The diagnostic accuracy of Technetium 99m labelled erythrocyte scintigraphy in the investigation of hepatic mass lesions

Special reference to

hepatic cavernous haemangioma
and hepatocellular carcinoma

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Dedication

To my wife Doris,

my son Graem

and my daughter Jaidé

With thanks for your love, support and understanding

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TABLE OF CONTENTS

Chapter 1 : Review of the literature

Chapter 2 : Patients, materials and methods

Chapter 3 : Results

INTRODUCTION

The distinction between cavernous haemangiomas of the liver (which are the second most common hepatic mass lesions) from malignant lesions, is often difficult. An incorrect diagnosis of cavernous haemangioma, in a patient with malignancy, may adversely influence the outcome of subsequent treatment in these patients, due to delay in therapy. Although previous studies have suggested that ^{99m}Tc erythrocyte blood pool scintigraphy is both highly sensitive and specific for haemangiomas, a basic flaw in all previous studies has been the small number of control patients studied. Bayesian analysis clearly shows that specificity for a test is dependant on the pre-test probability of the lesion being present. Thus all the studies done to date, may reflect an inappropriately high specificity for ^{99m}Tc scintigraphy, in diagnosing cavernous haemangiomas, because they have mainly studied patients with haemangiomas and relatively few patients with other lesions.

This study was thus undertaken to clarify the true accuracy of this technique, in distinguishing haemangiomas from other hepatic mass lesions, by studying a large number of patients with haemangiomas and other hepatic mass lesions.

Chapter 1

REVIEW OF THE LITERATURE

HISTORY

The first description of haemangiomas of the liver in the medical literature appeared in 1861. In his treatise on liver disease, Frerichs (1861) said that hepatic haemangiomas were described by Dupuytren, Cruveilhier and Meckel, but that Virchow and Rokitansky were the first to examine these lesions carefully. While a few authors considered the liver cavernous haemangioma to be rare (Peck, 1921; Mantle, 1903), others considered it to be common and probably the best known and most common of all new growths in the liver (Major and Black, 1918). The consensus of the early authors was that hepatic cavernous haemangiomas were usually asymptomatic and of negligible clinical importance (Frerichs, 1861; Schmieden, 1900; Mantle, 1903; Major and Black, 1918). Several autopsy reports appeared in the literature at the turn of the century, including a description by Major and Black (1918) of the largest haemangiomatous liver (18160 grams) reported up to that time. The major emphasis in the literature at the end of the 19th century and in the first half of the 20th century however, was on large symptomatic haemangiomas and their surgical excision (Pfannenstiel, 1898; Langer, 1901; Fillipini, 1901; Mantle, 1903; Von Generisich, 1908; M'Weeney, 1912; Rubin, 1918; Peck, 1921; Eckles, 1927; Shumacker and Baltimore, 1942; Wilson and Tyson, 1952; Henson *et al.*, 1956b).

An annotated bibliography of the historically relevant papers is given in Appendix 1.

AETIOLOGY AND PATHOGENESIS

The primordial network of endothelium and blood spaces in the human embryo develops in the third week from the mesoderm overlying the yolk sac, at the junction of the foregut and the hindgut. It is here that the vascular tree

takes root with the major structures of heart, aorta and hepatic vessels first appearing, growth following by extension from this central mesenchymal network. Haemangiomas follow the central and peripheral growth zones of the vascular system in their distribution (Geschickter and Keasbey, 1935).

Two major hypotheses of pathogenesis subsequently evolved:

(i) One of a hamartomatous origin (Schmieden, 1900; Borst, 1911; Major and Black, 1918; Feldman, 1958; Kojima-hara, 1986; Craig *et al.*, 1989; Watson and McCarthy, 1940);

(ii) The other of an angiomatous origin (Moore, 1944; O'Donoghue and Nicosia, 1950; Boyd, 1970; Robbins, 1974; Conter and Longmire, 1988).

A hamartoma, by definition, is a mixture of tissue commonly present in an organ, but present in a disordered arrangement. In contrast, an angioma is a true benign neoplasm of blood (or lymph) vessels. An intermediate hypothesis, in which a hamartomatous origin is accepted but with additional growth by proliferation of endothelial structures rather than simple enlargement by ectasia alone, is assumed by others (Ribbert, 1898; Eckles, 1927; Borst, 1911; Major and Black, 1918; Roggenbau, 1910; Robbins, 1974).

Hypotheses on the mechanism of growth or expansion of the cavernous haemangioma in the literature fall into two major schools. The *hypothesis of ectasia* postulates that expansion occurs initially with growth of the liver, followed by ectasia of pre-existing vascular channels without hyperplasia or hypertrophy (Trastek *et al.*, 1983; Adson, 1986; Nichols *et al.*, 1989). The *hypothesis of new growth* postulates the extension of newly-formed endothelial buds from intrinsic vascular structures into surrounding tissue, which is displaced by the constant formation of new vessels. Solid cords undergo canalization and establish communication with the parent vessel, but do not invade or communicate with surrounding normal vessels. (Ribbert 1898, cited by Watson and McCarthy, 1940; O'Donoghue and Nicosia, 1950; Conter and Longmire, 1988).

Coexistence of hepatic cavernous haemangioma and focal nodular hyperplasia has been observed by several workers and suggests that these

lesions are pathogenetically related (Benz and Baggenstoss, 1953; Mathieu *et al.*, 1989; Ndimbie *et al.*, 1990) and developmental in origin (Wanless and Mawdsley, 1985). See Appendix 14.

The possible association between oral contraceptives and benign hepatic tumours was brought to light for the first time in 1974 (Baum *et al.*, 1973). Subsequently, reports have appeared in the literature of the diagnosis of focal nodular hyperplasia and liver cell adenoma (Nissen *et al.*, 1976), liver hamartomas (O'Sullivan and Wilding, 1974; Nissen *et al.*, 1976), and liver haemangiomas (Tait *et al.*, 1992, Sinanan and Marchioro, 1989) in patients receiving oral contraceptive steroids (OCS) or exogenous oestrogen replacement therapy. These findings suggest a possible aetiological role of these hormones. The presence of moderate liver damage and hepatomegaly with periportal sinusoidal dilatation, demonstrated histologically in females on long term treatment with OCS, further suggest a role in the pathogenesis of vascular tumours of the liver (Winkler and Poulsen, 1975; Conter and Longmire, 1988). An aetiological role of OCS and anabolic steroids in the rare diffuse hepatic haemangiomatosis or peliosis hepatis has been suggested (Klatskin, 1977; Gordon *et al.*, 1960; McGiven, 1970).

Hepatic cavernous haemangiomas may increase in size and become symptomatic in response to exogenous oestrogens and OCS (Morley *et al.*, 1974; Tait *et al.*, 1992), but this situation is also documented in the complete absence of endogenous and exogenous oestrogen stimulation (Du Pre and Fincher, 1992). It has been suggested that exogenous oestrogen withdrawal, and possibly oestrogen receptor blockade by specific antagonists, may slow growth of the lesion (Sinanan and Marchioro, 1989). Recurrence following ablative therapy has been associated with exogenous oestrogen therapy (Conter and Longmire, 1988). A higher frequency of HCH has been reported in multiparous women (Ninard, 1950; Abrams *et al.*, 1950; McLoughlin, 1971). HCH may become symptomatic and/or undergo rapid enlargement during pregnancy (Rubin, 1918; Nichols *et al.*, 1989; White, 1983; Creasy *et al.*, 1985; Schwartz and Husser, 1987). The effect of pregnancy on the growth of HCH is considered to be inconsistent by some authors (Kato *et al.*, 1975; Schwartz and Husser, 1987). Sewell and Weiss (1961) described spontaneous rupture of a HCH, an otherwise rare complication, occurring in a pregnancy.

While the exact role of exogenous/endogenous oestrogenic steroids in the aetiology and pathogenesis of hepatic cavernous haemangioma remains unclear, the bulk of evidence seems to support a stimulatory role in the enlargement of pre-existing haemangiomas and the appearance of symptoms (Conter and Longmire, 1988; Zafrani, 1989). It could be speculated that the well known association between oestrogen use, or pregnancy, and worsening of angiomas of the skin/gingiva, may also exist within the hepatic parenchyma (Conter and Longmire, 1988; Edmondson, 1958).

The earliest hypotheses on the pathogenesis of HCH before 1900 are summarised in Appendices 2, 3, 4 and 5. An annotated bibliography of the aetiological role of OCS, exogenous oestrogens and pregnancy in HCH is given in Appendices 6 and 7.

PATHOLOGY

Gross pathology

Macroscopically, the hepatic cavernous haemangioma characteristically appears red, blue or purple (Edmondson, 1958; Goodman, 1987; Geschickter and Keasbey, 1935; Berk and Priest, 1965; Major and Black, 1918; Henson *et al.*, 1956*b*; Ochsner and Halpert, 1958; Ishak and Rabin, 1975; Craig *et al.*, 1989; Robbins, 1974; Frerichs, 1861; Edmondson, 1958; Aspray, 1945), but may be grey or whitish in appearance depending on the amount of fibrosis or calcification present (Harataki *et al.*, 1992; Plachta, 1962).

The HCH is circumscribed (Geschickter and Keasbey, 1935; Plachta, 1962; Mantle, 1903; Ishak and Rabin, 1975; Kew, 1990), and well demarcated from the surrounding liver tissue (Aspray, 1945; Harataki *et al.*, 1992; Henson *et al.*, 1956*b*; Berk and Priest, 1965). Although generally non-encapsulated (Ishak and Rabin, 1975; Mantle, 1903; Kew, 1990; Robins, 1974; Aspray, 1945), a fibrous capsule may be present and may be accompanied by compression of the surrounding liver parenchyma (Frerichs, 1861; Adam *et al.*, 1970; Wakeley, 1925). The absence of a fibrous capsule in the majority of haemangiomas and the fact that most haemangiomas are small, suggests that formation of a capsule occurs by compression of adjacent parenchyma, especially in larger and/or expanding lesions. When a capsule is lacking, the

cavernous spaces abut directly on the liver parenchyma, forming a very soft tumour, while the presence of a fibrous capsule is probably required to render a haemangioma readily palpable per abdomen (Wakeley, 1925). Liver haemangiomas may be elevated, depressed or pedunculated, irregular or lobulated masses (Ochsner and Halpert, 1958; Shumacker and Baltimore, 1942; Henson *et al.*, 1956*b*; Major and Black, 1918; Adam *et al.*, 1970; Berk and Priest, 1965; Aspray, 1945). The consistency is soft or spongy (Ochsner and Halpert, 1958; Edmondson, 1958; Henson *et al.*, 1956b; Berk and Priest, 1965; Robbins, 1974; Geschickter and Keasbey, 1935) and the masses are compressible (Robbins, 1974; Nichols *et al.*, 1989; Shumacker and Baltimore 1942), although they may be firm when large amounts of fibrous tissue or extensive calcification is present (Harataki *et al.*, 1992; Henson *et al.*, 1956*b*; Berk and Priest, 1965; Adam *et al.*, 1970; Plachta, 1962).

When sectioned, they partially collapse due to the escape of blood (Ishak and Rabin, 1975; Goodman, 1987; Robbins, 1974; Edmondson, 1958), appear round, oval or angular with a honeycomb or sponge-like cut surface (Ochsner and Halpert, 1958; Adam *et al.*, 1970; Ishak and Rabin, 1975; Craig *et al.*, 1989; Mantle, 1903; Goodman, 1987; Major and Black, 1918; Frerichs, 1861; Edmondson, 1958). There may be evidence of recent or old thrombosis (Ishak and Rabin, 1975; Craig *et al.*, 1989; Goodman, 1987; Frerichs, 1861; Tait *et al.*, 1992; Harataki *et al.*, 1992), with regressive or involutional changes such as fibrosis, calcification or necrosis (Ishak and Rabin, 1975; Craig *et al.*, 1989; Goodman, 1987; Harataki *et al.*, 1992; Aspray, 1945; Plachta, 1962; Berry, 1985).

Liver cavernous haemangiomas are usually solitary, but the prevalence of multiple liver haemangiomas varies between 7 and 44 % (mean 22%). The probable reason for the variability in the reported prevalence of multiple vs. solitary haemangiomas is the selection bias in the studies reporting the higher prevalences (Trastek *et al.*, 1983; Tait *et al.*, 1992; Schmieden, 1900). In the studies of Tait *et al.* (1992) and Trastek *et al.* (1983), clear selection bias was present in that retrospective analysis was performed only of patients with an established diagnosis of HCH. It is therefore likely that in these selected groups, more patients with multiple HCH were included than would be found in the general population or in an unselected autopsy series. In the study of Schmieden (1900), an unequivocal selection bias is present in that selected autopsy haemangioma specimens were examined to investigate

structure and genesis, and the frequency of multiple haemangiomas cannot be representative of that obtained in unselected autopsy series. The 9% prevalence of multiple HCH found in the two large unselected autopsy series of Ochsner and Halpert (1958) and Feldman (1958) and quoted by Edmondson (1958) and Craig *et al.* (1989), also based on large autopsy series, probably represents the true prevalence. While the study of Henson *et al.* (1956*b*) has no or at most only partial bias, the number of patients is small, and the 17 - 18 % prevalence of multiple HCH may be overestimated (See Appendix 8). Rarely, the is liver diffusely involved by great numbers of small haemangiomas (Edmondson, 1958; Wilson and Tyson, 1952).

The size of haemangiomas ranges from a few millimetres to greater than 20 cm in diameter. In *unselected* autopsy and clinical series the majority are less than 4 cm in size (Edmondson, 1958; Feldman, 1958; Goodman, 1987; Ochsner and Halpert, 1958; Henson *et al.*, 1956*b*). The large lesions found in several surgical series reflect a bias introduced by selection of patients with large and usually symptomatic HCH for resection, and therefore does not reflect the average size distribution in the general population (See Appendices 9 and 10). Lesions exceeding 4 cm in diameter have been defined as massive or giant cavernous haemangiomas by Adam *et al.* (1970), based on their finding that no symptomatic tumour was encountered which was less than this size. (See Appendix 10).

Haemangiomas occur most frequently in the right lobe of the liver (Frerichs, 1861; Edmondson, 1958; Nelson and Chezmar, 1990; Kato *et al.*, 1975; Ochsner and Halpert, 1958; Trastek *et al.*, 1983; Henson *et al.*, 1956*b*; Adam *et al.*, 1970; Schwartz and Husser 1987; Andersson and Bengmark, 1988; Alper *et al.*, 1988; Wilson and Tyson, 1952; Shumacker and Baltimore, 1942; Peck, 1921), which is probably simply due to the volume difference between right and left lobes (See Appendix 11).

It is frequently stated that haemangiomas are more frequently found in a sub-capsular location than deep within the parenchyma (Frerich, 1861; Abrams *et al.*, 1969; Geschickter and Keasbey, 1935; Feldman, 1958; Watson and McCarthy, 1940; Ochsner and Halpert, 1958). In the study of Tait *et al.* (1992), an inversion of this commonly quoted high subcapsular/parenchymal ratio was reported with a higher percentage of deeply situated asymptomatic HCH and a higher percentage of symptomatic HCH situated in a subcapsular

location. This suggests that symptomatic lesions are large and subcapsular, while asymptomatic lesions are mostly deep. Seen as a whole, however, the available data in the limited number of studies is inconclusive and further study is required in this area (See Appendix 12). A predilection for the under surface is reported by some authors (O'Donoghue and Nicosia, 1950; Feldman, 1958).

Histopathology

Liver cavernous haemangiomas are composed of blood filled spaces of variable size and shape which are lined by a single layer of flat endothelium and separated by septa of moderately cellular fibrous connective tissue (Craig *et al.*, 1989; Edmondson, 1958; Robbins, 1974; Major and Black, 1918; Mantle, 1903; Berk and Priest, 1965; Henson *et al.* 1956*b*; Ochsner and Halpert, 1958; Adam *et al.*, 1970; Harataki *et al.*, 1992; Goodman, 1987; O'Donoghue and Nicosia, 1950; Nichols *et al.*, 1989; Geschickter and Keasbey, 1935; Ishak and Rabin, 1975; Frerichs, 1861; M'Weeney, 1912). The endothelial cells are without atypia or increased cellularity (Craig *et al.* 1989; Aspray, 1945; M'Weeney, 1912), supporting the clinical finding that these lesions are benign. Occasional reports of haemangiomas containing large and pale endothelial cells with elongated nuclei and of multiple endothelial cell layers have appeared (O'Donoghue and Nicosia, 1950; Lewin *et al.*, 1992).

The septa separating the loculi vary greatly in thickness, but are usually thin and often incomplete, poorly cellular and may have a myxoid appearance (Craig *et al.*, 1989; Edmondson, 1958; Frerichs, 1861; Ochsner and Halpert, 1958; M'Weeney, 1912). The stromal trabeculae may contain lymphocytes, smooth muscle cells and lipid-laden phagocytes (Adam *et al.* 1970; Major and Black, 1918; Frerichs, 1861). Occasionally papillary in-foldings into the cavernous spaces are present (Craig *et al.*, 1989; Mantle, 1903; Geschickter and Keasbey, 1935). Major arterial branches and small bile ducts may be present in larger septa (Craig *et al.*, 1989; Edmondson, 1958). Some large portal tract arteries have branches that merge with the cavernous spaces, producing arteriovenous shunting (Craig *et al.*, 1989).

The large, variably sized and convoluted blood spaces of the haemangioma result in sluggish blood flow, which is reflected on red cell scintigraphy by the

characteristic progressively increasing activity within the lesion. Physiologically, both ingress and egress of blood are slow and variable, and thus considerable time is usually required before the non-radioactive blood within the haemangioma is replaced by new inflowing (radioactive) blood (Good *et al.*, 1978; Wilcox and Joo, 1980; Front *et al.*, 1983). The flow dynamics further underlie the typical appearance of HCH, where decreased activity is found in the lesion relative to the adjacent parenchyma on radionuclide angiography. Visualisation in the venous phase depends on the volume of contained radioactive blood at any one time, as well as the presence and extent of fibrosis, necrosis or haematoma (Front *et al.*, 1984; Rabinowitz *et al.*, 1984).

Arteriovenous shunts, as described by Craig *et al.* (1989), where portal tract arteries have branches that merge with the cavernous spaces, may explain, at least in part, the early arterial activity seen in the atypical appearance HCH during radionuclide angiography, but do not explain the continued high activity retained in the lesion in the late arterial and early venous phases, over and above the characteristically heightened activity in the mid to late venous phases. An additional explanation for an atypical appearance may be the presence of large bore cavernous spaces with a lesser degree of convolution, allowing rapid ingress and egress of radioactive blood A reversing vascular pattern was described by Hardoff *et al.* (1989), whereby a small central portion of a haemangioma revealed increased arterial flow initially and reduced blood pool activity subsequently, while the periphery of the lesion revealed decreased arterial flow initially and increased blood pool activity subsequently. In explanation he proposed a double vascular arrangement, with the presence of separate larger diameter vessels of lesser tortuousity supplying the central portion, surrounded by tortuous cavernous spaces. This however, fails to explain persistence of increased activity within an entire lesion or part thereof, from perfusion to late blood pool phases. The correlation between the atypical "arterialized" appearance HCH and the blood supply requires further clinicopathologic investigation, particularly in view of the necessary distinction of this entity from malignant neoplasm.

Although most cavernous haemangiomas are well circumscribed and demarcated from adjacent liver tissue (Craig *et al.*, 1989; Robbins, 1974; Goodman, 1987; Ochsner and Halpert, 1958), the connective tissue at the periphery may penetrate into the adjacent hepatic parenchyma, with liver cell

cords or lobules situated between adjacent blood spaces (Frerichs, 1861; Ochsner and Halpert, 1958; Goodman, 1987; M'Weeney, 1912; Geschickter and Keasbey, 1935; Craig *et al.*, 1989). The adjacent hepatic parenchyma is usually not distorted or compressed (Ochsner and Halpert, 1958; Kato *et al.*, 1975), although O'Donoghue and Nicosia (1950) found compression of adjacent liver parenchyma in their case report.

Marked septal fibrosis or hyalinisation and calcification may rarely occur (Harataki *et al.*, 1992; Aspray, 1945; Plachta, 1962; Edmondson, 1958). The cavernous spaces may contain fresh or organising thrombi (Craig *et al.*, 1989; Goodman, 1987), which may form and lyse constantly (Goodman, 1987), due to the sluggish blood flow, and sometimes may undergo calcification or ossification (Craig *et al.*, 1989; Edmondson, 1958).

Blood supply

The origin of the blood supply to the cavernous haemangioma is variable and controversial. Using dye injection techniques, Frerichs (1861) showed that the haemangioma was supplied by the smaller branches of the portal vein, while the hepatic artery supplied only the trabecular vessels and the vasa vasorum of the adjoining hepatic veins, without supplying blood to the cavernous spaces per se (Frerichs, 1861). M'Weeney (1912) demonstrated microscopic pouching and evaginations of the medium sized hepatic veins and suggested that these were the vessels supplying the cavernous haemangioma. However, although Frerichs, (1861), Ribbert (1898) and Mantle (1903) demonstrated the presence of large hepatic venous channels in the neighbourhood of hepatic cavernous haemangioma, they were all unable to demonstrate any communication with the surrounding blood vessels.

Despite the controversy regarding blood supply, as already proposed by Frerichs in 1861, it is now generally accepted that the cavernous spaces of the haemangioma are supplied with blood from radicles of the portal vein. The hepatic artery may provide the vasa vasorum and septae with a nutrient blood supply, but normally do not supply the cavernous spaces with blood. The exception to this rule is the presence of arteriovenous shunting produced by branches of some large portal tract arteries that merge with the cavernous spaces (Craig *et al.*, 1989). Thus, while the presence of such arteriovenous

shunts may produce increased perfusion in a haemangioma or part thereof, in effect these lesions are without arterialization as opposed to hepatocellular carcinoma, which is principally if not exclusively supplied via branches of the hepatic artery (the portal component is virtually absent). While the haemangioma is thus perfused via the portal vein system, they typically reveal hypoperfusion or at most slow perfusion in radionuclide angiography, owing to the sluggish inflow of blood into and circulation through the tortuous cavernous spaces, requiring gradual replacement of the large volume of non-radioactive blood contained within the lesion with labelled blood (Good *et al.*, 1978; Wilcox and Joo, 1980; Front *et al.*, 1983). Visualisation of the entire extent of the lesion by scintigraphy in the venous phase, requires complete mixing of the labelled erythrocytes with the non-labelled blood contained within the haemangioma. Characteristically, owing to an equally sluggish outflow of labelled blood from the tortuous cavernous spaces, the haemangioma reveals retention of labelled erythrocytes relative to adjacent parenchyma in the late venous phase (1-2 hours post injection). In contrast, hepatocellular carcinoma and metastases usually do not retain the labelled erythrocytes and characteristically become isoactive or hypoactive relative to adjacent parenchyma in the late venous phase. This forms the basis for the distinction between these lesions and the cavernous haemangioma on labelled erythrocyte blood pool scintigraphy.

In addition to arteriovenous shunting, further variations in blood supply include arterio-portal shunting, usually a finding associated with angiosarcoma (Ando *et al.*, 1984; Schima *et al.*, 1989) and multiple small porto-hepatic venous shunts (Matsumoto *et al.*, 1990).

Morphological variants

While fibrosis and calcification may be present in cavernous haemangioma (Edmondson, 1958), total sclerosis, hyalinisation or calcification is rare, (Harataki *et al.*, 1992; Aspray, 1945; Plachta, 1962). Fibrous nodules with necrotic centres and identifiable vascular structures within the fibrous stroma, are considered to represent sclerosing haemangiomas (Berry, 1985; Shepherd and Lee, 1983). Pedunculation may be found in up to 33% of cases (Shumacker and Baltimore, 1942). Necrosis in hepatic cavernous haemangioma may result from involution and the lesion may mimic metastatic tumour (Berry, 1985; Shepherd and Lee, 1983). Infarction was suggested by

Bornman *et al.* (1987) to be the probable cause of the hitherto undescribed clinical triad of rigors, pyrexia and right upper quadrant tenderness, with or without hepatomegaly, in these patients. Diffuse systemic haemangiomatosis is a rare disease in adults, with multiple small haemangiomas in multiple organs, including bone, lung and liver (Kane and Newman, 1973; Sugimura *et al.*, 1986). Haemangiomas of the liver may be associated with haemangiomas in other organs. See Appendix 13.

Malignancy

A single case of angiosarcoma associated with hepatic cavernous haemangioma has been described (Drouot *et al.*, 1990), which may merely represent a chance association with a common tumour.

Differential diagnosis

Haemorrhagic vascular lesions which may mimic haemangiomas histologically include metastatic Kaposi's sarcoma, angiosarcoma, peliosis (angiomatosis) hepatis and possibly hereditary haemorrhagic telangiectasia (Edmondson, 1958; Craig *et al.*, 1989). **Angiosarcoma** is characterised by the presence of atypical hypertrophic pleomorphic stratified lining cells with large elongated or angulated hyperchromatic nuclei, which is a hallmark of this tumour (Craig *et al.*, 1989; Edmondson, 1958). **Kaposi's sarcoma** may appear bland histologically, composed of spindle cells and a few vascular spaces, involving portal areas (Craig *et al.*, 1989). **Infantile haemangioendothelioma** (a rare finding in adults with 90% being discovered in the first 6 months of life), usually is not as haemorrhagic as cavernous haemangioma and has more solid fibrous nodules (Craig *et al.*, 1989). **Malignant epithelioid haemangioendothelioma** consists of densely fibrotic nodules containing scattered elongated cells with vacuolated cytoplasm; at the periphery of the sclerotic mass, plump pleomorphic epithelioid cells with abundant densely eosinophilic cytoplasm and large mitotic nuclei extend into adjacent sinusoids (Craig *et al.*, 1989). **Peliosis hepatis** is characterised by the presence of multiple small (< 5-10 mm diameter) dilated, blood filled cavities, not necessarily lined by endothelium, with liver cords and sinusoidal walls ending abruptly at the margins of the cavities; a supporting stroma is lacking, which aids histological distinction

from haemangioma (Craig *et al.*, 1989; Edmondson, 1958). **Hereditary haemorrhagic telangiectasia** (Osler Weber Rendu disease) is rarely associated with liver involvement, but when present, exists as diffuse liver involvement with dilated (portal) vascular channels that lack the supporting stroma found in cavernous haemangioma (Craig *et al.* 1989).

