyogenic liver abscess differ from those of amoebic liver abscess, these diseases cannot be distinguished from each other on the basis of ultrasonography alone (Kuligowska et al., 1982; Ralls et al., 1987).

The highly variable ultrasonographic appearances of hepatocellular carcinoma and metastatic carcinoma may also make it difficult to distinguish one disease from the other; metastatic carcinoma may be solitary, multiple, echogenic, hypoechoic, totally echo-free, or demonstrate mixed patterns of increased and decreased echogenicity or "bulls-eye" (centrally echogenic surrounded by hypoechoic rim) lesions (Green et al., 1977; Scheible et al., 1977). When the ultrasonographic morphology in hepatocellular carcinoma was compared to that of metastatic carcinoma, it was noted that lesions which were echogenic or of mixed echogenicity occurred in both diseases (31% vs 18% and 41% vs 12% respectively). In addition, "bulls-eye" lesions were present in both conditions (16% and 71% respectively) (Wong et al., 1985). Although these workers do not discuss this point, it is evident that each disease can simulate the other. This contention is supported in a paper on ultrasonography in hepatocellular carcinoma, in which the author stated that in some patients, distinction between hepatocellular carcinoma and metastatic malignancy proved difficult; the number of patients was not stated (Boultbee, 1979).

The author is not aware of any publications which suggest that problems in differentiating between amoebic liver abscess and metastatic carcinoma may occur. However, on the basis of the foregoing information, it is likely that diagnostic difficulties may exist. This was found to be the case in the present study; in one patient, amoebic liver abscess was misdiagnosed as metastatic carcinoma at ultrasonography, and in another, the opposite occurred.

Interobserver differences may influence the results of imaging studies (Conn and Spencer, 1972; Nishiyama et al., 1975). In the present study, interobserver differences between the two senior radiologists were present most frequently when ultrasound scans of patients with diffuse liver disease and scintigraphic scans of normal individuals were examined (25.5% and 14.5% respectively). The interobserver variation between the initial observer and the two senior radiologists was only slightly higher than that between the two senior radiologists. It is evident that the possible lack of experience of the registrar-in-training did not affect the results of scans substantially. This could be due to the fact that the person who initially performs the procedure has access to the request form which provides clinical details of the patient being examined.

Ultrasonography has made important contributions to the detection and management of patients with focal liver disease. It is used in the early detection of hepatocellular carcinoma in communities which are at risk of developing this tumour (Sheu et al., 1985), and in screening for metastatic malignancy in patients with extrahepatic neoplasia (Schreve et al., 1984; Smith et al., 1982; Taylor, 1982). It has also simplified the management of uncomplicated and complicated amoebic liver abscess (Berry et al., 1986; Gupta et al., 1987; Maharaj et al., 1987b). However, the diagnostic pitfalls that may be encountered as a result of an overlap between the features of these space-occupying lesions need to be remembered. Accordingly, liver biopsy or aspiration might be required to determine the cause of focal disease in selected patients in whom space-occupying lesions are detected on ultrasonography. Scintigraphy can also be used to detect space-occupying lesions, but information on morphology will not be obtained. On the other hand, neither scintigraphy nor ultrasonography is sensitive enough to be used in screening for diffuse liver disease. In addition, ultrasonography provides little useful or specific information about parenchymal liver disease. Therefore, when diffuse parenchymal liver disease is suspected, liver biopsy would be needed to determine the presence and nature of the disease in developing countries.

CHAPTER 6

COMPLICATIONS ASSOCIATED WITH LIVER BIOPSY

Introduction

Liver biopsy, an important diagnostic procedure in patients in whom either diffuse or focal liver disease is suspected, is associated with complications, the major one being intra-peritoneal haemorrhage. Liver tissue is usually obtained by percutaneous biopsy, or at peritoneoscopy. However, the latter procedure is not widely available in developing countries.

When percutaneous needle biopsy of the liver is carried out, a single specimen is usually obtained. It has been shown that the diagnostic yield of liver biopsy is improved when two specimens are taken, and can be improved further by taking a third biopsy specimen during the procedure (Maharaj et al., 1986b). It appeared that this could be achieved without exposing the patient to a greater risk of complications provided that standard precautions were taken. Since this study was carried out in a small group of patients, and since there was a paucity of data on the frequency and nature of complications that occur when 2 or more consecutive biopsy specimens are taken, a retrospective study was conducted to provide further data on the safety of this procedure, as well as that of peritoneoscopic biopsy at King Edward VIII Hospital, Durban.

Patients and Methods

A list of all patients in whom liver biopsy had been carried out at King Edward VIII Hospital, Durban during the period 1984-1987 (inclusive) was obtained from the Department of Anatomical Pathology.

The clinical records of all patients, other than those admitted to the paediatric wards, were examined and a note made of the type of biopsy done, and the presence and nature of complications. When percutaneous biopsy had been performed, the number of specimens taken during the procedure was also recorded.

Percutaneous liver biopsies were carried out in the general medical and surgical wards of the hospital by interns after consent for the procedure was obtained from the patient. A platelet count greater than $100 \times 10^9/l$ and a prothrombin index greater than 75% was considered a prerequisite for the performance of this procedure. After infiltration of the skin and subcutaneous tissue with 2% lignocaine, the biopsy was performed using a "Tru-Cut" needle. Based upon their individual preferences, the doctors would take either 1, 2 or 3 specimens; the additional specimens were obtained by redirecting the biopsy needle through a single entry site (Maharaj et al, 1986b). Thereafter, the nursing staff were requested to monitor the pulse rate and blood pressure. Some interns prescribed an opioid analgesic, usually pethidine, before the procedure. Patients were kept in hospital for at least 24 hours after biopsy.

Peritoneoscopy was carried out under local anaesthesia in an operating theatre by specialist gastro-enterologists. The precautions described for percutaneous biopsy were also taken for peritoneoscopy. After completion of the procedure, the patients were returned to their respective general medical or surgical wards, where the nursing staff were required to monitor the patients' vital signs.

Results

A total of 1525 percutaneous biopsies were carried out during the study period. A single specimen was obtained in 484 patients, two specimens in 578 patients and three in 463 patients. The morbidity and mortality rates associated with this procedure were 2.0% and

0.3% respectively. The nature and frequency of complications are shown in Table 1e. Patients in whom 2 or 3 specimens were obtained did not have a higher incidence of fatalities, pain, hypotension or biliary peritonitis, than those in whom a single specimen was taken.

The final diagnosis and number of specimens obtained in the 5 patients who died were as follows: hepatocellular carcinoma (n=2; 1 specimen); Kaposi's sarcoma (n=1; 3 specimens); disseminated tuberculosis plus alcoholic hepatitis (n=1; 3 specimens); pelvic and lung abscesses (n=1; 1 specimen).

Intraperitoneal bleeding was the cause of death in all patients; hypotension developed within 4 hours. Only one patient had been adequately monitored after the procedure. A gradual drop in blood pressure had been noted, but was not acted upon until shortly before his death. In the other 4 patients, the first blood pressure measurement was made when it was apparent that the patient had developed a complication. Resuscitation measures were successful in returning the blood pressure to normal in 2 patients. However, one patient refused surgery and in the other, there was a delay in the implementation of a decision made by the surgeons who had been consulted, to do a laparotomy. In the other 2 patients, all attempts at restoring the circulating blood volume failed.

