THE ROLE OF IMAGING WITH IODINE-131-META-IODOBENZYLGUANIDINE IN THE DIAGNOSIS AND LOCALISATION OF SUSPECTED PHAEOCHROMOCYTOMA

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INTRODUCTION

THE ROLE OF IMAGING WITH IODINE-131-META-IODOBENZYLGUANIDINE IN THE DIAGNOSIS AND LOCALISATION OF SUSPECTED PHAEOCHROMOCYTOMA

Phaeochromocytoma is a potentially lethal disorder. The secretion of increased amounts of catecholamines into the circulation by the metabolically active tumour can be life-threatening. Both benign and malignant tumours have this capability. Surgical removal of the majority of these tumours (other than the malignant, metastastic ones) is curative. Thus the detection and localisation of the phaeochromocytoma are vitally important.

The decade of the 1980's saw the development of ^{131}I-meta-iodobenzylguanidine(^{131}I-MIBG),a radiopharmaceutical reported to allow for the scintigraphic detection and localisation of the phaeochromocytoma. Wieland and his colleagues at the University of Michigan Medical School produced images of the adrenal medullas of dogs and monkeys using ^{131}I-MIBG.[1;2] Sissons et al working at the same medical school produced the first scintigraphic images in patients soon afterwards.[3] They claimed that scintigraphy was both safe and reliable for the localisation of phaeochromocytomas. Subsequent studies appear to have confirmed this initial impression.[4;5;6;7;8]

This study is an evaluation of the role of ^{131}I-MIBG scintigraphy and the results of our experience at the Groote Schuur Hospital over the last 4 years. The study entailed a review of literature on phaeochromocytomas, the characteristics of ^{131}I-MIBG and its scintigraphic appearances. In addition, a retrospective study of patient records is presented. The clinical, biochemical and scintigraphic features of the patients are compared with with the findings of other researchers in this field.

CHAPTER ONE

FEATURES OF PHAEOCHROMOCYTOMA

ORIGIN AND DISTRIBUTION

Phaeochromocytomas arise from chromaffin cells.These cells are of neuroectodermal origin. In the first trimester of fetal life, cells of the neural crest migrate from the thoracic region to form the sympathetic chain and to invade the developing adrenal cortex, where they become the adrenal medulla. Chromaffin cells are widespread during fetal life but degenerate from the age of three years. The major residual clusters of chromaffin cells comprise the adrenal medulla.

Thus approximately 90% of phaeochromocytoma arise from the adrenal medulla. Extra-adrenal phaeochromocytomas are found in sites ranging from the carotid body to the pelvic floor. The majority are associated with paravertebral sympathetic ganglia, the organ of Zuckerkandl near the aortic bifurcation in the abdomen, and with ganglia in the posterior mediastinum. These extra-adrenal phaeochromocytomas are more likely to be malignant than adrenomedullary phaeochromocytomas.

Cryer[9] and others[10] refer to all extra-adrenal phaeochromocytomas as paragangliomas while Smit et al[11] uses the term, paraganglioma when the tumour is extra -adrenal and nonfunctional but prefers the term, phaeochromocytoma for tumours

which secrete catecholamines, whether they are intra- or extra-adrenal. Khafagi[12], on the other hand, reserves the term phaeochromocytoma for functional tumours of the adrenal medulla, and uses "functional" and "nonfunctional" paragangliomas for extra-adrenal tumours according to whether or not they secrete catecholamines and produce "the clinical syndrome of phaeochromocytoma".

In this paper, all chromaffin tumours (with the exception of Carcinoid tumours which arise from enterochromaffin cells) are referred to as phaeochromocytomas, and specific mention is made as to whether these are adrenomedullary or extra-medullary and whether they are metabolically active or not.

Multiple phaeochromocytomas occur in up to 10% of sporadic cases. However, bilateral adrenomedullary phaeochromocytomas are the rule in familial phaeochromocytoma associated with multiple endocrine neoplasia (MEN) type 2a and type 2b syndromes. MEN 2a (Sipple's syndrome) includes medullary carcinoma of the thyroid, primary hyperparathyroidism and phaeochromocytoma. MEN 2b includes medullary carcinoma of the thyroid, multiple mucosal neuromas and phaeochromocytoma. Familial phaeochromocytomas also occur in association with neurofibromatosis and in the von Hippel-Lindau syndrome.

INCIDENCE

The incidence of phaeochromocytoma in the adult population has

been reported as being between Ø.Ø1% and Ø.ØØ1%.[13,14] The incidence in hypertensive patients is thought to be in the order of Ø.1%-Ø.Ø1%.[14] Approximately 1Ø% occur in children, 1Ø% are extraadrenal and 1Ø% are malignant[13] .Sutton[15] in a series of autopsy-proven cases discovered that the disorder was multiple in 19%, extra-adrenal in 9% and malignant in 11%. Phaeochromocytomas present most commonly in the fourth and fifth decades when they occur predominantly sporadically. Multifocal tumours occur in 35% of children. No sex predominance has been noted.

BIOCHEMISTRY

The substrate of catecholamine synthesis is tyrosine which is hydroxylated to L-DOPA (Dihydroxyphenylalanine). The enzyme PNMT (Phenylethanolamine methyl transferase) converts norepinephrine to epinephrine. (See Figure 1 on page 6)[13] Epinephrine is the major hormonal product in the adrenal medulla. Norepinephrine acts as a neurotransmitter at sympathetic nerve endings.

Norepinephrine and epinephrine are stored in granules which release their contents when the sympathetic nervous system is activated.These catecholamines are inactivated by re-uptake and by metabolic degradation. Metabolites include VMA (vanillylmandelic acid), metanephrine and NMA (normetanephrine). Free catecholamines and their metabolites are excreted in the urine. Norepinephrine may be excreted by intra- and extra-adrenal tumours, whereas 95% of epinephrine-secreting tumours are intra-

FIGURE 1

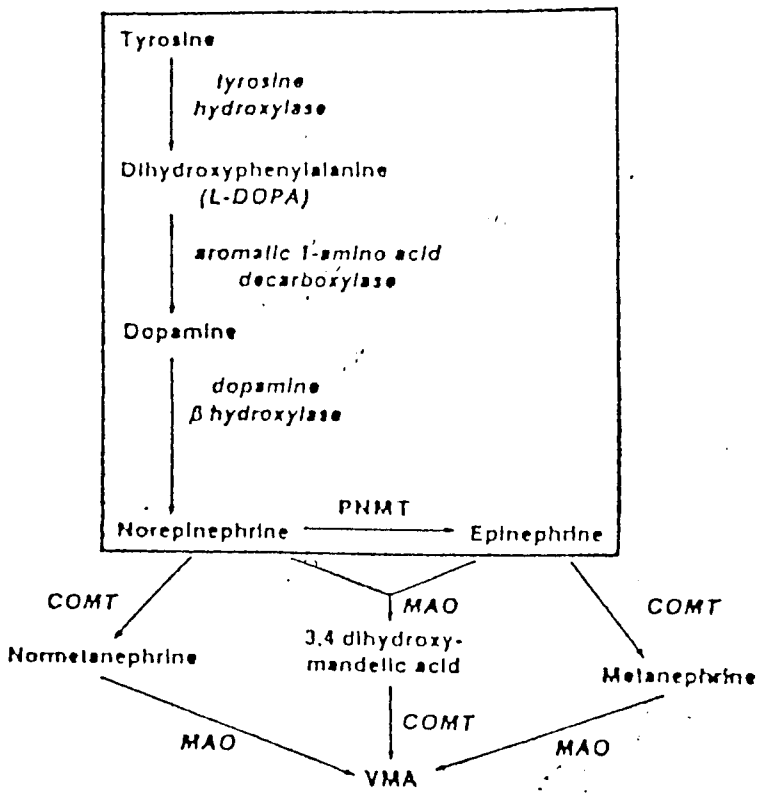


Fig 1 Biosynthesis and metabolism of catecholamines. Biosynthetic pathways are enclosed within the square. PNMT, phenylethanolamine-*n*-methyl transferase; MAO, monoamine oxidase; COMT, catechol-*O*-methyl transferase; VMA, vanillylmandelic acid.

adrenal.[13]

CLINICAL FEATURES

The clinical manifestations of phaeochromocytomas are due mainly to the effects of the catecholamines they produce. Phaeochromocytomas release noradrenaline predominantly, but some adrenaline is also released. Rarely do the mass effects of the tumour give rise to symptoms. Some phaeochromocytomas are discovered at autopsy or incidentally at surgery. A review of autopsy-proven cases of phaeochromocytoma seen at the Mayo Clinic over a 50 year period showed that only 24% of patients were correctly diagnosed in life.[15]

Common symptoms of phaeochromocytomas are headache, palpitations, diaphoresis and anxiety. Other symptoms include abdominal or chest pain, gastrointestinal symptoms, weakness or visual symptoms. Symptoms are typically paroxysmal and associated with increases in blood pressure. Paroxysms usually last only a few minutes but may persist for up to an hour or more.

Hypertension is often sustained but may be intermittent. Persistent hypertension is found in 55%[13,15] of patients. In these cases there may be marked fluctuations in the blood pressure with peaks occurring during symptomatic episodes. These

episodes are explained on the basis of intermittent catecholamine release- plasma catecholamine levels are higher during hypertensive episodes than during asymptomatic, less hypertensive or normotensive intervals. What precipitates the episodic catecholamine release is unknown and the relationship between plasma noradrenaline levels and blood pressure is not a constant one.[16]

Convulsions, visual disturbances, weight loss, and vomiting all occur more frequently in children[13].

Metabolic features of phaeochromocytoma include an increased metabolic rate (patients may complain of heat intolerance and weight loss), limitation of insulin secretion and an insulin resistant state. Glucose intolerance occurs but overt diabetes is unusual.

The rare, predominantly adrenaline-releasing phaeochromocytomas can produce different paroxysms. These may include systolic hypertension, tachycardia, hypotension, non-cardiac pulmonary oedema and cardiac arrythmias.

DIAGNOSIS

Phaeochromocytomas produce catecholamines which give rise to typical symptoms when released into the circulation. The diagnosis of a clinically suspected phaeochromocytoma is dependent upon the detection of these catecholamines and their metabolites in the plasma and urine. The most widely used

screening procedures for the detection of phaeochromocytoma are measurements of urinary catecholamines or their metabolites, such as vanillylmandelic acid (VMA) or total metanephrines. However, some feel that these tests are erratic and plasma catecholamine concentrations have been found to be more reliable predictors of phaeochromocytoma.[16]

The diagnosis of phaeochromocytoma is suspected on the basis of clinical manifestations and is confirmed biochemically. Phaeochromocytomas are suspected in patients with paroxysmal symptoms and hypertension that is intermittent, labile or resistant to conventional therapy. Persons with a familial history of phaeochromocytoma should be thoroughly evaluated. Nuclear medicine and radiographic studies are used to confirm the diagnosis and localize phaeochromocytomas once the diagnosis is strongly suspected on the basis of clinical and biochemical evidence.

Fluorometric assays of catecholamines or spectrophotometric measurement of total metanephrines or VMA in 24-hour urine collections are the most common approach to the biochemical diagnosis of phaeochromocytoma. The urinary catecholamines can be fractionated into adrenaline and noradrenaline if predominant adrenaline release is suspected. The excretion of all these substances is significantly increased in the majority of patients with phaeochromocytoma.[14] Catecholamine excretion is an index of released catecholamine whereas

catecholamine degradation within the tumour also contributes to the excreted VMA.