Pathology of hepatocellular carcinoma and hepatocellular adenoma

The gross pathology and histopathology of primary hepatocellular carcinoma and hepatocellular adenoma (Craig et al., 1989; MacSween 1980; Edmondson and Peters, 1977) are included in the pathological differential diagnosis of hepatic cavernous haemangioma, as these lesions frequently form part of the clinical and scintigraphic differential diagnosis.

Hepatocellular carcinoma is a malignant tumour derived from the hepatocyte and occupies a unique position among neoplasms because of it's propensity to arise in an organ that is already damaged by another disease - cirrhosis (Edmondson and Steiner, 1954). More rarely, primary hepatocellular carcinoma may arise in a non-cirrhotic liver.

Primary hepatocellular carcinoma may be massive, nodular or diffuse. The right lobe is more frequently involved in both the massive and the nodular forms. In the massive type, the right lobe particularly may be largely replaced by a well-circumscribed, soft yellow-brown tumour. This type is more common in non-cirrhotic livers. Small secondary nodules are sometimes present in other parts of the liver. In the nodular type, there is usually one mass which is larger, appears older, is more circumscribed than any other lesion, and can be regarded as the primary lesion. Usually, nodules of smaller size are present throughout the remainder of the liver. Invasion of branches of the portal vein is probably responsible for the rapid spread to other parts of the liver. The nodular type may arise in multicentric foci (Fraumeni et al., 1968). The nodules often bulge beneath Glisson's capsule, are much softer to palpation than are areas of nodular regeneration and are rarely umbilicated. The presence of haemorrhage, necrosis and bile staining may produce wide variation in the coloration of the nodules, while considerable variation in consistency, size and growth pattern is also possible. Most commonly, hepatocellular carcinoma is golden yellow in colour, but may present a mixture of colours including green, pink, pearl-grey, red and black. The golden areas occasionally contain fat. The green colour is due to bile retention and haemorrhagic areas impart a red colour. The consistency of the tumour reflects the microscopic growth pattern. A soft smooth texture indicates a solid growth pattern with little or no trabecular formation. A tumour with a dry granular and friable cut surface usually has well defined trabecular pattern. A haemorrhagic tumour often reflects blood flow through widened trabeculae. White or grey coloration reveals the extent of collagenation, duct-

like transformation and a lesser pooling of blood within the trabecular structures.

Invasion of branches of the portal vein may result in the presence of solid tumour masses in the portal trunk and portal hypertension. Less often, the hepatic veins are invaded and a tumour thrombus may extend into the inferior vena cava, by which route the carcinoma may metastasize to the lungs and more distant structures.

The microscopic appearance of hepatocellular carcinoma is highly variable between different tumours and even within the same tumour. Several biological factors contribute to the histological pattern. The relationship of the tumour to non-tumour parenchyma is reflected by the formation of nodules that extend or bulge into and enlarge within non-tumour liver parenchyma. A fibrous capsule is sometimes present. Tumour spread into the hepatic sinusoids has been reported by Nakashima *et al.* (1993). This occurred only in some poorly differentiated hepatocellular carcinomas, however. Sinusoidal tumour spread is more commonly seen in metastatic carcinoma than in hepatocellular carcinoma in the experience of Craig *et al.* (1989), while spread of hepatocellular carcinoma into the portal and hepatic veins is relatively common, especially in the cirrhotic liver.

The tumour cells simulate normal liver cells, being characterised by large, round hyperchromatic nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The relationship of the tumour cells to each other is reflected by their cohesiveness and a tendency toward arrangement in trabeculae that are usually two to eight cells in width. A microtrabecular pattern is present when the cell plates are less than 8 cells in thickness, whereas a macrotrabecular pattern is thicker. Necrosis occurring in some macrotrabecullae forms a gland-like space that mimics metastatic adenocarcinoma. An acinar or pseudoglandular pattern is present when a small lumen (canaliculus) is present, which often contains bile. Another feature indicative of origin from hepatocytes is the coverage of the trabecullae by a thin basement membrane envelope (as are the liver cords), with endothelial cells external to this. This arrangement is particularly noticeable when the tumour grows into blood vessels. The space surrounding the trabecullae is analogous to the sinusoidal spaces and carries arterial blood, and the vascular supply is abundant in most tumours. In the massive carcinomas, the trabecular pattern

is less obvious. Some hepatocellular carcinomas grow in solid sheets with few vascular channels and resemble squamous carcinoma. This pattern is called compact or solid type. Regardless of variations in pattern, most hepatocellular carcinomas are composed only of malignant cells and a capillary stroma. While stromal components of most hepatocellular carcinomas are minimal, and the excessive connective tissue characterising most adenocarcinimas is absent, some tumours incite a strong stromal reaction in the vascular component. The collagen formation results in a tubular or acinar pattern which may become glandular in appearance. Glandular transformation may thus develop in some trabecullar areas, while a small number of hepatocellular carcinomas have a marked glandular dilatation that resembles a thyroid acinus (adenoid pattern). Acini may or may not contain bile. Rarely, a papillary pattern is present as one of several patterns. The variation of histological patterns may result in misdiagnosis of metastatic carcinoma, on a small sample. Various degrees of sclerosis occur and if abundant in numerous sections, the term sclerosing hepatocellular carcinoma is applied, although this pattern accounts for less than 2 % of all hepatocellular carcinomas. A few carcinomas of hepatocyte origin are highly undifferentiated, forming spindle and giant cell types. In some carcinomas complicating cirrhosis, there is a combination of hepatocyte and bile duct carcinoma, with the former predominating as a rule.

In the grading of hepatocellular carcinoma, criteria include degree of cytoplasmic acidophilia, nuclear chromatism, nuclear/cytoplasmic ratio, cell cohesiveness, cell function (bile production) and histological architecture.

Grade I hepatocellular carcinoma: the nuclear/cytoplasmic ratio is nearly normal and this grade is recognised by the presence of a bulging nodule formation and compression of adjacent liver cords. In the presence of metastasis and/or vein invasion or the presence of other areas of grade II hepatocellular carcinoma, grade I hepatocellular carcinoma is clearly distinguished from hepatocellular adenoma.

Grade II hepatocellular carcinoma has larger hyperchromatic nuclei, more eosinophilic cytoplasm and acini. In addition, formulation of trabecullae and papillae may be present.

Grade III hepatocellular carcinoma has yet larger hyperchromatic and more variable nuclei, with multiple nucleoli and comparatively less cytoplasm. There may be loss of trabecullar arrangement and syncytial giant cells are more numerous. Bile plugs are less evident.

Grade IV hepatocellular carcinoma has less mature cells with large nuclei and little cytoplasm. This tumour grade may be hard to recognise as hepatocellular in origin. Trabecullae are rare and intravenous invasion by solid tumour may be found. Bile plugs are also rare.

Many hepatocellular carcinomas have more than one grade of tumour, often separated by thin fibrous septae.

Many of the functions of normal hepatocytes are retained in the malignant cells, such as the ability to secrete bile and to store glycogen. Cytoplasmic inclusions in hepatocellular carcinoma include Mallory bodies or alcoholic hyaline (Keely et al., 1972), pale bodies, α-1 antitrypsin bodies, and hyaline. Nuclear inclusions may be cytoplasmic invaginations. Fatty change may occur within the tumour cell cytoplasm, even though the non-tumour liver shows no significant fatty change. Calcification in hepatocellular carcinoma may occur due to tumour necrosis and degeneration. Although dystrophic calcification is rare, it may be extensive and may be detected by radiographic examination (Moenander, 1974; Chin et al., 1986). An unusual case of ossification of a hepatocellular carcinoma was reported by Maeda *et al.* (1986).

Electron microscopy may be useful in distinguishing hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma. Although the ultrastructural features of hepatocellular carcinoma are variable, the cytoplasmic organelles resemble those of normal hepatocytes, while atypical inclusions are present. The histological grade is usually related to the amount and type of cytoplasmic organelles. Well differentiated hepatocellular carcinomas have feature of normal hepatocytes, whereas moderately differentiated hepatocellular carcinomas have nuclear invagination and loss of cytoplasmic organization, with variable numbers of mitochondria that often contain mitochondrial inclusions. The rough endoplasmic reticulum may be increased or distended and the smooth endoplasmic reticulum often forms a whorled pattern called „fingerprinting“ or „myelin“ figures (Ordonez and

Mackay, 1983; Schaff et al., 1971). Electron dense bodies may be numerous and appear to correspond to α-1 antitrypsin (by immunohistochemical staining). Bile canaliculi are present, but are diminished in number.

Hepatocellular adenoma is a circumscribed, often but not always encapsulated, grey-brown bulging tumour composed of hepatocytes arranged in cords, and occasionally forms bile. The tumour is devoid of portal tracts and terminal hepatic veins. The tumours are usually very vascular and necrosis and haemorrhage are frequently present in larger tumours, which may undergo rupture. Although usually solitary, hepatocellular adenoma may be multiple.

The oestrogen-associated hepatocellular adenomas are usually detected in young women with more than 5 years of oestrogen intake (Edmondson et al., 1976). The tumours are usually somewhat lighter in colour than the surrounding liver. Glisson's capsule is usually smooth and glistening in those tumours which have not ruptured, although irregular bulging is usually present. A variegated, irregular, bulging cut surface of tan-coloured tissue is noted in those tumours without degenerative change or rupture. The bulging configuration is not the result of septae, but solid hepatocellular growth. Some hepatocellular adenomas have a homogeneous texture which is pitted by numerous tiny blood vessels and, rarely, fibrous septae. Resected hepatocellular adenomas often show variation in colour due to haemorrhage or infarction. The hepatocellular component is a lighter tan colour than the surrounding hepatic parenchyma. Varying degrees of infarction and haemorrhage may be present, particularly in the central portions. Infarction may be present with little or no haemorrhage. Ruptured tumours have abundant haemorrhage, recognised by bright to dark red clots, while old haemorrhage imparts a dark brown coloration. Degenerative changes, consisting of gelatinous areas or brown-grey connective tissue and pseudocyst formation, are common in larger tumours.

The hepatocytes within the hepatocellular adenoma bear a close resemblance to those of the adjacent non-neoplastic parenchyma. The neoplastic hepatocytes grow in a discernible cord pattern, forming regular trabeculae two to three cells thick. Bile canaliculi are present and appear normal, although bile ducts are absent and there is no evidence of portal triads. In many tumours, however, the cords are closely approximated,

resulting in a sheet-like pattern. Hepatocellular adenomas are composed of four distinct types of neoplastic hepatocytes, that are referred to as neohepatocytes because of their similarity to normal hepatocytes, the absence of malignant cytological features, and their presence only within the hepatocellular adenoma and not within the adjacent normal hepatic parenchyma. The common neohepatocyte, occurring in one-third of hepatocellular adenomas associated with oestrogen intake, resembles a normal hepatocyte (except for it's presence within a hepatocellular adenoma) and has acidophilic cytoplasm. A second type of neohepatocyte is 'hydropic' and the cellular organelles appear to be concentrated around tiny canaliculi. This hydropic type usually grows at the margin of the adenoma or just below the capsule. A third type of neohepatocyte is called the pleomorphic type because of it's larger size and abnormally large nucleus with dense chromatin. Giant cell formation may occur in approximately 10% of hepatocellular adenomas. The overall growth pattern must be observed carefully to exclude malignant change, which is recognised by nodule-within-nodule growth and by the presence of large trabeculae. The fourth type of neohepatocyte has a centrally located nucleus and clear cytoplasm with abundant glycogen.

Cytoplasmic changes of other types may be noted in many hepatocellular adenomas. Alcoholic hyaline may be abundant. Cholestasis is often present, especially in the non-hydropic type. fatty hepatocytes are occasionally present and may be prominent in some hepatocellular adenomas.

The architectural framework of hepatocellular adenoma consists of blood vessels and associated connective tissue that is usually scanty, but may form thin septae. Blood vessels are often very prominent at the margins and within the tumour. Although intimal fibrosis is present in capsular vessels, arterial branches within the tumour are free of such intimal thickening. The arteries within the hepatocellular adenoma are closely accompanied by veins. Degenerative changes may be present in the centre of the tumour, especially in larger hepatocellular adenomas (larger than 10 cm) characterised by necrosis, haemorrhage, densely collagenous scarifications, perivascular oedema, and occasionally, angiomatoid vascular ectasia. Wide dilatation of the sinusoids is also common and results in peliosis hepatis. A distinctive fibrodegenerative lesion composed of poorly cellular masses of amorphous eosinophilic material within the dilated sinusoids may be observed. The

formation of a fibrous capsule occurs at the periphery of most tumours; although thin and incomplete, it is composed of poorly cellular collagenous connective tissue.

Electron microscopic study of the hepatocellular adenoma has not disclosed diagnostic features. Intramitochondrial inclusions have been recorded, but are not specific.

The neohepatocyte types in spontaneous hepatocellular adenoma in women are similar to those present in oestrogen-associated tumours. These tumours rarely undergo infarction and haemorrhage, however. One patient in the series of Craig *et al.* (1989) revealed prominent macrovesicular fatty change and another large, deeply acidophilic neohepatocytes associated with striking peliosis hepatis.

Although adenomas occur occasionally in infants, in children or in men, they are not complicated by haemorrhage and rupture as those in women taking oral contraceptives. In spontaneous hepatocellular adenoma in men, the growth pattern is often characterised by nodularity due to fine fibrous septation. In one case in the series of Craig *et al.* (1989), the growth pattern was that of small nodules within larger ones, with associated infarction. In all cases, the cytoplasm is predominantly acidophilic with fewer hydropic forms. In spontaneous hepatocellular adenoma in children, the cytoplasm is also predominantly acidophilic and a mixture of hydrophilic forms is usually present. Occasionally, the neohepatocytes are dispersed in sheets with no definite cord pattern, while in some, the cord pattern is well defined and pericanalicular lipochrome may be present. In hepatocellular adenoma associated with metabolic disease, the histological appearance is identical to that of the more common oestrogen-related hepatocellular adenoma, with a predominantly acidophilic small cell growth pattern, although macrovesicular fat may predominate in the neohepatocytes (Coire et al., 1987).

Pathological associations

Hepatic cavernous haemangioma is frequently associated with cysts in the liver or pancreas (Feldman, 1958). Although Benz and Baggenstoss (1953) and Mathieu *et al.* (1989) found a high (20%) association of HCH with focal nodular hyperplasia (FNH), Ishak and Rabin (1975) found an association in

only 2,3% of livers and Ndimbie *et al.* (1990) observed only two cases (See Appendix 14). Matthieu *et al.* (1989) found no association between HCH and hepatocellular adenoma (HA).

EPIDEMIOLOGY

Prevalence

Benign tumours of the liver, other than haemangiomas, are rare (Edmondson, 1958; Ishak and Rabin, 1975; Nichols *et al.*, 1989; Adam *et al.*, 1970; Malt *et al.*, 1970; Gold *et al.*, 1978; Henson *et al.*, 1956*a*) (See Appendix 15).

The autopsy prevalence of benign liver tumours other than cavernous haemangioma is low, reported as 0.07 - 0.39 % in two major autopsy series (Edmondson, 1958 and Craig *et al.*, 1989). Benign bile duct tumours in consecutive necropsies or liver needle biopsies has been reported in 0.6 - 2.8% of cases (Thommesen, 1978; Chung, 1970), while Poulsen and Christofferson (1979) found focal nodular hyperplasia in 1 - 2% of necropsy specimens.

The most common benign liver tumour is the cavernous haemangioma (Geschickter and Keasbey, 1935; Henson *et al.*, 1956*b*; Ochsner and Halpert, 1958; Feldman, 1958; Ishak and Rabin, 1975; Adam *et al.*, 1970; Walt, 1977; Karhunen, 1986; Wishnow, 1989; Hobbs, 1990; Gandolfi *et al.*, 1991; Yamamoto *et al.*, 1991; Iwatsuki *et al.*, 1990). Of all the internal organs, the liver is the organ most commonly involved by cavernous haemangioma (Frerichs, 1861; Eckles, 1927; Major and Black, 1918; Shumacker and Baltimore, 1942; Henson *et al.*, 1956*b*; Adam *et al.*, 1970). Liver haemangiomas accounted for 109 of the 570 haemangiomas documented in a series at the Johns Hopkins Hospital (Geschickter and Keasbey, 1935). Hepatic haemangiomas are evenly distributed world-wide (Kew, 1990).

After metastases, cavernous haemangioma is the most common of all the hepatic neoplasms, (Edmondson, 1958; Grieco and Miscall, 1978; Kew, 1990). The high prevalence of metastases is very important when considering the predictive value of radionuclide imaging. Craig *et al.* (1989), in a review of 91 000 autopsies reported a prevalence of liver metastases of 7.7%, while

Iwatsuki *et al.* (1990) reported a prevalence of 33.8% in a surgical series of 547 patients.

The prevalence of HCH varies from 0.35 - 7.3% in autopsy series, with a mean of 0.87% (Edmondson, 1958; O'Donoghue and Nicosia, 1950; Craig *et al.*, 1989; Adami, 1910; Ochsner and Halpert, 1958; Feldman, 1958), although one autopsy series of 95 prospective consecutive medicolegal autopsies on men reported a prevalence of 20% (Karhunen, 1986). Two surgical series in which HCH was diagnosed in patients referred for resection of suspected neoplastic liver disease with a prevalence of 20%, may suffer from selection bias (Sinanan and Marchioro, 1989; Iwatsuki *et al.* 1990). The 52% prevalence of HCH reported by Little *et al.* (1990) in a study of hepatic lesions incidentally discovered on ultrasonography and/or CT imaging in 36 patients and referred to a surgical unit for evaluation, may also reflect a selection bias. See Appendix 16.

An increasing prevalence of HCH and other benign liver tumours reported in the literature probably reflects advances in diagnostic technology, rather than a true increase (Nichols *et al.*, 1989).

Age distribution

Haemangiomas of the liver occur in all age groups (Frerichs, 1861; Wilson and Tyson, 1952; Nichols *et al.*, 1989; Ishak and Rabin, 1975; Edmondson, 1958; Berliner *et al.*, 1983; Du Pre and Fincher, 1992; Kato *et al.*, 1975; Conter and Longmire, 1988), but are rare in infants and children (O'Donoghue et Nicosia, 1950; Edmondson, 1958; Niemann and Penitschka, 1957) and increase in frequency with advancing age (O'Donoghue and Nicosia, 1950; Frerichs, 1861; McLoughlin, 1971; Karhunen, 1986). Symptoms are reported to occur most commonly between the ages of 45 - 50 years (Tait *et al.*, 1992; Conter and Longmire, 1988; Berk and Priest 1965). The peak prevalence of HCH is in the third to sixth decades of life (Wilson and Tyson, 1952; Shumacker and Baltimore, 1942; Gandolfi *et al.*, 1991; Nichols *et al.*, 1989; Du Pre and Fincher, 1992; Conter and Longmire, 1988; Kato *et al.*, 1975; Starzl *et al.*, 1980). (See Appendix 17).

Sex distribution

A female preponderance of HCH with a mean female to male ratio of 2.8:1 is reported in several surgical series (resection of symptomatic HCH), two clinical series (symptomatic HCH), one angiographic series and one autopsy study of 12 calcified (complicated) haemangiomas (Kato *et al.*, 1975; Starzl *et al.*, 1980; Wilson and Tyson, 1952; Adam *et al.*, 1970; Reading *et al.*, 1988; Lise *et al.*, 1992; Vishnevsky *et al.*, 1991; Nichols *et al.*, 1989; Trastek *et al.*, 1983; Schwartz and Husser, 1987; Iwatsuki *et al.*, 1990; Bornman *et al.*, 1987; Shumacker and Baltimore, 1942; McLoughlin, 1971; O'Donoghue and Nicosia, 1950; Alper *et al.*, 1988; Plachta, 1962; Sinanan and Marchioro, 1989). (See Appendix 17). In contrast, Edmondson (1958) and Craig *et al.* (1989) reported a male preponderance in their large autopsy series, with a mean female to male ratio of 0.65:1. See Appendix 17. In both series, however, patients under 40 years of age with HCH were predominantly female.

Henson *et al.* (1956*b*), found a female to male ratio of 10:1 for his subgroup of patients with symptomatic haemangiomas, but the ratio for the subgroup with incidentally discovered haemangiomas was 3.8:1 (5:1 for the entire group). Trastek *et al.* (1983), in a clinical study of patients with liver cavernous haemangioma larger than 4 cm, found that the female group had a mean age of 40 years as opposed to 55 years for the male group. In summary, the discordance of the female to male ratio between series of large and/or symptomatic HCH or surgical resection of HCH and autopsy series, support the opinion in the literature that haemangiomas in females are more prone to become clinically manifest and at an earlier age than in males, (Edmondson, 1958; Shumacker and Baltimore, 1942; Nichols *et al.*, (1989). This may reflect the effects of oestrogens on the development and growth of haemangiomas.

CLINICAL PRESENTATION

The great majority of cavernous haemangiomas of the liver are small, asymptomatic and discovered incidentally on abdominal examination, at laparotomy, autopsy (Shumacker and Baltimore, 1942; Park and Philips, 1970; Bornman *et al.*, 1987; Ishak and Rabin, 1975), or by ultrasonography, computerised tomography or angiography performed for other reasons in patients who have symptoms unrelated to the tumour itself (Johnson *et al.*, 1981; Adson, 1986; Freeny *et al.*, 1979; Bornman *et al.*, 1987; Reading *et al.*, 1988; Park and Philips, 1970). The frequency of asymptomatic forms in the literature varies from 68.6% to 86.5% (Adam *et al.*, 1970; Henson *et al.*, 1956*a*; Park and Philips, 1970). This may be due to the availability of ultrasonography and computerised tomography which detects lesions that would previously have been missed. In the evaluation of the oncological patient, incidentally found haemangiomas frequently raise concern about metastases (Scatarige *et al.*, 1987; Shimizu *et al.*, 1990; Wishnow *et al.*, 1989; Mydlo *et al.*, 1991).

Liver haemangiomas rarely become symptomatic, even when large and palpable (Kato *et al.*, 1975). The percentage of patients with liver haemangiomas who are symptomatic range in the literature from 6.5 to 13.5% (Gandolfi *et al.*, 1991; Park and Philips, 1970). Clinical studies have reported symptomatology developing only in patients with liver haemangiomas exceeding 4 cm (Adam *et al.*, 1970) or 10 cm (Nichols *et al.*, 1989) in diameter. When haemangiomas reach a size sufficient to exert pressure on, to displace, or to interfere with the normal functioning of adjacent viscera and organs, they may present with a sensation of pressure, weight, fullness or dragging discomfort in the upper abdomen and may be associated with anorexia, nausea and vomiting or dysphagia (Morley *et al.*, 1974; Issa, 1968; Wilson and Tyson, 1952; Grieco and Miscall, 1978; Ishak and Rabin, 1975; Abrams *et al.*, 1969). Liver haemangiomas may present with an increasing abdominal girth or an upper abdominal mass, non-specific abdominal pain almost always located in the right upper quadrant or epigastrium with frequent radiation to the back and right shoulder (Morley *et al.*, 1974; Grieco and Miscall, 1978; Iwatsuki *et al.*, 1990; Bornman *et al.*, 1987). Pain is probably due to stretching and inflammation of Glisson's capsule (Nichols *et al.*, 1989), which may be caused by recurrent or intermittent thromboses causing the lesion to swell and producing focal fibrinous serositis, or due to

compression of adjacent organs such as the stomach, gallbladder or bile ducts (Nichols *et al.*, 1989; Goodman, 1987; Taitelbaum *et al.*, 1982; Gandolfi *et al.*, 1991). The primary symptoms are increased abdominal girth, vague abdominal pain and non-specific digestive disturbances (Levitt *et al.*, 1955) and about half of the patients coming to surgery are aware of an enlarging abdomen or a localized abdominal swelling (Morley *et al.*, 1974).

Although physical examination is often unremarkable (Du Pre and Fincher, 1992; Nichols *et al.*, 1989), the most common physical finding is that of a palpable mass in the right upper quadrant connected to the liver, the tumour moving with respiration (Shumacker and Baltimore, 1942; Henson *et al.*, 1956*b*; Morley *et al.*, 1974; Berk and Priest, 1965). The liver itself may or may not be enlarged, or may reveal the fine nodularity and firm consistency of cirrhosis (Berk and Priest, 1965). The lesion is usually non-tender, smooth and varies considerably in size (Berk and Priest, 1965; Grieco and Miscall, 1978). Haemangiomas may be soft, spongy and compressible (depending on the amount of fibrosis of the haemangioma and/or its capsule, liver haemangiomas may occasionally be of firm or hard consistency (Wakeley, 1925)). Occasionally a bruit or venous hum is audible (Berk and Priest, 1965; Grieco and Miscall, 1978; Morley *et al.*, 1974; Nichols *et al.*, 1989; Levitt *et al.*, 1955).