Hypotension, unassociated with death, occurred in 15 patients. Treatment with intravenous fluids, freeze-dried plasma and/or blood transfusions restored the blood pressure to normal in all cases. In the 3 patients in whom pain accompanied the hypotension, analgesics were also given. Another 15 patients had pain after their biopsy - in only 1 had 3 specimens been taken.

Of the 217 patients in whom peritoneoscopic biopsies were performed, complications were encountered in 5 (2.3%); all developed hypotension which responded when intravenous fluids, freeze-dried plasma or blood was given. One patient (0.5%), who had hepatocellular carcinoma, died as a result of intraperitoneal bleeding. The blood pressure had been restored to normal before a decision against surgical intervention to stop bleeding was made because the prognosis was considered to be poor. In all six patients, the blood pressure had not been monitored after the procedure.

Table 1e. MORBIDITY AND MORTALITY FOLLOWING PERCUTANEOUS LIVER BIOPSY WHEN ONE, TWO OR THREE SPECIMENS WERE TAKEN.

	NUMBER OF PATIENTS			
	One specimen	Two specimens	Three specimens	Total
Pain	8	6	1	15
Hypotension	6	4	5	15
Biliary peritonitis	0	1	0	1
Death	3	0	2	5
TOTAL	17	11	8	36

Discussion

Blind percutaneous needle biopsy of the liver is a valuable method of detecting hepatic disease in developing countries (Atoba and Junaid, 1980; Maharaj et al., 1986a; 1987a). However, important pathology can be overlooked when liver biopsy is performed in the conventional manner because of the influence of sampling variability (Abdi et al., 1979; Maharaj et al., 1986b). The diagnostic yield of this procedure is improved when two or three consecutive biopsy specimens are obtained by introducing the biopsy needle through a single entry site and redirecting it by about 20° to 30° from the initial position (Maharaj et al., 1986b).

The present study in 1525 patients indicates that this can be achieved without an increase in morbidity and mortality; patients in whom two or three specimens were taken (578 and 463 patients, respectively) did not have a higher incidence of fatalities, pain, hypotension, or biliary peritonitis than those in whom a single specimen was obtained (484 patients). These findings are in agreement with those of an earlier investigation in which 344 patients required between 2 and 11 biopsies; an increased frequency of complications, all minor in nature, were observed after more than 3 consecutive biopsies were performed (Perrault et al., 1978). A similar conclusion was reached by a group of workers who performed multiple liver biopsies under ultrasonographic guidance on 95 patients with carcinoid and endocrine pancreatic tumours (Andersson et al., 1987). The only major complication in this study, intrahepatic haematoma, occurred in 3 patients who had required more than three biopsies. Thus, it appears that the safety of both blind and imaging-guided needle biopsy of the liver is adversely affected by taking more than three consecutive specimens.

Fifteen (1.0%) patients in this study complained of either abdominal or thoracic pain after percutaneous liver biopsy. The incidence of pain in 3 studies involving 288, 1000 and 68276 patients was 1.4, 4.5, and 1.2% respectively (Atoba and Junaid, 1980; Perrault et al.,

1978; Piccinino et al., 1986). Pain was usually experienced soon after the biopsy and responded to analgesics (Piccinino et al., 1986). In the present study, pain was least frequently noted in patients in whom 3 biopsy specimens were taken. A probable reason for this anomaly is that the doctors who obtained 3 specimens during the biopsy made greater use of opioid analgesics before the procedure.

Hypotension developed in 1% (15) of patients in this study. This complication was corrected by the administration of intravenous fluids, freeze-dried plasma or blood. None of the patients needed a laparotomy. When pain accompanied the hypotension (3 patients), analgesics were also given. Perrault and co-workers encountered hypotension in 2.8% of the 1000 patients in their study (Perrault et al., 1978). Hypotension and pain occurred together in 14 of their patients and five patients required blood transfusions because of a reduction in haemoglobin level of up to 4g/dl. Clinically significant haemorrhage requiring either blood transfusion or laparotomy, or both, was observed in 2.1% of 288 patients reviewed by Atoba and Junaid (Atoba and Junaid, 1980) and in 1.5% of 200 patients who underwent biopsy as a day-case procedure (Westaby et al., 1980). This complication was also encountered in 40 (0.6%) of 6379 patients studied by Sherlock and colleagues (Sherlock et al., 1984), in 8 (0.2%) of 4000 patients reported by Hegarty and Williams (Hegarty and Williams, 1984), and in 6 (0.5%) of 1174 patients studied by Knauer (Knauer, 1978). Of the 24 significant complications among 7532 biopsies recorded by Terry, 16 (0.2%) were due to bleeding (Terry, 1952). In a large multicentre study of 68276 patients, haemoperitoneum developed in 16 (0.02%) of patients (Piccinino et al., 1986).

The mortality rate in the present study was 0.3%; 3 patients who had a single specimen and 2 who had 3 specimens taken during the biopsy, died as a result of the procedure. The cause of death in all five patients was intraperitoneal bleeding. There were 5 (1.7%) deaths among the 288 patients reviewed by Atoba and Junaid, 3 were due to haemorrhage (Atoba and Junaid, 1980). There were no fatalities in 3 studies of 1174 (Knauer, 1978),

1000 (Perrault et al., 1978), and 200 patients (Westaby et al., 1980) respectively. The mortality rate in two early large series of 10600 (Terry, 1952) and 20016 (Zamcheck and Klausenstock, 1953) patients was 0.12% and 0.17% respectively. More recently, a review of 79381 biopsies has given a figure of 0.015% (Lindner, 1967). Haemorrhage was the major cause of mortality in these studies. There were 2 fatalities in the group studied by Sherlock and co-workers (Sherlock et al., 1984), and one in the series reported by Hegarty and Williams (Hegarty and Williams, 1984), yielding a mortality rate of 0.03% for both groups. Bleeding was the cause of death in the latter patient. The mortality rate in the recent large multicentre study of 68276 patients was 0.009%; all six fatalities were due to haemoperitoneum (Piccinino et al., 1986).

Biliary peritonitis developed in one (0.07%) of the 1525 patients studied. This patient required a laparotomy. The incidence of this complication in the series reported by Terry in 1952 and by Piccinino and others in 1986 was 0.09% and 0.02% respectively.

The morbidity and mortality rates in the 217 patients who were subjected to peritoneoscopic biopsies were 2.3% and 0.5% respectively; 5 patients developed hypotension which responded to treatment with intravenous fluids, freeze-dried plasma or blood transfusion, and one patient died as a result of intraperitoneal bleeding. A review of 917 peritoneoscopic biopsies revealed that 1 (0.1%) fatality occurred; haemorrhage was the cause of death (De Groen et al., 1987). In addition, 4 (0.4%) patients developed bleeding which required intravenous fluids or blood transfusions. No complications or deaths were recorded in 2 studies of 250 (Hall et al., 1980) and 102 (Rattan et al., 1987) peritoneoscopic biopsies. The only complication that was attributed to the liver biopsy in a study of 238 patients who had peritoneoscopy was bile leakage (Barry et al., 1978). This was discovered incidentally at laparotomy in one patient. In a prospective study of 603 peritoneoscopies, haemorrhage from the biopsy site and death (due to this complication) occurred in 6 (1%) and 2 (0.3%) patients, respectively (Kane and Krejs, 1984). A report

on 415 peritoneoscopic and 92 percutaneous biopsies indicated that the only major complication, intrahepatic haemorrhage, developed in one patient (Celle et al., 1988). However, the type of biopsy carried out in this patient was not mentioned. Reynolds and Cowan have recorded their experience with 2400 peritoneoscopies (Reynolds and Cowan, 1985). Two patients with hepatocellular carcinoma died after bleeding from the liver biopsy site. The mortality rate associated with peritoneoscopic biopsy cannot be calculated because the number of patients who had a biopsy during the examination is not given.