The development of highly sensitive and specific single and dual radioisotope methods for plasma catecholamine assays has resulted in these being used in the diagnosis of phaeochromocytoma in certain institutions.[16] These assays obviate the need to collect 24-hour urine specimens; blood can be conveniently collected before and after a provocative test, and catecholamine levels correlated with blood pressure response; and spontaneous or provoked changes in catecholamine production can be correlated with cardiovascular status. However, care must be taken to ensure that the patient is in a resting state when the blood is taken as even minimal stress can result in an elevation of catecholamine levels.

Bravo and his colleagues[16] use the following diagnostic approach:

1. total plasma catecholamine levels are measured with the patient at rest and in a supine position. A value of 1ØØØ ng per litre or less rules out phaeochromocytoma and values between 1ØØØ and 2ØØØ ng per litre are equivocal.

2. a glucagon test is performed only if the clinical findings are highly suggestive of phaeochromocytoma. A positive glucagon test requires a rise in the systolic blood pressure of at least 15-2Ø mm Hg above the response to a cold pressor test, and a clear increase (at least threefold or greater than 2ØØØ ng per

litre) in simultaneously measured plasma catecholamines. However, provocative tests like these are dangerous and are rarely used for diagnostic purposes today.

Bravo and his colleagues[16] claim that the plasma catecholamine measurements are superior to measurements of urinary catecholamines because there is less overlap between affected and unaffected hypertensive patients. But the two approaches yield different information. Urinary measurements provide an index of catecholamine production and release over a period of 24 hours. They might reflect intermittent catecholamine elevations that could be missed by plasma measurements which provide information relevant to a comparatively short time period of a few minutes.

Careful sample collection, handling and storage are essential for reliable results. A knowledge of the sources of biological variation of catecholamines and the effects of drugs is vital if diagnostic error is to be avoided.(See Table 1 on page 12)[13]

It must however be emphasised that most patients with phaeochromocytomas have elevated plasma and urinary catecholamine levels.

TABLE 1

BIOCHEMICAL TESTS FOR PHEOCHROMOCYTOMA AND INTERFERING SUBSTANCES

URINARY	VMA	METANEPHRINES	CATECHOLAMINES
Normal values	< 6.5 mg/24 h	< 1.3 mg/24 h	< 100 ug/ 24h
G.S.H.	0-40 µmol/24h	0-5 µmol/24h	E < 20 ug/24h NE < 80 ug24h
Increase	Catecholamines	Catecholamines	Catecholamines
	Drugs containing catecholamines	Drugs containing catecholamines	Drug containing catecholamines
	Amphetamines	Amphetamines	Amphetamines
	Methyldopa Levodopa	Methyldopa	Methyldopa
	Clonidine withdrawal	Clonidine withdrawal	Clonidine withdrawal
		Ethanol	Ethanol
	Methacarbanol	Diatrizoate	Erythromycin
	Glyceryl guaiacolate	MAO inhibitors	Tetracycline
	Nalidixic acid		Chlorpromazine
			Quinine
Decrease	Metyrosine	Metyrosine	Metyrosine
	Reserpine	Reserpine	Reserpine
	Guanethidine	Guanethidine	Guanethidine
	MAO inhibitors		
	Clofibrate		
	Disulfiram		
	Ethanol		

E, epinephrine: NE, norepinephrine

MANAGEMENT

The treatment of choice for unifocal and multifocal phaeochromocytoma is surgical removal. For surgery to be successful localisation of all existing tumour sites is essential. Computerised tomography (CT) is very sensitive for diagnosing intraadrenal phaeochromocytomas over 2 cm in size. However, smaller lesions and extraadrenal foci may defy identification by CT.[8,17] Even if CT delineates an extraadrenal tumour, the nature of the anatomic abnormality remains uncertain.

^{131}I-MIBG Scintigraphy was introduced by Sissons and his colleagues[3] in 1981 as a non-invasive whole body screen for imaging and localising phaeochromocytoma. They claimed that:

"Scintigrams are appealing because they not only locate the anatomic position of the disease but also shed light on the nature of the disturbance by providing evidence of function."

They also noted that ^{131}I-MIBG localised in malignant as well as benign phaeochromocytomas.

CHAPTER TWO

^{131}I-META-IODOBENZYLGUANIDINE

^{131}I-MIBG was first used to image the human adrenal medulla in 1981.[3] Sisson and his colleagues[3] produced images of phaeochromocytomas in 8 patients with known tumours using ^{131}I-MIBG although the normal adrenal medulla was not visualised.

CHEMISTRY

^{131}I-MIBG is a radioiodinated aralkylguanidine and an analogue of norepinephrine and guanethidine(a potent adrenergic neuron blocking agent).(See Figure 2 on page15)[13] It was first synthesised by Wieland et al in 1979.[18] The meta- isomer showed less liver and thyroid uptake indicating that it was more stable in vivo than the para-isomer.[1;2] Subcellular fractionation of the adrenal medulla showed sequestration of ^{131}I-MIBG in the chromaffin granules.[2]

MIBG is reacted with cyanamide and dissolved in potassium bicarbonate to precipitate MIBG bicarbonate. This is then reacted with normal sulphuric acid and purified by recrystallization to form MIBG sulphate as colourless crystals. Radioiodination is achieved with ^{123}I, ^{125}I or ^{131}I. A radiochemical yield of 60%-80% is achieved and

FIGURE 2

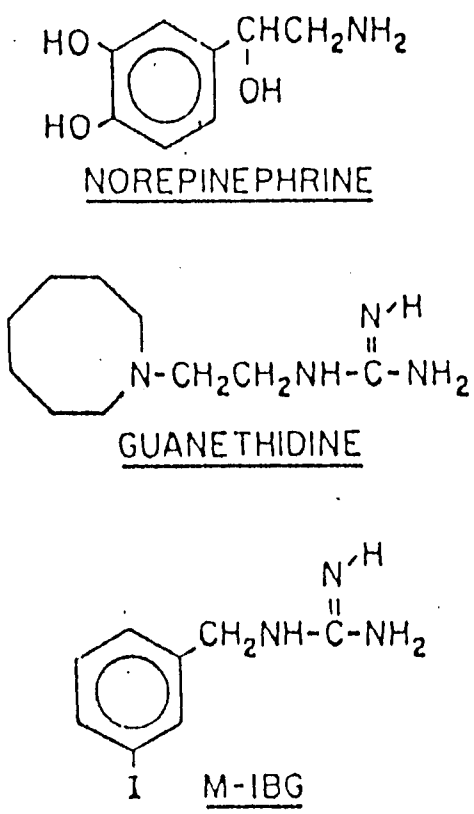


Fig 2 Comparison of the structurs of norepinephrine, guanethidine, and meta-iodobenzylguanidine.

specific activities up to 37Ø Mega Becquerels(MBq)/mg (1Ø mCi/mg).[1] Specific activities in excess of 148Ø MBq (4Ø mCi) /mg have now been achieved for therapeutic purposes.[13] Amino-iodobenzylguanidine, an analogue of MIBG, has been developed.[19] This agent is reported to show an affinity for the heart and adrenal medulla which is similar to that of MIBG in dogs and monkeys. It is available in a kit-form but has not yet been tested in humans.

METABOLISM

MIBG shares the same mode of uptake and retention as norephrine in peripheral adrenergic nerves.In vitro studies have shown that MIBG is avidly sequestered by the uptake carrier that transports norepinephrine. Sisson et al[3] showed that the percentage of the dose of ^{131}I-MIBG accumulating in phaeochromocytomas was 2% or less. They found no correlation between this percentage and the types or magnitudes of hormones in plasma and urine, or with the concentrations of norepinephrine and epinephrine within the tumours. Mangner et al[2Ø] found that 97% to 1ØØ% of the radioactivity extracted from the tumours of two patients was in the form of ^{131}I-MIBG. One tumour contained a small amount of free radioiodide.

Mangner et al[20] evaluated the excretion and metabolism of ^{131}I-MIBG in nine patients with phaeochromocytomas. They found that the major route of excretion is by the urinary tract. Forty to 55% of the administered activity appeared in the urine within 24 hours and 70% to 90% was recovered within 4 days. Using reverse high performance liquid chromatography they discovered unaltered ^{131}I-MIBG to be the major radioactive urinary component, accounting for 75% to 90% of the total radioactivity in 8 of the 9 patients investigated. ^{131}I-iodide and ^{131}I-m-iodohippuric acid were minor components in the urine samples. They found no correlation between plasma or urinary catecholamine levels, the presence of urinary metabolites and the location of tumours.[20] Less than 1% of the administered dose was detected in the faeces.[20]

These findings suggest that ^{131}I-MIBG is not appreciably metabolized and that it is excreted by the kidneys primarily as the unaltered compound. Furthermore, the analysis of the radioactivity extracted from the phaeochromocytomas following ^{131}I-MIBG administration indicates that MIBG is solely responsible for the images observed in humans.

MECHANISM OF UPTAKE

^{131}I-MIBG localizes within the intracellular, storage granules of the sympatho-adrenal system. The mechanism of uptake remains to be clearly defined but experiments with cultured human phaeochromocytoma cells and cultured bovine adrenomedullary cells have indicated that this occurs through the sodium-dependent Type 1 catecholamine uptake mechanism.[21;22] This uptake mechanism is shared by norepinephrine which is a competitive inhibitor of MIBG. Uptake is characterised by high affinity, low capacity, saturability, temperature, and ouabain sensitivity.[21] It is an active process which is inhibited by desmethylimipramine and cocaine.[22]

Shapiro et al[4] investigated 400 patients with phaeochromocytoma and discovered that the uptake of ^{131}I-MIBG by phaeochromocytoma is variable and ranges from no detectable activity (and hence false negative scans) through minimal uptake to intense uptake (true positive).These patterns occur in tumours which are apparently indistinguishable from each other in terms of location, histology, and levels of plasma and urinary catecholamine.

The uptake and storage mechanism of ^{131}I-MIBG does not always parallel the synthesis and secretion of catecholamines.

DOSIMETRY

Dosimetry calculations in humans are based upon tissue distribution data derived from experimental work on rats. It has been calculated that the largest absorbed dose from ^{131}I-MIBG is delivered to the adrenal gland.[13] The adrenal medulla is subjected to an estimated 100 rad/37 MBq(mCi) of ^{131}I-MIBG. The use of ^{123}I-MIBG significantly reduces the radiation dose to 0.8 rads/37 MBq for "pure" ^{123}I-MIBG. However ^{125}I contamination of ^{123}-I increases the dose to the adrenal medulla to 2.76 rads/37 MBq, that is by a factor of 3.5.[13]

A radiation dose of approximately 35 rads/37 MBq is delivered to the unblocked thyroid gland by ^{131}I-MIBG. This emphasises the importance of effectively blocking thyroid uptake. Far lower dosimetry estimates have been made for the heart (0.7 rads/37 MBq), liver (0.40 rads/37 MBq), ovaries (1.0 rads/37 MBq) and spleen (1.6 rads/37 MBq).[13] The total body absorbed dose has been estimated at 0.1 rads/37 MBq for ^{131}I-MIBG and 0.02 for ^{123}I-MIBG.[13]

^{131}I-MIBG SCINTIGRAPHY

PATIENT SELECTION

There should be a strong suspicion of phaeochromocytoma before a patient is selected for ^{131}I-MIBG scintigraphy. Shapiro et al[4] use the following criteria:

1. Labile, severe or uncontrolled hypertension and/or

2. Spells manifested by headache, palpitations, sweating, or abdominal pain and/or

3. Basal plasma norepinephrine.>6ØØ pg/ml and epinephrine >15Ø pg/ml or

4. Persistent urinary excretion rates for catecholamine that are greater than 3 s.d. above the mean for normal subjects.

5. Patients in whom there is historical, clinical or laboratory evidence of a syndrome associated with an increased frequency of phaeochromocytoma but who manifest only minor symptoms and/or intermittent or borderline laboratory abnormalities of phaeochromocytoma.