Less common presentations include episodes of acute abdominal pain which may be caused by congestion, thrombosis or infarction (Bornman *et al.*, 1987; Ishak and Rabin, 1975; Taitelbaum *et al.*, 1982; Kew, 1990; Berk and Priest, 1965), acute haemorrhage into the haemangioma (Issa, 1968), or an acute abdominal crisis due to haemoperitoneum resulting from spontaneous or traumatic rupture (Ishak and Rabin, 1975; Kew, 1990; Nichols *et al.*, 1989, Taitelbaum et al., 1982; Stayman et al., 1976; Kawarada and Mizumoto, 1984). Rupture is a catastrophic event and carries a 67% to 70% mortality (Taylor *et al.*, 1981; Sewell and Weiss, 1961; Niemann and Penitschka, 1957). The reported incidence of spontaneous rupture ranges from 0.9% to 4.5% (Adam *et al.*, 1970; Shumacker and Baltimore, 1942) From the small number of cases reported in the literature, this complication appears to be extremely rare (Taylor *et al.*, 1981; Sewell and Weiss, 1961; Zafrani, 1989; Trastek *et al.*, 1983; Yamamoto *et al.*, 1991). See Appendix 18.

Rupture of the haemangioma may present with a sudden unexplained shock or may mimic the presentation of an acute abdominal emergency such as acute appendicitis, perforated peptic ulcer, acute diverticulitis or ruptured tubal pregnancy (Wilson and Tyson, 1952; Levitt *et al.*, 1955). Diagnostic liver biopsy or incision at operation can result in massive haemorrhage which may be fatal (Levitt *et al.*, 1955).

Other rare complications of haemangiomas include obstructive jaundice (Kato *et al.*, 1975), biliary colic (Levitt *et al.*, 1955), obstruction of the gastric cardia (Wakeley, 1925), torsion of pedunculated haemangiomas (Berk and Priest, 1965; Tran-Minh *et al.*, 1991) and abscess formation following percutaneous liver biopsy (Klein *et al.*, 1980). Berliner *et al.* (1983) reported abscess formation 6 months following biopsy, raising the possibility of spontaneous formation.

A clinical triad of rigor, pyrexia and right upper quadrant tenderness, with or without hepatomegaly in the presence of a normal leucocyte count, with or without abnormal liver function tests and with a raised ESR and serum fibrin(ogen) breakdown products, suggests that the haemangioma has been complicated by infective bleeding, thrombosis and/or infarction. These manifestations return to normal following resection of the haemangioma. These features are also commonly found in hepatocellular carcinoma complicated by necrosis and therefore this triad should prompt aggressive investigation to exclude carcinoma (Bornman *et al.*, 1987; Pateron *et al.*, 1991).

LABORATORY INVESTIGATIONS

As with other benign hepatic tumours, hepatic function tests are usually normal and thus of little help in the diagnosis (Berk and Priest, 1965; Henson *et al.*, 1956*b*; Shockman *et al.*, 1963; Nichols *et al.*, 1989; Park and Philips, 1970; Schwartz and Husser, 1987; Taitelbaum *et al.*, 1982). However, Little *et al.* (1990) showed that one or more values of bilirubin, serum alkaline phosphatase, serum alanine amino transferase or serum gamma glutamyl transpeptidase, were abnormal in 8 of 21 patients with incidentally discovered benign liver lesions. Occasionally, slight elevation of bilirubin level (Henson *et al.*, 1956*b*; Gandolfi *et al.*, 1991), alkaline phosphatase (Bornman *et al.*, 1987), alkaline phosphatase and serum gamma glutamyl transferase (Pateron *et al.*, 1991; Reading *et al.*, 1988) or of all three (Gandolfi *et al.*, 1991) have been reported in patients with large symptomatic haemangiomas. (See Appendix 19).

Compression of bile ducts due to large or enlarging central haemangiomas, particularly in the presence of greater rigidity produced by acute haemorrhage, thrombosis and/or fibrosis, may cause raised bilirubin, ALP and/or GGT. Portal vein compression has been demonstrated angiographically in some cases (Gandolfi *et al.*, 1991). Enzyme activity and bilirubin return to normal following radiotherapy (Henson *et al.*, 1956*b*) and surgical resection (Pateron *et al.*, 1991; Bornman *et al.*, 1987). Whereas abnormal liver function tests are only infrequently found associated with hepatic cavernous haemangioma, primary or secondary malignant tumours of the liver are commonly associated with abnormal liver function tests (Kemeny *et al.*, 1982; Chu and Douglass, 1986).

Tumour markers such as alpha fetoprotein and carcinoembryonic antigen are negative in isolated haemangioma (Reading et al., 1988; Little *et al.*, 1990; Bornman *et al.*, 1987).

Rarely, large hepatic haemangiomas may cause the Kasabach-Merritt syndrome, a thrombocytopaenia microangiopathic haemolytic anaemia consumptive coagulopathy, attributed to sequestration and destruction of platelets and red cells in haemangiomas (Shimitsu *et al.*, 1990; Inceman and Tangün, 1969; Cooper and Martin, 1962). Kawarada and Mizumoto (1984) reported the prompt cure of Kasabach-Merritt syndrome in two patients

following resection of large haemangiomas.

Hypofibrinogenaemia may also occur and is associated with increased fibrin(ogen) degradation products, indicating a fibrin(ogen)olytic process (Behar *et al.*, 1963; Martinez *et al.*, 1973; Shimitsu 1990; Inceman and Tangün, 1969). This is thought to be secondary to coagulation and fibrin clot deposition in the haemangioma (Behar *et al.*, 1963), or to primary activation of fibrinolysis possibly by a plasminogen activator released by the endothelium, with little or no activation of intravascular coagulation (Martinez *et al.*, 1973).

Microangiopathic haemolytic anaemia (decreased erythrocytes, haemoglobin and haptoglobin, increased indirect bilirubin and red cell fragments) in association with chronic defibrination may occur in cavernous haemangioma (Inceman and Tangün, 1969; Shimitsu *et al.*, 1990). This is usually associated with thrombocytopaenia (Inceman and Tangün, 1969) but rarely with a normal platelet count, possibly due to increased platelet turnover (Shimitsu *et al.*, 1990).

Rarely, polycythaemia may occur secondary to abnormal secretion of a biologically active erythropoietin by haemangiomas. However, erythrocytosis associated with hepatic tumour is most commonly seen with hepatocellular carcinoma (Taillan *et al.*, 1989; Davidson, 1976).

TECHNETIUM 99M ERYTHROCYTE BLOOD POOL SCINTIGRAPHY

Labelling of erythrocytes with Technetium 99m (^{99m}Tc) provides a suitable intravascular blood pool imaging agent. This is in contrast to the previously used agents such as ^{113m}Indium transferrin, ^{131}Iodine- and ^{99m}Tc - labelled human serum albumin and ^{51}Chromium labelled erythrocytes, which were not suitable for modern gamma cameras, had low labelling efficiency and diffused out of the intravascular space (Front *et al.*, 1984). High labelling efficiency is achieved by consecutive treatment of the red cells with stannous ion and ^{99m}Tc pertechnetate and is complemented by the favourable physical properties and efficient detection of the ^{99m}Tc emissions by the modern Anger camera. The Technetium is bound to the beta chain of the haemoglobin molecule (Dewanjee, 1974) with maintenance of cellular integrity and high stability of the cellular label both in vivo and in vitro. Labelling may be performed in vivo, by a combined in vivo/in vitro technique or by an in vitro technique, with labelling efficiency increasing respectively from former to latter method. Labelling performed in vitro is associated with little free ^{99m}Tc pertechnetate, as opposed to in vivo labelling, providing a higher target to backround ratio and thus improving sensitivity of detection, especially for small and/or thrombotic or fibrotic liver haemangiomas (Floyd, 1986; Rabinowitz *et al.*, 1984; Brodsky *et al.*, 1987).

Hepatic blood pool scintigraphy can be performed as planar scintigraphy in isolation or augmented by single photon emission computerized tomography (SPECT).

Planar blood pool scintigraphy comprises three phases. Methods described in the literature are varied:

1. The perfusion, blood flow or dynamic phase (radionuclide angiography), during which data is acquired at a framing rate of between 1 and 5 seconds per frame for 30 to 120 seconds, following rapid bolus administration of labelled erythrocytes. The projection chosen for radionuclide angiography is that which best visualizes the mass lesion; its position having been determined by other methods.

2. The early blood pool phase, during which images are acquired in one or more projections immediately following the perfusion phase, with or without additional images acquired at variable intervals up to 30 minutes.

3. The late blood pool phase, during which images are acquired at 1 to 2 hours following administration of labelled erythrocytes.

Radionuclide angiography was performed in the majority of studies reviewed, although certain authors have excluded the perfusion phase and relied entirely on information obtained from late blood pool imaging, with or without early blood pool phase imaging (Birnbaum *et al.*, 1990; Brown *et al.*, 1987; Guze and Hawkins, 1989; Krause *et al.*, 1993; Kudo *et al.*, 1989; Langsteger *et al.*, 1989; Lipman and Tumeh, 1990; Malik, 1987).

Planar blood pool scintigraphy is performed with the acquisition of 500 000 to 3 000 000 (usually 1000 000) counts on a large field of view Anger camera equipped with a low energy high resolution or general purpose collimator, on a 128 by 128 or 256 by 256 acquisition matrix.

Single photon emission computerised tomography (SPECT) is typically performed on a single rotating head Anger camera with the acquisition of 64 to 128 angular projections over a 360 degree rotation, with images acquired for 10 to 45 seconds (usually 20 to 30 seconds) or 300 000 counts per projection, on a 64 by 64 acquisition matrix. SPECT performed on a dual head rotating camera typically comprises the acquisition of 64 angular projections with 32 angular intervals of 40 seconds each over 180 degrees (Krause *et al.*, 1993). SPECT acquired on a three headed camera typically comprises the acquisition of 120 angular projections over 360 degrees (Ziessman *et al.*, 1991). SPECT acquisition may be performed at 1 to 2 hours following labelled erythrocyte administration. Brunetti *et al.* (1988) performed acquisition at 10 minutes following administration and found superior sensitivity to planar scintigraphy performed at 1 hour post administration. Langsteger *et al.* (1989) performed acquisition at 30 and 120 minutes and found that although enhanced activity was evident in all the haemangiomas studied, the accumulation of labelled erythrocytes was greater in the 2 hour study. Reconstruction of SPECT data is performed by filtered backprojection, but consensus regarding the filter type is lacking in the literature and filters include ramp, Hanning, ramp-Hanning and Butterworth. Correction for centre

of rotation and camera non-uniformity is performed commonly, while correction for attenuation is performed in a minority of studies (Brunetti *et al.*, 1988; Kudo *et al.*, 1989). Generation of orthogonal planes in three axes (transaxial, sagittal and coronal) of one pixel (6 mm) width or successive merging of two adjacent pixels (12 mm) may be performed.

In the blood pool phase, early and delayed planar scintigraphy are commonly performed alone (Front *et al.*, 1981; Front *et al.*, 1984; Lisbona *et al.*, 1989; Moinuddin *et al.*, 1985; Rabinowitz *et al.*, 1984; Rossleigh *et al.*, 1984) or in combination with delayed SPECT (Brodsky *et al.*, 1987; Groshar *et al.*, 1992; Kudo *et al.*, 1989; Lipman and Tumeh, 1990; Farlow *et al.*, 1990; Tumeh *et al.*, 1985; Tumeh *et al.*, 1987; Birnbaum *et al.*, 1990; Intenzo *et al.*, 1988; Swayne *et al.*, 1991; Ziessman *et al.*, 1991). Less common imaging methods include delayed planar scintigraphy only (Brown *et al.*, 1987), delayed planar scintigraphy and SPECT without early planar scintigraphy (Malik, 1987; Krause *et al.*, 1993) and delayed SPECT only (Guze and Hawkins, 1989; Langsteger *et al.*, 1989).

Planar blood pool scintigraphy

The *perfusion blood pool mismatch*, generally considered diagnostic for hepatic cavernous haemangioma (Rabinowitz *et al.*, 1984; Engel *et al.*, 1983; Drane *et al.*, 1987; Intenzo *et al.*, 1988; Moinuddin *et al.*, 1985; Front *et al.*, 1983; Groshar *et al.*, 1992), embraces the combination of absent or only partial perfusion of the lesion and slow progressive filling with labelled erythrocytes over time, i.e. complete or near complete in the late blood pool phase (at 1-2 hours post injection), reflecting a lesion with slow perfusion but large blood pool. A mismatch may also be present between the early blood pool phase (immediately following the dynamic or perfusion phase up to approximately 30 minutes post injection) and the late blood pool phase. The basis of the perfusion blood pool mismatch and also of an early blood pool/late blood pool mismatch, may be the sluggish circulation of blood through the tortuous cavernous spaces of the haemangioma, producing slow ingress and egress of the label, with the radioactive blood entering the haemangioma being rapidly diluted initially by the large volume of non-radioactive blood contained therein (Good *et al.*, 1978; Wilcox and Joo, 1980; Front *et al.*, 1983). Hence, hepatic cavernous haemangioma *typically* reveals decreased activity relative to the adjacent parenchyma in the dynamic phase

and *characteristically* reveals activity increased relative to adjacent hepatic parenchyma in the late blood pool phase, with or without progressive increase of lesion activity intensity from early to late blood pool phases. Visualisation of the entire extent of the lesion requires complete mixing of the labelled erythrocytes with the non-labelled blood contained within the haemangioma. The extent to which the lesion is visualised depends upon the degree of admixture achieved which in turn depends upon the size of the haemangioma, i.e. the contained volume, as well as the length of time between injection and imaging (Front *et al.*, 1984). In small haemangiomas, admixture with the non-labelled blood is more rapid and they can be visualised in the early blood pool phase (Groshar *et al.*, 1992), often earlier than large cavernous haemangiomas, where the larger contained volume of non-radioactive blood delays visualisation. In the former, activity may be intense in the early blood pool phase and remains constant into the late blood pool phase. Calculation of peak filling rates reveals that maximal labelled erythrocyte accumulation typically occurs within 30-50 minutes after injection (Drane, 1991). If early blood pool images are performed before mixing is complete, and late blood pool images are not done, the slowly filling pool of blood, typical of haemangiomas, will be missed, giving a false negative result (Good *et al.*, 1978; Wilcox and Joo, 1980). This emphasizes the importance of late blood pool imaging, since it is only at this stage that the entire extent of the lesion, often underestimated by ^{99m}Tc sulphur colloid scintigraphy, is visualised (Front *et al.*, 1984). Even so, non-visualization of the haemangioma in the late blood pool phase may occur with extensive thrombosis, fibrosis or infarction of the haemangioma, or with small lesions (< 1.5 cm), especially when deeply situated in the liver tissue (Rabinowitz *et al.*, 1984).

Variable appearance of HCH in dynamic and early blood pool phases

1. Haemangiomas, especially smaller or deeply situated lesions, may appear isoactive with the adjacent parenchyma in the dynamic phase. During the early blood pool phase, a variable portion of the lesion may reveal some degree of activity accumulation.

2. While peripheral contrast enhancement is found frequently with cavernous haemangioma on dynamic bolus CT imaging (Freeny and Marks, 1986*b*), peripheral followed by centripetal filling is rarely seen with blood pool scintigraphy, but when demonstrated is highly suggestive if not

pathognomonic, of hepatic cavernous haemangioma (El Desouki *et al.*, 1991; Kim *et al.*, 1987; Drane and Weatherby, 1988). The reason for the discrepancy between these techniques is due to fundamental differences between planar (blood pool) and cross sectional (CT) imaging. Planar imaging of a peripherally filling spherical mass would show activity throughout the mass, because the surface of the mass is presented *en face* to the camera, as opposed to the true cross sectional visualization seen with CT imaging (Drane and Weatherby, 1988). In a sufficiently large haemangioma, greater superimposition of the marginal than the central activity may render an appearance of greater detectable activity in the outer margin than in the centre of the lesion on planar scintigraphy. The pattern of fill-in also appears to be size dependant, with larger lesions (greater than 10-11 cm) revealing peripheral followed by centripetal filling and smaller lesions equilibrating uniformly (Groshar *et al.*, 1992; Lisbona *et al.*, 1989). Single photon emission computerized tomography (SPECT) is not expected to increase the detection of early peripheral and progressive centripetal filling, in spite of its cross sectional nature, principally because SPECT imaging is usually performed at 60-120 minutes post-injection, at which stage the greatest amount of admixture and central filling has already been attained (Drane and Weatherby, 1988).

3. The uncommon *atypical* appearance of HCH consists of increased activity either in the early (arterial) or the mid dynamic phase, usually in a small portion of the haemangioma, but occasionally involving most of the lesion (Front *et al.*, 1984; Brodsky *et al.*, 1987). Usually the atypical appearance is associated with unchanging or increasing activity intensity from the dynamic through to the delayed blood pool phase (Larcos *et al.*, 1989). It is unclear why some haemangiomas demonstrate increased early activity in addition to progressive or persistent heightened blood pool activity, but it may be related to the presence of larger less tortuous sinusoidal cavernous spaces or arteriovenous communications within the haemangioma, which may permit rapid ingress of radioactive blood, yet with sufficiently delayed outflow to allow activity to persist in the delayed blood pool. Hardoff *et al.* (1989) described a reversing vascular pattern, whereby a small central portion of a haemangioma revealed increased arterial flow initially and reduced blood pool activity subsequently, while the periphery of the lesion revealed decreased arterial flow initially and

increased blood pool activity subsequently. This pattern suggests the presence of a separate blood supply with larger diameter vessels of lesser tortuousity in the central portion surrounded by the usual tortuous cavernous spaces.

False positive blood pool scintigraphy - hepatocellular carcinoma and metastases

While hepatocellular carcinoma and some vascular metastases may demonstrate increased activity in the perfusion and immediate blood pool phases, they usually demonstrate isoactivity or hypoactivity relative to adjacent liver parenchyma in the late blood pool phase (Front *et al.*, 1984; Swayne *et al.*,1991; Kudo *et al.*, 1989; Rabinowitz *et al.*, 1984). Four cases of hepatocellular carcinoma with increased activity in the perfusion and the late blood pool phases, are described in the literature (Intenzo *et al.*, 1988; Rabinowitz *et al.*, 1984; Drum, 1982). Conversely, none of the 46 hepatocellular carcinomas in the study of Kudo *et al.* (1989), had delayed blood pool activity on planar or SPECT imaging. One case of metastatic colon carcinoma and one of metastatic adenocarcinoma, both with increased activity relative to adjacent parenchyma on delayed SPECT have been reported, but in both cases, the labelled erythrocyte accumulation is considered to have occurred in immediately adjacent areas of focal sinusoidal dilatation and congestion, rather than in the metastasis itself (Swayne *et al.*, 1991; Ali *et al.*,1994). These non-specific reactive changes are commonly seen in the vicinity of space-occupying hepatic lesions (Gerber *et al.*, 1986).

Decreased perfusion was not present in any of the hepatocellular carcinomas or metastases described in the literature demonstrating false positive increased activity in the late blood pool phase. This substantiates the consensus in the literature that the presence of such a perfusion blood pool mismatch is considered pathognomonic for HCH. These tumours revealed increased (the hepatocellular carcinomas) and normal (the metastases) perfusion, but lesion activity which was increased in the late blood pool phase, a pattern which may be confused with that of a hepatic cavernous haemangioma. When increased perfusion is present in a lesion, the observation of clearly progressive accumulation of activity over time from the perfusion to the late blood pool phase, may help distinguish between an atypical haemangioma and a hepatocellular carcinoma or vascular

metastasis (Larcos *et al.*, 1989; Drane, 1991). Owing to the nature of the (slow) portal blood supply and prolonged mixing phase of haemangiomas as opposed to the hepatic arterial supply of hepatocellular carcinoma, quantitative analysis (by the utilization of time activity curves obtained from a region of interest around the lesion) of early and late blood pool phase activity intensity may improve accuracy, but requires further validation (Moinuddin *et al.*, 1985).

False positive blood pool scintigraphy - angiosarcoma

Ginsberg *et al.* (1986) reported an angiosarcoma which presented with an early blood pool - late blood pool mismatch, thereby mimicking the appearance of hepatic cavernous haemangioma. He postulated that the scintigraphic features may have occurred due to histological similarities between the highly vascularized angiosarcoma and hepatic cavernous haemangioma.

False negative blood pool scintigraphy - isoactive lesion pattern of HCH

A pattern of blood pool isoactivity may occur in patients with HCH if the lesion is small (< 2 cm), deep seated location, or if partial thrombosis, infarction or fibrosis is present. The low tracer concentration in the lesion leads to poor resolution because of high background activity inherent in blood pool studies (Engel *et al.*, 1983; Rabinowitz *et al.*, 1984). While blood pool scintigraphy may be negative in the presence of HCH, primary or metastatic carcinoma of the liver usually give an isoactive blood pool image (Engel *et al.*, 1983; Taylor *et al.*, 1976). An isoactive late blood pool image obtained in the presence of a known mass lesion, therefore indicates the need for further investigation.

False negative blood pool scintigraphy - hypoactive lesion pattern of HCH

When a liver haemangioma is largely replaced by thrombosis, infarction or fibrosis, an area of persistent hypoactivity or a mixed pattern of photopaenia with focal areas of increased activity contained therein, may be seen on blood pool images (Karimeddini and Klein, 1991; Intenzo *et al.*, 1988; Rabinowitz *et al.*., 1984). Either pattern requires further investigation to distinguish a complicated haemangioma from hepatocellular carcinoma or vascular metastasis with variable irregular necrosis and patchy late pooling.

Differentiation of HCH from other lesions

Focal nodular hyperplasia and hepatic adenomas usually reveal normal or increased activity in the early perfusion phase, with activity equal to adjacent parenchyma in the blood pool phase.

SPECT blood pool scintigraphy

Planar hepatic blood pool scintigraphy is thought to be a sensitive, specific and reliable technique for the evaluation of hepatic haemangioma and in distinguishing these from other benign and malignant hepatic lesions (Brunetti *et al.*, 1988; Farlow *et al.*, 1990; Front *et al.*, 1981; Rabinowitz *et al.*, 1984). The SPECT technique may be more accurate than planar scintigraphy where haemangiomas are extensively fibrosed, and little pooling of labelled erythrocytes occurs (Rabinowitz et al., 1984), and in detecting small, deeply situated cavernous haemangiomas (Langsteger *et al.*, 1989; Tumeh *et al.*, 1987; Intenzo *et al.*, 1988; Brodsky *et al.*, 1987; Drane, 1991; Rubin and Lichtenstein, 1993), and/or where small haemangiomas are obscured by adjacent normal vascular structures (Brunetti *et al.*, 1988).

SPECT provides two major advantages over conventional planar imaging (Keyes, 1989):

Improved image contrast is achieved by SPECT, as superimposed tissue activity is removed (Keyes, 1989; Guze and Hawkins, 1989; Tumeh *et al.*, 1987; Brodsky *et al.*, 1987; Bonnano *et al.,* 1991; Intenzo *et al.*, 1988; Langsteger *et al.*, 1989; Malik, 1987). The smallest haemangioma identified on SPECT was 1.4 cm and by planar imaging 1.7 cm (Kudo *et al.*, 1989).

SPECT has a low sensitivity for detecting lesions smaller than 10-15 mm and planar imaging lesions less than 25-40 mm. (Langsteger *et al.*, 1989).

Advances in SPECT imaging techniques include dynamic three view display, high resolution SPECT and dynamic SPECT. Dynamic three view display is superior to conventional static display (Krause *et al.*, 1993), while high resolution three headed SPECT may allow visualization of 20-30% of haemangiomas of 0.5 - 1.3 cm in diameter (Ziessman *et al.*, 1991). Small haemangiomas (### 5 mm) may be difficult to distinguish from normal vascular anatomy and variation in hepatic blood pool background (Drane, 1991). Dynamic three headed SPECT, with sequential acquisitions over time, permits the visualization of cavernous haemangiomas 5 mm in diameter while avoiding confusion over normal vascular anatomy, and the calculation of peak filling rates. This method combines the increased sensitivity of high resolution SPECT with the increased specificity and characterization value of analyzing progressive RBC accumulation (Drane, 1991).

Correlation of SPECT with other cross sectional imaging modalities such as ultrasound and CT imaging, particularly in the evaluation and precise anatomic location of small lesions (Brunetti *et al.*, 1988; Brodsky *et al.*, 1987; Birnbaum *et al.*, 1990), is also better. The SPECT technique may, in addition, give better resolution of the size, relative position, anatomy and the delineation of small lesions adjacent to vascular structures, by virtue of its ability to provide a three dimensional map of liver tracer distribution (Guze and Hawkins, 1989; Brunetti *et al.*, 1988; Oyamada *et al.*, 1984; Brodsky *et al.*, 1987; Birnbaum *et al.*, 1990; Ziessman *et al.*, 1991). The three dimensional image is obtained because the gamma camera collects data from a volume, and not a single slice, as is the case in conventional transmission X-ray and computerised tomographic (CT) techniques (Keyes, 1989; Brunetti *et al.*, 1988). The three dimensional resolution of SPECT also improves correlation of scintigraphy with CT and ultrasound techniques, allowing precise localisation of lesions (Guze and Hawkins, 1989; Brunetti *et al.*, 1988; Oyamada *et al.*, 1984; Brodsky *et al.*, 1987; Birnbaum *et al.*, 1990; Ziessman *et al.*, 1991).

Sensitivity of ^{99m}Tc blood pool scintigraphy for HCH

The reported sensitivity for detection of HCH by planar blood pool scintigraphy varies between 33 and 89% depending on the size of the lesion (Brunetti *et al.*, 1988; Engel *et al.*, 1983; Kudo *et al.*, 1989; Langsteger *et al.*, 1989; Malik, 1987; Rabinowitz *et al.*, 1984; Farlow *et al.*, 1990; Tumeh *et al.*, 1987). Sensitivity was 16 - 50% for lesions smaller than 3 cm (Langsteger *et al.*, 1989; Malik, 1987; Kudo *et al.*, 1989) and 10% for lesions smaller than 1.5 cm (Brunetti *et al.*, 1988).