The mortality rate from both percutaneous and peritoneoscopic liver biopsies in the present study is high. Four of the 6 patients who died had malignant disease; 3 had hepatocellular carcinoma and one Kaposi's sarcoma. Although it could be argued that the prognosis in these patients was extremely poor (Kew and Geddes, 1982), a critical evaluation of the factors that could have predisposed to their deaths is essential because it could yield important information which might help in preventing serious complications in other patients having a liver biopsy. Haemoperitoneum was the cause of death in all patients. None had a contraindication to the biopsy (Losowsky, 1982). A platelet count greater than $100 \times 10^9/l$ and a prothrombin index greater than 75% was present in all patients in this study, including those who died and those who developed hypotension; bleeding occurred despite taking these precautions. It is generally accepted that there is an increased risk of bleeding in patients who are deficient in clotting factors or have thrombocytopaenia (Milward-Sadler and Whorwell, 1985; Sherlock, 1985). However, a number of authors have stated that haemorrhage is usually a random event which cannot be predicted with methods that are currently available (Ewe, 1981; McGill, 1981), and that it usually develops when least expected, and when, at the time of biopsy, the risk seemed small (Sherlock, 1985). Therefore, doctors need to be prepared for the possible development of bleeding in all patients who are subjected to liver biopsy, even those who have no

contraindications, or are not considered to be at "high-risk" for bleeding. In some institutions two units of blood are routinely available before the procedure (Milward-Sadler and Whorwell, 1985). This has not been the practice in our hospital.

Although there is no data confirming this hypothesis, available evidence suggests that there could be an increased risk of bleeding after liver biopsy in patients with hepatocellular carcinoma. Piccinino and colleagues reported that haemoperitoneum was more frequent in patients with neoplastic disease; the nature of these tumours was not mentioned (Piccinino et al., 1986). In addition, it is known that hepatocellular carcinoma may rupture spontaneously or following trauma, resulting in an acute haemoperitoneum which necessitates an emergency laparotomy (Chen et al., 1988; Maraj et al., 1988). Accordingly, it is possible that needle puncture during biopsy may precipitate rupture of the tumour.

The "Tru-Cut" needle was used for all percutaneous liver biopsies in the present study. Some workers have observed an increased incidence of serious complications and death after biopsy with the "Tru-Cut" needle (Piccinino et al., 1986), while others have not found this to be the case (Perrault et al., 1978). The incidence of haemorrhage and deaths in a study of 4000 patients who were biopsied with a "Tru-Cut" needle (Hegarty and Williams, 1984) was not higher than that reported in a group of 6379 patients in whom the Menghini needle was used (Sherlock et al., 1984). In studies that have compared the yield of "Tru-Cut" and Menghini needle biopsies in patients with cirrhosis, a frequent cause of unexplained hepatomegaly in developing countries (Atoba and Junaid, 1980; Bahl et al., 1975; Maharaj et al., 1986a; Patel and Lwanga, 1971), the "Tru-Cut" biopsies were found to be longer, less fragmented and superior for the diagnosis of this disease (Colombo et al., 1988; Vargas-Tank et al., 1985).

Hypotension developed within 4 hours in all patients who died. Only one patient had been adequately monitored after liver biopsy; a gradual reduction in blood pressure had been detected, but no remedial measures were instituted until shortly before his death. In the other patients, the first blood pressure measurement was made when it was apparent that a complication had occurred. A similar observation was made in the 5 patients who developed hypotension after peritoneoscopic biopsy. Examination of the case records of all patients in this study revealed that in the majority of patients, the after-care and monitoring were either inadequate or non-existent. This important duty in our hospital is delegated to nurses, who are already overcommited as a result of staff shortages and overcrowding of wards. In order to reduce the mortality associated with liver biopsy, the doctor who carries out a percutaneous biopsy or requests a peritoneoscopic biopsy will need to assume responsibility for monitoring the patient, for at least the first 4 hours after the biopsy - the period during which most of the serious complications are likely to become manifest (Perrault et al., 1978; Piccinino et al., 1986). This will ensure that resuscitation and other appropriate measures will be instituted timeously. Further, though less frequent, observations should be made over the next 18 hours because some patients may show signs of complications during this period (Piccinino et al., 1986; Sherlock, 1985). It is noteworthy that a marked increase in blood pressure has been recorded very early after biopsy in some patients with haemorrhage (Middleton et al., 1977). It is generally accepted that successful needle biopsy of the liver without complications demands good technique (Hegarty and Williams, 1984; Milward-Sadler and Whorwell, 1985; Sherlock, 1985; Zamcheck and Klausenstock, 1953). Accordingly, interns must always be adequately trained.

Piccinino and colleagues stated that the retrospective nature of their study allowed an accurate evaluation only in patients developing very serious complications; the number of patients developing minor or asymptomatic complications could be larger (Piccinino et al., 1986). Their comments are also applicable to the present study.

Blind percutaneous needle biopsy of the liver is an important and valuable method for detecting liver disease in developing countries, especially those in which facilities for hepatic imaging and peritoneoscopy are not widely available (Atoba and Junaid, 1980; Maharaj et al., 1986a). A trained operator should perform the procedure and two specimens should be taken (Maharaj et al., 1987a) by redirecting the needle through a single entry site as this improves the diagnostic yield of the biopsy (Maharaj et al., 1986b) without increasing the risk of complications. Greater awareness of the hazards of liver biopsy and their prevention is needed; good technique, careful monitoring, and prompt and aggressive resuscitation are essential if the mortality rate is to be reduced.

CHAPTER 7

"TRU-CUT" NEEDLE BIOPSY OF THE LIVER: IMPORTANCE OF THE CORRECT TECHNIQUE

Introduction

Percutaneous needle biopsy of the liver is a useful method for detecting the presence and nature of hepatic disease. The specimens obtained need to be of an adequate length for histological diagnosis because pathology is often missed due to the small size of the sample (Sherlock, 1985).

The "Tru-Cut" needle (Travenol Laboratories, Deerfield, USA) is used for this purpose at King Edward VIII Hospital, Durban. The author recently discovered that the technique that he had been using for liver biopsy was a modification of the one recommended by the manufacturer for breast biopsy (Travenol Laboratories, 1980), and that the method suggested by them (Travenol Laboratories, 1980) was one of two he had discouraged colleagues from using because the length of specimens obtained was inadequate.

In view of the importance of the length of the liver tissue specimen submitted for histological examination, a study comparing the three techniques was conducted in cadavers.

Patients and Methods

"Tru-Cut" Biopsy Techniques

The "Tru-Cut" needle consists of an inner solid needle, the obturator and an outer hollow needle, the cannula. The obturator has a pointed end for tissue penetration and immediatley behind this is a notch for the biopsy specimen. The cannula serves as a cutting sheath.

The manufacturers of the "Tru-Cut" needle recommend one technique for what they term "usual biopsy procedures" and another for breast biopsy (Travenol Laboratories, 1980). In both cases, preparation of the biopsy site, adequate anaesthesia and incision of the skin with a scalpel is advised. The latter step is necessary because the needle is not designed to puncture the skin.