In their series of 4ØØ patients , Shapiro and his colleagues found no evidence of phaeochromocytoma in

patients with symptoms not typical of phaeochromocytoma and with normal catecholamine levels.

Indications[13] for imaging include:

1. Confirmation of adrenal disease if CT is equivocal;
2. Excluding coexisting extra-adrenal disease;
3. Identification of recurrent or extra-adrenal tumours;
4. Detection of unsuspected multifocal disease;
5. Assessment of malignant phaeochromocytoma;
6. Investigation of patients with a strong family history of phaeochromocytoma.

IMAGING PROTOCOL AND TECHNIQUE

This aspect is discussed in detail in Chapter 3.

IMAGING PATTERNS

NORMAL DISTRIBUTION

A thorough knowledge of the normal distribution of ^{131}I-MIBG is essential for the correct interpretation of the scintigraphs.

ADRENAL MEDULLA

The normal adrenal medulla is not visualized by ^{131}I-MIBG in the majority of patients but there have been reports of faint uptake in a few patients.[25] ^{123}I-MIBG scintigraphy, however, permits the routine visualization of normal adrenal medulla.[23;24] This is due to the fact that the ^{123}I-MIBG dose used is 20 times greater than that of the ^{131}I-MIBG.

LIVER

There is uniform uptake of ^{131}I-MIBG by the liver which is maximal at 24 hours and clears substantially by 72 hours.[13] The liver activity declines more rapidly than most phaeochromocytomas thus reducing the chances of the liver activity obscuring a phaeochromocytoma.

SPLEEN

The rich sympathetic innervation of the spleen results in early uptake which clears over 72 hours.

URINARY BLADDER

The renal excretion of ^{131}I-MIBG results in bladder activity which may obscure extraadrenal phaeochromocytoma in the bladder or pelvis. Despite the fact that 55% of injected

activity is excreted within 24 hours the bladder must be emptied prior to performing pelvic scintigraphy.[13]

LARGE BOWEL

Large bowel uptake has been found in up to 20% of studies.[25] The mechanism of uptake is uncertain but activity is known to increase in severe constipation and in renal insufficiency. Gut uptake may be sufficient to obscure or be confused with tumour uptake.

SALIVARY GLANDS

Their rich sympathetic innervation allows for the salivary glands to be visualized in almost all patients. The mechanism of uptake is thought to be due to neuronal uptake.[25]

HEART

Cardiac visualisation of ^{131}I-MIBG is variable and Nakajo et al[25] has shown that the intensity of uptake is greater in patients with no phaeochromocytoma. Cardiac uptake is due to its rich sympathetic innervation. Some suggest that visualization of the myocardium at 24 hours makes the diagnosis of phaeochromocytoma unlikely.[13]

^{123}I-MIBG uptake by the heart is sufficiently high for this agent to be used for myocardial scintigraphy.[26]

LUNGS

High uptake is present within 2 hours of administration of the radiopharmaceutical but this disappears rapidly and does not interfere with inter- pretation. Nakajo et al[25] found that the lower lobes of the lungs are visualised more frequently (in 68% of normals) than the middle lobes (in 24% of normals). The upper lobes were visualised in only 2% of normals. They feel that these differences in frequency and intensity of uptake may be due to the relative lung volumes and vascularity in these zones.

THYROID

If the thyroid gland is adequately blocked before the administration of ^{131}I -MIBG visualization of the gland is uncommon.

ABNORMAL UPTAKE

PHAEOCHROMOCYTOMA

Phaeochromocytomas are characterized by their ability to concentrate ^{131}I-MIBG and are visualized as foci of increased uptake whether they are situated intra- or extra-adrenally.

Phaeochromocytomas metastases are identified for the same reason. The commonest site of metastatic spread is to bone.[13] Liver metastases have also been reported.[13] Follow-up bone and liver scintigraphy is useful for determining the spread of the disease.[5] Both benign and malignant tumours concentrate the ^{131}I-MIBG and scintigraphy is unable to distinguish between these. Scintigraphy therefore screens for multifocal or bilateral disease and metastases.

THE ROLE OF ^{123}I-MIBG SCINTIGRAPHY

Lynn[23] and Shapiro[24] have found ^{123}I-MIBG to be superior to ^{131}I-MIBG as an imaging agent. 37Ø MBq (1Ø mCi) of ^{123}I-MIBG have a radio-dosimetry similar to that of 18.5 MBq (Ø.5 mCi) of ^{131}I-MIBG and provide a greater, more useful (159 KeV energy) photon flux. They have shown a better delineation of lesions and the detection of smaller lesions.[23;24] Lynn demonstrated 3 lesions on ^{123}I-MIBG which were not visualised on the ^{131}I-MIBG images.[23] Shapiro demonstrated additional lesions in 5 of 19 patients in whom a comparative study was done.[24] They performed successful single photon emission tomography (SPECT) studies on 8 patients using ^{123}I-MIBG.[24]

In addition ^{123}I-MIBG permits the visualisation and quantification of uptake in the normal adrenal medulla.[23;24;27] Bomanji et al[27] using ^{123}I-MIBG in 18 hypertensive patients who had no evidence of phaeochromocytoma visualised the adrenal medullas in all the patients except one. They quantitated the uptake in the adrenal medullas and found a range of Ø.Ø1-Ø.22% of the administered dose.27

Some feel that ^{123}I-MIBG should be used in the investigation of patients in whom clinical suspicion is high but who have negative or equivocal ^{131}I-MIBG scintigraphy.[4]

However, ^{123}I is far more costly and less readily available for general use.

NONPHAEOCHROMOCYTOMA IMAGING

^{131}I-MIBG uptake has been found to occur in a range of neuroendocrine tumours (apudomas) including neuroblastoma, carcinoid tumours, and medullary carcinoma of the thyroid.[28-37]

NEUROBLASTOMA

A number of reports have noted the excellent uptake of ^{131}I-MIBG by neuroblastomas.[28-31;33] Munkner[28] has shown that this technique is highly sensitive for the detection of local and extensive disease. Ikekubo et al[29] used ^{131}I-MIBG to locate both the primary abdominal tumour and a distant metastatic orbital tumour. Imaging also demonstrated significant resolution of these tumours following treatment.[29] Hoefnagel et al detected neuroblastomas in 47 patients using ^{131}I-MIBG, and found the investigation to be 95% sensitive and 100% specific.[30]

The use of ^{131}I-MIBG as a therapeutic agent for this condition is being investigated in a number of centres. Huberty[31] and his colleagues are using this method in children with stage IV disease who have failed conventional

therapy but it is still too early to assess the efficacy of this therapy.

CARCINOID TUMOUR

^{131}I-MIBG uptake by carcinoid tumours have been reported.[30;32;34;37] Hoefnagel and his colleagues[32] report a case of metastatic gastric carcinoid tumour concentrating the radiopharmaceutical. Both the primary tumour and the liver mets were detected by ^{131}I-MIBG. Fischer et al[34] also showed the presence of liver metastases using ^{131}I-MIBG. Hoefnagel et al[30] demonstrated carcinoid tumours in 6 of 12 patients with this disorder. Feldman et al visualised carcinoid tumours in 14 of 23 patients with these tumours and they made the observation that the ^{131}I-MIBG concentrated most avidly in tumours of midgut origin.[37]

MEDULLARY CARCINOMA OF THE THYROID

Troncone et al[35] demonstrated uptake in both the primary tumour and metastases in patients with medullary carcinoma of the thyroid. Ansari et al[36] report ^{131}I-MIBG uptake in this carcinoma in a patient with type 2b MEN syndrome.

CHAPTER THREE

THE USE OF ^{131}I-MIBG AT GROOTE SCHUUR HOSPITAL

A total of 28 patients had ^{131}I-MIBG scintigraphy at GSH during the period from mid-1983, when this investigation was first instituted, to 1987. The study is a retrospective one and includes a review of patient clinical records and scintigrams.

MATERIALS AND METHODS

Twenty-eight patients had ^{131}I-MIBG scintigraphy. Thyroidal uptake of ^{131}I was blocked by Lugol's iodine solution, 30 mg per day, given 24 hours before the administration of the radiopharmaceutical. This treatment was continued for a minimum of 5 days.

Drugs like reserpine, the tricyclic antidepressants and phenylpropanolamine preparations were stopped at least a week prior to scintigraphy as they interfere with the uptake of ^{131}I-MIBG.[3;13]

ADMINISTRATION

18.5 MBq of ^{131}I-MIBG obtained from the Atomic Energy Corporation was administered by slow intravenous infusion over 20 to 30 seconds as the possibility of a hypertensive

crisis exists due to norepinephrine displacement from the storage granules. The patients were monitored for alterations in vital signs for at least 3Ø minutes following the injection.

The unfavourable radio-dosimetry of ^{131}I-MIBG limits the dose to 18.5 MBq/1.7m^2. 37Ø MBq of ^{123}I-MIBG has the equivalent dosimetry and gives superior images.

ACQUISITION

Images were obtained using an Elscint Apex 415 gamma camera with a medium energy, high sensitivity, parallel hole collimator. Imaging was performed at 24 and 48 hours after the administration of the ^{131}I-MIBG. Multiple posterior overlapping views of at least 5Ø ØØØ counts from the skull to the bladder were obtained. Anterior and lateral views were obtained when it became necessary to localise lesions. As the bulk of the ^{131}I-MIBG excretion occurs via the urinary tract, the bladder was emptied before the pelvis was scanned to avoid confusion.

Anatomical orientation and localisation of the sequential images was achieved by simultaneous scintigraphic demonstration of the kidneys using technecium-99m (^{99m}Tc) labelled diethylenetriaminepentacetic acid (DTPA).

DATA ANALYSIS

The scintigrams were evaluated by experienced nuclear medicine physicians. This was followed by a review of the medical records of the patients for urinary and plasma catecholamine and VMA and NMA levels all measured by the previously described methods. The clinical histories of the patients were scrutinised and the results of radiological studies e.g. computerised tomography and ultrasound were reviewed.

Clinical, biochemical and scintigraphic data on each patient are tabulated below. Scintigraphic results were divided into:

1. POSITIVE: where there is a clearly defined abnormal focus or foci.

2. NEGATIVE: where there is no evidence of an abnormal focus.

3. INDETERMINATE: where an ill-defined area of low-intensity makes a definitive diagnosis difficult or, where it is difficult to distinguish between a pelvic focus and normal ^{131}I-MIBG excretion in the urine.

RESULTS

(For details see Table 2 at the end of this chapter)

TOTALS:

(See Pie diagram on next page)

1. TOTAL NUMBER OF PATIENTS SCANNED: 28

* 2. TOTAL NUMBER OF POSITIVE SCINTIGRAMS: 5

3. TOTAL NUMBER OF NEGATIVE SCINTIGRAMS: 18

4. TOTAL NUMBER OF INDETERMINATE SCANS: 4

(1 of which was positive on histology).