Reported sensitivity for SPECT blood pool scintigraphy varies between 58 and 100% (Brunetti *et al.*, 1988; Kudo *et al.*, 1989; Langsteger *et al.*, 1989; Malik, 1987; Farlow *et al.*, 1990; Tumeh *et al.*, 1987; Birnbaum *et al.*, 1990), with up to 92% of lesions smaller than 3 cm (Langsteger *et al.*, 1989; Malik, 1987) and 28% of lesions smaller than 1.5 cm (Brunetti *et al.*,1988) being detected. Kudo *et al.* (1989) found a sensitivity of 85% for lesions larger than 1.4 cm. Ziessman *et al.* (1991), demonstrated improved sensitivity with high resolution three-headed SPECT over previously reported results obtained with single-headed SPECT, and improved ability to detect small hepatic cavernous haemangiomas. Sensitivities of 100% for lesions greater or equal to 1.4 cm, 33% for lesions 0.9 -1.3 cm and 20% for lesions smaller than 0.8 cm were demonstrated, while the smallest lesion visualized was 0.5 cm.

Planar and SPECT blood pool scintigraphy (Langsteger *et al.*, 1989; Malik, 1987) have similar sensitivity for lesions > 3 cm.

Specificity of ^{99m}Tc blood pool scintigraphy for HCH

Of critical importance in the investigation of HCH, is the specificity of the test used in diagnosis. A false positive diagnosis of HCH as a benign lesion which usually does not require further treatment, may result in further investigation and management being stopped. Specificity of the test for HCH is thus of greater importance than sensitivity, as a false negative test for HCH will lead to further investigation, if clinically indicated.

Despite the clear clinical importance of test specificity in HCH, all studies on the diagnostic accuracy of red-cell labelled blood pool scintigraphy done to date, have examined surprisingly few patients with lesions other than

haemangiomas. Clearly, if only HCH lesions are studied, only HCH will be detected, and test specificity will be 100%. Bayesian analysis (Patrick, 1979) clearly shows that the specificity of a test is dependant on the pre-test probability of the lesion being present and that the probability of a false positive result is directly proportional to the number of non-haemangiomatous cases studied. In addition, it is critical to avoid diagnosing HCH exclusively on the basis of a positive scintigraphic test. This bias was introduced in some of the studies of the accuracy of scintigraphy in HCH. The specificity and positive predictive value reported in the literature for planar and SPECT blood pool scintigraphy are 100% (Engel *et al.*, 1983; Brunetti *et al.*, 1988; Krause *et al.*, 1993; Intenzo *et al.*, 1988; Farlow *et al.*, 1990; Tumeh *et al.*, 1987; Kudo *et al.*, 1989; Ziessman *et al.*, 1991). In these studies, the number of haemangiomas detected ranged between 11 and 108 (mean 36) and the number of patients between 9 and 77 (mean 26.5) respectively. Proportionately fewer non-HCH lesions were studied, with a range of 5 to 46 (mean 18.6), in 5 to 29 patients (mean 14) respectively. The study with the largest non-haemangiomatous lesion group was that of Kudo *et al.* (1989) - 29 patients with a total of 46 hepatocellular carcinomas, as opposed to 77 patients with a total of 108 haemangiomas. The small numbers of control patients means that the specificity of scintigraphy has never been adequately tested. In addition, in the studies by Engel et al (1983), Intenzo et al (1988), Kudo et al (1989) and Ziessman et al (1991), it is not clear that patients who received a diagnosis of HCH by scintigraphy, had this diagnosis confirmed by other means. It is thus not clear from these studies whether patients with non-HCH lesions were included in the HCH group. This would also give a falsely high specificity for the test.

INVESTIGATION WITH OTHER RADIONUCLIDES

^{99m}Tc Sulphur Colloid (SC)

The appearance of cavernous haemangioma, metastasis, hepatoma and the vast majority of hepatic adenomas on ^{99m}Tc sulphur colloid scintigraphy, is that of a photopaenic defect, thus rendering differentiation difficult (Drane *et al.*, 1987; Antar *et al.*, 1989; Kerlin *et al.*, 1983; Lubbers *et al.*, 1987). The double sequential in vivo labelling of the reticuloendothelial system and of erythrocytes, provides high accuracy detection of haemangiomas as focal defects on the colloid scintigraphy that subsequently fill in with labelled erythrocytes (Piga *et al.*, 1990).

Focal nodular hyperplasia may reveal decreased (in up to 30% of cases), normal or increased activity uptake (Drane *et al.*, 1987; Welch *et al.*, 1985; Rogers *et al.*, 1981). Intense colloid uptake, seen in 10% of cases, is specific for focal nodular hyperplasia (Piers *et al.*, 1980).

^{99m}Tc Diisopropyldiacetic Acid (DISIDA)

Metastases and cavernous haemangiomas appear as photopaenic defects on ^{99m}Tc-DISIDA scintigraphy, although the latter may appear isoactive in the early images due to the amount of tracer activity present in the enlarged blood pool (Drane *et al.*, 1987; Lecklitner and Dornbluth, 1985; Makler *et al.*, 1983).

Hepatoma is usually photopaenic in the early part of the study (first 30 min), but may reveal uptake on the 1-5 hour delayed images without washout occurring. Focal nodular hyperplasia and hepatic adenoma reveal uptake and accumulation with poor washout and without washout respectively (Drane *et al.*, 1987).

^{99m}Tc Diethylenetriaminepentaacetic Acid (DTPA)

Accumulation of ^{99m}Tc-DTPA in hepatic cavernous haemangiomas, probably a reflection of the enlarged blood pool, has been identified incidentally on renal scintigraphy (Moreno *et al.*, 1987; Cabahug *et al.*, 1989).

^{99m}Tc Methylenediphosphonate (MDP)

Hepatic cavernous haemangiomas, occasionally accumulate ^{99m}Tc-MDP either on the basis of expanded and uncleared blood pool activity or septal calcification (Burkhalter *et al.*, 1986; Le Bel *et al.*, 1988). Hepatocellular carcinoma has also been shown to accumulate ^{99m}Tc-MDP on the basis of calcification, or in the absence of demonstrable microscopic or macroscopic calcification, on the basis of other, as yet poorly elucidated and probably multiple, pathophysiological factors operative in neoplasms (Desai, 1983).

Gallium 67-Citrate

Liver cavernous haemangiomas appear photopaenic on Gallium scintigraphy (Drane *et al.*, 1987). Metastases are photopaenic in about 50% of cases, most of the remainder revealing uptake similar to normal liver tissue, while occasionally metastases, including malignant melanoma and diffuse histiocytic lymphoma, may demonstrate increased activity uptake (Drane *et al.*, 1987). Most hepatomas have gallium uptake equal to or greater than that of adjacent liver tissue (Cornelius and Atterbury, 1984; Drane *et al.*, 1987). Focal nodular hyperplasia may reveal isoactivity or hyperactivity but photopaenic lesions do occur, while the patterns of activity uptake in hepatic adenoma are variable and poorly studied (Drane *et al.*, 1987).

INVESTIGATION WITH OTHER IMAGING MODALITIES

Ultrasound (US)

The increased availability of real-time ultrasound has led to increased detection of benign focal liver lesions, particularly hepatic haemangiomas (Lipman and Tumeh, 1990). The classic sonographic appearance of the liver haemangioma is that of a homogeneously hyperechoic lesion with a well-defined and smooth margin (Birnbaum *et al.*, 1990; Reading et al., 1988; Tumeh *et al.*, 1987). Although this typical appearance is seen in 50 - 60% of cases and sensitivities of 83 - 100 % are reported, the specificity is relatively low (Sandler *et al.*, 1981; Bree *et al.*, 1983; Prakash *et al.*, 1987). The differential diagnosis of solitary, homogeneous hyperechoic lesions includes metastases, hepatocellular carcinoma, hepatic adenoma and focal nodular hyperplasia (Bree *et al.*, 1983; Birnbaum *et al.*, 1990; Sandler *et al.*, 1981; Green *et al.*, 1977; Kamin and Bernadino 1979; Scheible and Gosink, 1977; Taylor *et al.*,1987).

The echogenicity of hepatic cavernous haemangioma results from the multiple interfaces between the walls of the cavernous sinuses and the contained blood. Most haemangiomas measure less than 2 cm in diameter and in this size usually have a typical appearance. The internal architecture, however, differs in larger lesions and may be complicated by haemorrhage, thrombosis, myxomatous change, fibrosis and calcification (Lipman and Tumeh, 1990). These changes alter the sonographic pattern, producing variable echogenicitiy, hypoechoic and occasionally large anechoic areas, varying degrees of posterior acoustic enhancement attributed to variable vascularity, and acoustic shadows produced by foci of calcification (Birnbaum *et al.*, 1990; Gillebert *et al.*, 1980; Bruneton *et al.*, 1983; Taboury *et al.*, 1983; Prakash *et al.*, 1987).

The ultrasonographic appearance of cavernous haemangioma can be divided into three groups (Wiener and Parulekar 1979; Ohto *et al.*, 1987): (i) hypoechoic; (ii) hyperechoic; and (iii) complex. A diagnosis of haemangioma can only be reliably entertained when a hyperechoic pattern is found, and because of the great variability of the sonographic appearance, ultrasound is not the modality of choice for the diagnosis of hepatic cavernous haemangioma (Mirk *et al.*, 1982; Gandolfi *et al.*, 1991; Rubin and

Lichtenstein, 1993). Pulsed doppler ultrasound may have advantages in the differentiation of haemangioma from hepatocellular carcinoma but does not enable distinction from metastases and has not yet been adequately evaluated (Taylor *et al.*, 1987).

Computer Tomography (CT)

On incremental dynamic bolus CT, the appearance of small (< 1 cm) foci of globular enhancement is suggestive of HCH, analagous to areas of contrast material puddling seen on angiography (and on dynamic contrast enhanced MRI), but sensitivity and specificity of this method still have to be determined (Quin and Benjamin, 1992). To meet the established diagnostic criteria for hepatic cavernous haemangioma, single level, dynamic bolus CT scanning is necessary, in which the liver is first scanned prior to contrast and then repeatedly on the same level after rapid bolus contrast administration. Freeny and Marks (1986*a,* 1986*b*) described a triad of morphological diagnostic criteria for the diagnosis of hepatic cavernous haemangioma:

- Diminished attenuation on non-contrast enhanced scans (excluding lesions arising in a fatty liver);

- Peripheral contrast enhancement during the bolus dynamic phase (using rapid intravenous administration of 150 ml of a 60% contrast medium);

- Complete isodense fill-in on delayed scans obtained up to 60 min following contrast medium administration.

Diminished attenuation on non-contrast scans is found in 96% of haemangiomas (Freeny and Marks, 1986*a;* Freeny and Marks, 1986*b;* Ashida *et al.*, 1987). Haemangioma present in a liver with diffuse fatty infiltration may be isodense or even hyperdense on a pre-contrast scan (Freeny and Marks, 1986*a*). Freeny *et al.* (1986*a*) reported peripheral contrast enhancement during the bolus dynamic phase in 74% of cases. This results from the high early arteriovenous attenuation difference (within the first two minutes following bolus contrast media administration), resulting in enhancement of the lesion periphery, while the lesion centre remains unenhanced; if more delayed scans are obtained, the pattern of enhancement may change from

peripheral to diffuse enhancement or to a mixed or heterogeneous pattern (Freeny and Marks 1986*b*). Freeny and Marks (1986*a*) found fill-in to be absent in 5 of 54 (9.3%) of cases, partial in 11 of 54 (20.4%) cases and complete in 38 of 54 (70.4%).

Freeny *et al.* (1986*a*) found a pattern of peripheral contrast enhancement and complete isodense fill-in, in 54% of the haemangiomas in their study, while Freeny and Marks (1986*b*) found all three diagnostic criteria in 55% of the haemangiomas studied, indicating a significant loss of sensitivity. If more liberal criteria for the CT diagnosis of haemangioma had been used (such as central or mixed patterns of contrast enhancement or incomplete isodense fill-in with central clefts), the sensitivity certainly would have been increased but at the expense of a loss of specificity, resulting in metastases being diagnosed incorrectly as haemangiomas (Freeny and Marks, 1986*a*; Bree *et al.*, 1987). Specificity is also hampered by the appearance of some hepatomas and metastases as hypodense lesions with centripetal contrast enhancement (Barnett *et al.*, 1980; Burgener and Hemlin, 1983).

Ashida *et al.* (1987) expanded the criteria to five, including progressive centripetal opacification, a delay of at least 3 minutes before total opacification, and isodense fill-in with or without non-opacified clefts. 79% of lesions fulfilled all five criteria, but if the data is applied to the classic (three criteria) model of Freeny and Marks, only 45% of the lesions would be diagnosed as cavernous haemangiomas (Lipman and Tumeh, 1990).

Further complicating the CT diagnosis of haemangioma is the presence of central fibrosis, thrombosis and haemorrhage, which results in delayed or absent central opacification and the presence of non-enhancing central clefts in large haemangiomas (Johnson *et al.*, 1981; Scatarige *et al.*, 1987; Ashida *et al.*, 1987). Small lesions may be difficult to study dynamically owing to respiratory artifact, while characterization of multiple lesions is tedious and could even be hazardous as safe dosages of contrast material may be exceeded (Farlow *et al.*, 1990; Brodsky *et al.*, 1987).

Hepatic angiosarcoma can reveal findings similar to those of cavernous haemangioma on dynamic CT, angiography and MRI (Itai and Teraoka, 1989).

In summary, rapid bolus contrast enhanced CT scans are less sensitive and specific than SPECT blood pool scintigraphy in the diagnosis of hepatic cavernous haemangiomas. The latter is also cheaper and easier to perform (especially when several lesions are present), and can be safely applied in patients with contrast agent intolerance and in hyperthyroid patients (Moinuddin *et al.*, 1985; Front *et al.*, 1984; Langsteger *et al.*, 1989).

Magnetic Resonance Imaging (MRI)

MRI has emerged as an accurate and safe, though expensive method for the diagnosis of hepatic cavernous haemangioma (Stark *et al.*, 1985).

Haemangiomas classically appear as homogeneous lesions of high signal intensity on T2-weighted images (Wittenberg *et al.*, 1988). Since fluids have a long T2 value and the haemangioma is essentially a lake of flowing blood, these lesions are more distinctive on long echo time (TE) T2-weighted sequences, and Stark *et al.* (1985), using a multi-echo technique, found a TE of 120 ms to yield the most useful images. However, all hepatic neoplasms become hyperintense relative to adjacent liver on T2-weighted images, so that it is the degree of hyperintensity (the so-called light bulb sign) that is characteristic of haemangioma (Ziessman *et al.*, 1991; Itai *et al.*, 1985). A mean T2 time greater than 80 m sec is reported to be characteristic of hepatic cavernous haemangioma, at both 0.35 and 1.5 Tesla field strength, and sensitivities of 83-90 % (specificities of 95-98 %) have been reported in series of patients based purely on T2-weighted properties (Itai *et al.*, 1985; Ohtomo *et al.*, 1985; Ohtomo *et al.,* 1988). In addition to haemangiomas being brighter than hepatocellular carcinoma on T2-weighted images, the signal intensity increase from T1- to T2-weighted images is greater for haemangioma than for hepatocellular carcinoma (Ho *et al.*, 1992). In addition to a long T2 value, the homogeneity and sharp margins of haemangioma on MRI images help to distinguish this lesion from malignant disease (Stark *et al.*, 1985). However, inhomogeneity in haemangiomas produced by fibrosis, thrombosis and ossification, would result in a less typical appearance (decreased T2 value) while liquefaction or necrosis in a hepatoma could produce an image simulating a haemangioma (i.e. increased T2 value) (Ros *et al.*, 1987). Hepatocellular carcinoma with dense acinar formation (pseudoglandular type) is associated with T2 prolongation based on the

abundant intra-acinar fluid, and this could render differentiation from haemangioma difficult (Ohtomo *et al.*, 1990).

Differentiation of haemangioma from certain hypervascular metastases, such as metastatic carcinoid, phaeochromocytoma, islet cell tumour, adenocarcinoma of the pancreas uterus and lung, and vascular sarcomas may be difficult, since they may also appear as homogeneous, hyperintense lesions on T2-weighted images (Wittenberg *et al.*, 1988; Li *et al.*, 1988; Birnbaum *et al.*, 1990). Successful differentiation of haemangiomas from metastases may be possible utilizing T2 calculations with ultra fast MRI as opposed to conventional MRI T2-weighted imaging (Goldberg *et al.*, 1991; Lombardo *et al.*, 1990). Successful differentiation may also be demonstrated with a combination of a dynamic MRI study and delayed post contrast T1-weighted imaging (Hamm *et al.*, 1990).

On MRI imaging with intravenous injection of gadolinium-DTPA, haemangiomas are characterised by a hypointense appearance before injection, followed by peripheral intensity enhancement after injection and by subsequent progressive hyperintense fill-in and hyperintensity in the late phase; it is suggested that dynamic contrast enhanced MRI is an effective method to facilitate the differential diagnosis when pre-contrast T2 weighted images are equivocal (Olivetti *et al.*, 1992; Ho *et al.*, 1992; Murakami *et al.*, 1992).

MRI imaging has a greater sensitivity than ^{99m}Tc blood pool SPECT with a slightly greater overall accuracy, particularly in the detection of haemangiomas smaller than 2 cm in diameter and in the detection of haemangiomas smaller than 2.5 cm that are adjacent to the heart or major intrahepatic blood vessels (Birnbaum *et al.*, 1990; Itai *et al.*, 1985). The specificity of MRI for haemangiomas is thought to be good, despite the inability to categorically differentiate haemangiomas from hypervascular metastases. The main contraindication to its wide use, is the high cost, and SPECT may be useful in the diagnosis of haemangiomas larger than 2 to 2.5 cm in diameter (Birnbaum *et al.*, 1990; Li *et al.,* 1988). MRI may serve as a complementary technique for the non-invasive characterization of haemangiomas demonstrating an atypical scintigraphic appearance and considered to be indeterminate (Birnbaum *et al.*, 1990).

Angiography

Traditionally considered the gold standard, angiography is both sensitive and specific for the diagnosis of hepatic cavernous haemangioma, but is an invasive procedure and requires the use of contrast materials (Johnson *et al.*, 1981). With the availability of accurate non-invasive modalities, there is a limited role for angiography in the evaluation of liver cavernous haemangioma, reserved for diagnostically equivocal cases and for preoperative assessment where it provides vital hepatic vascular anatomic information (Bornman *et al.*, 1987).

The classic angiographic appearance of haemangioma (Freeny *et al.*, 1979; Freeny, 1983; McLoughlin, 1971) includes:

- The main hepatic artery and its branches are of normal calibre, but may be displaced to one side and crowded together.
- The feeding vessels are of normal calibre and taper normally to form a fine vascular network within the haemangioma, but the individual vessels have a normal appearance
- Arteriovenous shunts and draining veins are rare and there is no tumour neovascularity
- During the early arterial phase, small lakes of contrast media accumulate around the periphery of the lesion, forming a C- or ring-shaped configuration.
- The contrast material in the vascular spaces persists throughout the capillary and late venous phases.

Atypical angiographic features may be encountered in liver haemangiomas:

- Arterioportal shunting, usually an angiographic finding pathognomonic of malignancy and commonly present in angiosarcoma. However this may occasionally be present in haemangioma (Ando *et al.*, 1984; Winograd and Pulabinskas, 1977; Weiler *et al.*, 1992; Shima *et al.*, 1989);

- Diffuse intense contrast enhancement may be present (Mikulis *et al.*, 1985).

Angiography may occasionally be normal even in the presence of symptomatic haemangioma, and lesions in the left lobe overlying the spine may be difficult to visualize on angiography (Davis *et al.*, 1990; Bornman *et al.*, 1987). Selective left hepatic arteriography, although requiring special expertise in technique and interpretation, or intra-arterial digital subtraction, may be of value in the evaluation of lesions in the left lobe (Flauniger *et al.*, 1983).

NON-IMAGING INVESTIGATIVE MODALITIES

Biopsy

Biopsy of hepatic cavernous haemangioma and haemangioendothelioma with needles of outside diameter greater than 1 mm is associated with a relatively high risk of serious or even fatal haemorrhage (Kato *et al.*, 1975; Zamcheck and Klausenstock 1953; Haaga and Vane, 1979; Walt 1977; Karpas and Pavon, 1971). As a result, biopsy of hepatic cavernous haemangioma with large bore needles is contraindicated (Solbiati *et al.*, 1985).

In contrast biopsy of liver cavernous haemangioma with fine needles of outside diameter less than 1 mm under ultrasonographic guidance, has shown adequate results with no significant risk to the patient, provided that subcapsular lesions are biopsied through interposed liver tissue and not by a direct route (Spamer *et al.*, 1986; Solbiati *et al.*, 1985; Taavitsainen and Kivisaari, 1987; Cronau *et al.*, 1988; Bree *et al.*, 1983; van Sonnenberg *et al.*, 1981). Terriff *et al.* (1990), however, reported a fatality following fine needle aspiration biopsy of a hepatic cavernous haemangioma.

The criteria to establish a diagnosis of liver cavernous haemangioma are the aspiration of fresh blood and endothelial cells and/or agglomerates of capillaries (Solbiati *et al.*, 1985; Bree *et al.*, 1983). However, fine needle aspiration biopsy lacks specificity and biopsies of other malignant vascular tumours such as haemangiosarcoma and hepatocellular carcinoma, with histology mimicking cavernous haemangioma, have been documented (Bornman *et al.*, 1987). Fine needle aspiration biopsy is said to have a high accuracy in some hands (Cronau *et al.*, 1988; Xu, 1989; Kaw and Esparza, 1991; Nakaizumi *et al.*, 1990).

Laparoscopy

Laparoscopy may be useful in the diagnosis of haemangioma when the lesion is subcapsular, especially in the presence of a palpable mass. Although this may prove useful in selected cases, the depth and extent cannot be determined, and the presence of fibrosis and/or necrosis in the haemangioma may give an atypical laparascopic appearance (Kato *et al.*, 1975; Ando *et al.*, 1984).

TREATMENT

Asymptomatic haemangiomas

The asymptomatic incidentally discovered cavernous haemangioma can safely be observed with serial studies as long as the lesion is small (< 2 cm in diameter) and the diagnosis of HCH is reasonably certain. The risk of unmanageable growth and spontaneous haemorrhage is small compared with the low but significant morbidity and potential mortality attendant a prophylactic resection (Iwatzuki *et al.*, 1990; Starzl *et al.*, 1980; Reading *et al.*, 1988; Trastek *et al.*, 1983; Andersson and Bengmark, 1988; Schwartz and Husser, 1987; Adam *et al.*, 1970; Trastek *et al.*, 1983). Alteration of the character or size of the lesion requires thorough reinvestigation with appropriate reassessment of the management strategy (Iwatzuki *et al.*, 1990; Starzl *et al.*, 1980). Alternatively, in the presence of an equivocal diagnosis, hepatic resection may be indicated as the risk of missed diagnosis of cancer should not be underestimated (Lise *et al.*, 1992; Iwatzuki *et al.*, 1990; Starzl *et al.*, 1980). This finding supports our contention that studies of the specificity of scintigraphy have been inadequate. Resection should also be considered in asymptomatic cases at diagnostic laparotomy, provided that the haemangioma location is amenable to resection with minimal risk, but asymptomatic lesions requiring major surgery should be treated expectantly (Bornman *et al.*, 1987).

Symptomatic and/or large haemangiomas

Large haemangiomas (larger than 4 cm in diameter) may be considered for resection in some individuals, even when asymptomatic, owing to the increased incidence of central necrosis, acute haemorrhage into the lesion and possible rupture, either spontaneous or induced by blunt abdominal trauma (Reading *et al.*, 1988; Vishnevsky *et al.*, 1991; Riesener *et al.*, 1990*a*; Nichols *et al.*, 1989; Kanazawa *et al.*, 1990). Large symptomatic haemangiomas are treated effectively and safely by excisional therapy, with relief of symptoms in the majority of cases, a low operative morbidity and a zero operative mortality rate for elective surgery (Starzl *et al.*, 1980; Iwatzuki *et al.*, 1990; Schwartz and Husser, 1987; Adam *et al.*, 1970; Kawarada and Mizumoto, 1984; Yamagata *et al.*, 1991; Riesener *et al.*, 1990*b*). Thus, the

majority of patients with symptomatic and complicated haemangiomas are treated with hepatic resection, except when a significant risk is present due to difficult anatomic location, or systemic disease, where continued conservative treatment is appropriate (Bornman *et al.*, 1987; Starzl *et al.*, 1980). During formal lobar or segmental resection, the intraoperative blood loss can be extensive and it is essential that major vessels entering or leaving the specimen are controlled before the parenchymal resection is begun (Starzl *et al.*, 1980; Schwartz and Husser, 1987).

An alternative to resection is enucleation through dissection along the fibrous capsule or compressed adjacent parenchyma, with direct control of blood vessels entering or leaving the haemangioma and without resection of normal adjacent liver parenchyma (Alper *et al.*, 1988; Adson, 1986).

Hepatic arterial embolization may improve symptoms, but rarely reduces the size or subsequent vascularity of the haemangioma; and may be associated with necrosis and secondary infection of the lesion (Allison *et al.*, 1985; Reading *et al.*, 1988; Bornman *et al.*, 1987; Trastek *et al.*, 1983). Hepatic arterial ligation may similarly reduce symptoms, but precludes future embolization should revascularisation of the haemangioma cause a recurrence of symptoms (Nishida *et al.*, 1988; Reading *et al.*, 1988). Both hepatic arterial embolization and ligation may control acute bleeding (Yamamoto *et al.*, 1991) and give symptomatic relief, but these procedures should be reserved for selected cases (Hobbs, 1990).

Radiotherapy has historically been used in the management of non-resectable haemangioma of the liver (Park and Phillips, 1970, McKay *et al.*, 1989), but the lack of objective evidence of benefit and the risks of radiation hepatitis, have largely precluded its further use (Trastek *et al.*, 1983; Reading *et al.*, 1988).