Thereafter, if a breast biopsy is desired, the obturator is retracted fully to cover the specimen notch (i.e. the needle is closed), the T-shaped cannula handle is held firmly while the device is inserted up to the tissue to be biopsied, and the obturator advanced as far as possible. Finally, the obturator is held firmly to stabilise the assembly, the cannula handle (outer sheath) is advanced to cut the tissue which has prolapsed into the specimen notch, and the device withdrawn (Technique 1) (Figure 1).

For the usual biopsy procedures, the manufacturer recommends that with the obturator fully retracted and held firm, the needle is inserted into the tissue being biopsied, the cannula is retracted (to expose the specimen notch) and then advanced (to cut the tissue which has prolapsed into the specimen notch), and the assembly withdrawn (Technique 2) (Figure 2). Another possible technique involves inserting the closed needle into the liver and advancing and then retracting the obturator (Technique 3) (Figure 3).

In the present study, one modification was made to the breast biopsy technique - the needle was inserted into, rather than up to, the liver; the rest of the procedure was unchanged.

Figure 1
Schematic representation of the
breast biopsy technique using the "Tru-Cut" needle

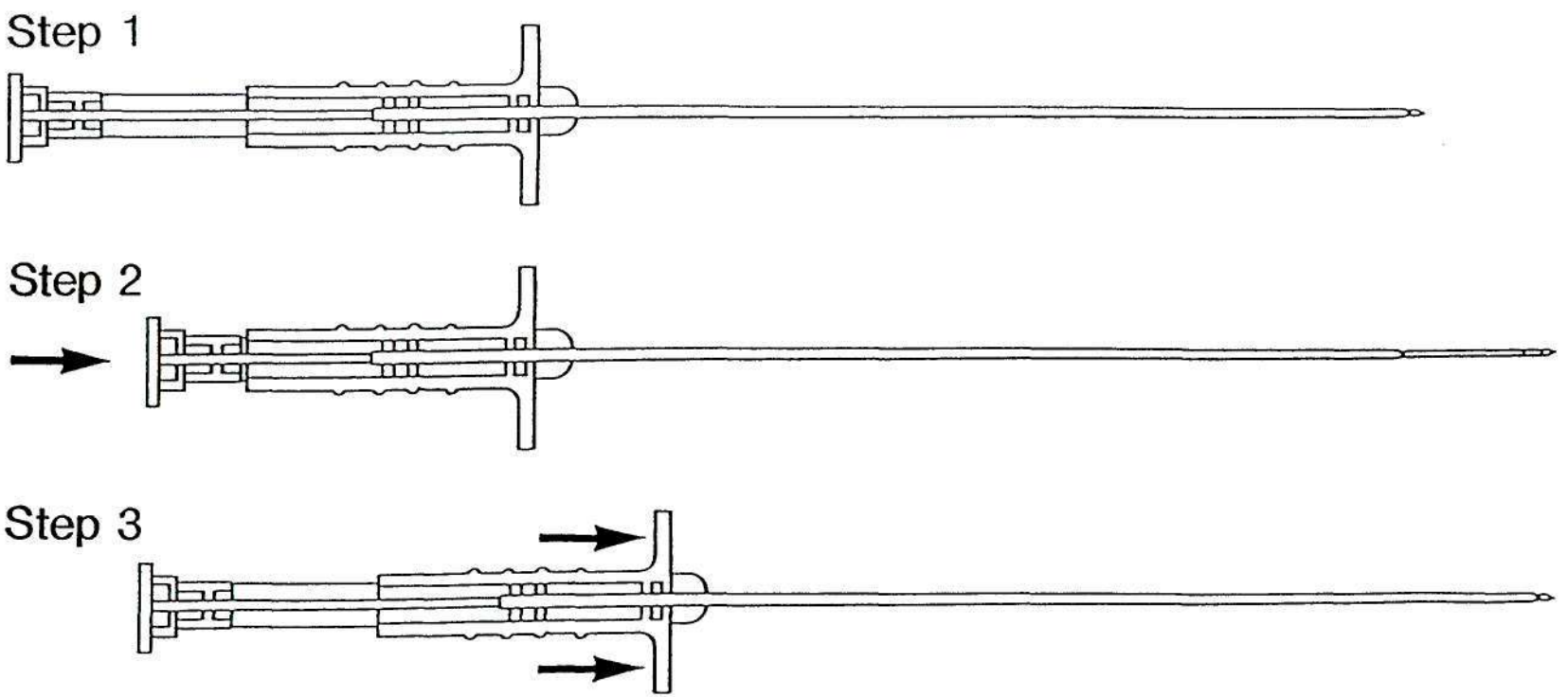


Figure 2
Schematic representation of "usual"
biopsy technique using the "Tru-Cut" needle