5. SCINTIGRAPHY RESULT NOT AVAILABLE: 1

* 6. HISTOLOGICALLY-PROVEN CASES: 11

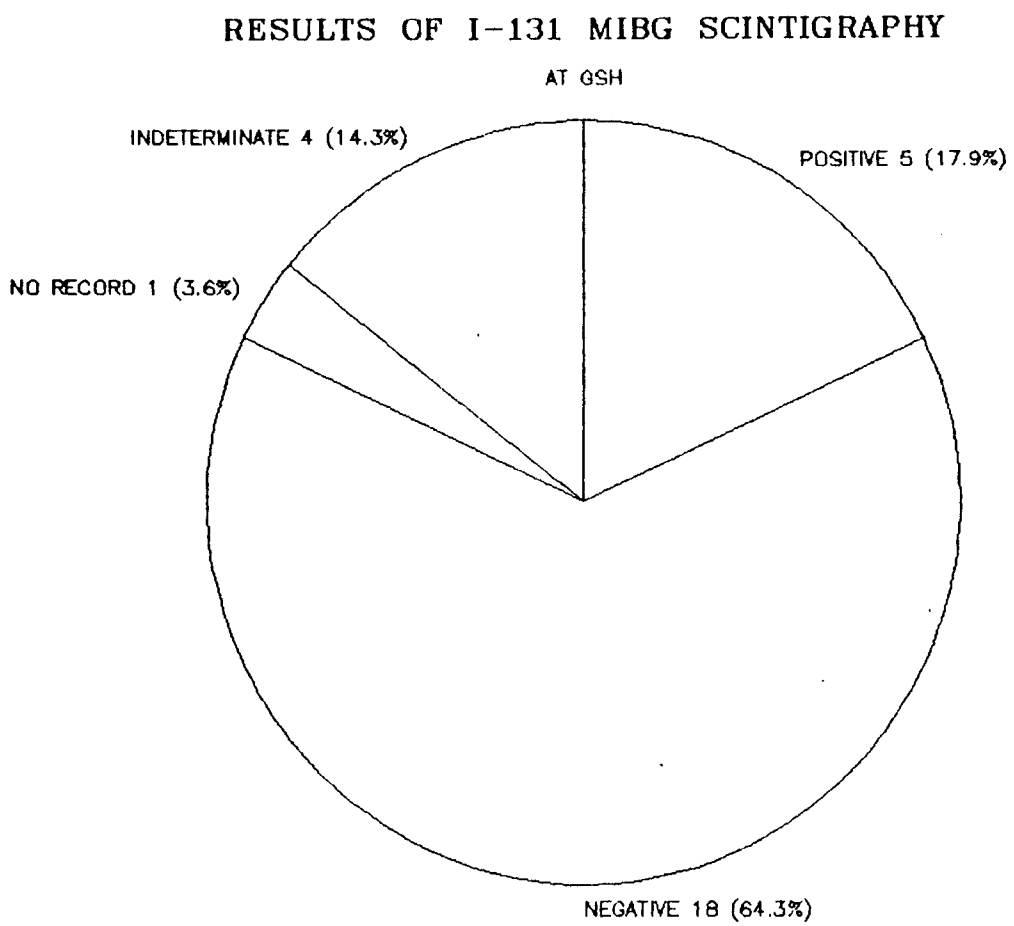
(1 of which had no scintigraphy result).

SENSITIVITY: 5Ø%

TRUE POSITIVE TEST RESULTS/ALL PATIENTS WITH THE DISEASE[38]

5 positive scans (group 2 above) out of 1Ø proven cases (group 6 above). One patient had no scintigraphy result and was therefore excluded.

PIE CHART


RESULTS OF I-131 MIBG SCINTIGRAPHY
AT GSH
INDETERMINATE 4 (14.3%)
POSITIVE 5 (17.9%)
NO RECORD 1 (3.6%)
NEGATIVE 18 (64.3%)

SPECIFICITY: 100%[38]

TRUE NEGATIVE TEST RESULTS/ALL PATIENTS WITHOUT THE DISEASE

There were no false positive studies in this series.

A. POSITIVE ^{131}I-MIBG SCINTIGRAMS

(See Histogram 1)

1. CLINICAL FEATURES

AGE:

Third decade: 3 patients

Fifth decade: 2 patients

SEX:

Females:3

Males: 2

MAIN CLINICAL PROBLEM:

Persistent hypertension: 2

Abdominal masses: 2 (one of these had polycythemia)

Paraplegia: 1

BLOOD PRESSURE:

Persistent hypertension: 2

Episodic hypertension: 2

Normotensive: 1

BLOOD PRESSURE RANGE: 12Ø/8Ø-18Ø/11Ø mm Hg

Of the 11 patients with proven phaeochromocytoma:

(See Histogram 2)

Persistent hypertension: 5

Labile hypertension: 3

normotensive: 3

FEATURES OF FAMILIAL PHAEOCHROMOCYTOMA:

1 patient with evidence of cafe au lait spots and cutaneous neurofibromata presented with an abdominal swelling and was found to have bilateral phaeochromocytomas.

2. BIOCHEMICAL FINDINGS

Normetadrenalin (NMA) and/or vanillylmandelic acid (VMA) levels in the urine were measured in 4 of the 5 patients with positive ^{131}I-MIBG scintigraphy.

VALUES:

NORMAL NMA= Ø-5 micromol/24 hours

1+= 5-1Ø micromol/24 hours

2+= 1Ø-2Ø micromol/24 hours

3+= >2Ø micromol/24 hours

NORMAL VMA= 1Ø-4Ø micromol/24 hours

1+= 4Ø-1ØØ micromol/24 hours

2+= 1ØØ-2ØØ micromol/24 hours

3+= >2ØØ micromol/24 hours

RESULTS:

NMA and/or VMA levels >1+: 4 patients

No results: 1 patient

Of the 11 patients with histologically-proven disease:

NMA and/or VMA levels >1+: 5 .....4 hypertensive

Normal NMA and/or VMA : 4 .....3 hypertensive

No biochemical results: 2

There was no correlation between the severity of the blood pressure and the urinary catecholamine and VMA levels.

3. COMPUTERISED TOMOGRAPHY

Positive CT scans: 4

No result: 1

Of the 11 patients with proven phaeochromocytoma:

Positive CT scans: 9

4.TYPES OF PHAEOCHROMOCYTOMA

Malignant, metastastic phaeochromocytoma: 3

Patient 1: Primary tumour in the thoracic sympathetic chain with metastatic lesions in the skull, spine ,right hemipelvis and inferomedial to left kidney. These lesions were found to be surgically inoperable and the patient was treated with ^{131}I-MIBG.

Patient 2: Primary tumour in the right adrenal with initial metastases in the region of the left kidney. After surgery 3 further metastatic lesions were identified and the patient was treated with ^{131}I-MIBG.

Patient 3: Inoperable malignant tumour with multiple bone and soft tissue metastases. The primary tumour was not identified.

Benign, extra-adrenal pheaochromocytoma: 1

This patient had an operable tumour situated in the region of the left kidney arising from the great vessels.

Benign, bilateral (familial) phaeochromocytoma: 1

This patient was found to have a right adrenal phaeochromocytoma and another tumour in the region of the lower pole of the left kidney. These were surgically removed.

Of the 11 patients with proven disease:

Benign, intra-adrenal tumours: 2

One patient had a right adrenal tumour which was surgically removed. The other patient has been discussed above (familial disease).

Benign, extra-adrenal tumours: 6

Patient 1: This patient had a retrovesical tumour which was surgically removed.

Patient 2: A tumour was located below the left renal hilum and was surgically removed.

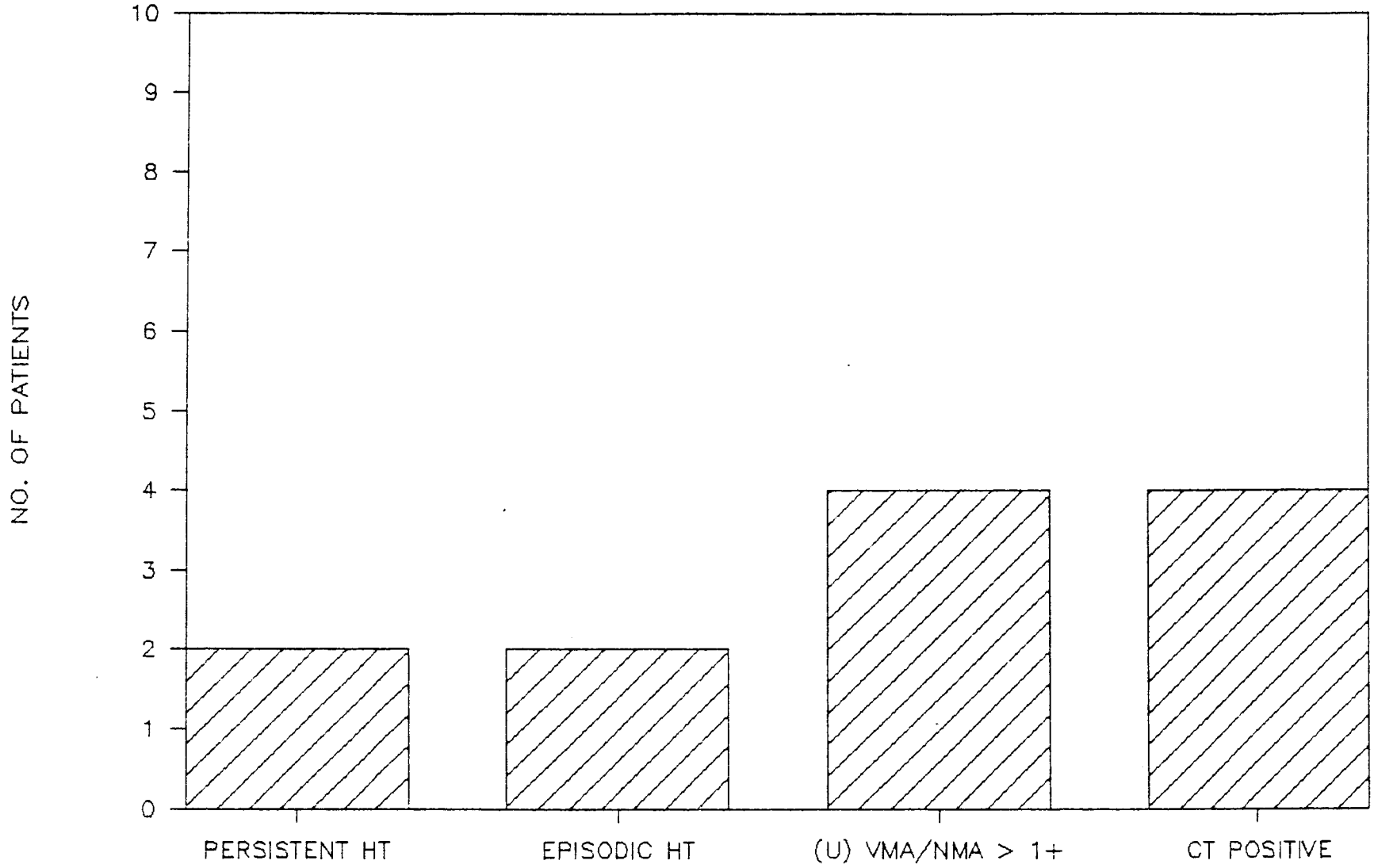
Patient 3: An inoperable retroperitoneal tumour was discovered in this patient.

Patient 4: Irresectable bilateral carotid body tumours were found in this patient.