Chapter 2

PATIENTS, MATERIALS AND METHODS

PRIMARY AIM

To assess the specificity of ^{99m}Tc labelled erythrocyte blood pool scintigraphy (incorporating radionuclide angiography, planar and SPECT imaging) in the diagnosis of hepatic cavernous haemangiomas by including adequate numbers of control patients with hepatic mass lesions not due to HCH.

SECONDARY AIMS

1. To establish the sensitivity of planar and SPECT imaging in the diagnosis of HCH at Groote Schuur Hospital.

2. To describe the *appearances* of hepatic mass lesions on Technetium labelled erythrocyte scintigraphy.

3. To establish if SPECT provides additional information over planar imaging in the investigation of hepatic mass lesions.

STUDY DESIGN

Forty five patients (21 male, 24 female), aged 21 to 75 years (mean 54 years) presenting to the liver and hepatobiliary clinics at the Groote Schuur Hospital between January 1991 and December 1992, were prospectively studied following demonstration of solitary or multiple focal hepatic mass lesions (excluding hydatid cysts) on ultrasonography and/or computed tomography. Patients were fully prospectively evaluated by clinical and radiological investigations, including various combinations of magnetic resonance imaging, contrast enhanced bolus CT scans, angiography, aspiration cytology and/or biopsy or surgical resection. All patients also underwent hepatic ^{99m}Tc erythrocyte scintigraphy.

Final diagnosis

All patients had a diagnosis based on clinical and non-scintigraphic studies to avoid introducing bias in the case of positive scintigraphic studies. The final clinical diagnosis was used as the reference against which the results of scintigraphy were compared.

The usual process followed to establish the diagnosis was evaluation of clinical, biochemical and ultrasonographic data, followed by the evaluation of the radiological data excluding the scintigraphic data and thereafter by the evaluation of follow-up and histological data.

The diagnosis of the hepatic mass lesion based on these criteria was then compared to the diagnosis made by scintigraphy.

Scintigraphic data was evaluated separately by three observers; two were blinded to clinical and other data. Inter-observer variation was established to determine the accuracy of the observations.

Erythrocyte labelling

The labelling of autologous erythrocytes was performed with 900 MBq of ^{99m}Tc pertechnetate by an in vitro technique:

1. A vial of stannous pyrophosphate containing 1,092 mg of $SnCl_2$ and 59,4 mg of $Na_4P_2O_7$ (Atomic Energy Corporation, SA) was reconstituted at room temperature with 10 ml 0.9% sodium chloride solution BP;

2. 1 ml of the reconstituted stannous pyrophosphate solution was diluted in 9 ml of 0.9% sodium chloride solution BP to make up 10 ml;

3. 0.5 ml of the reconstituted diluted stannous pyrophosphate solution was aspirated into a heparinized 20 ml syringe;

4. 10 ml of blood from the patient was then aspirated into this pre-prepared 20 ml syringe;

5. Pre-tinning and centrifugation:

   (a) The blood-heparin-stannous-pyrophosphate mixture was injected into a sterile vial; and

   (b) incubated for 5 min at room temperature while being gently agitated;

   (c) 1 ml of 4.4% EDTA[1] solution was injected into the vial which was gently agitated for 30 seconds;

   (d) then centrifuged for 5 min at 2000 rpm;

   (e) Two millilitres of packed red blood cells were then aspirated from the vial; and

   (f) transferred into a sterile vial containing approximately 1200 MBq ^{99m}Tc pertechnetate;

   (g) This mixture was incubated at room temperature for 10 min while being gently agitated;

   (h) 900 MBq ^{99m}Tc labelled red blood cells were then reinjected into the patient.

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[1] EDTA chelates extracellular free stannous ions, thereby preventing reduction of pertechnetate before it penetrates the erythrocyte membrane (preventing formation of radionuclidic impurities such as Sn:Tc colloid and/or labelled plasma proteins), resulting in improvement of the labelling yield and the in vitro and in vivo stability of the label (Mock and Wellman, 1984; Srivastava and Chervu, 1984)

Radionuclide imaging system

Dynamic, planar and SPECT imaging were performed on the same system (General Electric Starcam 400 AC) consisting of a rotating single head, large field of view (40 cm) Anger camera, equipped with a low energy high resolution parallel-hole collimator. Planar imaging was performed on all 45 patients while SPECT imaging was performed on 41.

Acquisition technique

1. Radionuclide angiography was performed with a framing rate of one frame per second for 90 seconds on a 64 x 64 acquisition matrix in the most appropriate projection, based upon ultrasonographic or CT lesion localization.

2. Planar imaging was performed on a 256 x 256 acquisition matrix with acquisition preset for 1'000'000 counts per image.

   a) Anterior and right lateral images were acquired immediately following the dynamic phase.

      (i) When a lesion was visible on the initial images, an image was acquired in the projection of best visualization (anterior or right lateral) at 7 min post-injection. Thereafter, images were acquired in the anterior, right lateral and posterior projections at 10, 20 and 30 min post-injection.

      (ii) When a lesion was not visible on the initial images, images were acquired in the anterior and right lateral projections at 5 min intervals, starting at 10 min post-injection and continuing until 30 min post-injection. If a lesion became visible during this imaging interval, the imaging protocol reverted to that described under (i).

   b) Images in the anterior, right lateral and posterior projections were acquired at 2 hours post-injection.

3. SPECT was performed at two hours post injection, immediately following acquisition of the two hour planar images. Data was acquired on a 64 x 64 matrix in 64 angular projections over a 360° elliptical rotation, in step and shoot mode, with the patients arms raised above the head. The optimal image projection interval was determined for each patient individually as the time required to reach a mean pixel count of between 180 and 200 in the liver on the anterior projection image.

DATA PROCESSING

1. Summation of the 1 sec/frame dynamic acquisition data to 3 sec/frame images.

2. Reconstruction of SPECT data by an integrated computer system, using software provided by the manufacturer and utilizing a filtered back projection technique. Transverse sections, with a thickness of 1 pixel (0.63 mm) were obtained first and sagittal and coronal section one pixel thick were obtained subsequently.

3. The study was prefiltered using a Hanning filter with a critical frequency of 0,8 cm^{-1} and it was filtered using a back projection ramp filter with a critical frequency of 0,0 cm^{-1}.

IMAGE ANALYSIS AND INTERPRETATION

Scintigraphic image analysis and interpretation (dynamic three view computer display) were performed at the time of investigation by observer 1 (SL) with knowledge of the clinical data and lesion location. Analysis and interpretation (dynamic three view computer display) were performed by observers 2 and 3 at a second stage without knowledge of clinical data, lesion location or final diagnosis.

Criteria for the diagnosis of hepatic cavernous haemangioma:

1. Activity in the lesion must be increased relative to the adjacent hepatic parenchyma on the planar and/or SPECT images in the late blood pool phase (at 2 hours post injection);

   and;

2. Activity in the lesion must have increased or remained constant relative to the adjacent hepatic parenchyma from the dynamic to the late blood pool phase.

Categorization of cavernous haemangiomas according to scintigraphic appearance:

A study was categorized as having a *characteristic* appearance, if the lesion's activity increased relative to adjacent hepatic parenchyma in the late blood pool phase, with or without progressive increase of intensity from early to late blood pool phases. If, in addition, the lesion's activity was decreased relative to adjacent parenchyma in the dynamic phase (early post injection), the study was categorized as being characteristic and typical. If the less common feature of increased lesional activity in the dynamic phase was present, the study was classified as characteristic but atypical.

STATISTICAL ANALYSIS OF SCINTIGRAPHIC RESULTS

True positives were defined as scintigraphic tests in which the scintigraphic studies correctly diagnosed HCH as confirmed by other clinical, radiological and histological studies.

True negative tests were defined as those tests where scintigraphic data correctly identified a lesion as not being HCH.

False positive tests were defined as those where the scintigraphic data incorrectly identified a lesion as being HCH, but where other clinical, radiological and histological data definitively characterised the lesion as not being HCH.

False negatives were defined as tests where scintigraphic data incorrectly identified a lesion as not being a haemangioma, but where other data showed the lesion to be an haemangioma.

Reproducibility of scintigraphic analysis was assessed by measuring inter-observer variability. Each study was interpreted by three observers, two of whom were blinded to all clinical and other radiological data. Inter-observer variability was determined using the Mantel-Haenzel chi-square test.

Chapter 3

RESULTS

PATIENTS

Forty-five patients (21 male), mean age 54 (range 21-75), presenting with focal hepatic mass lesions (HML) were studied.

Of the 45 patients, the final diagnosis was indeterminate in 8, and these patients were excluded from the statistical analysis. Of the remaining 37 patients, clinically 30 haemangiomas were found in 18 patients, while 37 non-haemangiomatous lesions (20 metastatic carcinoma, 11 primary hepatocellular carcinoma, 3 focal nodular hyperplasia, 2 probably malignant liver neoplasms and 1 chronic hepatic abscess), were diagnosed in 19 patients.

Of the 17 patients with HCH who underwent ultrasonography, hyperechoic lesions (typical for HCH) were found in 13 patients (76%), hypoechoic lesions in 1 and complex lesions in 3.

Of the 14 patients with a final diagnosis of HCH who underwent dynamic CT, 8 patients had lesions compatible with HCH, 5 patients had lesions characteristic of HCH, while 1 patient had a lesion not typical of HCH. All lesions in these 14 patients were low density on CT.

MRI was performed in only one patient (final diagnosis of HCH), and revealed features compatible with HCH.

Of the 6 patients who underwent angiography, 1 patient (final diagnosis HCH) revealed features compatible with haemangioma.

HCH was diagnosed by histology in 3 patients (1 by liver biopsy, 2 by resection), whereas in one patient with an initial clinical diagnosis of HCH, liver biopsy revealed features of a lymphangioma.

The control group consisted of 19 patients (Appendix 25).

Eight patients had metastatic liver disease [1 adenocarcinoma breast, 1 adenocarcinoma colon, 1 adenocarcinoma of undetermined origin, 1 carcinoma bronchus, 1 poorly differentiated carcinoma (? melanoma), 1 transitional cell carcinoma, 1 sarcoma, 1 spindle cell tumour (?leiomyosarcoma)]. Seven patients had hepatocellular carcinoma, 1 had a (benign) liver neoplasm, 2 had focal nodular hyperplasia and 1 had a liver abscess.

Of the six patients undergoing angiography, features compatible with focal nodular hyperplasia were found in 1 patient, neovascularity in 2 patients (final diagnosis hepatocellular carcinoma), and hypervascularity in 1 patient (final diagnosis of hepatocellular carcinoma).

Of the 12 patients from the control group undergoing liver aspiration cytology, no malignant cells were found in 3 patients, highly atypical cells were found in 1 (final diagnosis low grade malignancy/HCC), malignant cells compatible with HCC in 3, metastatic carcinoma in 3, metastatic sarcoma in 1 and inflammatory cells compatible with abscess in 1 patient. Liver biopsy was obtained in two patients in the control group, both revealing HCC.

SCINTIGRAPHY

Basic analysis of scintigraphic features (observers I, II, III)

Observer I found 25 haemangiomatous lesions in 18 patients. Observer II found 24 haemangiomatous lesions in 17 patients, and observer III found 18 haemangiomatous lesions in 14 patients. Scintigraphic features typical of HCH were found in 7 patients with hepatic malignancy by observer I (5 hepatocellular carcinomas, 2 metastatic carcinomas), in 6 of these 7 patients by observer II, in 2 patients of these 7 patients by observer III (Tables 1,3). In addition, scintigraphic features characteristic of HCH were found in 1 patient with hepatic abscess (false positive prominent portal vein activity) by observer II and in 1 patient with metastatic sarcoma by observer III (Table 3). Five of the 7 false positive cases had histological or cytological confirmation of the diagnosis, the diagnosis in the remaining two established on clinical and biochemical (alpha fetoprotein) grounds.

TABLE 1. Sensitivity, specificity and diagnostic accuracy of scintigraphy for HCH, according to 3 observers.

STATISTICAL ANALYSIS		Observer I	Observer II	Observer III
True positive (TP)		18	17	14
True negative (TN)		12	12	16
False positive (FP)		7	7	3
False negative (FN)		0	1	4
Specificity / true negative ratio	TN/(TN+FP)	0.632	0.632	0.842
Sensitivity / true positive ratio	TP/(TP+FN)	1.000	0.944	0.778
Positive predictive value	TP/(TP+FP)	0.720	0.708	0.824
Negative predictive value	TN/(TN+FN)	1.000	0.923	0.800
False positive ratio (1-specificity)	FP/(TN+FP)	0.368	0.368	0.158
False negative ratio (1-sensitivity)	FN/(TP+FN)	0.000	0.056	0.222
Accuracy	(TP+TN)/(TP+FP+FN+TN)	0.811	0.784	0.811
Disease prevalence	(TP+FN)/(TP+TN+FP+FN)	0.486	0.486	0.486

TABLE 2. Inter-observer variation

INTEROBSERVER VARIATION	Fischer Test	Mantel-Haenzel Chi-Square Test	Contingency Coefficient
Observer I-II	*p=1.000*	*p=0.861*	0.117
Observer I-III	*p=0.084*	*p=0.175*	0.288
Observer II-III	*p=0.267*	*p=0.233*	0.240

False positive results

The right hand column indicates the total number of patients incorrectly diagnosed by any one of the three observers and the bottom column the total number by each individual observer.

TABLE 3. Lesions diagnosed incorrectly as HCH, by 3 independent observers.

FALSE POSITIVES	I	II	III	*TOTAL*
Hepatocellular carcinoma	5	5	2	*5*
Metastatic carcinoma	2	1	-	*2*
Liver abscess	-	1	-	*1*
Metastatic sarcoma	-	-	1	*1*
TOTAL	*7*	*7*	*3*	

Detailed analysis of scintigraphic features (observer I)

All of the 25 haemangiomatous lesions demonstrated scintigraphically revealed increased activity in the lesion relative to the adjacent hepatic parenchyma in the late blood pool phase, at 1-2 hours p.i. The scintigraphic features of the true and false positive lesions in the dynamic phase are presented in Table 4. In 14 lesions, the dynamic phase revealed normal flow. Activity was decreased in the lesion relative to adjacent hepatic parenchyma in 2 lesions and increased relative to adjacent parenchyma in 5 lesions, in the dynamic phase. A mixed pattern was present as a small area of increased flow either contained within, or situated adjacent to and contiguous with a large area of decreased flow, in 4 lesions. Only one patient with cavernous haemangioma (patient 26) showed peripheral-centripetal filling-in the dynamic phase. In this patient, activity surrounding a large photopaenic area in the right lobe, appeared within 3 seconds of aortic activity and was followed by progressive centripetal fill-in of the greater part of the cold area in the late blood pool phase. All 11 mass lesions in the 5 patients with hepatocellular carcinoma, and all 4 mass lesions in the 2 patients with metastatic disease, which were interpreted as being false positive for HCH,

demonstrated increased activity in the lesion relative to the adjacent hepatic parenchyma in the late blood pool phase. Eight of the 11 hepatocellular carcinoma lesions demonstrated increased perfusion in the dynamic phase.

TABLE 4. Scintigraphic features of the true and false positive lesions in the dynamic phase

TRUE AND FALSE POSITIVES	Normal Perfusion	Decreased Perfusion	Increased Perfusion	Decreased and Increased Perfusion	*TOTAL NUMBER OF LESIONS*	*NUMBER OF PATIENTS*
Cavernous haemangioma	14	2	5	4	*25*	*18*
Hepatocellular carcinoma	3	-	8	-	*11*	*5*
Metastatic carcinoma	4	-	-	-	*4*	*2*

The scintigraphic patterns of the true negative lesions are presented in Table 5. In the 12 patients of the control group with lesions true negative for haemangioma, 4 patients had normal flow and normal blood pool (1 HCC, 2 metastatic carcinoma, 1 liver neoplasm), 1 patient had normal flow and decreased blood pool (metastatic carcinoma), 6 patients had decreased flow and decreased blood pool (1 HCC, 1 metastatic carcinoma, 1 metastatic sarcoma, 1 metastatic spindle cell tumour, 1 abscess, 1 low grade malignancy/FNH) and 1 patient had increased flow and decreased blood pool (FNH). The lesion in one patient (patient 4, final diagnosis of focal nodular hyperplasia), displayed a transient arterial activity blush in the very early dynamic phase, with activity increased relative to adjacent parenchyma, appearing within 5 seconds of aortic activity and becoming isoactive with adjacent parenchymal activity 10 seconds following aortic activity appearance. The planar static images revealed a rounded cold focus corresponding to the site of the preceding arterial blush.

TABLE 5. Scintigraphic patterns - entire group

SCINTIGRAPHIC PATTERNS	Characteristic	Characteristic and typical	Characteristic and atypical	Characteristic with separate typical and atypical lesions	Characteristic with mixed typical and atypical lesions	Normal flow and normal blood pool	Normal flow and decreased blood pool	Decreased flow and decreased blood pool	Increased flow and decreased blood pool	*PATIENT TOTAL*
Cavernous haemangioma	10	-	2	2	4	-	-	-	-	*18*
Hepatocellular carcinoma	1	-	4	-	-	1	-	1	-	*7*
Metastatic carcinoma	2	-	-	-	-	2	1	1	-	*6*
Metastatic sarcoma	-	-	-	-	-	-	-	1	-	*1*
Abscess	-	-	-	-	-	-	-	1	-	*1*
Metastatic spindle-cell tumour	-	-	-	-	-	-	-	1	-	*1*
Focal nodular hyperplasia	-	-	-	-	-	-	-	1	1	*2*
Liver neoplasm (benign)	-	-	-	-	-	1	-	-	-	*1*
Indeterminate	1	1	-	-	-	5	-	1	-	*8*
PATIENT TOTAL	*14*	*1*	*6*	*2*	*4*	*9*	*1*	*7*	*1*	*45*

LEGEND		
Characteristic	**Typical**	**Atypical**
Activity increased in the lesion relative to the adjacent hepatic parenchyma in the late blood pool phase (1-2 hours)	Activity *decreased* in the lesion relative to the adjacent hepatic parenchyma in the dynamic phase	Activity *increased* in the lesion relative to the adjacent hepatic parenchyma in the dynamic phase

The number of lesions demonstrated scintigraphically is presented in Table 6. Twelve patients had solitary haemangiomas while 6 had two haemangiomas. In the control group, solitary lesions were found in 10 patients, two lesions in 2 and more than two lesions in 3, while no lesion was detectable scintigraphically in 4.

TABLE 6. Scintigraphic lesion number

LESION NUMBER	Patients with no detectable lesions	Patients with solitary lesions	Patients with two lesions	Patients with ### two lesions	*TOTAL NUMBER LESIONS*	*TOTAL NUMBER PATIENTS*
Haemangioma group	-	12	6	-	*25*	*18*
Non-haemangioma group	4	10	2	3	*23*	*19*
Indeterminate group	5	1	1	1	*7*	*8*
Entire group	9	23	9	4	*56*	*45*

The location of lesions demonstrated scintigraphically is presented in Table 9. The greater majority of haemangiomas were present in the right lobe (20), whereas lesions in the left lobe totalled only 5. In the control group, the same tendency was found, with 20 lesions present in the right lobe (although 3 of these lesions revealed extension into the medial segment of the left lobe), and 3 lesions in the left lobe.

TABLE 7. Scintigraphic lesion location

LESION LOCATION	Patients with lesions in both lobes	Lesions in (R) lobe	Lesions in (L) lobe medial segment	Lesions in (L) lobe lateral segment	*TOTAL NUMBER LESIONS*	*TOTAL NUMBER PATIENTS*
Haemangioma group	3	20	4	1	*25*	*18*
Non-haemangioma group	3	20	3	-	*23*	*19*
Indeterminate group	-	5	2	-	*7*	*8*
Entire group	6	45	9	1	*56*	*45*

Planar imaging was performed in all 45 patients, SPECT in 41. The results of the comparison between planar versus SPECT imaging obtained from the subgroup where both planar and SPECT imaging were performed, is detailed in Table 8. All 8 cold areas were detected by both modalities. SPECT detected 42 foci of increased activity as opposed to 33 detected by planar imaging. In the haemangioma subgroup, SPECT detected 22, planar imaging 21, while in the non-haemangioma subgroup, SPECT detected 13, planar imaging 10. The differences are not statistically significant (Fischer test, *p=0.801*). In the haemangioma group, four small lesions were seen with greater clarity on the SPECT images and in one patient with an indeterminate final diagnosis, four small hot foci were only visible on the SPECT images.

TABLE 8. Planar versus SPECT imaging

GROUP	Planar	SPECT	*TOTAL NUMBER PATIENTS*
COLD FOCI :			
Entire Group	8	8	*41*
HOT FOCI :			
Haemangioma group	21	22	*16*
Non-haemangioma group	10	13	*17*
Indeterminate group	2	7	*8*
Entire group	33	42	*41*

CASE REPORTS (FALSE POSITIVE LESIONS)

A. Hepatocellular carcinoma

Five patients with hepatocellular carcinoma were misdiagnosed as having cavernous haemangioma (Table 7).

Case 1 (patient 17) presented with a history of alcoholism, loss of weight, right upper quadrant pain and massive hepatomegaly. The AST and ALT were 2x normal and the alpha fetoprotein was > 100 ng/ml (normal = 10 ng/ml). Ultrasonography revealed a single well defined partially encapsulated lesion of mixed echogenicity (complex pattern) 11 cm in diameter, in the right lobe. CT revealed a 15 x 12 cm lesion of mixed density in the right lobe; the dynamic contrast enhanced study was not typical of cavernous haemangioma. Angiography revealed a large hypervascular lesion in the right lobe with bizarre, irregular internal vascularity and neovascularity. Cytology of the liver aspirate demonstrated malignant cells. A diagnosis of hepatocellular carcinoma was made. Scintigraphy demonstrated increased activity in the dynamic phase and in the late blood pool phase. The focal increased activity was present in the superolateral part of the right lobe in the dynamic phase, the activity increasing in intensity over time in the planar images and confirmed in the SPECT images. The activity in the adjacent hepatic parenchyma was inhomogeneous.

Case 2 (patient 18) presented with loss of weight, abdominal pain and ascites with a nodular firm and tender hepatomegaly extending 6 cm below the costal margin. The alpha fetoprotein was > 1000 ng/ml. A diagnosis of HCC was made. Scintigraphy demonstrated increased activity in the late blood pool phase. The perfusion phase revealed an area of increased activity in the inferior part of the right lobe and the medial segment of the left lobe, appearing in the mid to late perfusion phase. In the planar images, areas of activity increased relative to the adjacent parenchymal activity were seen as two contiguous foci inferiorly and one inferolaterally in the right lobe and one focus in the medial segment of the left lobe. The activity in these foci increased slightly in the early blood pool phase but then remained constant into the late phase. The foci were confirmed in the SPECT images. ^{99m}Tc sulphur colloid

scintigraphy revealed multiple photopaenic areas in both lobes. A large, rounded, partially photopaenic area was present in the medial segment of the left lobe, encroaching upon the medial part of the right lobe. Increased activity was present in the rim of this area, superiorly (diffuse) and inferiorly (as two focal areas, one inferomedially in the medial part of right lobe and one inferiorly in the medial segment of the left lobe). Further photopaenic areas were present in the right lobe superiorly, posteriorly and laterally.

Case 3 (patient 28) presented with a history of alcoholism, marked weight loss over 6 months and right upper quadrant pain with a hard nodular hepatomegaly extending 20 cm below the costal margin. A bruit was present over the liver. The liver function tests were abnormal and the alpha fetoprotein > 85 ng/ml. Ultrasonography demonstrated an enlarged inhomogeneous liver with cystic and/or necrotic areas in the right lobe. Cytology of the liver aspirate revealed malignant cells compatible with hepatocellular carcinoma. Scintigraphy demonstrated focal increased activity in the inferior part of the right lobe in the early dynamic phase with subsequent persistence of increased activity throughout the planar images into the late blood pool phase. The SPECT images revealed an area of irregular increased activity (with an appearance of 3 contiguous foci) surrounding a central cold area, situated in the anteroinferior part of the right lobe. Activity throughout the remainder of the right lobe was inhomogeneous. ^{99m}Tc sulphur colloid scintigraphy revealed irregular photopaenia in the anteroinferior part of the right lobe laterally and in the superolateral part.

Case 4 (patient 29) presented with sudden onset right upper quadrant pain after 3 days of heavy alcohol drinking and was in a state of hypovolaemic shock on admission to hospital. A three cm firm hepatomegaly was present on examination. The liver function tests and alpha fetoprotein were normal. Ultrasonography revealed a lesion of mixed echogenicity (complex pattern) in the right lobe posterior segment, 9 x 8 x 6 cm in diameter. Two satellite lesions were observed in the right lobe anterior segment. The CT demonstrated a low density lesion in the inferomedial part of the right lobe which revealed increased size in a second study one month later. Angiography displayed a hypervascular lesion in the posterior segment of the right lobe, a second lesion in the

anterior segment of the right lobe and an obstructed right portal vein branch. Histology of the liver biopsy confirmed hepatocellular carcinoma. Scintigraphy, in the early dynamic phase in the posterior projection, demonstrated focal increased activity in the posterior segment of the liver superomedial to the right kidney, relative to the activity in the remainder of this segment. This increased activity subsequently persisted unchanged into the blood pool phase. Focal increased activity was also present anteroinferiorally in the right lobe, on anterior and lateral projections, relative to activity in the part of the right lobe medial to a large cold area situated superolaterally (subcapsular haematoma on CT imaging). Foci were confirmed on the SPECT study.