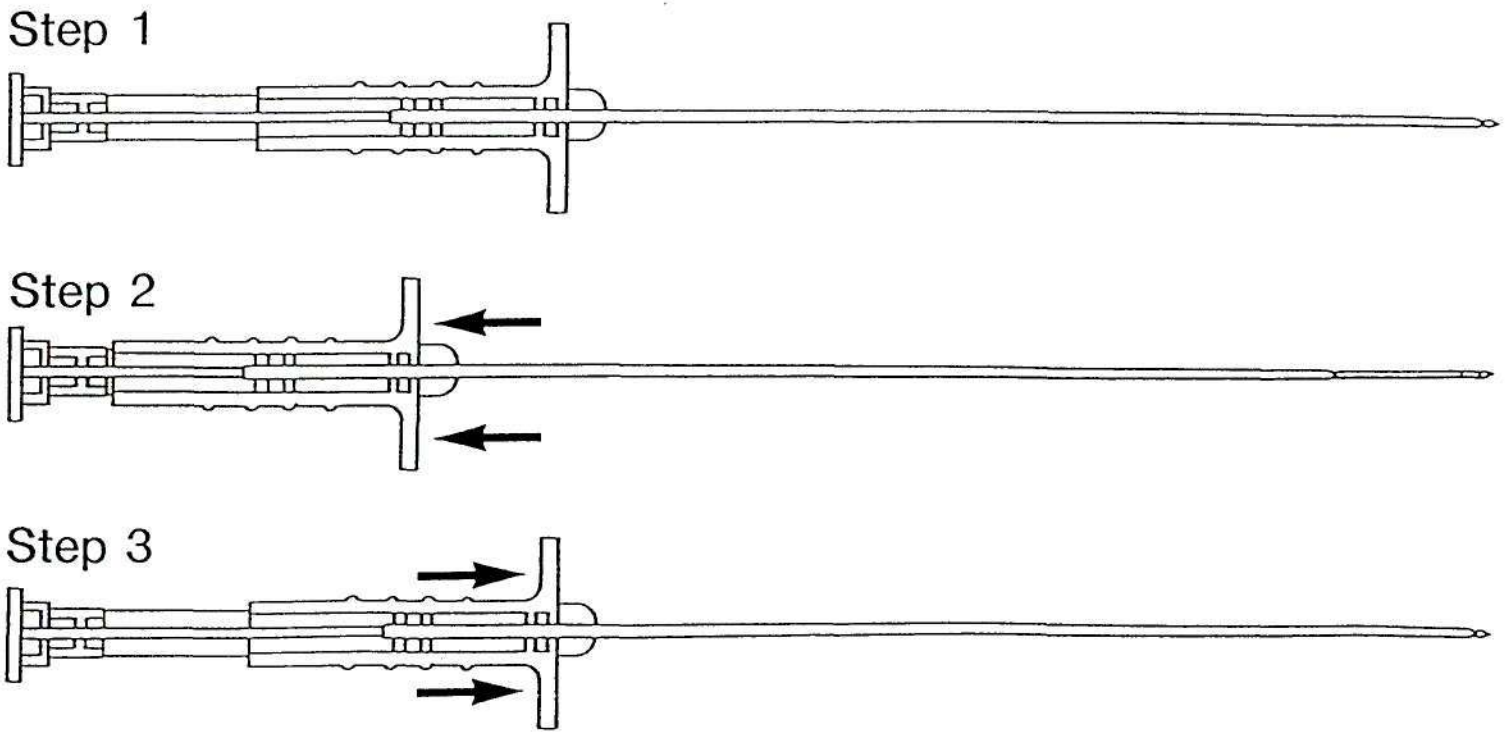
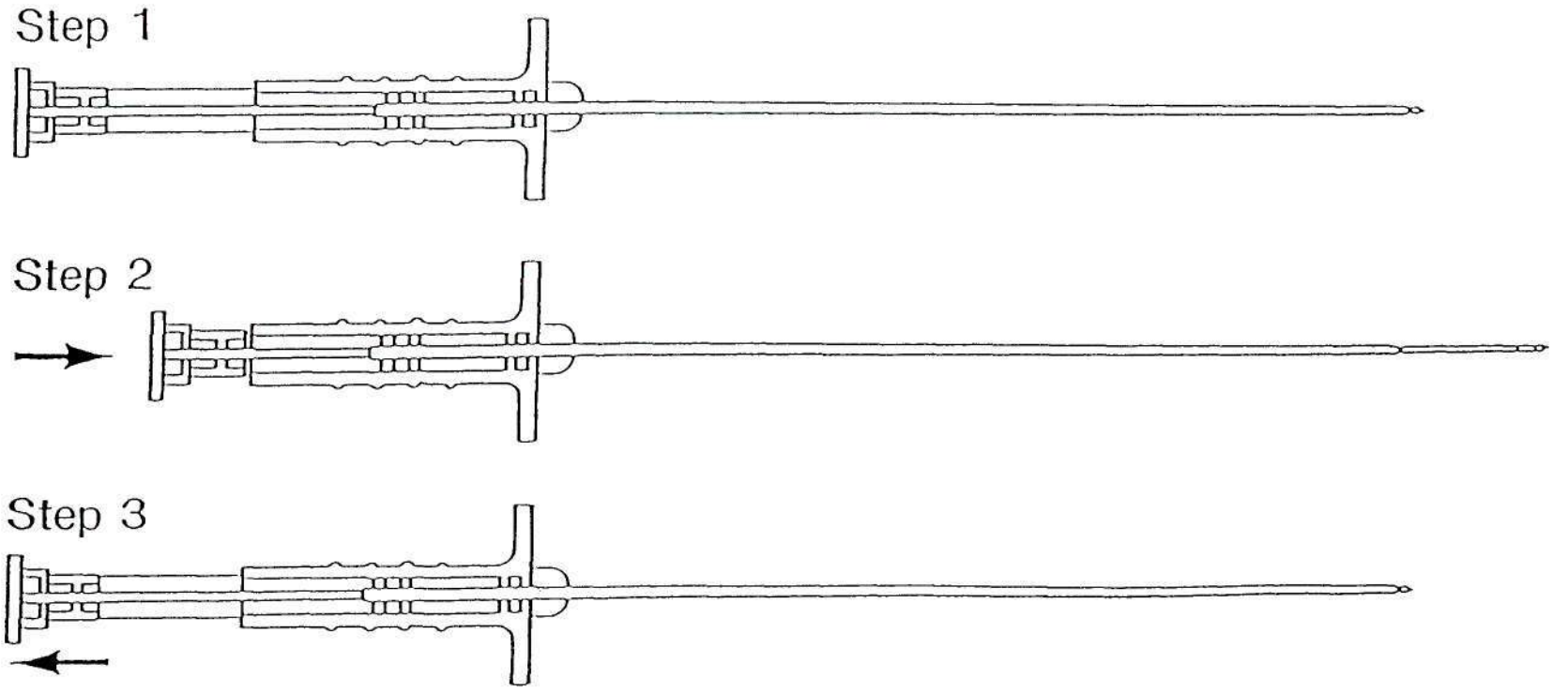


Figure 3

Schematic representation of an "alternative" biopsy technique using the "Tru-Cut" needle



Study Design

Twenty adults who had died of non-natural causes were studied after the liver had been exposed at autopsy and found to be normal macroscopically. Each liver was biopsied four times, under direct vision, using one "Tru-Cut" needle. The modified breast biopsy technique (technique 1) either preceded or followed technique 3 in a random manner. Thereafter, the biopsies were repeated using the alternative sequence. All biopsies were carried out by a single operator. The length of the specimens was measured immediately after each biopsy, and after they had been immersed in formalin. The latter step was taken to determine if fragmentation of the specimens occurred with either technique. Technique 1 was compared to technique 2 in a similar manner in 10 livers. These specimens were not placed in formalin.

Results

The results are presented in Tables 1f and 2f.

The mean length of the liver biopsy specimens that were obtained using the modified breast biospy technique was 16.3mm (range: 8-20mm). The corresponding figures for technique 3 were 2.7mm (range: 0.5-8mm). Three of the 40 specimens (7.5%) obtained using the latter technique fragmented when placed in formalin; this did not occur in any of the 40 specimens taken using the alternative method (Table 1f). The average length of specimens using technique 2 was 7.7mm (Table 2f).

TABLE 1f. LENGTH OF LIVER BIOPSY SPECIMENS OBTAINED WITH A "TRU-CUT" NEEDLE USING TECHNIQUE 1 AND 3.

Patient No.	LENGTH OF SPECIMENS (MILLIMETRES)			
	Technique 1		Technique 3	
	First biopsy	Second biopsy	First biopsy	Second biopsy
1	18 (17)	20 (19)	3 (3)	3 (2)
2	20 (20)	15 (15)	1 (1)	1 (1)
3	19 (19)	8 (8)	2 (2)	2 (2)
4	16 (16)	13 (12)	1 (1)	4 (4)
5	13 (12)	12 (12)	1 (1)	2 (2)
6	13 (12)	12 (11)	2 (2)	5 (5)
7	20 (20)	16 (15)	1 (1)	1 (1)
8	20 (20)	10 (10)	1 (1)	1 (1)
9	13 (12)	14 (13)	3 (3)	4 (2,1,1)**
10	10 (10)	14 (14)	1 (1)	3 (3)
11	8 (7)	11 (11)	1 (1)	1 (1)
12	20 (20)	12 (12)	8 (8)	3 (3)
13	20 (20)	20 (20)	3 (3)	4 (3)
14	20 (20)	14 (14)	3 (3)	5 (5)
15	20 (20)	11 (11)	4 (2,1,1)**	4 (3)
16	15 (15)	20 (20)	1 (1)	3 (3)
17	17 (17)	20 (20)	3 (3)	1 (1)
18	19 (19)	18 (18)	6 (5)	4 (4)
19	20 (20)	16 (16)	3 (3)	2 (1,0.5,0.5)**
20	20 (20)	18 (18)	5 (5)	3 (2)
Mean	17.1 (16.8)	14.7 (14.5)	2.7 (2.5)	2.8 (2.4)
SD	3.8 (4.1)	3.7 (3.7)	1.9 (1.9)	1.4 (1.4)

* figures in brackets indicate the length of specimens after immersion in formalin.