Patient 5: A left carotid body tumour was discovered which

POSITIVE I-131 MIBG SCINTIGRAMS

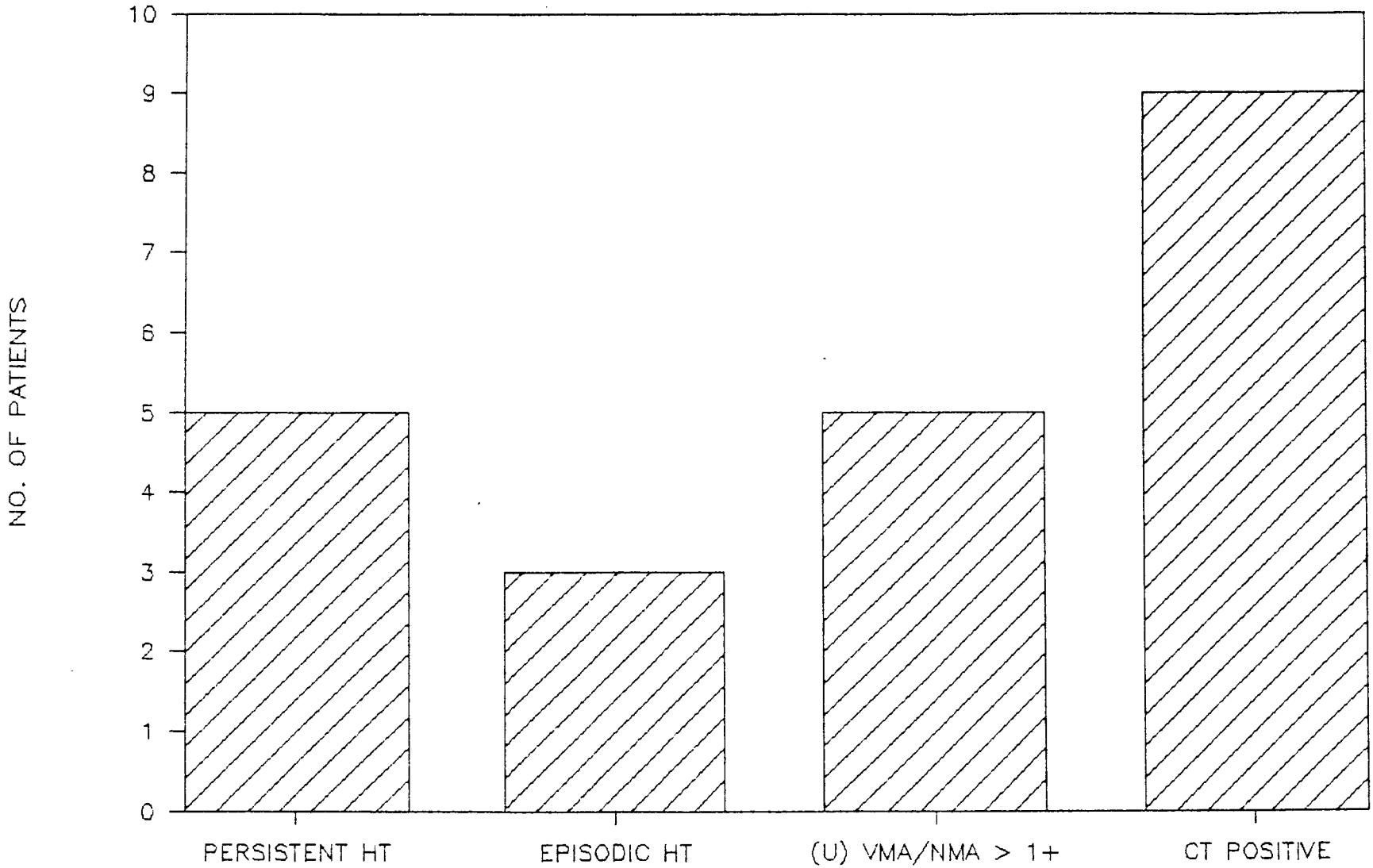
5 PATIENTS



HISTOGRAM 1

HISTOLOGICALLY PROVEN CASES

11 PATIENTS



was surgically removed.

Patient 6: This patient has been discussed above (familial disease).

Malignant, metastatic tumours: 3

These patients have been discussed above.

B. NEGATIVE ^{131}I-MIBG SCINTIGRAMS

(See Histogram 3)

Eighteen patients had negative scintigraphy. The vast majority of these patients had no biochemical evidence for phaeochromocytoma - only one patient had elevated catecholamines. Although CT was positive in 6 patients, these were found to have other disease on histology.

1. CLINICAL FEATURES

BLOOD PRESSURE:

Persistent hypertension: 7

Labile hypertension: 2

Hypertension ? type: 1

The majority of these complained of headaches, palpitations and sweating.

Normotensive: 7

Five of these presented with paroxysmal symptoms including, dizziness, sweating, palpitations and flushing. One was discovered to have bilateral adrenal masses while having a CT for abdominal pain, and the other presented with bilateral swelling of the neck.

One patient had no available blood pressure recording.

2. BIOCHEMICAL FINDINGS

Normal VMA and/or NMA levels: 13

Elevated NMA levels: 1.....? due to phenothiazine No results available: 4

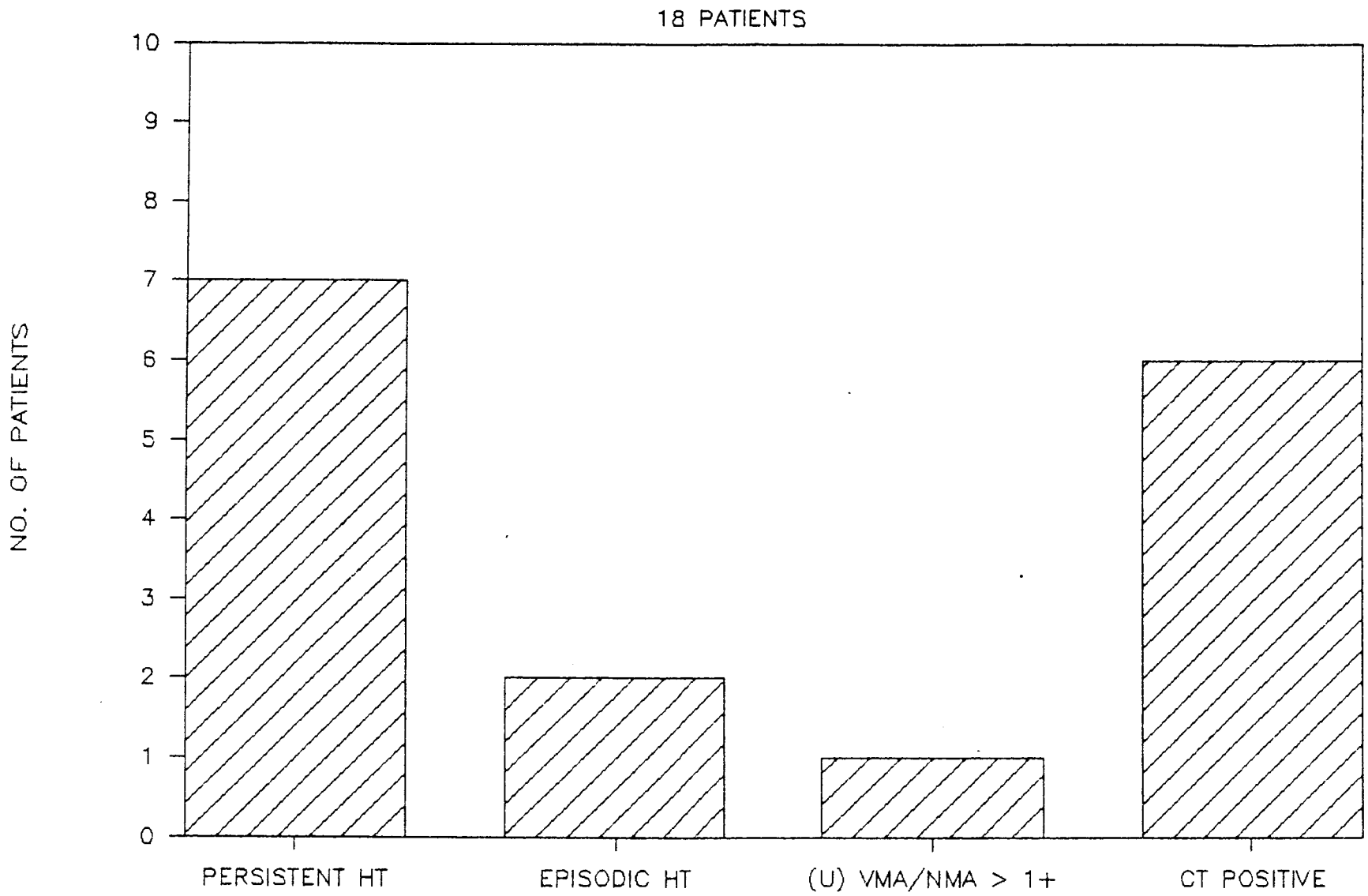
3. COMPUTERISED TOMOGRAPHY (CT) AND ULTRASOUND(US)

Positive CT scans: 6

Negative CT and/or US scans: 8

No available record: 4

NEGATIVE I-131 MIBG SCINTIGRAMS



HISTOGRAM 3

C. INDETERMINATE SCINTIGRAMS

(See Histogram 4)

Four patients had indeterminate scintigrams.

1. CLINICAL FEATURES

BLOOD PRESSURE:

Persistent hypertension: 2

Labile hypertension: 2

Three of the 4 patients presented with sweating, palpitations and headaches. The fourth was asymptomatic, hypertension being discovered on routine examination.

2. BIOCHEMICAL FINDINGS

NMA and/or VMA levels >1+: 2

NMA and/or VMA levels =1+: 1

Normal NMA and/or VMA : 1

3. COMPUTERISED TOMOGRAPHY

Positive CT scans: 1

Negative CT scans: 2

No available record: 2

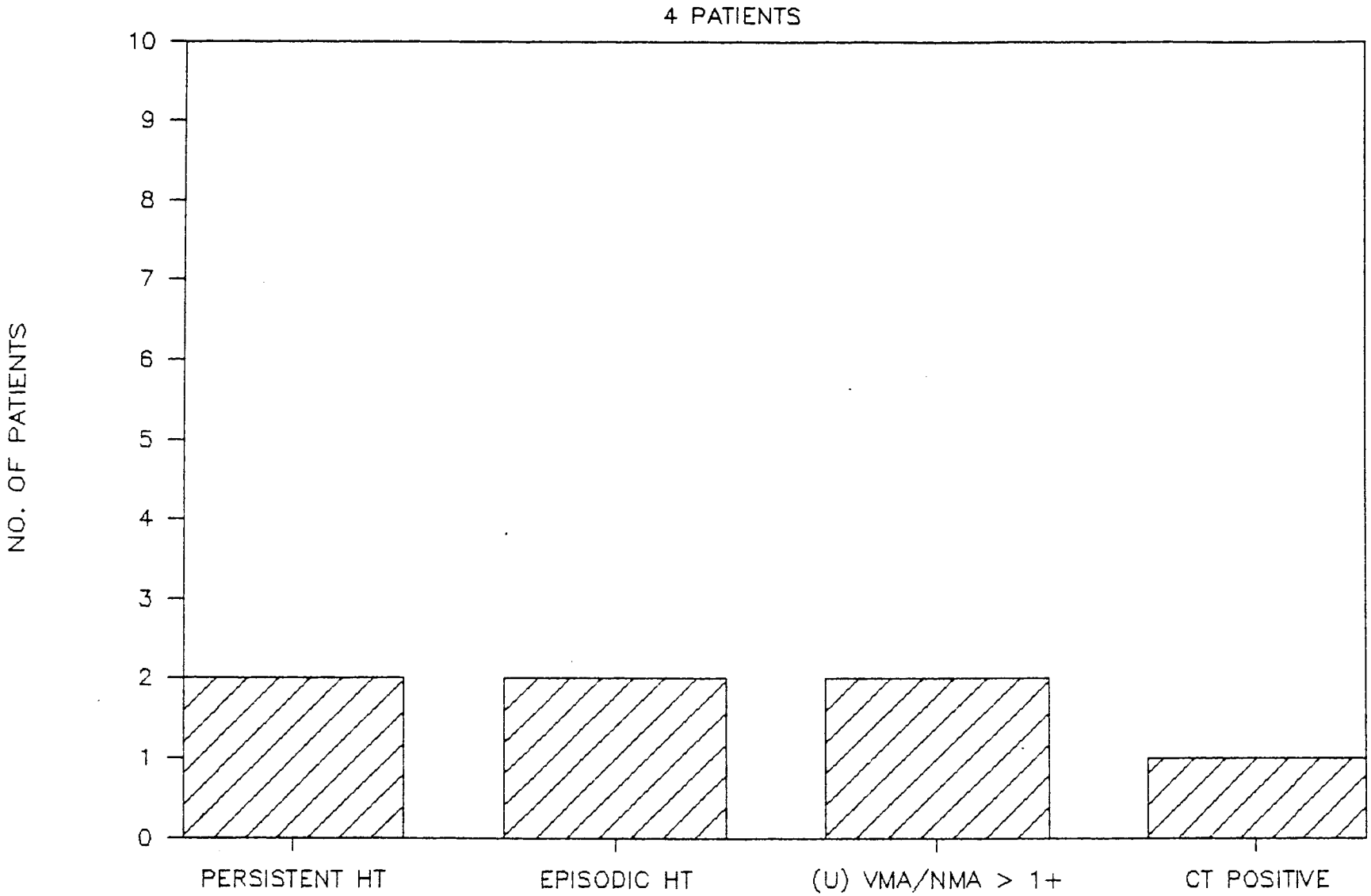
One patient with severe hypertension and normal biochemistry