Case 5 (patient 31) presented clinically with right upper quadrant pain, progressive abdominal distension and ascites, with a firm hepatomegaly extending 5 cm below the costal margin. The liver function tests were abnormal and the alpha fetoprotein was > 1000 ng/ml.. Ultrasonography revealed an inhomogeneous right lobe and multiple hyperechoic lesions with hypoechoic halos in the left lobe. Cytology of the liver aspirate revealed malignant cells compatible with an hepatocellular carcinoma. Scintigraphy demonstrated focal increased activity relative to adjacent parenchyma in the upper part of the right lobe anterolaterally and in the medial segment of the left lobe, appearing constant in early and late blood pool phases. The activity in the adjacent hepatic parenchyma was inhomogeneous.

B. Metastatic carcinoma

Two patients with metastatic carcinoma were misdiagnosed as having cavernous haemangioma (Table 7).

Case 6 (patient 3) presented with a history of alcoholism and weight loss, with a smooth non-tender hepatomegaly extending 3 cm below the costal margin. Ultrasonography revealed multiple hyperechoic lesions (up to 2 cm in diameter) throughout the liver. Histology of transbronchial biopsy material demonstrated bronchial carcinoma, but cytology of the liver aspirate revealed no malignant cells. A diagnosis of bronchial carcinoma with probable hepatic metastases was made. Scintigraphy demonstrated

a small focus of increased activity in the inferior tip of the right lobe in the early blood pool phase, which increased in intensity in the late phase.

Case 7 (patient 45) presented with jaundice and abnormal liver function tests. Ultrasonography revealed a lesion 7 x 8.8 cm in diameter in the porta hepatis region. CT demonstrated a low density lesion in the porta hepatis lesion with irregular peripheral contrast enhancement. Cytology of the liver aspirate revealed cells compatible with metastatic adenocarcinoma. Scintigraphy, in the dynamic phase, demonstrated an ovoid ring of increased activity surrounding a cold area in the right lobe, appearing simultaneously with aortic activity and subsequently rapidly becoming isoactive with adjacent hepatic parenchyma, the central photopaenia persisting. On the SPECT images, a large photopaenic area was situated in the superomedial part of the right lobe with 3 foci of increased activity located in the periphery of this area (inferior, postero-superior and postero-inferior). The inferior focus was seen in the early and late blood pool phases of the planar images, remaining constant in intensity.

C. Liver abscess

Case 7 (patient 36) presented with a history of pyrexial illness and abdominal pain. A non-tender smooth hepatomegaly was found on examination. The liver function tests were abnormal. Ultrasonography revealed a single 6 cm diameter hyperechoic lesion with an echolucent rim, in the right lobe. Cytology of the liver aspirate revealed the presence of inflammatory cells consistent with abscess. Scintigraphy demonstrated an irregular area of decreased flow and decreased blood pool in the right lobe medially, but a focus of increased flow and persistent increased blood pool activity was present in the right lobe medially, in retrospect shown to represent false positive prominent portal vein activity.

D. Metastatic sarcoma

Patient 42 presented with loss of weight, right and left upper quadrant pain and a non-tender hepatomegaly. Ultrasonography revealed an inhomogeneous lesion 9 x 6 cm in diameter in the left lobe. CT demonstrate a low density lesion 8 x 4.7 cm in diameter in the left lobe. Cytology of the liver aspirate revealed features of a metastatic sarcomatoid tumour (Appendix 20). Scintigraphy revealed a large area of decreased flow and decreased blood pool in the left lobe, but filling in of this area in the blood pool phase was observed by observer III.

ULTRASONOGRAPHY

Ultrasonography was performed on 40 patients (haemangioma group, n=17; non-haemangioma group, n=16; and indeterminate group, n=7).

TABLE 9. Lesion number

LESION NUMBER	Patients with no focal lesions	Patients with solitary lesions	Patients with two lesions	Patients with ### two lesions	*TOTAL NUMBER PATIENTS*
Haemangioma group	-	10	3	4	*17*
Non-haemangioma group	1	8	1	6	*16*
Indeterminate group	1	4	1	1	*7*
Entire group	2	22	5	11	*40*

TABLE 10. Lesion location

LESION LOCATION	Patients with no focal lesions	Patients with (R) lobe lesions	Patients with (L) lobe lesions	Patients with lesions in both lobes	*TOTAL NUMBER PATIENTS*
Haemangioma group	-	12	-	5	*17*
Non-haemangioma group	1	8	1	6	*16*
Indeterminate group	1	3	2	1	*7*
Entire group	2	23	3	12	*40*

Lesion diameter was documented ultrasonographically in 21 patients (haemangioma group, n=10; non-haemangioma group, n=7; and indeterminate group, n=4). The largest lesional diameter ranged from 1.3 to 20 cm (mean 6.6 cm) for the entire group, 2.0 to 20 cm (mean 8.1 cm) for the haemangioma group, 2.0 to 11 cm (mean 7.2 cm) and for the non haemangioma group.

TABLE 11. Lesion diameter

LESION DIAMETER	Range (cm)	Mean (cm)	*NUMBER OF PATIENTS*
Haemangioma group	2.0-20	8.1	*10*
Non-haemangioma group	2.0-11	7.2	*7*
Indeterminate group	1.3-2.5	2.0	*4*
Entire group	1.3-20	6.6	*21*

Of the 40 patients undergoing ultrasound, 58% revealed hyperechoic lesions. In the haemangioma group, 76% of haemangiomas were hyperechoic, whereas the sonographic pattern in the non-haemangioma group was more variable. However, the differences between the two groups are not statistically significant (Fischer test, $p=0,277$), implying that ultrasonography has little or no diagnostic value in distinguishing the lesions of these two groups.

TABLE 12. Sonographic pattern

SONOGRAPHIC PATTERN	Patients with hyperechoic lesions	Patients with hypoechoic lesions	Patients with complex lesions	Patients with isoechoic lesions	Patients lesion not described	Patients with no lesion	*TOTAL NO. OF PATIENTS*
Haemangioma group	13	1	3	-	-	-	*17*
Non-haemangioma group	6	1	5	1	2	1	*16*
Indeterminate group	5	1	-	-	-	1	*7*
Entire group	24	3	8	1	2	2	*40*

COMPUTER TOMOGRAPHY

CT imaging was performed in 32 patients. (haemangioma group, n=14; non-haemangioma group, n=12; and indeterminate group, n=6).

TABLE 13. Lesion number

LESION NUMBER	Patients with no focal lesions	Patients with solitary lesions	Patients with two lesions	Patients with ### two lesions	*TOTAL NO. OF PATIENTS*
Haemangioma group	-	10	2	2	*14*
Non-haemangioma group	-	7	1	4	*12*
Indeterminate group	4	1	1	-	*6*
Entire group	4	18	4	6	*32*

TABLE 14. Lesion location

LESION LOCATION	Patients with no focal lesions	Patients with (R) lobe lesions	Patients with (L) lobe lesions	Patients with lesions in both lobes	*TOTAL NO. OF PATIENTS*
Haemangioma group	-	10	-	4	*14*
Non-haemangioma group	-	5	1	6	*12*
Indeterminate group	4	1	1	-	*6*
Entire group	4	16	2	10	*32*

Dynamic (single level large bolus contrast injection) CT was performed in 18 patients, and the results are presented in Table 15. Of the 14 patients from the haemangioma group, 8 revealed a contrast pattern compatible with cavernous haemangioma, 5 a contrast pattern characteristic of cavernous haemangioma, while one revealed a contrast pattern not typical of cavernous haemangioma. All 3 patients of the non-haemangioma group revealed contrast enhancement not typical of cavernous haemangioma. The bias towards the haemangioma group in Table 15 reflects the referral pattern to dynamic CT preferentially of patients with a high suspicion of HCH for confirmation of the diagnosis. The non-haemangioma group is too small to be significant.

TABLE 15. Dynamic CT contrast enhancement pattern

DYNAMIC CT PATTERN	Patients with lesions compatible with HCH	Patients with lesions characteristic of HCH	Patients with lesions not typical of HCH	*TOTAL NO. OF PATIENTS*
Haemangioma group	8	5	1	*14*
Non-haemangioma group	-	-	3	*3*
Indeterminate group	-	-	1	*1*
Entire group	8	5	5	*18*

The CT lesion density was documented in 28 patients and is presented in Table 16. In all but one patient, a low density in both haemangioma and non-haemangioma groups was present. Lesion contrast density must be considered as showing no specificity as a diagnostic criterion.

TABLE 16. Lesion contrast density

CONTRAST DENSITY	Patients with low density lesions	Patients with mixed density lesions	Patients with high density lesions	*TOTAL NO. OF PATIENTS*
Haemangioma group	14	-		*14*
Non-haemangioma group	11	1	-	*12*
Indeterminate group	1	-	1	*2*
Entire group	26	1	1	*28*

ANGIOGRAPHY

Angiography was performed in 6 patients, revealing features compatible with haemangioma in one patient, focal nodular hyperplasia in one patient, neovascularity in 2 patients (final diagnosis hepatocellular carcinoma and probable hepatocellular carcinoma), hypervascularity in one patient (hepatocellular carcinoma) and conventional hepatic arterial anatomy in one patient (indeterminate diagnosis) (Appendix 23).

Chapter 4

DISCUSSION

It has been widely advocated in the literature that ^{99m}Tc erythrocyte blood pool scintigraphy is highly sensitive and specific for hepatic cavernous haemangiomas. The specificity and positive predictive value reported in the literature for planar and SPECT blood pool scintigraphy are 100% (Engel *et al.*, 1983; Brunetti *et al.*, 1988; Krause *et al.*, 1993; Intenzo *et al.*, 1988; Farlow *et al.*, 1990; Tumeh *et al.*, 1987; Kudo *et al.*, 1989; Ziessman *et al.*, 1991). Some investigators recommend that a positive scan is sufficient to make the diagnosis and that further investigations can therefore be terminated once a positive result has been obtained (Engel *et al.* 1983; Krause *et al.* 1993; Moinuddin *et al.* 1985).

In the investigation of HCH, the specificity of the test used in diagnosis is of greater importance than sensitivity. A false positive diagnosis of HCH as a benign lesion which usually does not require further treatment, may result in further investigation and management being stopped, whereas a false negative test for HCH will lead to further investigation, if clinically indicated. However, with regard to specificity, all studies to date have been flawed because insufficient non-haemangiomatous hepatic mass lesions have been studied. Bayesian analysis (Patrick, 1979) clearly shows that the specificity of a test is dependant on the pre-test probability of the lesion being present and that the probability of a false positive result is directly proportional to the number of non-haemangiomatous cases studied, i.e. if only cases of hepatic cavernous haemangiomas are studied, no false positives will be found. The probability of a false positive test increases with the number of non-HCH patients studied. It is important to avoid introducing bias by basing the diagnosis of HCH exclusively on a positive scintigraphic test, as occurred in some of the studies of the accuracy of scintigraphy in HCH. In the studies quoting a specificity of 100% (Engel *et al.*, 1983; Brunetti *et al.*, 1988; Krause *et al.*, 1993; Intenzo *et al.*, 1988; Farlow *et al.*, 1990; Tumeh *et al.*, 1987; Kudo *et al.*, 1989; Ziessman *et al.*, 1991), the number of haemangiomas detected ranged between 11 and 108 (mean 36) and the number of patients between 9 and 77 (mean 26.5) respectively. Proportionately fewer non-HCH lesions were studied, with a range of 5 to 46 (mean 18.6), in 5 to 29 patients

(mean 14) respectively. The study with the largest non-haemangiomatous lesion group was that of Kudo *et al.* (1989) - 29 patients with a total of 46 hepatocellular carcinomas, as opposed to 77 patients with a total of 108 haemangiomas. The small numbers of control patients relative to the number of patients with hepatic cavernous haemangioma, has resulted in a bias towards indicating high specificity of erythrocyte blood pool scintigraphy.

Furthermore, the studies by Engel *et. al* (1983), Ziessman et. al (1991), Brunetti *et. al* (1988), it is not clear that patients in whom a diagnosis of HCH was made by scintigraphy, had this diagnosis confirmed by other means. It thus remains unclear from these studies whether patients with non-HCH lesions were included in the HCH group. This would also give a falsely high specificity for the test.

Our study confirms the high sensitivity of the ^{99m}Tc labelled erythrocyte blood pool scintigraphy in the detection of hepatic cavernous haemangiomas, as quoted in the literature, by obtaining a high sensitivity (1.000/0.944), high negative predictive value (1.000/0.923) and low false negative ratio (0.000/0.056).

With regard to specificity and positive predictive value, the results of this study stand in marked contrast to the results widely published in the literature. The low specificity (0.632), low positive predictive value (0.720/0.708) and the high false positive ratio (0.368) must also be seen in the context of a 48% disease prevalence, reflecting the matched number of patients with haemangiomatous (n=18) and non-haemangiomatous (n=19) lesions in the patient population studied. The finding of 7 false positive diagnoses of hepatic cavernous haemangioma in 37 patients (19%), clearly indicates that ^{99m}Tc erythrocyte blood pool scintigraphy is not sufficiently specific to distinguish the mostly innocuous cavernous haemangioma from malignant mass lesions of the liver. As hepatocellular carcinoma is common in the geographical area where the investigation was performed, but relatively rare in most other places, the series has probably been slanted towards hepatocellular carcinoma. This factor is however a constant feature in this area, posing an obvious diagnostic problem.

This study was designed to minimise observer bias. To this end two independent observers, experienced in interpretation of ^{99m}Tc blood pool scintigraphy, interpreted the scintigrams without prior knowledge of clinical or

patient data. In addition, every effort was made to use non-scintigraphic data to clarify the nature of the lesion. Therefore the diagnosis of the lesion was based on clinical, biochemical, ultrasound, CT, MRI, cytological and histological basis in the majority of cases. The scintigraphic data was not used in the diagnosis of the hepatic mass lesions. Of particular importance is the fact that 5 of the 7 false positive cases who had characteristic scintigraphic features of cavernous haemangiomas, had histological or cytological confirmation of the diagnosis. There can be no doubt about the malignant nature of the disease in these patients. One of the patients with false positive scintigraphy (patient 18) had an alpha fetoprotein level of > 1000 ng/ml, which was considered diagnostic and which was followed by rapid clinical deterioration, thereby supporting the clinical diagnosis of HCC. One of the patients with false positive scintigraphy (patient 3), in whom histology of transbronchial biopsy material demonstrated bronchial carcinoma but cytology of the liver aspirate revealed no malignant cells, had a diagnosis of bronchial carcinoma with probable hepatic metastases established on the basis of the clinical data and ultrasonographic appearance.

It is possible that some patients who were diagnosed as having cavernous haemangioma by clinical and other criteria with confirmation on scintigraphy, may indeed also have been false positive and that the lesions may not have been cavernous haemangiomas. Therefore, this study indicates that the maximum specificity is 0.632. We cannot exclude that the specificity is in fact lower than this, as histological confirmation was obtained in only 3 patients diagnosed as having HCH, and in one patient the biopsy material revealed features compatible with lymphangioma.

Statistically, the results of observers I and II are near identical (Fischer test, p=1.000; Mantel-Haenzel chi-square test, p=0.861), and the correlation was high (contingency coefficient, 0.117). Although the statistical difference between the results of observers I and III, and between II and III were not significant (Fischer test, p=0.084 and 0.267; Mantel-Haenzel chi-square test, p=0.175 and 0.233), the correlation was poorer between both sets of results (contingency coefficient, 0.288 and 0.240). The results of observer III, consistently at variance with the results of both observer I and II, with a lower false positive and a higher false negative ratio (4 of the 5 false negative diagnoses out of 3 observers arising from observer III) may reflect the difficulties incumbent in the interpretation of erythrocyte blood pool images with limited experience of the method.

All the haemangiomas in the current study revealed the characteristic scintigraphic pattern of increased activity in the late blood pool phase, with or without progressive increase in activity intensity. The rarity of the peripheral-centripetal filling, as reported in the literature, was confirmed with the finding of only one large haemangioma demonstrating this phenomenon. Only 2 (of 25) lesions demonstrated isolated or pure decreased activity in the dynamic perfusion phase. This is in marked contrast to the frequency with which this pattern is described in the literature. Indeed, 5 haemangiomas had increased activity in the dynamic perfusion phase, which is generally considered to be rare (Larcos *et al.* 1989), and 4 haemangiomas demonstrated a mixed pattern in the perfusion phase, with small areas of increased activity, either contained within or situated adjacent to and contiguous with, a large(r) area of decreased activity. This atypical pattern has previously been described by Front *et al.* (1984) and Brodsky *et al.* (1987). The relative frequency of increased and paucity of decreased activity found in the dynamic phase in this study, is at variance with the findings in the literature. The pathophysiology of this finding is uncertain, but may be a reflection of rapid ingress (and egress) of radiolabelled blood, permitted by the presence of larger less-tortuous cavernous spaces or the presence of arteriovenous fistulae. However, the rapid ingress/egress required for visualization of increased perfusion in the dynamic phase is incongruent with the pathophysiological requirement of delayed egress necessary for unchanging or increasing intensity in the late blood pool phase. The reversing vascular pattern described by Hardoff *et al.* (1989) suggesting a double vascular arrangement, does not explain persistence of increased activity within an entire lesion or part thereof, from perfusion to late blood pool phases. This is an area requiring further scintigraphic and histologic correlative study, to define the pathophysiology and the underlying histological basis.

The atypical appearance haemangioma, although described rarely in the literature, was seen in isolation in 5 haemangiomas, and contiguous with or contained within 4 haemangiomas also revealing typical reduced perfusion, in our study. It is important that this entity, more common than previously assumed, be seen in the light of the eight lesions/foci (corresponding to five or six hepatocellular carcinomas) in four patients, demonstrating similar increased activity in the dynamic perfusion phase and late blood pool phase. While the increased late blood pool phase activity is the characteristic pattern of haemangiomas (here false positive), the increased perfusion seen in these lesions, well described in HCC, was taken to represent the *atypical*

scintigraphic appearance of HCH. In each of two of these patients, three foci were closely adjacent, probably representing multiple areas of increased vascularity and pooling in one neoplasm, rather than distinct or separate neoplasms. In two of the four patients, the lesions revealed an increase in lesional activity intensity between early and late blood pool phases, while in the other two patients the intensity remained constant. When increased perfusion is present in a lesion, the observation of clearly progressive accumulation of activity over time from the perfusion to the late blood pool phase, may help distinguish between an atypical haemangioma and a hepatocellular carcinoma or vascular metastasis (Larcos *et al.*, 1989; Drane, 1991). However, the increasing lesional activity intensity seen in 2 of the four patients with false positive HCC between early and late blood pool phases, suggests that even this pattern must be interpreted with caution, especially in the presence of increased perfusion. Quantitative analysis of early and late blood pool phase activity intensity may improve accuracy, but requires further validation (Moinuddin *et al.*, 1985).This pattern, of atypical increased perfusion but characteristic late pooling, may therefore suggest the presence of a malignant hepatic mass lesion rather than an atypical haemangioma. This should prompt further investigation. The additional scintigraphic demonstration of inhomogeneous activity distribution in the adjacent parenchyma, as found in all five patients with hepatocellular carcinoma, may be a clue to the presence of a malignancy. The distinction of normal versus abnormal parenchymal vascularity is complicated by the fact that the adjacent parenchyma may be abnormal itself, making it difficult to use as a reference. The finding of increased perfusion and pooling in relation to adjacent (tumourous) parenchyma on blood pool scintigraphy, could be due to normal vascularity in remaining normal parenchyma appearing abnormal due to the decreased reference parenchymal activity. This may contribute to the generation of false positive blood pool scintigraphy.

The remaining false positive three hepatocellular carcinomas and four metastatic lesions/foci lesions with normal perfusion, seen as separate and discrete lesions, presented a scintigraphic pattern characteristically associated with hepatic cavernous haemangioma. Lesional activity intensity remained constant except in one patient with two metastatic lesions, where activity intensity increased between early and late blood pool phases. The presence of an early arterial activity blush, as seen in one of the two patients with false positive metastases, may suggest a malignant vascular neoplasm, despite characteristic features of haemangioma.

While planar hepatic blood pool scintigraphy is shown to be a sensitive technique for the evaluation of hepatic haemangioma (Brunetti *et al.*, 1988; Farlow *et al.*, 1990; Front *et al.*, 1981; Rabinowitz *et al.*, 1984), the SPECT technique may be more accurate than planar scintigraphy where haemangiomas are extensively fibrosed, and little pooling of labelled erythrocytes occurs (Rabinowitz *et al.*, 1984), and in detecting small, deeply situated cavernous haemangiomas (Langsteger *et al.*, 1989; Tumeh *et al.*, 1987; Intenzo *et al.*, 1988; Brodsky *et al.*, 1987; Drane, 1991; Rubin and Lichtenstein, 1993), and/or where small haemangiomas are obscured by adjacent normal vascular structures (Brunetti *et al.*, 1988).

In this study, comparison of SPECT versus planar imaging demonstrated no statistical difference in the detection of hot or cold foci, although SPECT provided better clarity and allowed more precise localization of lesions. In the non-haemangioma group, three small foci were only seen on SPECT, suggesting that SPECT has a greater sensitivity but decreases specificity in the investigation of HCH.

Scintigraphically, haemangiomas were found to be more frequently solitary and located in the right lobe. A similar tendency was however found with the non-haemangiomatous lesions. Thus, no differences were found in the number or location of lesions in the haemangioma and non-haemangioma groups.

In summary, the efficacy of ^{99m}Tc erythrocyte blood pool scintigraphy in the investigation of hepatic mass lesions, as a first or second line investigation to distinguish cavernous haemangioma from hepatocellular carcinoma and liver metastases, is based upon the apparently high specificity and positive predictive value of this investigation for cavernous haemangioma, reported in the literature. While the order in which investigations for hepatic mass lesions are performed are still being debated, the necessity for confirmation of a scintigraphic diagnosis of hepatic cavernous haemangioma by other imaging modalities (to exclude a potentially catastrophic false positive diagnosis), should be reconsidered in the light of the findings of the current study. In contrast to several authors who advocate the termination of investigations upon the finding of scintigraphic features characteristic for haemangioma (Engel *et al.*, 1983; Krause *et al.*, 1993; Moinuddin *et al.*, 1985), our study has shown that scintigraphy is non-specific, and that this recommendation may be dangerous. When the classical perfusion blood pool mismatch, with

decreased activity in the dynamic phase (decreased perfusion) and increased or increasing activity in the late blood pool phase, considered pathognomonic for HCH, is found, the diagnosis of HCH is relatively certain. This pattern was however found in isolation in only 2 and in combination with atypical increased perfusion in 4 of 25 haemangiomas in this study, and should therefore be considered the exception rather than the rule. In the absence of decreased perfusion, the presence of lesion activity increased in the late blood pool phase alone, or lesion activity which has increased or remained constant relative to the adjacent hepatic parenchyma from the dynamic to the late blood pool phase, are sensitive but non-specific criteria for HCH. These features do not exclude an underlying (potentially treatable) malignancy.

Chapter 5

CONCLUSION

It has been widely accepted in the literature that ^{99m}Tc erythrocyte blood pool scintigraphy is a sensitive and specific tool for diagnosing cavernous haemangiomas of the liver and that this investigation distinguishes these benign lesions from hepatic malignancy. Previous studies have been based on flawed methodology. This study has clearly demonstrated that ^{99m}Tc erythrocyte blood pool scintigraphy yields a false positive rate of 36% in patients with hepatocellular carcinoma and hepatic metastases. Observer bias was reduced by the observers examining these studies in a blinded fashion and the correlation between two independent observers was excellent. The high false positive rate for scintigraphy in patients with hepatocellular carcinoma and hepatic metastases indicates that ^{99m}Tc erythrocyte blood pool scintigraphy is probably less specific for the diagnosis of hepatic cavernous haemangioma than expected, and that a major diagnostic ambiguity exists particularly in the case of hepatocellular carcinoma, especially in an area where this carcinoma is common. It is therefore essential for patients with positive scintigraphic studies to have confirmatory studies done if any doubt exists on clinical, biochemical or other radiological examination regarding the diagnosis, as incorrect diagnoses could have severe consequences for these patients. The exception would be patients with lesions demonstrating the classical perfusion blood pool mismatch, with absent or only partial perfusion, considered diagnostic for HCH. Lesions demonstrating atypical increased perfusion, either in part or in their entirety, in addition to features characteristic of HCH, by contrast fall into a high risk category. The performance of radionuclide angiography (dynamic perfusion phase) is therefore essential to maximise the specificity of the method. While the performance of SPECT is documented to improve the sensitivity, the risk of increasing the number of false positive lesions detected must be taken into consideration.

Finally, while the role of ^{99m}Tc labelled red cell blood pool scintigraphy in the diagnosis of hepatic mass lesions needs to be re-evaluated, improvement of diagnostic accuracy would be provided by the additional performance of dynamic CT and/or MRI, or at best, implementation of multimodality imaging with image fusion.

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APPENDICES

APPENDIX 1

Early History of Hepatic Cavernous Haemangioma

STUDY	DESCRIPTION / EMPHASIS
Frerichs (1861)	First description of HCH in the medical literature.
Virchow (1863)	Described a HCH 4 cm in diameter and proposed hypotheses of pathogenesis.
Payne (1869)	Case report of haemangiomatous liver weighing 2700 gm in association with haemangiomas of adrenal capsules, uterus and ovaries.
Langhans (1879)	Case report of associated liver and spleen haemangiomas.
Birch-Hirschfeld (1895)	Reported a case of large HCH in which the abdomen resembled that of a pregnant woman.
Keen (1897)	Reported surgical pedicle formation and elastic ligature of a HCH, exteriorization and extra-abdominal excision after six days.
Schmieden (1900)	Described gross and microscopic features of 32 incidental autopsy findings of HCH asymptomatic during life.
Langer (1901)	Reported resection of a HCH measuring 21 x 21 x 11 cm and weighing 5000 gm.
Fillipini (1901)	Described a HCH the size of a human head.
Mantle (1903)	Reported resection of a HCH measuring 30 x 16 x 4 cm and involving virtually the entire right lobe.
Von Genersich (1908)	Described a HCH as large as a child's head.
Chiari (1909)	Described a HCH as large as a man's head.
Roggenbau (1910)	Described a HCH measuring 22 x 9 x 33 cm.
M'Weeney (1912)	Described a HCH measuring 25 x 25 x 10 cm in a liver weighing 5100 gm.
MacCallum (1917)	Described a large pedunculated HCH measuring 24 cm in diameter.
Major and Black (1918)	Described a haemangiomatous liver weighing 18160 gm and discussed pathogenesis of HCH.
Rubin (1918)	Reported resection of a large pedunculated HCH measuring 61 x 41 x 10 cm, weighing 2155 gm and causing obstetric difficulty.