** indicates fragmented specimen.

TABLE 2f. LENGTH OF LIVER BIOPSY SPECIMENS OBTAINED WITH A "TRU-CUT" NEEDLE USING TECHNIQUE 1 AND 2.

Patient No.	LENGTH OF SPECIMENS (MILLIMETRES)			
	Technique 1		Technique 2	
	First biopsy	Second biopsy	First biopsy	Second biopsy
1	11	16	4	6
2	15	16	2	11
3	20	18	8	10
4	18	14	11	11
5	15	19	12	2
6	15	17	3	3
7	20	18	10	5
8	15	15	11	6
9	18	20	14	7
10	16	18	5	12
Mean	16.3	17.1	8.0	7.3
SD	2.8	1.9	4.2	3.5

Discussion

The diagnostic yield of percutaneous needle biopsy of the liver is influenced by the length of the specimen (Sherlock, 1985); diagnostic accuracy improves as increasing amounts of tissue become available for histological examination (Holund et al., 1980).

The present investigation indicates that, when the "Tru-Cut" needle is used for liver biopsy, the modified breast biopsy technique should be used, because the specimens obtained were much longer and adequate for histological diagnosis; the average length was 16.3mm. The shortest specimen obtained measured 8mm and none of the specimens was fragmented. This data lends support to the recommendation of a number of workers that this technique should be used for liver biopsy (Hegarty and Williams, 1984; Walters and Paton, 1980).

However, the limitations of the alternative methods, including that recommended by the manufacturer (Travenol Laboratories, 1980), have not been emphasised in the literature. The average length of specimens obtained with technique 2 (cannula retracted and advanced) and technique 3 (obturator advanced and retracted) was 7.7mm and 2.7mm respectively. The longest specimen obtained with technique 3 measured 8mm. In addition, 7.5% of specimens were fragmented.

It is not only diagnostic accuracy of the procedure that is compromised by poor technique, but also safety. Hegarty and Williams have stated that successful liver biopsy without complications demands good technique and that inadequate specimens and serious complications are the hallmarks of the inexperienced operator (Hegarty and Williams, 1984). Thus, the importance of the correct technique during needle biopsy of the liver cannot be stressed enough, especially in developing countries where the procedure is carried out by relatively junior medical staff in general medical or surgical wards.

CHAPTER 8

SUMMARY

The causes of hepatomegaly at King Edward VIII Hospital, Durban: A prospective study of 240 black patients.

In this prospective study of 240 black patients with liver enlargement admitted to the medical wards of King Edward VIII Hospital, Durban, a cause for the hepatomegaly was found in 92.5% of patients (63.8% without recourse to biopsy, 28.7% after liver biopsy). The commonest cause was congestive heart failure (36.7%), followed by amoebic liver abscess (7.1%), hepatocellular carcinoma (5.8%) and cirrhosis (5.4%).

Liver biopsy provided the diagnosis in 90.8% of patients with initial unexplained hepatomegaly. It appeared that the diagnostic yield of liver biopsy could be increased by submitting 3 biopsy specimens for histological examination without increasing the risk of complications.

Hepatic tuberculosis was present in 9.2% of patients who underwent biopsy. There were no consistent clinical findings in these patients. Therefore, in communities in which tuberculosis is endemic, all patients with unexplained hepatomegaly require liver biopsy since it provides the only means of making this diagnosis.

Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver.

In an investigation to determine the influence of sampling variability on the diagnostic yield of liver biopsy, 3 consecutive samples were obtained from each of 75 patients by redirecting the biopsy needle through a single entry site. In 14.7% of patients all 3 specimens were normal, and in 36% there were similar abnormalities in all 3 specimens. In the other

patients, sampling variability between specimens was present. In those patients with cirrhosis, hepatocellular carcinoma, metastatic carcinoma, or hepatic granulomas the histological abnormality was present in all 3 biopsy specimens in only 50%, 54.5%, 50%, and 18.8% of patients respectively. No complications were recorded. These findings show that important pathology can be overlooked if only a single biopsy specimen is taken, and that the method of obtaining 3 consecutive specimens improves the diagnostic yield of liver biopsy without an associated increase in complications.

A prospective study of hepatic tuberculosis in 41 black patients.

Forty-one black patients aged 21 to 75 years with hepatic tuberculosis diagnosed at liver biopsy were studied prospectively. The liver varied in size and consistency and was tender in 44 per cent of patients. Abdominal symptoms, weight loss, pyrexia, hepatomegaly, splenomegaly and anaemia were absent in 54, 39, 37, 5, 68 and 27 per cent of patients respectively. Twenty-two percent of chest radiographs were normal. Liver function tests were of little diagnostic value and hepatic imaging techniques often gave normal results. Acid-fast bacilli, caseation and co-existent liver disease were detected in 59, 51 and 37 per cent of patients respectively.

Since there is no consistent clinical pattern, a high index of suspicion is necessary if this disease is to be detected in communities in which tuberculosis is endemic. In patients with unexplained hepatomegaly or hepatosplenomegaly, and patients with pyrexia of unknown origin, liver biopsy provides the only means of making this diagnosis.

The role of ultrasonography and scintigraphy in detecting focal and diffuse liver disease in developing countries.

In a study conducted to determine the value of hepatic ultrasonography and scintigraphy in detecting liver disease, a total of 425 ultrasound scans and 304 scintigraphic scans of patients who had either focal or diffuse liver disease, or who had normal livers were reviewed by two senior radiologists who worked independently of each other, and who were unaware of the patients' clinical details, results of investigations or final diagnosis.

The accuracy of both ultrasonography and scintigraphy in distinguishing between normal and diseased livers was low (68% and 74% respectively). Both techniques performed better at detecting focal than diffuse liver disease; the sensitivity of ultrasonography and scintigraphy in focal and diffuse disease were 88% and 92%, and 27% and 54% respectively. The specificity of both procedures was high for both types of liver disease (range 91-96%). Overlap between the ultrasonographic features of amoebic liver abscess, hepatocellular carcinoma and metastatic carcinoma resulted in a correct final diagnosis being made in only 81% of patients with amoebic liver abscess, 29% with hepatocellular carcinoma and 43% of patients with metastatic carcinoma who had an ultrasound scan.

The sensitivity of ultrasonography and scintigraphy in detecting cirrhosis (diffuse liver disease) in patients in whom hepatocellular carcinoma and cirrhosis co-existed was 41% and 67% respectively. Inter-observer differences between the senior radiologists were present in 25.5% of ultrasound scans and 11% of scintigraphic scans of patients with diffuse liver disease, 8.8% and 5.7% of scans of patients with focal disease, and 7.9% and 14.5% of scans of patients with normal livers respectively.

This study indicates that these techniques were neither accurate in detecting diffuse liver disease nor capable of determining the cause of diffuse liver disease. Therefore, when diffuse parenchymal liver disease is suspected, liver biopsy would be needed to determine the presence and nature of the disease. Although the accuracy of both imaging modalities in detecting focal disease is high, overlap between the ultrasonographic features of the common causes of space-occupying lesions may result in an incorrect final diagnosis being made in certain patients. Accordingly, liver biopsy or aspiration might be required to determine the cause of focal disease in selected patients with space-occupying lesions on hepatic imaging studies.