was found to have a phaeochromocytoma at surgery after having a positive CT scan.

Of the three remaining patients one was found to have a renal artery stenosis while the other 2 were diagnosed as having essential hypertension.

(See Histogram 5 for a comparison of patient features).

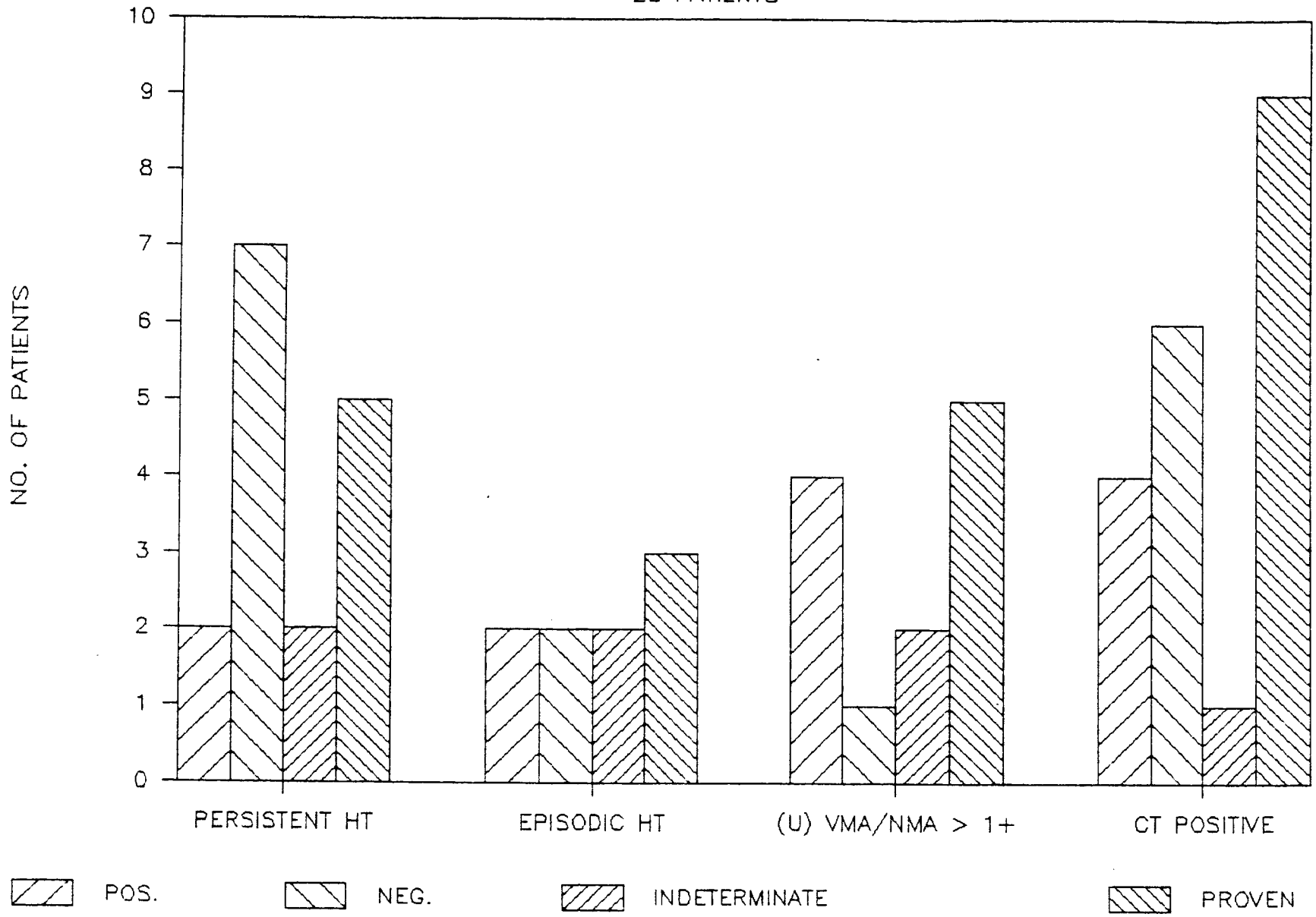
INDETERMINATE I-131 MIBG SCINTIGRAMS



HISTOGRAM 4

SUMMARY OF PATIENT FEATURES

28 PATIENTS



HISTOGRAM 5

TABLE 2

RESULTS

Age/Sex	Clinical Features	Catecholamines	MIBG	Other
1. 53/m	Headache;Dizzy Persistent Ht B.P. 200/105	VMA(U) - TOT(U) -	Neg	Neg CT
2. 38/m	Headache;Dizzy Palpitations Sweating;Flush Cafe au lait Labile Ht B.P. 240/170	VMA(U) - NMA(U) -	Neg	Neg CT
3. 51/m *	Headache Palpitations Labile Ht B.P. 240/140	VMA(U) - TOT(U) -	Ind	Pos CT
4. 19/f *	Headache;Flush Sweating;SOB B.P. 210/160	NMA(U) ++ TOT(U) ++	NR	Pos CT
5. 24/f	Headache;Flush Dizzy;Nausea Sweating Labile Ht B.P. 160/135	VMA(U) - TOT(U) +	Ind	RAS
6. 23/m	Recurrent TIA Persistent Ht	VMA(U) -	Neg	Neg
7. 73/f	Persistent Ht	NR	Neg	NR
8. 18/m	Headache Convulsions B.P. 130/90	NR	Neg	NR
9. 34/m	Asymptomatic B.P. 160/110	NMA(U) + TOT(U) ++	Ind	Neg CT
10. 63/m *	Hoarse RUQ pain B.P. 140/80	NMA(U) - NMA(S) -	Neg	PosCT
11. 47/m	Palpitations Chest pain TIA B.P. 140/90	VMA(U) -	Neg	Pos CT

Age/Sex	Clinical Features	Catecholamines	MIBG	Other
12. 23/f	Palpitations Dizzy Sweating B.P. 140/80	VMA(U) - TOT(U) -	Neg	Neg CT
13. 25/f * *	Paramediast- inal mass B.P. 130/100	NMA(U) ++ VMA(U) ++	Pos	Pos CT +B.S.
14. 23/f * *	Headache;Dizzy Sweating;Flush Palpitations Abdominal pain Abdominal mass Episodic Ht B.P. 140/110	NMA(U) +++ VMA(U) +	Pos	Pos CT
15. 68/f	Sweating Palpitations Persistent Ht B.P. 200/120	NMA(U) + NMA/CR ++	Ind	Neg CT
16. 33/m	Malignant Ht B.P. 240/160	NMA(U) ++ TOT(U) -	Neg	Neg US
17. 68/f *	Abdominal pain Abdominal mass Persistent Ht B.P. 200/110	VMA(U) -	Neg	Pos CT
18. 36/f	Headache Palpitations Paroxysmal Ht B.P. 180/110	VMA(U) -	Neg	Neg CT
19. 44/m * *	Abdominal mass Cafe au lait Neurofibromatosis B.P. 120/80	VMA(U) +++ NMA(U) -	Pos	Pos CT
20. 69/m	Medullary Ca of Thyroid	NMA(U) -	Neg	NR
21. 45/f	Palpitations Headache;Flush Tremor;Sweating B.P. 130/90	NMA(U) - NMA(U) +	Neg	Neg CT
22. 25/f *	Bilateral neck swellings B.P. 140/90	Nil	Neg	Pos CT + MRI

Age/Sex	Clinical Features	Catecholamines	MIBG	Other
23. 19/f	Abdominal pain Persistent Ht B.P. 220/160	NMA(U) - VMA(U) -	Neg	Neg CT
24. 69/f *	Neck swelling Dysphasia Persistent Ht B.P. 180/100	NMA(U) - VMA(U) - CAT(S) -	Neg	Pos CT
25. 70/m	Abdominal pain Persistent Ht B.P. 170/110 L.O.A.+ L.O.W.	NMA(U) -	Neg	Pos CT
26. 26/f *	Persistent Ht * B.P. 1	NMA(U) ++	Pos	Pos CT
27. 40/m	NR	NR	Neg	NR
28. 41/m *	Sweating * Persistent Ht B.P. 180/110	NR	Pos	NR

---

* Histologically-proven Phaeochromocytoma

*

* Proven cases with positive ^{131}I-MIBG scintigraphy

NR No record available

US Ultrasound

RAS Renal artery stenosis

MRI Magnetic resonance imaging

CT Computerised tomography

B.S.Bone scan

(U) Urinary

(TOT) Total catecholamines

B.P. Blood Pressure

Ht Hypertension

TIA Transient Ischemic Attack

RUQ Right Upper Quadrant

LOA Loss of Appetite

LOW Loss of Weight

CHAPTER FOUR

DISCUSSION

SENSITIVITY

The low sensitivity of 50% obtained at Groote Schuur Hospital for ^{131}I-MIBG scintigraphy differs significantly from results at other centres in the U.S.A. and Europe. Shapiro and his colleagues in Michigan[4] report a sensitivity of 87% while Brown et al report a figure of 79% from a study at the Mayo Clinic[6] and Ackery in Southampton[5], a sensitivity of 89%. Baulieu et al working in Tours, France[7] report a sensitivity of 91% and Chatal of the French MIBG Study Group[8], a sensitivity of 91%.

The reasons for this discrepancy are:

1. PATIENT SELECTION:

There were 4 false negative scans out of the 10 proven cases of phaeochromocytoma and 1 scan was indeterminate. The latter one will also be considered as a false negative for the purposes of this discussion. (One patient's scintigraphy result could not be found).

Four of these 5 patients had normal biochemistry while the fifth had no biochemical investigations done. Four of these had no typical symptoms; 2 patients with carotid body

tumours presented with neck swellings, and the other 2, with atypical abdominal pain one of whom had an associated mass.The phaeochromocytomas in these patients were probably non-secretory and non-funcional and thus did not take up the ^{131}I-MIBG or secrete catecholamines.