APPENDIX 1 (continued)

Early History of Hepatic Cavernous Haemangioma

STUDY	DESCRIPTION / EMPHASIS
Peck (1921)	Reported resection of a HCH measuring 26 x 20 x 9 cm, weighing 1700 gm.
Tokushige (1940)	Reported an autopsy case with an HCH twice the size of a man's head and weighing 2800 gm.
Shumacker and Baltimore (1942)	Presented analysis of 67 operative cases of HCH, resection performed in 56.
Wilson and Tyson (1952)	Reported 3 resections of HCH and found 84 operative cases of HCH in the literature.
Henson *et al.* (1956*b*)	Reported on 35 resections of HCH at the Mayo Clinic from 1907 to 1954.

APPENDIX 2

Pathogenesis of Hepatic Cavernous Haemangioma - Early Hypotheses

AUTHOR	HYPOTHESIS
Virchow (1863)	Pathogenesis a process of increased liver connective tissue, followed by disappearance of organ secretory paths. Dilatation of connective tissue vessels with thickening of walls and fusion with surrounding connective tissue. Destruction of liver tissue keeps pace with growing angioma and no liver volume increase occurs.
Rindfleisch (1886) Burckhard (1894)	Proposed a hypothesis of connective tissue origin in agreement with that of Virchow and considered as important an accompanying cavernous metamorphosis of blood vessels.
Beneke (1890)	Considered biliary obstruction with biliary capillary (ductular) dilatation as the origin of HCH.
Scheffen (1897)	Suggested passive hepatic venous congestion with cavernous dilatation of blood vessels over time to be the pathogenetic mechanism.

APPENDIX 3

Pathogenesis of Hepatic Cavernous Haemangioma - Hypothesis of Hamartomatous Origin

AUTHOR	HYPOTHESIS
Schmieden (1900)	Rejected many earlier hypotheses and concluded that: 1. Liver cavernoma does not arise from primary connective tissue or vascular tumourous growth and that vascular obstruction, primary liver tissue atrophy, bile obstruction or haemorrhage cannot produce liver cavernoma. 2. Pathogenesis is one of local tissue malformation during liver anlage development, with the final form being attained through regressive changes. 3. Liver cavernoma is to be considered different from cavernous angiomas of other organs (considered to be true angiomas).
Mantle (1903)	Proposed origin of a large liver cavernous haemangioma examined at autopsy to be from dilatation of pre-existing vessels rather than new-vessel formation, shown by the presence of hepatic cells and bile ducts throughout the lesion and by dilatation of vessels in the uninvolved lobe.
Borst (1911)	Proposed embryonal maldevelopment of liver tissue without growth of new blood vessels as the origin of HCH.
Ochsner and Halpert (1958)	Vascular hamartoma, not angioma. Possesses no growth potential and undergoes retrogressive changes (thrombosis, organization, hyaline change) when there is interference with the blood circulation.
Feldman (1958)	Developmental abnormality, based on the frequent (19%) association of cysts with liver haemangiomas.
Kojimahara (1986)	Hamartoma, based on the ultrastructural demonstration of a basement membrane beneath the lining endothelium.

APPENDIX 4

Pathogenesis of Hepatic Cavernous Haemangioma - Hypothesis intermediate between Hamartomatous and Angiomatous Origin

AUTHOR	HYPOTHESIS
Ribbert (1898)	Neoplasms caused by aberrant growth of sequestered vascular mesoderm.
Borst (1911)	Considered HCH to be hamartomatous but found evidence of genuine (rare) cavernous angioblastomata of the liver (growth in the form of endothelial sprouts and tubes).
Robbins (1974)	Suggested a hamartomatous origin or origin as a neoplasm (angioma) in a congenital defect.

APPENDIX 5

Pathogenesis of Hepatic Cavernous Haemangioma - Hypothesis of Angiomatous Origin

AUTHOR	HYPOTHESIS
Moore (1944)	Speculated on origin as a neoplasm developing in areas of focal hepatic tissue necrosis with subsequent regeneration.
O'Donoghue and Nicosia (1950)	Proposed origin as a neoplasm of blood vessels with independent vascular growth, new vessels originating from budding of atypical angioblasts.
Boyd (1970)	Speculated that the neoplasm may consist of distinct new blood vessels and should be differentiated thus from telangiectatic dilatation of pre-existing vessels.
Robbins (1974)	Speculated on a spontaneous origin as a true neoplasm in children or adults.
Conter and Longmire (1988)	Emphasised the hypothesis of new cellular tissue origin by growth rather than ectasia of pre-existing vessels, based on recurrence of HCH in 4 patients following ablative treatment (radiotherapy in 2 and resection in 2).

APPENDIX 6

The Aetiological Role of Oral Contraceptive Steroids (OCS) and Exogenous Oestrogens in Hepatic Cavernous Haemangioma

AUTHOR	AETIOLOGICAL RELATIONSHIP
Nissen *et al.* (1976)	Reported benign liver neoplasia in 67 patients receiving OCS - FNH 23 (34%), LCA 27 (40%), hamartoma 11 (16%).
O'Sullivan and Wilding (1974)	Described three cases of liver hamartomas in females who had received OCS for long periods of time.
Tait *et al.* (1992)	In a 10 year review of patients with liver haemangioma, found that in 25 women, 10 had a history of OCS use and 2 a history of progesterone use. All four patients having resection of increasingly symptomatic HCH had at some time used OCS. Symptoms developed in 2 patients while using OCS and cessation of OCS use did not reduce their symptoms or slow symptom progression. One male patient had received oestrogenic medication for treatment of prostatic carcinoma.
Sinanan and Marchioro (1989)	Eight of 12 patients with diagnosed liver haemangioma reported prior or concomitant oestrogen replacement after oophorectomy (6 patients) or OCS (2 patients).
Morley *et al.* (1974)	Reported the rapid growth of a liver haemangioma in a patient receiving exogenous oestrogens.
Conter and Longmire (1988)	Reported extensive recurrence of liver haemangioma after ablative therapy in four patients, three of which were women receiving oral oestrogen therapy prior to their original surgery, and who continued with oestrogen replacement until their recurrence was diagnosed.

APPENDIX 7

The Aetiological Role of Pregnancy in Hepatic Cavernous Haemangioma

STUDY	AETIOLOGICAL RELATIONSHIP
Rubin (1918)	Rapid enlargement of liver haemangioma in 33 year old woman in her 10th pregnancy (13 children borne of 9 pregnancies, 8 of twin pregnancies), requiring resection of a pedunculated HCH measuring 61 x 41 x 10 cm and weighing 2155 gm.
Nichols *et al.* (1989)	Documented growth of a liver haemangioma in a patient during three pregnancies prior to referral for resection of a symptomatic 23 cm diameter lesion.
White (1983)	Sudden increase in size of a previously diagnosed liver haemangioma in a patient during the last trimester of pregnancy, symptoms necessitating resection of a 6000 gm lesion 1 month postpartum.
Creasy *et al.* (1985)	Enlargement of liver haemangioma in a patient from 4 cm in early pregnancy to 6 cm before delivery.
Schwartz and Husser (1987)	Unequivocal rapid growth of a liver haemangioma in a patient in her first trimester of pregnancy, although the patient's first pregnancy was unassociated with growth of the lesion.
Sewell and Weiss (1961)	Spontaneous rupture of a 10 cm liver haemangioma in a 21 year old woman in the fourth month of pregnancy.

APPENDIX 8

Solitary vs. Multiple Hepatic Cavernous Haemangioma

STUDY	PATIENTS WITH HCH	SOLITARY (%)	MULTIPLE (%)	COMMENTS
Schwartz and Husser (1987)	28	93	7	Retrospective skewed clinicopathologic series. *Selection bias* - patients with a previous diagnosis of HCH referred for hepatic surgery.
Ochsner *et al.* (1958)	55	91	9	Large autopsy series (n=2400). *No selection bias.*
Feldman (1958)	96	91	9	Large autopsy series (n=1319). *No selection bias.*
Henson *et al.* (1956*b*)	24	83	17	Group B: HCH discovered incidentally at surgical exploration for some other condition. *No selection bias.*
Henson *et al.* (1956*b*)	11	82	18	Group A: HCH discovered at surgical exploration for symptomatic indeterminate hepatic masses. *No selection bias.*
Trastek *et al.* (1983)	49	67	33	Retrospective skewed clinicopathologic series. *Selection bias* - only patients with HCH > 4 cm examined.
Tait *et al.* (1992)	61	62	38	Retrospective skewed clinicopathologic series. *Selection bias* - only patients with HCH were examined.
Schmieden (1900)	32	56	44	Selected pathological series. *Selection bias* - selected autopsy HCH specimens examined to investigate structure and genesis.
All studies	356	78	22	Mean
All studies	356	56-93	7-44	Range

APPENDIX 9

Size of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	SIZE RANGE (cm)	MEAN SIZE (cm)	COMMENTS
Tait *et al.* (1992)	61	1 - 16	3.5	Ten year retrospective review. Symptomatic HCH (n=7), 6 > 4 cm. HCH excised due to symptomatology (n=4), measured 5, 6.5, 8 and 16 cm. Asymptomatic HCH (n=54), 19 > 4 cm.
Schwartz and Husser (1987)	12	3 - 8	4.7	Surgical series - nonoperative group. Pain in 10 patients related to other pathology such as gallbladder disease.
Lise *et al.* (1992)	51	5 - 20	8.5	Patients referred for surgical treatment. Symptomatic (n=22), asymptomatic (n=29), surgery performed in 25 patients.
Bornman *et al.* (1987)	4	3 - 15	8.3	Surgical resection. Pain and mass (n=2), mass (n=1), incidental finding at laparotomy (n=1).
Trastek *et al.* (1983)	49	4 - 22	9	Surgical resection in 13 patients. Symptomatic (n=6), asymptomatic (n=4), incidental (n=2), haemorrhage post-biopsy (n=1).
Andersson and Bengmark (1988)	8	5 - 15	10	Surgical resection: Suspected abdominal tumour or hepatic metastases (n=5), enlargement of known HCH (n=2) and spontaneous rupture of HCH (n=1).

APPENDIX 9 (continued)

Size of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	SIZE RANGE (cm)	MEAN SIZE (cm)	COMMENTS
Schwartz and Husser (1987)	16	4 - 32	10	Surgical series - operative group (skewed, referral for hepatic surgery). Pain (n=5), pain and mass (n=4), mass and ITP (n=1), mass (n=2), mass with rapid enlargement in pregnancy (n=1), preoperative diagnosis of HCC (n=1), preoperative diagnosis of metastasis (n=1), incidental (n=1). HCH excised due to symptomatology (n=9), measured 5, 6, 7 (2), 9, 10 (2), 14 and 18 cm.
Shumacker and Baltimore (1942)	18	9 - 32	12	Surgical resection.
Alper *et al.* (1988)	9	8 - 23	13.3	Surgical resection. Pain (n=3), pain and mass (n=3), mass (n=1), asymptomatic incidental (n=2).
Henson *et al.* (1956*b*)	11	4 - 40	15	Group A: Surgical resection for symptomatic HCH.
Adam *et al.* (1970)	22	6 - 45	17.2	Surgical resection for symptomatic HCH (n=18). Incidental finding at laparotomy for other conditions (n=4).
Vishnevsky *et al.* (1991)	16	15 - 31	19	Surgical resection for symptomatic HCH.
All studies	356	-	10.2	Mean of the mean values.
All studies	356	0.4-45	-	Range.

APPENDIX 10

Giant Hepatic Cavernous Haemangioma

STUDY	SIZE (cm)	WEIGHT (gm)	COMMENTS
Sewell and Weiss (1961)	10	-	Spontaneous rupture (fatal haemorrhage).
Aspray (1945)	12 x 6	-	Autopsy. Calcified.
O'Donoghue and Nicosia (1950)	16 x 14	-	Surgical resection of symptomatic liver mass.
Shimizu *et al.* (1990)	18 x 12 x 8	1490	Surgical resection of symptomatic liver mass.
Langer (1901)	21 x 21 x 11	5000	Surgical resection.
McCallum (1917)	24	-	Autopsy. Pedunculated.
M'Weeney (1912)	25 x 25 x 10	-	Surgical resection.
Peck (1921)	26 x 20 x 9	1700	Surgical resection for pain and abdominal enlargement.
Mantle (1903)	30 x 16 x 4	-	Surgical resection.
Shumacker and Baltimore (1942)	32 x 22 x 9	2500	Surgical resection.
Schwartz and Husser (1987)	32	-	Surgical resection. Liver mass and pain.
Roggenbau (1910)	33 x 22 x 9	-	Autopsy.
Adam *et al.* (1970)	45x 25 x 25	-	Surgical resection. Large abdominal mass with RUQ tenderness.
Rubin (1918)	61 x 41 x 10	2200	Surgical resection of a pedunculated HCH reaching down into the pelvis, presenting with rapid growth and accompanied by pain (in pregnancy).
Tokushige (1940)	-	2800	Autopsy.

APPENDIX 11

Lobar Distribution of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	(R) LOBE (%)	(L) LOBE (%)	(R) & (L) LOBES (%)	UNRECORDED / OTHER (%)	COMMENTS
Andersson and Bengmark (1988)	8	7 (88)	1 (12)	-	-	Surgical.
Schwartz and Husser (1987)	12	10 (84)	1 (8)	1 (8)	-	Non-operative.
Trastek *et al.* (1983)	49	34 (69)	3 (6)	12 (25)	-	Surgical.
Adam *et al.* (1970)	22	13 (59)	3 (14)	6 (27)	-	Surgical.
Ochsner and Halpert (1958)	50	28 (56)	13 (26)	-	9 (18)	Autopsy. Solitary.
Alper *et al.* (1988)	9	5 (56)	4 (44)	-	-	Surgical.
Henson *et al.* (1956*b*)	11	6 (55)	4 (36)	1 (9)	-	Surg. Symptomatic.
Henson *et al.* (1956*b*)	24	11 (46)	7 (29)	4 (17)	2 (8)	Surg. Incidental.
Peck (1921)	21	7 (33)	11 (52)	1 (5)	2 (10) Not recorded 1 Spigelian lobe 1	Surgical.
Shumacker and Baltimore (1942)	56	18 (32)	30 (54)	5 (9)	3 (5) Spigelian lobe 1 Accessory lobe 1 Schnurrlappen 1	Surgical.
Schwartz and Husser (1987)	16	4 (25)	8 (50)	3 (19)	1 (6) Quadrate lobe	Operative.
Bornman *et al.* (1987)	4	1 (25)	1 (25)	2 (50)	-	Surg. Small series.
Ochsner and Halpert (1958)	5	1 (20)	-	4 (80)	-	Autopsy. Multiple.
Wilson and Tyson (1952)	3	-	2 (67)	1 (33)	-	Surg. Small series.
All studies	290	145 (50)	88 (30)	40 (14)	17 (6)	Right lobe predominance.

APPENDIX 12

Depth Distribution of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	SUB - CAPSULAR	DEEP	NOT STATED	COMMENTS
Ochsner and Halpert (1958)	50	29	4	17	Autopsy. Solitary HCH. Inconclusive.
Ochsner and Halpert (1958)	5	4	-	1	Autopsy. Multiple HCH.
Tait *et al.* (1992)	7	6	1	-	Clinical. Symptomatic HCH. Giant HCH (5/7).
Tait *et al.* (1992)	54	11	43	-	Clinical. Asymptomatic HCH. Inversion of the common high subcapsular / parenchymal ratio.
All studies	116	50	48	18	Inconclusive

APPENDIX 13

Association of Hepatic Cavernous Haemangioma with Cavernous Haemangioma in other Organs

STUDY	ORGANS INVOLVED
Ullmann	Liver and skin.
Payne (1869)	Liver, adrenals, ovaries and uterus.
Langhans (1879)	Liver and spleen.
Roggenbau (1910)	Liver and scrotum.
Von Falkowski (1914)	Liver, spleen and skin.
Major and Black (1918)	Liver, skull and bilateral (cystic) adrenal glands.
Wunschmann *et al.* (1987)	Liver, intestine and mesentery.

APPENDIX 14

Association of Hepatic Cavernous Haemangioma with Focal Nodular Hyperplasia and Hepatic Adenoma

STUDY	PATIENTS WITH FNH	PATIENTS WITH HA	% LIVERS WITH HCH	COMMENTS
Ishak and Rabin (1975)	130	-	2.3	Autopsy.
Benz and Baggenstoss (1953)	34	-	20.6	Autopsy. Retrospective.
Mathieu *et al.* (1989)	26	-	23.1	Clinicopathologic. FNH diagnosed histologically after surgical resection. HCH (n=8, in six patients). HCH in same lobe or segment - resected with FNH and diagnosed histologically (n=6); HCH in same lobe - not resected with FNH diagnosed by preoperative U/S and dynamic CT.

APPENDIX 15

Relative Prevalence of Benign Liver Tumours

STUDY	BENIGN NEOPLASMS TOTAL	HCH (%)	FNH (%)	HEPATO - ADENOMA (%)	CHOLANGIO - ADENOMA (%)	CHOLANGIO - HEPATO - ADENOMA (%)	CYSTADENOMA	CYSTS	OTHERS	COMMENTS
Gold *et al.* (1978)	45	Excl.	21 (47)	12 (27)	11 (24)	-	-	-	1 Mesenchymal Hamartoma (2)	Surgical-pathological and autopsy series. (1950-1976). Selection excludes HCH.
Malt *et al.* (1970)	26	11 (42)	3 (12)	4 (15)	-	-	-	7 (27)	1 Mesenchymal Hamartoma (4)	Pathology records. (1947-1968).
Henson *et al.* (1956*a*)	124	35 (28)	-	4 (3)	7 (6)	2 (2)	5 (4)	71 (57)	-	Surgical records of the Mayo Clinic. (1907-1954).

APPENDIX 16

Prevalence of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	PATIENTS WITH HCH (%)	COMMENTS
Edmondson (1958)	50 000	175 (0.35)	Autopsy series.
O'Donoghue and Nicosia (1950)	20 029	140 (0.7)	Autopsy series.
Craig *et al.* (1989)	91 000	850 (0.9)	Autopsy series.
Adami (1910)	1 400	20 (1.4)	Autopsy series.
Gandolfi *et al.* (1991)	21 280	292 (1.4)	Ultrasonographic series.
Ochsner and Halpert (1958)	2 400	55 (2.3)	Autopsy series.
Feldman (1958)	1 319	96 (7.3)	Autopsy series.
Karhunen (1986)	95	19 (20)	Prospective consecutive medicolegal autopsies.
Sinanan and Marchioro (1989)	60	12 (20)	Clinical retrospective study. HCH diagnosed in patients referred for surgery of neoplastic liver disease.
Iwatsuki *et al.* (1990)	547	114 (20.8)	Prospective series of consecutive hepatic resections for neoplastic liver disease.
Little *et al.* (1990)	64	33 (52)	Prospective clinical series of incidental hepatic lesions referred for diagnosis and management.

APPENDIX 17

Age and Sex Distribution of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	AGE RANGE (YRS)	AGE MEAN (YRS)	F/M RATIO	COMMENTS
Lise *et al.* (1992)	51	27-72	35	1.7:1	Selected surgical series. Resection of HCH > 5 cm. Symptomatic (n=22).
Reading *et al.* (1988)	24	27-65	43.5	1.4:1	Clinical series.
Henson *et al.* (1956*b*)	11	1.2-58	43.6	10:1	Selected series. Surgical exploration for symptomatic HCH.
Shumacker and Baltimore (1942)	67	6-76	44	4.5:1	Literature review of HCH in which surgery was performed.
Iwatsuki *et al.* (1990)	114	21-77	46	3.2:1	Surgical resection of HCH.
Bornman *et al.* (1987)	4	40-54	46.3	4F	Surgical series.
Vishnevsky *et al.* (1991)	16	25-61	48	1.7:1	Surgical resection of symptomatic HCH.
Alper *et al.* (1988)	9	36-56	48.2	8:1	Selected surgical series. Treatment of symptomatic HCH by enucleation.
Tait *et al.* (1992)	61	26-85	49 (median)	3.4:1	Selected clinical series. Patients with HCH referred for assessment.
Sinanan and Marchioro (1989)	12	29-77	50	12F	Surgical series. Evaluation for surgery of neoplastic disease.
Adam *et al.* (1970)	22	0.3-77	50.1	1.2:1	Selected series of HCH > 4 cm. Symptomatic (n=18).
Starzl *et al.* (1980)	15	40-65	51.3	1.1:1	Selected surgical series. Excisional treatment of HCH.
Schwartz and Husser (1987)	28	29-80	50.4	3:1	Retrospective clinical series.

APPENDIX 17 (continued)

Age and Sex Distribution of Hepatic Cavernous Haemangioma

STUDY	PATIENTS	AGE RANGE (YRS)	AGE MEAN (YRS)	F/M RATIO	COMMENTS
Henson *et al.* (1956*b*)	24	34-75	53.8	3.8:1	Surgical series. HCH found incidentally at laparatomy for some other condition.
Karhunen (1986)	19	35-69	53.9	19M	Autopsy series (males only).
McLoughlin (1971)	12	33-80	57.6	5:1	Angiographic series. Symptomatic (n=2).
Wilson and Tyson (1952)	84	22d-76	Data not available	F > M	Literature review of HCH in which surgery was performed.
Plachta (1962)	13	67-86	Data not available	12:1	Selected series of calcified HCH.
Edmondson (1958)	175	Data not available	57.7	0.77:1	Autopsy series.
Craig *et al.* (1989)	850	Data not available	Data not available	0.63:1	Autopsy series.

APPENDIX 18

Spontaneous Rupture of Hepatic Cavernous Haemangioma

STUDY	COMMENTS
Haefen (1898)	Described the first case of spontaneous rupture of hepatic haemangioma, discovered at autopsy.
Karp (1931)	Reported the first case of ruptured hepatic haemangioma treated with hepatic resection. The patient died on 10th post-operative day.
Tinker (1935)	Reported the first successful resection of a ruptured hepatic haemangioma.
Shumacker and Baltimore (1942)	Reported rupture having occurred in only 3 of 67 reviewed patients (4.5%), all three of whom had had large tumours, symptomatic for more than 5 years.
Sewell and Weiss (1961)	Reviewed 12 cases of spontaneous rupture reported in the literature (including one case of his own), only 4 having survived (mortality 67%).
Adam *et al* (1970)	Reported spontaneous rupture in one (0.9%) and incisional rupture in one (0.9%) of 106 patients seen over a 31 year period.
Trastek *et al* (1983)	Found 21 cases of spontaneous rupture reported in the literature since 1898.
Yamamoto *et al* (1991)	Found 28 cases of spontaneous rupture reported in the literature, including one of his own. Of the 9 children, only 3 survived (mortality 67%). Ruptured haemangiomas ranged from 3 to 25 cm in diameter and many were located on the inferior surface of the liver.

APPENDIX 19

Abnormal Liver Function Tests in Hepatic Cavernous Haemangioma

STUDY	PATIENTS	↑ BILIRUBIN	↑ ALP	↑ ALP γ GT	ABNORMAL UNSPECIFIED	COMMENTS
Henson *et al.* (1956*b*)	11	3	-	-	-	Large symptomatic haemangiomas. Bilirubin returned to normal in two patients following radiotherapy.
Pateron *et al.* (1991)	2	-	-	2	-	Selected case reports presenting with pain, fever and abnormal LFT. ALP and γ GT normalised following surgical resection.
Bornman *et al.* (1987)	4	-	1	-	-	Large haemangiomas (symptomatic - n=3, asymptomatic - n=1). ALP normalised following surgical resection.
Reading *et al.* (1988)	24	-	-	1	3	Patients with unspecified abnormal LFT had evidence of underlying parenchymal liver disease in addition to haemangioma (autoimmune chronic active hepatitis, Gilbert's disease and alcoholic liver disease).
Adam *et al.* (1970)	22	-	-	-	1	Patient with concomitant common bile duct calculi.