Complications associated with liver biopsy

In order to determine the frequency and nature of complications associated with percutaneous and peritoneoscopic liver biopsies at King Edward VIII Hospital, Durban, patients in whom these procedures had been performed during the period 1984 - 1987 (inclusive) were studied. A total of 1525 percutaneous biopsies were carried out; a single specimen was obtained during the procedure in 484 patients, 2 consecutive specimens in 578 patients and 3 in 463 patients. The morbidity and mortality rates after percutaneous biopsy were 2.0 and 0.3% respectively; pain occurred in 15 patients, hypotension in 15 patients, and biliary peritonitis in 1 patient. The final diagnoses in the 5 patients who died were hepatocellular carcinoma (n=2), Kaposi's sarcoma (n=1), disseminated tuberculosis plus alcoholic hepatitis (n=1), pelvic and lung abscesses (n=1). Intraperitoneal bleeding was the cause of death in all patients. Patients in whom 2 or 3 specimens were obtained did not have a higher incidence of fatalities, pain, hypotension or biliary peritonitis.

Of the 217 patients in whom peritoneoscopic biopsies were performed, complications were encountered in 5 (2.3%); all developed hypotension. One patient (0.5%), who had hepatocellular carcinoma, died as a result of intraperitoneal bleeding.

All, except one, of the patients who died, and many patients who had developed hypotension, had not been adequately monitored. In the majority of patients who underwent both types of biopsy, after-care was either inadequate or non-existent.

This study demonstrates that by taking 2 or 3 consecutive specimens during percutaneous liver biopsy an increase in diagnostic yield is achieved without an increase in fatalities and complications, that the mortality and morbidity associated with percutaneous and peritoneoscopic biopsies are high, and that greater awareness of the hazards of biopsy and their prevention is needed; good technique, careful monitoring and prompt and aggressive resuscitation are essential if the mortality rate is to be reduced.

"Tru-Cut" needle biopsy of the liver: importance of the correct technique.

In order to determine which technique would provide adequate tissue for histological examination when the "Tru-Cut" needle is used for liver biopsy, the livers of cadavers were biopsied by a single operator, under direct vision, using a "Tru-Cut" needle. The modified breast biopsy technique either preceded or followed one of two alternative methods, one of which was recommended by the manufacturer, in a random manner. Thereafter, the biopsies were repeated using the alternative sequence.

The mean length of the liver biopsy specimens that were obtained using the modified breast biospy technique was 16.3 mm (range: 8-20mm). The corresponding figures for the manufacturer's method were 7.7 mm (range: 2-14mm), and for the third technique were 2.7 mm (range: 0.5-8mm). Three of the 40 specimens (7.5%) obtained using the latter technique fragmented when placed in formalin; this did not occur in any of the 40 specimens taken using the alternative method.

This investigation indicates that the modified breast biopsy technique should be used when "Tru-Cut" needle biopsy of the liver is performed. This provides specimens which are adequate for histological diagnosis. In addition, the safety of liver biopsy, which is compromised by poor technique, is improved. The alternative methods, including that recommended by the manufacturer, must be avoided.

CHAPTER 9

CONCLUSIONS AND RECOMMENDATIONS

In developing countries, a cause for liver enlargement should be sought in all patients in whom hepatomegaly is detected, including those in whom liver enlargement is incidental to the condition for which hospital admission is required. In the majority of patients, this is achieved by careful clinical examination, the appropriate use of laboratory or radiological investigations, and where applicable, evaluation of response to appropriate therapy. The remaining patients with unexplained hepatomegaly will require liver biopsy to determine the cause. Diseases which could otherwise go undetected, such as hepatic tuberculosis, are diagnosed when this approach is used.

Hepatic tuberculosis has a highly variable clinical picture; there are no characteristic findings. A high index of suspicion is needed and liver biopsy is essential in patients with unexplained hepatomegaly or hepatosplenomegaly, and patients with pyrexia of unknown origin as it provides the only means of making this diagnosis.

The following limitations of liver function tests need to be considered when interpreting the results of this investigation in patients suspected of having liver disease. Firstly, the presence of normal liver function tests does not exclude liver pathology. Secondly, with few exceptions, liver function tests are of little diagnostic value; they have a limited capacity for differential diagnosis.

Hepatic imaging studies also have limitations. Neither hepatic ultrasonography nor scintigraphy is useful in detecting or determining the cause of diffuse parenchymal liver disease; liver biopsy has to be used for this purpose. In addition, although both imaging modalities have a high accuracy in detecting focal liver disease, space-occupying lesions will not always be detected. Also, overlap between the ultrasonographic features of amoebic liver abscess, hepatocellular carcinoma and metastatic carcinoma will result in an

incorrect final diagnosis being made in a number of patients. Accordingly, liver biopsy or aspiration is required to determine the cause of focal liver disease in selected patients in whom space-occupying lesions are detected during hepatic imaging studies.

Liver biopsy is a valuable method for detecting the presence and nature of liver disease. The diagnostic yield of percutaneous liver biopsy is increased by obtaining two (or three) consecutive specimens for histological examination by redirecting the biopsy needle through a single entry site. This benefit is achieved without an increase in fatalities or complications. However, the overall morbidity and mortality rate in patients undergoing percutaneous or peritoneoscopic biopsy is high. Complications are not detected early because the after-care in the majority of patients is either non-existent or inadequate. The mortality rate will be reduced when doctors assume responsibility for monitoring patients; complications will be detected early, and resuscitation and other measures will be instituted timeously.

When the "Tru-Cut" needle is used incorrectly, the tissue specimens obtained are inadequate for histological diagnosis and the risk of serious complications is increased. Accordingly, greater emphasis on good technique and adequate training of operators is needed.

It is against this background that the following recommendations on percutaneous liver biopsy are made.

RECOMMENDATIONS ON PERCUTANEOUS "TRU-CUT" NEEDLE BIOPSY OF THE LIVER IN DEVELOPING COUNTRIES.

Precautions

1. A skilled operator is required:
   a. The technique is first taught on 500g margarine which has just been removed from a freezer.
   b. A number of "biopsies" can be done until both the teacher and operator are satisfied (The incorrect technique should also be demonstrated by the teacher to show the inadequacy of the sample obtained).
   c. Further practice can be obtained in the necropsy room, if required.
   d. Thereafter, the operator watches the procedure being carried out in a patient, performs the biopsy under supervision, and finally, does so on his own.

2. The prothrombin time must be checked.
   a. If the prothrombin time is prolonged more than 3 seconds over control values, biopsy should be postponed and vitamin K 10mg given intramuscularly for a few days.
   b. If the prothrombin time remains prolonged despite vitamin K, and biopsy is considered essential, fresh frozen plasma should be given (one unit before, one during, and one after the biopsy).
   c. If the prothrombin time is prolonged more than 6 seconds, then the procedure should not be carried out.

3. The platelet count must be checked.

   a. A platelet count greater than 100 x 10^9/l has been recommended, but in recent years, the minimum has, by general agreement, been reduced to 80 x 10^9/l.

   b. If the platelet count is reduced below this level, and biopsy is considered essential, platelet concentrates may be used. The bleeding time must be checked in these patients both before and after the platelet transfusion.