There have, however, been reports of uptake of ^{131}I-MIBG by "non-secreting"[11],"nonfunctional"[12] "paragangliomas" or phaeochromocytomas. Khafagi et al[12] demonstrated tumours in 2 patients , one with a carotid body tumour, despite normal urinary catecholamine and VMA levels. Smit et al[11] showed intense ^{131}I-MIBG uptake in a carotid paraganglioma in the presence of modest elevation of urinary catecholamines (thought to be due to cardiac failure) and normal plasma concentrations. They concluded that the uptake of ^{131}I-MIBG does not necessarily parallel catecholamine synthesis and secretion.

Shapiro and his colleagues[4] found that patients who did not exhibit typical symptoms of phaeochromocytoma and who had normal or borderline catecholamine levels "never harboured phaeochromocytomas." However, our experience has shown that patients with atypical symptoms and normal catecholamine levels do indeed harbour phaeochromocytomas, only these did not yield positive scintigraphy. However,this apparently contradictory finding may be a mere matter of definition. Shapiro et al[4] specifically excluded

nonfunctioning carotid body tumours from their series and what they termed "nonfunctioning paragangliomas". All our patients in the false negative group had normal biochemistry.1

The fifth patient had typical symptomatology but normal biochemistry. This was possibly due to the fact that the catecholamine levels were measured during a period when the phaeochromocytoma was quiescent. This patient was reported to have had elevated catecholamine levels at the hospital from which he was referred but this could not be confirmed. Moreover, the presence of an intravesical phaeochromocytoma compounded the problem as the ^{131}I-MIBG is excreted via the urinary tract.

2. BIOCHEMISTRY

In contrast to McEwan and his colleagues[13] who showed no relationship between urinary catecholamine values and false negative scintigraphic studies, at least 4 of the 5 patients with false negative studies at Groote Schuur Hospital had normal urinary catecholamine levels.

We conclude that had we used criteria for selection based mainly upon a high index of clinical suspicion and raised catecholamine levels, our results would compare favourably with the studies mentioned above. The criteria used by

Shapiro et al[4], outlined in Chapter Two would appear to provide too wide a margin for error.

SPECIFICITY

The specificity in our study was 100% i.e. there were no false positive studies. This compares favourably with the various series mentioned above. Most other series report false positives due to: uptake in other neuroendocrine tumours[8] and in non-endocrine tumours[39], and altered normal anatomy ,for example retention of radio-activity in a dilated renal pelvis mimicking a phaeochromocytoma[8]. The fact that our study was a comparatively small one may account for the absence of false positive images.

TRUE POSITIVE SCINTIGRAMS

BIOCHEMISTRY

Four of the 5 patients with positive scintigraphy had significantly elevated urinary catecholamine metabolites (2+ or greater).(No results were available for the other patient). This is consistent with findings in other studies. McEwan et al[13] found that positive ^{131}I-MIBG images are associated with significantly increased levels of catecholamines and catecholamine metabolites in the urine.

Many studies have shown the importance of urinary catecholamine and VMA concentrations in the assessment of phaeochromocytoma.Van Heerden et al[14] have found urinary metanephrines and VMA to be very sensitive diagnostic aids in phaeochromocytoma with accuracy rates of 95% and 89% respectively. And all the patients in Ackery's[5] series with confirmed phaeochromocytoma had significantly elevated urinary catecholamine concentrations. Sixteen of their 18 patients had positive ^{131}I-MIBG scintigrams.

Our results are consistent with those of McEwan[13] and Ackery[5] in that we found that positive ^{131}I-MIBG scintigraphy is associated with significantly elevated urinary catecholamine levels. It would appear that the increased uptake noted in the metabolically inactive tumours by Smit[11] and Khafagi[12] are the exception to the rule and not a common occurrence. This would suggest that although the active uptake process does not necessarily accompany the processes of catecholamine production and secretion in the same tumour, that these processes generally occur together in the same tumour.

CLINICAL PATTERNS

Two of the 5 patients with positive scintigraphy presented with hypertension and symptoms associated with increased catecholamine release. Two presented with symptoms related to the mass effects of the phaeochromocytoma. One of these patients required frequent venesections for polycythemia which was subsequently discovered to be due to erythropoeitin-producing ,metastatic phaeochromocytoma.This is an extremely unusual presentation. The fifth patient presented with a paraplegia, the result of a metastatic, spinal lesion.

Thus only 2 of our patients with positive scintigraphy presented with a typical clinical picture. It is less common for patients to present with the mass effects of the phaeochromocytoma and its metastases as was the case in 60% of our patients.A patient presenting with secondary polycythemia as a result of an erthropoeitin-producing tumour is very rare.

Three of these patients presented in their third decade, at a somewhat younger age than the fourth and fifth decades when these patients usually present.[13] Two of these were found to have metastatic, malignant disease.

TYPES OF PHAEOCHROMOCYTOMA

1. MALIGNANT PHAEOCHROMOCYTOMA

The three patients in this series with malignant, metastatic disease all had positive scintigraphy. This represents 60% of our patients with metabolically active disease, a very high figure when compared with the 10 - 15% incidence found in other studies.[4;14] The ^{131}I-MIBG proved to be a sensitive investigation for the detection of metastatic disease, and for assessing its progression, and repeat studies performed on 2 of these patients provided valuable information in this regard.

In 2 of the patients bone metastases were confirmed on bone scintigraphy. The skeleton is the commonest site for phaeochromocytoma metastases.[13] The other patient had multiple intra-abdominal lesions. On the basis of our study we would concur with Shapiro et al[4] that ^{131}I-MIBG scintigraphy appears to be superior to CT in the evaluation of metastastic disease as CT failed to show the metastatic lesions distant from the abdomen.

The intra-abdominal lesions were detected by CT but ^{131}I-MIBG scintigraphy provided information regarding the functional nature of these lesions which the CT is unable to do. In addition, bone metastases were easily located and

confirmed on bone scintigraphy. Shulkin et al[33] have demonstrated metastatic lesions in the appendicular skeleton of patients with phaeochromocytoma by doing whole body ^{131}I-MIBG scintigraphy. They found that focal lesions in the bones demonstrated by the ^{131}I-MIBG scan are more specific for metastases than the bone scan.

BENIGN EXTRAADRENAL TUMOUR

One patient had a tumour in the region of the left adrenal which was found to involve the renal vessels. Histology showed an extraadrenal, functioning phaeochromocytoma. Both the CT and ultrasound investigations showed evidence of a mass lesion in the region of the left kidney.

In this series CT proved reliable in detecting intraabdominal, extraadrenal tumours despite reports of false negative CT scans in other studies[17;40]. The CT also detected the presence of a bladder phaeochromocytoma which was difficult to evaluate due to the excretion of ^{131}I-MIBG via this route. However, the Tc-99m DTPA - ^{131}I-MIBG subtraction method used by Ackery[5] to demonstrate intravesical lesions was not used.

FAMILIAL PHAEOCHROMOCYTOMA

One patient with neurofibromatosis was found to have benign,bilateral phaeochromocytomas. The patient had numerous cafe au lait spots and cutaneous neurofibromata. The incidence of phaeochromocytoma in patients with neurofibromatosis is reported as being ten times higher than in the general population.[41] These tumours have been found to secrete adrenaline and noradrenaline in contrast to other phaeochromocytomas which secrete noradrenaline predominantly. This is thought to be due to a link with Type 2a MEN syndrome.[41]

Kalff et al[41] have shown the value of screening patients with neurofibromatosis who present with hypertension. Our patient was normotensive but the urinary VMA levels were elevated. Pantoja[42] believes that 5 -25% of all phaeochromocytomas occur in association with neurofibromatosis.Kalff[41] found that all their patients had either intraadrenal and/or paraadrenal tumours. Our patient, who had right adrenal and left "ectopic" paraadrenal phaeochromocytomas, conformed to this pattern.

This patient has a child with neurofibromatosis who will be required to undergo full investigation for phaeochromocytoma at a later stage. This is an important consideration as there is a known familial relationship with phaeochromocytomas.

TRUE NEGATIVE SCINTIGRAMS

The 18 patients with true negative scintigraphy were found in all but one case to have no biochemical evidence of phaeochromocytoma. Six patients had positive CT scans but histology showed the presence of other disease. The large number of true negative scans is due to the fact that the criteria for patient selection did not exclude those with normal biochemistry.

THERAPY WITH ^{131}I-MIBG

Phaeochromocytomas are resistant to chemotherapy and external beam radiotherapy[13].

The rationale for the use of this form of therapy is that the ^{131}I-MIBG is taken up selectively by the metabolically hyperactive malignant phaeochromocytoma. The radiation dose to the tumour is therefore theoretically very high while the dose to the surrounding normal tissue is acceptably low. Wieland et al[2] demonstrated a tumour to liver ratio of 68Ø:1 after the administration of ^{131}I-MIBG. Good metabolic uptake by the tumour tissue is a prerequisite for the trapping and retention of the approximately 2Ø,ØØØ rads neccessary to relieve clinical symptoms which are secondary to increased catecholamine secretion. Sisson et

al[43] believe that this radiation dose may result in the destruction of the tumour.

Two of the patients with multiple, metastatic disease underwent courses of ^{131}I-MIBG therapy. The response to the therapy was poor. Minimal alleviation of their symptoms occurred. One was readmitted within a year with residual active tumour and died the following year. The other was readmitted to hospital within 14 months of the treatment with a severe exacerbation of her symptoms. Scintigraphy showed new intraabdominal foci and 4 lesions were resected at surgery.

Sisson et al[43] treated 5 patients with malignant phaeochromocytoma with 2 to 4 doses of 3589-7289 MBq (97-197mCi) of ^{131}I-MIBG. Two patients showed improvement based upon the alleviation of symptoms, biochemistry and shrinkage in the size of their tumours. The other 3 patients showed no improvement. Significantly, the patients who failed to respond had bone metastases in contrast to the others who had mainly soft tissue involvement. The nonresponders were all under 34 years of age. Both of our patients had extensive bone metastases and, moreover, both of them were under 32 years of age.

A subsequent study performed by Sisson et al[44] demonstrated a favourable clinical or biochemical response,

or reduction in tumour size in 5 out of the 1Ø patients treated. Hoefnagel et al[3Ø] treated 2 patients with malignant phaeochromocytoma with 3219-7881 MBq (87-213 mCi) doses of ^{131}I-MIBG and noted relief of bone pain in one and radiological evidence of regression of lung matastases in the second.

Fischer and Vetter[45] treated 6 patients with malignant phaeochromocytoma with multiple doses of 24Ø5-777Ø MBq (65 - 21Ø mCi) of ^{131}I-MIBG. In four of the patients either tumour progression or new metastases occurred. They conclude that although certain patients may improve clinically for a period of weeks to years,"the treatment is probably not curative."

CONCLUSION

CONCLUSION

THE ROLE OF ^{131}I-MIBG IN PHAEOCHROMOCYTOMA

The study at Groote Schuur Hospital has shown that ^{131}I-MIBG scintigraphy is a safe, reliable method for the diagnosis and localisation of metabolically active benign and malignant phaeochromocytoma provided that patient selection for the investigation is based upon significantly elevated levels of urinary and/or plasma catecholamines or their metabolites. This is the key to obtaining a high sensitivity. Exceptions may be made if the clinical suspicion of the disorder remains high despite normal biochemistry, or if the patient is on medication which is known to interfere with the biochemical tests. Methyldopa, guanethidine and reserpine are antihypertensives which come to mind. ^{131}I-MIBG scintigraphy should not be used for the indiscriminate screening of patients who have hypertension with episodes of palpitations, sweating, headaches, but who have normal biochemistry.