APPENDIX 20

^{99m}Tc Erythrocyte Blood Pool Scintigram Interpretation

PATIENT	OBSERVER I	OBSERVER II	OBSERVER III	FINAL DIAGNOSIS
1	+	+	+	Cavernous haemangioma
2	+	+	+	Cavernous haemangioma
3	+	+	-	Metastatic carcinoma
4	-	-	-	Focal nodular hyperplasia
5	-	-	-	Indeterminate
6	+	+	+	Cavernous haemangioma
7	+	+	+	Cavernous haemangioma
8	+	+	+	Cavernous haemangioma
9	+	+	+	Cavernous haemangioma
10	-	-	-	Indeterminate
11	+	+	+	Indeterminate
12	-	-	-	Liver neoplasm (probably malignant)
13	+	+	+	Cavernous haemangioma
14	-	-	-	Indeterminate
15	-	-	-	Indeterminate

APPENDIX 20 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Interpretation

PATIENT	OBSERVER I	OBSERVER II	OBSERVER III	FINAL DIAGNOSIS
16	-	-	-	Metastatic carcinoma
17	+	+	-	Hepatocellular carcinoma
18	+	+	-	Hepatocellular carcinoma
19	+	+	+	Cavernous haemangioma
20	+	+	+	Cavernous haemangioma
21	-	-	-	Hepatocellular carcinoma
22	+	+	-	Indeterminate
23	+	+	+	Cavernous haemangioma
24	-	+	-	Indeterminate
25	+	+	+	Cavernous haemangioma (probable)
26	+	+	-	Cavernous haemangioma
27	+	+	+	Cavernous haemangioma (probable)
28	+	+	+	Hepatocellular carcinoma
29	+	+	-	Hepatocellular carcinoma
30	-	-	-	Hepatocellular carcinoma

APPENDIX 20 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Interpretation

PATIENT	OBSERVER I	OBSERVER II	OBSERVER III	FINAL DIAGNOSIS
31	+	+	+	Hepatocellular carcinoma
32	-	-	-	Low grade malignancy / FNH
33	+	+	-	Cavernous haemangioma (probable)
34	-	-	-	Metastatic spindle cell tumour
35	-	-	-	Metastatic adenocarcinoma (sigmoid)
36	-	+	-	Liver abscess (infected hydatid cyst)
37	-	-	-	Metastatic transitional cell carcinoma
38	+	+	+	Cavernous haemangioma (probable)
39	-	-	-	Metastatic adenocarcinoma (bronchus)
40	+	+	-	Cavernous haemangioma (probable)
41	-	+	-	Indeterminate
42	-	-	+	Metastatic sarcoma
43	+	+	+	Cavernous haemangioma
44	+	-	-	Cavernous haemangioma
45	+	-	-	Metastatic adenocarcinoma

APPENDIX 21

^{99m}Tc Erythrocyte Blood Pool Scintigram Description

PATIENT	NO. OF LESIONS	SITE OF LESIONS	DESCRIPTION	FINAL DIAGNOSIS
1	1	(R) lobe	Characteristic with a large area of typical and a small area of atypical appearance	Cavernous haemangioma
2	2	(R) lobe (L) lobe lateral segment	Characteristic and atypical (both)	Cavernous haemangioma
3	1	(R) lobe	Characteristic	Metastatic carcinoma
4	1	(R) lobe	Increased arterial flow Decreased blood pool	Focal nodular hyperplasia
5	-	-	Normal blood flow and blood pool	Indeterminate
6	1	(R) lobe	Characteristic	Cavernous haemangioma
7	1	(R) lobe	Characteristic with a large area of typical and a small area of atypical appearance	Cavernous haemangioma
8	2	(R) lobe (L) lobe medial segment	Characteristic (both)	Cavernous haemangioma
9	1	(R) lobe	Characteristic and atypical	Cavernous haemangioma
10	-	-	Normal blood flow and blood pool	Indeterminate

APPENDIX 21 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Description

PATIENT	NO. OF LESIONS	SITE OF LESIONS	DESCRIPTION	FINAL DIAGNOSIS
11	2	(L) lobe medial segment	Characteristic and typical	Indeterminate
12	-	-	Normal blood flow and blood pool	Liver neoplasm (? malignant)
13	2	(R) lobe	Characteristic (both)	Cavernous haemangioma
14	-	-	Normal blood flow and blood pool	Indeterminate
15	-	-	Normal blood flow and blood pool	Indeterminate
16	1	(R) lobe (L) lobe medial segment ext.	Decreased blood flow Decreased blood pool	Metastatic carcinoma
17	1	(R) lobe	Characteristic and atypical	Hepatocellular carcinoma (low grade)
18	3 (?4)	(R) lobe (L) lobe medial segment	Characteristic and atypical (all)	Hepatocellular carcinoma
19	1(?2)	(R) lobe	Characteristic and typical (anterior segment) Characteristic and atypical (posterior segment)	Cavernous haemangioma
20	1	(R) lobe	Characteristic with a large area of typical and a small area of atypical appearance	Cavernous haemangioma

APPENDIX 21 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Description

PATIENT	NO. OF LESIONS	SITE OF LESIONS	DESCRIPTION	FINAL DIAGNOSIS
21	1	(R) lobe (L) lobe medial segment ext.	Decreased blood flow Decreased blood pool	Hepatocellular carcinoma
22	4(?5)	(R) lobe	Characteristic (all)	Indeterminate
23	1	(R) lobe	Characteristic	Cavernous haemangioma
24	-	-	Normal blood flow and blood pool Prominent portal vein activity	Indeterminate
25	1	(R) lobe	Characteristic Early/late blood pool mismatch	Cavernous haemangioma (probable)
26	1	(R) lobe	Characteristic with a large area of typical and a small area of atypical appearance Early peripheral filling inferior half	Cavernous haemangioma
27	2	(R) lobe (L) lobe medial segment	Characteristic and typical (R) lobe Characteristic and atypical (L) lobe medial segment	Cavernous haemangioma (probable)
28	3	(R) lobe (clustered)	Characteristic and atypical (all)	Hepatocellular carcinoma
29	1 (2)	(R) lobe	Characteristic and atypical	Hepatocellular carcinoma
30	-	-	Normal blood flow and blood pool	Hepatocellular carcinoma

APPENDIX 21 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Description

PATIENT	NO. OF LESIONS	SITE OF LESIONS	DESCRIPTION	FINAL DIAGNOSIS
31	2	(R) lobe (L) lobe medial segment	Characteristic (both)	Hepatocellular carcinoma
32	1	(R) lobe (L) lobe medial segment ext.	Decreased blood flow Decreased blood pool	Low grade malignancy or focal nodular hyperplasia
33	2	(L) lobe medial segment	Characteristic (both)	Cavernous haemangioma (probable)
34	2	(R) lobe	Decreased blood flow Decreased blood pool (both)	Metastatic spindle cell tumour (? leiomyosarcoma)
35	1	(R) lobe	Normal blood flow Decreased blood pool	Metastatic adenocarcinoma (sigmoid colon)
36	1	(R) lobe	Decreased blood flow Decreased blood pool	Liver abscess (infected hydatid cyst)
37	-	-	Normal blood flow and blood pool	Metastatic transitional cell carcinoma
38	1	(R) lobe	Characteristic	Cavernous haemangioma (probable)
39	-	-	Normal blood flow and blood pool	Metastatic adenocarcinoma (bronchus)
40	2	(R) lobe	Characteristic (both)	Cavernous haemangioma (probable)

APPENDIX 21 (continued)

^{99m}Tc Erythrocyte Blood Pool Scintigram Description

PATIENT	NO. OF LESIONS	SITE OF LESIONS	DESCRIPTION	FINAL DIAGNOSIS
41	1	(R) lobe	Decreased blood flow Decreased blood pool	Indeterminate
42	1	(L) lobe	Decreased blood flow Decreased blood pool	Metastatic sarcoma
43	1	(R) lobe	Characteristic	Cavernous haemangioma
44	1	(R) lobe	Characteristic	Cavernous haemangioma
45	3	(R) lobe	Characteristic (all)	Metastatic adenocarcinoma

APPENDIX 22

^{99m}Tc Erythrocyte Blood Pool Scintigram Description - Terminology

Characteristic	Typical	Atypical
Activity increased in the lesion relative to the adjacent hepatic parenchyma in the late blood pool phase (1-2 hours)	Activity *decreased* in the lesion relative to the adjacent hepatic parenchyma in the dynamic phase	Activity *increased* in the lesion relative to the adjacent hepatic parenchyma in the dynamic phase

APPENDIX 23

Clinical and Diagnostic Data

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
1	66	F	Asymptomatic incidental US finding of liver mass Hepatomegaly 3 cm firm	Single complex lesion (R) lobe posterior segment 16 x 14 x 14 cm	Large low density lesion (R) lobe posterior segment Dynamic: compatible with cavernous haemangioma	MRI: compatible cavernous haemangioma	Histology: liver biopsy - lymphangioma	+	Cavernous haemangioma
2	47	F	RUQ pain	Single hypoechoic lesion (R) lobe	Two large low density lesions (R) and (L) lobes Dynamic: characteristic of cavernous haemangioma			+	Cavernous haemangioma
3	61	M	Weight loss History of alcoholism Hepatomegaly 5 cm smooth non-tender	Multiple hyperechoic lesions throughout liver largest 2 cm.			Cytology: liver aspirate - no malignant cells	+	Metastatic carcinoma
4	21	F	RUQ pain Oral contraceptive usage	Single isoechoic lesion (R) lobe 4 x 4.3 x 4.3 cm	Low density lesion (R) lobe Compatible with FNH	Angiography: compatible with FNH		-	Focal nodular hyperplasia

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
5	74	F	1. RUQ / Epigastric pain Hepatomegaly 3 cm tender 2. Asymptomatic (at 15 months)	1. Single hyperechoic lesion (R) lobe 2.3 x 1.7 x 1.5 cm 2. Unchanged				-	Indeterminate
6	45	M	Weight loss Chronic cough Night sweats Hepatomegaly 5 cm firm	Single hyperechoic lesion (R) lobe 2 cm	Low density lesion (R) lobe Dynamic: compatible with cavernous haemangioma			+	Cavernous haemangioma
7	51	F	RUQ pain Previous fibrosarcoma of forehead (excised)	Single complex lesion (R) lobe 12 x 18 cm	Large low density lesion (R) lobe Dynamic: compatible with cavernous haemangioma	Angiography: compatible with cavernous haemangioma	Histology: liver biopsy - haemangioma	+	Cavernous haemangioma
8	35	M	RUQ pain	Multiple hyperechoic lesions	Multiple low density lesions Dynamic: compatible with cavernous haemangioma			+	Cavernous haemangioma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
9	51	F	Asymptomatic Hepatomegaly 8 cm non-tender	Single hyperechoic lesion (R) lobe	Low density lesion (R) lobe 5 x 4 cm Dynamic: characteristic of cavernous haemangioma			+	Cavernous haemangioma
10	68	F	Epigastric pain Abnormal LFT	1. Single hyperechoic lesion (R) lobe 2 cm 2. Unchanged (at 12 months)	1. Low density lesion (R) lobe Dynamic: compatible with cavernous haemangioma 2. No lesion identified with and without contrast (at 12 months)			-	Indeterminate
11	45	M	RUQ pain Previous embryonal carcinoma of testis (orchidectomy)	Single hyperechoic lesion (L) lobe 2.5 x 2.5 x 2.3 cm	1. Two low density lesions (R) and (L) lobes (8 mm) Poorly defined lesion (L) lobe (2.5 cm) 2. Two small low density lesions (R) and (L) lobes again seen (7 days) Lesion in (L) lobe not demonstrated			+	Indeterminate

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
12	64	M	Emphysema Hepatomegaly 3 cm hard non-tender Abnormal LFT Alpha fetoprotein > 10 ng/ml	Hyperechoic liver No focal lesions	Two irregular low density lesions (R) and (L) lobes Dynamic: not typical of cavernous haemangioma	Angiography: neovascularity in (R) lobe - benign or malignant neoplasm; haemangioma unlikely	Cytology: liver aspirate - no malignant cells	-	Liver neoplasm (low grade malignant)
13	46	F	Asymptomatic Previous carcinoma breast	Several hyperechoic lesions both lobes (1.5 - 2.0 cm)	Three lesions - (R) lobe (2 cm) (L) lobe (1 cm and 1 cm) Dynamic: lesion (R) lobe compatible with cavernous haemangioma			+	Cavernous haemangioma
14	42	F	Upper abdominal discomfort for 1 year Hepatomegaly 5 cm tender	Single hypoechoic lesion (L) lobe 1.3 cm	Single high density lesion (L) lobe lateral segment 1.5 cm Dynamic: not typical of cavernous haemangioma	Angiography: conventional hepatic arterial anatomy	Cytology: liver aspirate - no malignant cells	-	Indeterminate

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
15	51	F	Unexplained episodic weight loss Insulin dependent diabetes mellitus Asymptomatic	Liver - no focal lesions Spleen - focal nodular lesions	1. Lesion (L) lobe lateral segment 5 cm 2. Lesion not demonstrated (at 2 months) 3. Unchanged (at 3 months)		Histology: liver biopsy - primary sclerosing cholangitis	-	Indeterminate
16	56	M	Previous nasal polyp ? plasmacytoma ? melanoma ? granulocytic sarcoma Loss of weight Hepatomegaly Abnormal LFT	Single solid complex lesion (L) lobe (entire) and (R) lobe anterior segment Central necrosis	Large low density lesions (R) lobe anterior segment and (L) lobe medial segment		Cytology: liver aspirate - malignant cells metastatic poorly differentiated carcinoma (? melanoma)	-	Metastatic carcinoma
17	71	M	RUQ pain History of alcoholism Loss of weight Hepatomegaly massive Abnormal LFT Alpha fetoprotein > 10 ng/ml	Single well defined partially encapsulated complex lesion (R) lobe 11 cm	Mixed density lesion (R) lobe 15 x 12 cm Dynamic: not typical of cavernous haemangioma	Angiography: large hypovascular lesion (R) lobe internal vascularity bizarre with irregular neovascularity	Cytology: liver aspirate - highly atypical cells Histology: liver biopsy - post-hepatitic fibrosis and early cirrhosis	+	Hepatocellular carcinoma (low grade)

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
18	60	M	Abdominal pain Loss of weight Hepatomegaly 6 cm nodular firm tender Ascites Alpha fetoprotein > 1000 ng/ml					+	Hepatocellular carcinoma
19	63	F	Previous cavernous haemangioma (L) lobe resected segmentectomy Second cavernous haemangioma (R) lobe left in situ Recurrence of RUQ pain after 7 years with progressive hepatomegaly		Huge low density lesion involving (R) and (L) lobes Dynamic: compatible with cavernous haemangioma			+	Cavernous haemangioma
20	40	F	Epigastric discomfort Massive hepatomegaly	Single well defined hyperechoic lesion (R) lobe 20 cm	Large low density lesion (R) lobe Dynamic: characteristic of cavernous haemangioma		Histology: (R) lobectomy - cavernous haemangioma	+	Cavernous haemangioma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
21	26	F	Loss of weight Hepatomegaly 7 cm hard nodular Abnormal LFT Alpha fetoprotein > 1000 ng/ml Lumbar X-ray bone scan and ^{99m}Tc sulphur colloid scan - metastasis in L4 vertebra CXR - lung metastases	Complex lesion in (R) lobe extending into (L) lobe Second separate lesion in (R) lobe			Cytology: liver aspirate - malignant cells compatible with hepatocellular carcinoma	-	Hepatocellular carcinoma
22	42	M	Emphysema Epilepsy Hepatomegaly 6 cm hard Abnormal LFT	Multiple hyperechoic lesions both lobes				+	Indeterminate
23	47	M	Jaundice recent onset Hepatomegaly 10 cm tender Abnormal LFT Ascites	Two hyperechoic lesions (R) lobe	Two low density lesions (R) lobe Dynamic: diagnostic of cavernous haemangioma (caudal lesion)			+	Cavernous haemangioma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
24	57	F	RUQ pain Loss of weight History of heavy smoking	Four hyperechoic lesions two in (R) lobe two in (L) lobe (cystic)	Two loculated cystic lesions (L) lobe No lesions demonstrated in (R) lobe before or after contrast			-	Indeterminate
25	56	M	Epigastric pain episodic worse after meals responsive to ranitidine Asymptomatic follow up (10 months)	Single well defined hyperechoic lesion (R) lobe inferiorly 4.3 x 3.7 cm	Low density lesion (R) lobe inferiorly No contrast enhancement			+	Cavernous haemangioma (probable)
26	43	M	RUQ pain Weight loss Hepatomegaly 15 cm firm tender	Complex lesion involving (R) lobe and part of (L) lobe	Inhomogenous low density lesion (R) lobe with central fluid density component Dynamic: compatible with cavernous haemangioma		Histology: (R) lobectomy - cavernous haemangioma	+	Cavernous haemangioma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
27	62	F	Abdominal pain acute onset (1 day)	Multiple hyperechoic lesions some intrahepatic some extrahepatic projecting from liver edge				+	Cavernous haemangioma (probable)
28	68	M	History of alcoholism Loss of weight (marked) RUQ pain Hepatomegaly 20 cm hard nodular Bruit abnormal LFT Alpha fetoprotein > 10 ng/ml	Enlarged inhomogeneous liver with cystic (? necrotic) area in (R) lobe			Cytology: liver aspirate - malignant cells compatible with hepatocellular carcinoma	+	Hepatocellular carcinoma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
29	43	M	RUQ pain sudden onset (3 days heavy drinking) Hypovolaemic shock Hepatomegaly 3 cm firm Alpha fetoprotein < 10 ng/ml	Complex lesion (R) lobe posterior segment 9 x 8 x 6 cm Two satellite lesions (R) lobe anterior segment Subcapsular collection superiorly (R) Large subphrenic collection (R)	1. Low density lesion (R) lobe inferomedially with anterolateral fluid collection (subcapsular haematoma) 2. (R) lobe lesion and subcapsular haematoma increased in size (at 1 month) Free intraabdominal fluid	Angiography: hypervascular lesion (R) lobe posterior segment; second lesion (R) lobe anterior segment; obstructed (R) portal vein branch	Histology: liver biopsy - hepatocellular carcinoma	+	Hepatocellular carcinoma
30	62	F	RUQ pain	Lesion (R) lobe	Lesion (R) lobe		Histology: liver biopsy - hepatocellular carcinoma	-	Hepatocellular carcinoma
31	64	M	RUQ pain Progressive abdominal distension with ascites Hepatomegaly 5 cm firm Abnormal LFT Alpha fetoprotein > 1000 ng/ml	Inhomogeneous (R) lobe Multiple hyperechoic lesions with hypoechoic halos (L) lobe			Cytology: liver aspirate - malignant cells compatible with hepatocellular carcinoma	+	Hepatocellular carcinoma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
32	59	F	RUQ pain intermittent over 10 years Hepatomegaly progressive over 4 years (3 cm to 10 cm) firm tender Mild loss of weight Abnormal LFT Alpha fetoprotein < 10 ng/ml	Multiple rounded hyperechoic lesions	Multiple poorly defined low density lesions (R) and (L) lobes Slight increase in size and number over 4 years		Cytology: liver aspirate - no malignant cells Histology: liver biopsy - fatty degeneration and diabetic liver change	-	Low grade malignancy or focal nodular hyperplasia
33	70	F	Congestive heart failure Chronic renal failure Non insulin dependent diabetes mellitus Hepatomegaly 4 cm	Two hyperechoic lesions (R) and (L) lobes (incidental)				+	Cavernous haemangioma (probable)
34	53	M	Weight loss Hepatomegaly 10 cm non-tender Abnormal LFT	Large mixed hypoechoic lesions throughout both lobes			Histology: liver biopsy - spindle cell tumour	-	Metastatic spindle cell tumour (? leiomyosarcoma)

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
35	43	F	Intermittent rectal bleeding (1 year) Loss of weight Hepatomegaly 3 cm Abnormal LFT	Five discrete hyperechoic lesions (R) lobe	CT-portography: multiple low density lesions throughout liver		Cytology: liver aspirate - malignant cells compatible with metastatic carcinoma Histology: sigmoid colon biopsy - adenocarcinoma	-	Metastatic adenocarcinoma (sigmoid colon)
36	54	M	History of pyrexial illness with abdominal pain and jaundice Hepatomegaly 5 cm smooth non-tender Mildly abnormal LFT	Single hyperechoic lesion with echolucent rim (R) lobe 6 cm			Cytology: liver aspirate - inflammatory cells consistent with abscess	-	Liver abscess (infected hydatid cyst)
37	74	M	RUQ pain Haematuria		Multiple low density lesions		Histology: bladder biopsy - transitional cell carcinoma	-	Metastatic transitional cell carcinoma

APPENDIX 23 (continued)

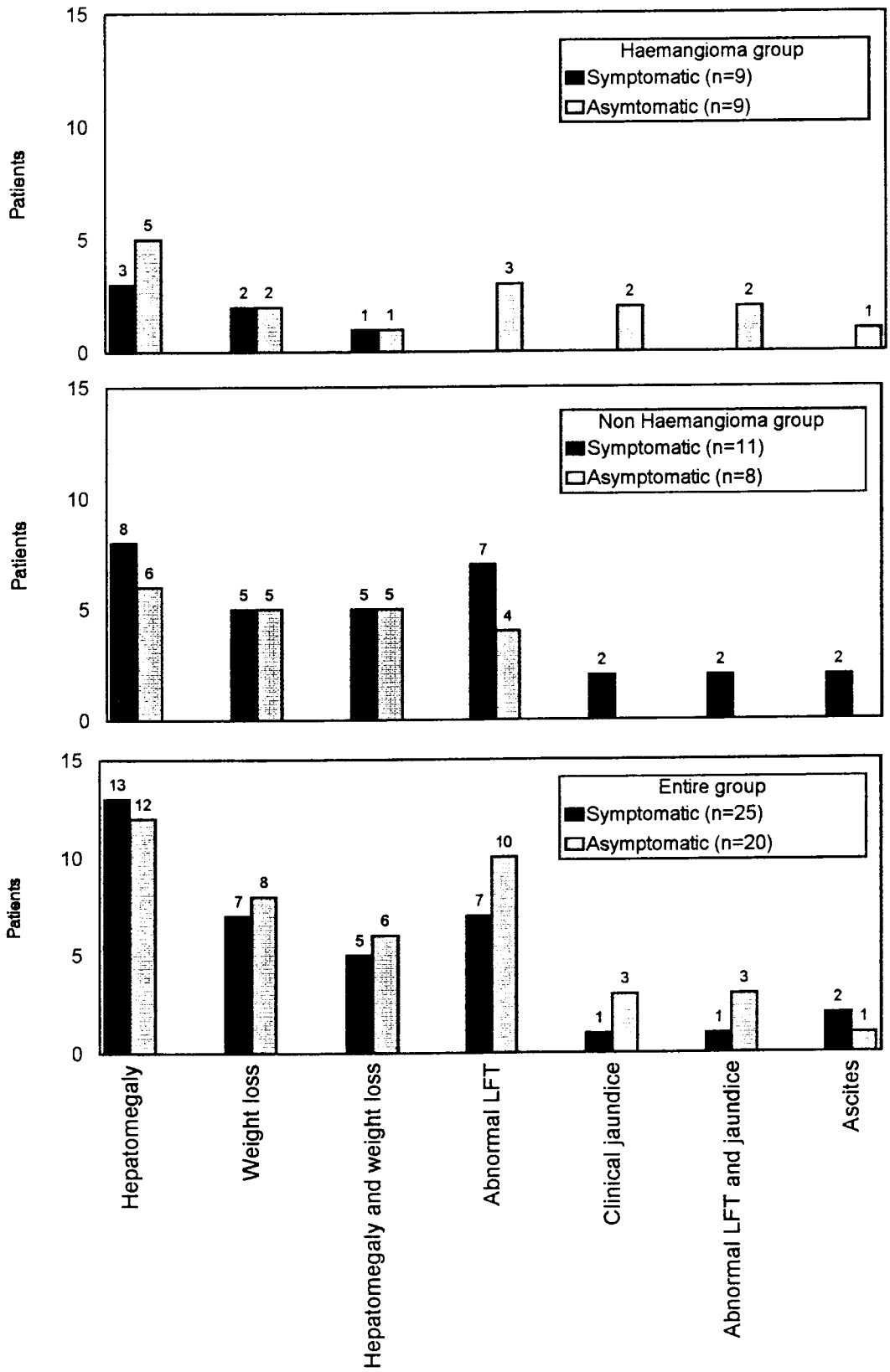
PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
38	48	M	Loss of weight (1 year) Diabetes mellitus End stage renal failure Mildly abnormal LFT	Three hyperechoic lesions (R) lobe (largest 3 cm)				+	Cavernous haemangioma (probable)
39	54	M	Chest pain and cough (3 months)		Three low density lesions (R) lobe (two) (L) lobe (one)		Histology: bronchial biopsy - adenocarcinoma	-	Metastatic adenocarcinoma (bronchus)
40	69	F	Diabetes mellitus Hypertension Ischaemic heart disease Jaundice Abnormal LFT Aldomet-induced hepatitis	Two hyperechoic lesions (R) lobe (2 cm) (8 cm)				+	Cavernous haemangioma
41	75	F	Carcinoma breast Sulphur colloid liver scan-cold focus (R) lobe		Atrophy (L) lobe medial segment No other abnormalities			-	Indeterminate
42	37	M	Loss of weight RUQ and LUQ pain Hepatomegaly non-tender	Complex lesion (L) lobe 9 x 6 cm	Low density lesion (L) lobe 8 x 4.7 cm		Cytology: liver aspirate - metastatic sarcomatoid tumour	-	Metastatic sarcoma

APPENDIX 23 (continued)

PATIENT	AGE	SEX	CLINICAL PRESENTATION	ULTRASOUND LIVER	CT LIVER	OTHER	PATHOLOGY	^{99m}Tc RBC STUDY	FINAL DIAGNOSIS
43	44	F	Pyelonephritis Pneumonia RUQ pain (occasional) Mild loss of weight	Single lesion hyperechoic (R) lobe 4 cm	Low density lesion (R) lobe 4 x 3 cm Dynamic: compatible with cavernous haemangioma			+	Cavernous haemangioma
44	75	F	Asymptomatic Previous carcinoma rectum	Single hyperechoic lesion with hypoechoic centre (R) lobe posterior segment 2.7 x 3.4 cm	Low density lesion (R) lobe posterior segment Dynamic: characteristic of cavernous haemangioma			+	Cavernous haemangioma
45	59	F	Abnormal LFT Obstructive jaundice	Lesion in porta hepatis region 7 x 8.8 cm	Low density lesion in porta hepatis region Irregular peripheral contrast enhancement		Cytology: liver aspirate - metastatic adenocarcinoma	+	Metastatic adenocarcinoma

APPENDIX 24

Clinical presentation - Graphical Representation



APPENDIX 25

Final Diagnoses - Graphical Representation