4. Blood should be available.

   a. Two units of blood should be cross-matched before the procedure.

   b. An intravenous cannula should be placed in-situ.

5. The path to the liver should be normal.

   a. If there is skin or chest infection, biopsy should be postponed.

   b. When ascites is appreciable, it should be treated first because ascites causes the liver to float away from an advancing needle.

6. The day of the week and time of biopsy should be carefully chosen.

   In the interests of safety, biopsies should not be carried out:

   a. After 11h00.

   b. On weekends.

   c. When the ward is "on-intake".

Procedure

The correct procedure should be used.

1. Preparation

    a. The patient should lie flat on the edge of the bed with the right hand placed behind the head.

    b. Except when it is necessary to biopsy a specific area, the intercostal route should be used.

    c. The site for biopsy is selected by craniocaudal percussion over the chest in the mid-axillary line until an intercostal space is reached where dullness is maximal at the end of expiration. The intercostal space below this is used. This usually involves traversing either the eight, ninth or tenth intercostal space.

2. Technique

    a. The skin is cleansed with a suitable antiseptic.

    b. 10 ml of 2% lignocaine is drawn up and infiltrated first subcutaneously, then into the intercostal area, and finally down to the diaphragm and capsule of the liver. Care must be taken to infiltrate each area adequately.

    c. The patient is trained to take several deep breaths in and out and to hold his breath in deep expiration for a long as he can.

    d. A small incision is made in the skin with a scalpel-blade to facilitate entry of the biopsy needle.

    e. With the patient breathing quietly, the needle is introduced and advanced until it is felt to give into the space overlying the liver.

f. The patient is told to breathe out and then stop breathing, and the biopsy is completed as follows.

   i. The "Tru-Cut" needle, which is in a closed position, is advanced 2-3cm into the liver.

   ii. With the outer cutting sheath (cannula) held still, the obturator (inner trocar) is advanced.

   iii. The obturator is then held steady, while the outer cutting sheath is advanced.

   iv. The whole needle is withdrawn quickly.

   Steps i to iii consist of 3 forward movements (see the figure)

   The entire maneouvre (step f) should take less than 3 seconds.

g. The biopsy specimen is removed from the notch and placed in formalin.

h. A second specimen is taken by reintroducing the needle through the same entry site and redirecting it by about 20^{o} to 30^{o} from the original position. Steps f and g are then repeated.

i. The skin incision is covered with plaster.

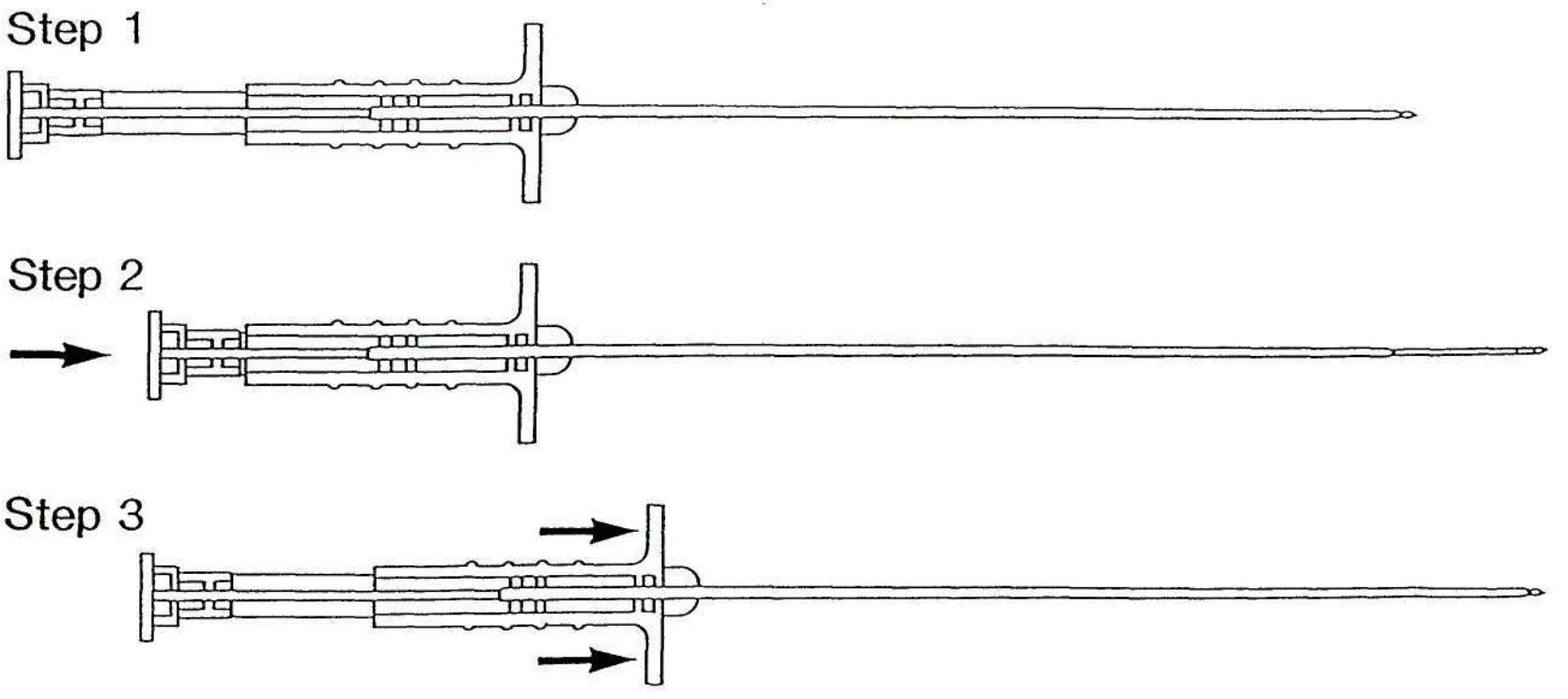
After-Care

1. The patient is asked to lie on his right side for 4 hours.
2. The patient is advised to rest in bed for 24 hours.
3. The doctor who performs the biopsy must assume responsibility for monitoring the patient for haemorrhage and other serious complications during the first 6 hours after the procedure. Blood pressure and pulse rate must be measured immediately after the biopsy, at 15 minute intervals for the first 2 hours, at 30 minute intervals for the next 2 hours, and at hourly intervals for the next two hours.
4. The nursing staff can be requested to assist with further observations.

Awareness of complications

1. The mortality rate after percutaneous liver biopsy is high.
2. Death is usually a result of haemorrhage into the peritoneum.
3. Strict observations should give an early indication of bleeding, and if blood transfusion fails to stabilise the situation, laparotomy has to be considered.
4. Adherence to the measures outlined above, prompt and aggressive resuscitation and early involvement of surgeons in the management of serious complications will reduce the mortality rate.
5. The complications that may be encountered after biopsy include pain, haemorrhage, biliary peritonitis, haemothorax, pneumothorax, perforation of the colon or gall bladder, and intrahepatic haematoma.

Schematic representation of the
correct technique using the "Tru-Cut" needle



Footnote

These conclusions and recommendations are based upon information which is presented in the foregoing chapters. In addition, during the preparation of recommendations on percutaneous liver biopsy, a number of papers which were relevant to the topic were consulted (Hegarty and Williams, 1984; Losowsky, 1982; Millward-Sadler and Whorwell, 1985; Sherlock, 1985; Walters and Paton, 1980).

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