The value of ^{131}I-MIBG as a therapeutic agent remains uncertain. The potential of a tumour-specific agent like ^{131}I-MIBG is great, but there is little evidence to indicate that the treatment provides significant relief of symptoms.

And there is no evidence to suggest that this form of therapy is curative. There are, however, a number of problem areas which have yet to be elucidated, for example, the variations in tumour uptake in different patients and sometimes at different sites in the same patient; optimal doses and the frequency at which these may be administered; the differences in response in patients with bone metastases as compared with soft tissue secondary deposits.

FUTURE PERSPECTIVES

^{123}I-MIBG has been found to be superior to ^{131}I-MIBG as an imaging agent providing a far greater photon flux and permitting better delineation of lesions and the detection of smaller lesions. It also permits single photon emission tomography (SPECT) to be done which may further improve its efficacy. Moreover, ^{123}I-MIBG has the advantage of a lower radiation dose to the patient. Furthermore, it permits the visualisation and quantitation of uptake of the normal adrenal medulla.

^{123}I-MIBG has the potential to become the agent of choice if the problems of expense and supply can be solved.

REFERENCES

1. Wieland DM, Wu JL, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WM: Radiolabeled adrenergic neuron blocking agents: Adrenomedullary imaging with ^{131}I-iodobenzylguanidine. J Nucl Med 21:349-353, 1980

2. Wieland DM, Brown LE, Tobes MC: Imaging the primate adrenal medulla with ^{123}-I and ^{131}I-MIBG. J Nucl Med 22:358-364, 1981

3. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, Tobes MC, Beierwaltes WM, Thompson NW: Scintigraphic localization of phaeochromocytoma. N Engl J Med 305:12-17, 1981

4. Shapiro B, Copp JE, Sisson JC, Eyre PL, Wallis J, Beierwaltes WH: Iodine-131 Metaiodobenzylguanidine for the Locating of Suspected Pheochromocytoma: Experience in 400 Cases. J Nucl Med 26:576-585, 1985

5. Ackery DM, Tippet P, Condon B, Sutton HE, Wyeth P: New approach to the localization of phaeochromocytoma: Imaging with ^{131}-MIBG. Br Med J 288:1587-1591, 1984

6. Brown ML, Sheps SG, Sizemore G: MIBG in the evaluation of suspected phaeochromocytoma: Mayo Clinic experience. J Nucl Med 25:P94, 1984 (abstr)

7. Baulieu JL, Guilloteau C, Canbon C, Viel C, Baulieu F, Itti R, Pourcelot L, Besnard JC: MIBG scintigraphy: A one-year experience. J Nucl Med 25:P111, 1984 (abstr)

8. Chatal JF and Charbonnel B: Comparison of Iodobenzylguanidine Imaging with Computed Tomography in Locating Phaeochromocytoma. J Clin Endocrinol Metab 61:769-772, 1985

9. Cryer PE: Phaeochromocytoma. Clinics in Endocrinology and Metabolism 14:203-221, 1985

10. Landsberg L and Young JB: Phaeochromocytoma. Harrison's Principles of Internal Medicine, International Edition, McGraw-Hill Book Company Chap 326:1775-1778, 1987

11. Smit AJ, Van Essen LH, Hollema H, Muskiet FAJ, Piers OA: ^{131}I-MIBG uptake in a non-secreting paraganglioma. J Nucl Med 25:984-986, 1984

12. Khafagi F, Egerton-Vernon J, van Doorn T, Foster W, McPhee IB, Allison RWG: Localization and Treatment of Familial Malignant Nonfunctional Paraganglioma with Iodine-131 MIBG: Report of Two Cases. J Nucl Med 28: 528-531, 1987

13. McEwan J, Shapiro B, Sisson JC, Beierwaltes WH, Ackery DM: Radio-iodobenzylguanidine for the Scintigraphic Location and Therapy of Adrenergic Tumors. Seminars in Nuclear Medicine, Vol XV, No 2:132-153, 1985

14. Van Heerden JA, Sheps SG, Hamberger B, Sheedy PF, Poston JG, ReMine WH: Phaeochromocytoma: Current status and changing trends. Surgery 91:367-373, 1982

15. St John Sutton MG, Sheps SG, Lie JT: Prevalence of clinically unsuspected phaeochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 56:354-360, 1981

16. Bravo EL, Tarazi RC, Gifford RW, Stewart BH: Circulating and urinary catecholamines in phaeochromocytoma: Diagnostic and pathophysiological implications. N Engl J Med 301:682-686, 1979

17. Adams JE, Johnson RJ, Rickards D, Isherwood I: Computed tomography in adrenal disease. Clin Radiol 34:39-49, 1983

18. Wieland DM, Swanson DP, Brown LE, Beierwaltes WM: Imaging the adrenal medulla with an I-131-labeled antiadrenergic agent. J Nucl Med 20:155-158, 1979

19. Lee H, Inbasekaran MN, Wieland DM, Sherman PS, Fisher SJ, Mangner TJ, Rogers WL, Clinthorne NH: Development of a Kit-Form Analog of Metaiodobenzylguanidine. J Nucl Med 27:256-267, 1986

20. Mangner TJ, Tobes MC, Wieland DW, Sisson JC, Shapiro B: Metabolism of Iodine-131 Metaiodobenzylguanidine in Patients with Metastatic Phaeochromocytoma. J Nucl Med 27:37-44, 1986

21. Jacques S, Tobes MC, Sisson JC, Baker JA: Mechanism of uptake of norepinephrine and meta-iodobenzylguanidine into cultured human phaeochromocytoma cells. J Nucl Med 25:P122, 1984 (abstr)

22. Tobes MC, Jacques S, Sisson JC: Mechanisms of uptake of NE and MIBG into cultured bovine adrenomedullary cells. Evidence for uptake 1. J Nucl Med 25:P124, 1984 (abstr)

23. Lynn MD, Shapiro B, Sisson JC, Swanson DP, Mangner TJ, Wieland DM, Myers LJ, Beierwaltes WH: Portrayal of phaeochromocytoma and normal human adrenal medulla by 123-I-meta-iodobenzylguanidine (123-I-MIBG). J Nucl Med 25:436-440, 1984

24. Shapiro B, Sisson JC, Eyre P, Lynn M, Beierwaltes WH: Scintigraphic Imaging of Pheochromocytomas by Means of Metaiodobenzylguaidine (MIBG). Nuclear Medicine in Clinical Oncology: Current Status and Future Aspects, Ed. C.Winkler. Springer-Verlag, P129-137, 1986

25. Nakajo M, Shapiro B, Copp J, Kalff V, Gross MD, Sisson JC, Beierwaltes WH: The normal and abnormal distribution of the adrenomullary imaging agent m[I-131]iodobenzylguanidine (131-I-MIBG) in man: Evaluation by scintigraphy. J Nucl Med 24:672-682, 1983

26. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, Beierwaltes WH: Myocardial Imaging in Man with I-123 Meta-iodobenzylguanidine. J Nucl Med 22:129-132, 1981

27. Bomanji J, Flatman WD, Horne T, Fettich J, Britton KE, Ross G, Besser GM: Quantitation of Iodine-123 MIBG Uptake by Normal Adrenal Medulla in Hypertensive Patients. J Nucl Med 28:319-324, 1987

28. Munkner T: ^{131}I-Meta-iodobenzylguanidine Scintigraphy of Neuroblastomas. Seminars in Nuclear Medicine, Vol XV:154-160, 1985

29. Ikekubo K, Habuchi Y, Jeong S, Yamaguchi H, Saiki Y, Ito H, Hino M, Higa T: A Follow-up Study Using Iodine-131 Metaiodobenzylguanidine Imaging in a Patient with Neuroblastoma. Clinical Nuclear Medicine 11:777-780, 1986

30. Hoefnagel CA, Voute PA, de Kraker J, Marcuse HR: Radionuclide Diagnosis and Therapy of Neural Crest Tumors Using Iodine-131 Metaiodobenzylguanidine. J Nucl Med 28:308-314, 1987

31. Huberty J, Matthay K, Engelstad B, Hattner R, Yano Y, Albin A: Considerations in the Development of an 131-I-MIBG Therapy Program for advanced Neuroblastoma. Clinical Nuclear Medicine 11:P14, 1986 (abstr)

32. Hoefnagel CA, Den Hartog Jager FCA, Van Gennip AH, Marcuse HR, Taal BG: Diagnosis and Treatment of a Carcinoid Tumor Using Iodine-131 Meta-iodobenzylguanidine. Clinical Nuclear Medicine 11:150-152, 1986

33. Shulkin BL, Wei Shen S, Sisson JC, Shapiro B: Iodine-131 MIBG Scintigraphy of the Extremities in Metastastic Phaeochromocytoma and Neuroblastoma. J Nucl Med 28:315-318, 1987

34. Fischer M, Kamanabroo D, Sanderkamp H, Proske T: Scintigraphic imaging of carcinoid tumours with ^{131}I-MIBG. Lancet 2:165, 1984 (letter)

35. Troncone L, Rufini V, Maussier ML, Valenza V, Fabiano A: The Possible Use of I-131-MIBG in Medullary Thyroid Carcinoma. Preliminary Results. J Nucl Med 28:P576, 1987 (abstr)

36. Ansari AN, Siegel ME, DeQuattro V, Gazarian LH: Imaging of Medullary Thyroid Carcinoma and Hyperfunctioning Adrenal Medulla Using Iodine-131 Metaiodobenzylguanidine. J Nucl Med 27:1858-186Ø,1986

37. Feldman JM, Blinder RA, Lucas KJ, Coleman RE: Iodine-131 Metaiodobenzylguanidine Scintigraphy of Carcinoid Tumors. J Nucl Med 27:1691-1696, 1986

38. Goldman L: Quantitative Aspects of Clinical Reasoning. Harrison's Principles of Internal Medicine, International Edition, McGraw-Hill Book Company, Chap2:7, 1987

39. Nakajo M, Taguchi M, Shimabukuro K, Shinohara S: Iodine-131 MIBG Uptake in a Small Cell Carcinoma of the Lung. J Nucl Med 27:1785-1786, 1986 (letter)

4Ø. Dunnick NR, Doppman JL, Gill JR, Strott CA, Keiser HR, Brennan MF: Localization of functional adrenal tumors by computed tomography and venous sampling. Radiology 142:429-433, 1982

41. Kalff V, Shapiro B, Lloyd R, Sisson JC, Holland K, Nakajo M, Beierwaltes WH: The spectrum of phaeochromocytoma in hypertensive patients with neurofibromatosis. Arch Intern Med 142: 2Ø92-2Ø98, 1982

42. Pantoja E, Llobet RE, Taveras JE: Neoplastic complications of neurofibromatosis. Cutis 22:677-68Ø, 1978

43. Sisson JC, Shapiro B, Beierwaltes WH, Glowniak JV, Nakajo M, Mangner TJ, Carey JE, Swanson DP, Copp JE, Satterlee WG, Wieland DM: Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med 25:197-2Ø6, 1984

44. Sisson JC, Shapiro B, Glowniak JV, Beierwaltes WH, Mangner TJ, Wieland DM, Carey JC, Petry NA, Copp JE, Eyre PL: ^{131}I-MIBG treatment of malignant pheochromocytoma. J Nucl Med 25:P72, 1984 (abstr)

45. Fischer M and Vetter H: Treatment of Pheochromocytomas with ^{131}I-Metaiodobenzylguanidine. Nuclear Medicine in Clinical Oncology: Current Status and Future Aspects, Ed. C.Winkler, Springer-Verlag, P327-33Ø, 1986