

Phaeochromocytoma and functioning paraganglioma in childhood and adolescence: role of iodine 131 metaiodobenzylguanidine

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Abstract. Phaeochromocytomas and functioning paragangliomas are rare tumours in childhood and adolescence. We review our experience of 43 cases (24 men, 19 women) who were first diagnosed at the age of ≤ 18 years. All patients were evaluated at some point in their illness with iodine 131 metaiodobenzylguanidine (¹³¹I-mIBG) scintigraphy. Eight patients (19%) had bilateral adrenal tumours, 12 (28%) had solitary extra-adrenal tumours, and 8 (19%) had multiple tumours. In 10 patients (23%), the tumours were associated with a familial neurocristopathic syndrome. Thirteen of 24 (54%) unifocal tumours which were initially considered to be benign ultimately proved to be multi-focal and/or malignant. The final prevalence of malignancy was 60% – 26 patients, of whom only 15 (57%) had obviously malignant tumours at the time of diagnosis. Primary tumour size ≥ 5 cm was more commonly associated with a malignant course in adrenal but not extra-adrenal tumours. No other clinical, biochemical or morphological characteristic was significantly associated with malignancy. Although the high prevalence of malignancy in this series at least partly reflects referral bias, the need for lifelong follow-up of these patients is underscored. ¹³¹I-mIBG scintigraphy was positive in 36 patients (84%), with a somewhat lower false-negative rate (12%) than X-ray computed tomography (20%). Eight patients with malignant tumours received therapeutic doses of ¹³¹I-mIBG, with partial tumour responses in 3. Thus, ¹³¹I-mIBG is an efficacious, non-invasive, localising agent and may be considered as a palliative therapeutic agent when alternatives have failed.

Key words: Phaeochromocytoma – Paraganglioma – Childhood – Adolescence – Metaiodobenzylguanidine

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Introduction

Phaeochromocytomas are catecholamine-secreting tumours arising from adrenal medullary tissue which produce a highly variable clinical syndrome typically characterised by the triad of hypertension, headache and sweating (Manger and Gifford 1982; Bravo and Gifford 1984; Shapiro and Fig 1989). Hypercatecholaminaemia and an identical syndrome may also result from functioning tumours arising in extra-adrenal chromaffin tissue within sympathetic and other autonomic ganglia and paraganglia (including such specialised structures as the carotid and aortic bodies); such tumours have variously been termed “extra-adrenal phaeochromocytomas” and “functioning paragangliomas” – the latter designation has been recommended by the Armed Forces Institute of Pathology (Glennier and Grimley 1974).

Phaeochromocytomas and functioning paragangliomas are rare tumours, with an estimated prevalence of 0.1%–0.5% of the hypertensive population and a peak incidence in the 3rd to 4th decades (Manger and Gifford 1982; Bravo and Gifford 1984; Shapiro and Fig 1989). It is generally held that approximately 10% of tumours are extra-adrenal, 10% of patients have multiple tumours, 10% of tumours are malignant, and 10% occur in childhood. Although the reported incidence of malignant tumours in childhood appears to be similar to that in adults, over 50% of children with the phaeochromocytoma syndrome have extra-adrenal, bilateral adrenal or multiple tumours (Hume 1960; Stackpole et al. 1963; Melicow 1977; Kaufman et al. 1983). Phaeochromocytomas and functioning paragangliomas are components of the autosomal dominant multiple endocrine neoplasia

(MEN) syndromes types 2a (medullary thyroid carcinoma, parathyroid hyperplasia or adenoma and pheochromocytoma) and 2b (marfanoid habitus, mucosal neuromata, medullary thyroid carcinoma and pheochromocytoma) and may occasionally appear in isolation as an autosomal dominant familial syndrome without other features of MEN (Głowniak et al. 1985). They are also associated with the neurocutaneous syndromes of von Recklinghausen's (neurofibromatosis) and Lindau-von Hippel disease (retinal and cerebellar angiomas and multiple hamartomas) more commonly than in the general population. Finally, paragangliomas may occur in association with gastric leiomyosarcomas and pulmonary chondromas to make up Carney's triad (Carney 1983). In all these syndromes, affected children are disproportionately over represented. Because of the rarity of the pheochromocytoma syndrome in the paediatric and adolescent age group, series reported from single institutions are necessarily small. We present the combined experience of two tertiary referral centres in evaluating patients whose original tumours were diagnosed in childhood.

Patients and methods

In this retrospective study, patients in whom the diagnosis of (adrenal) pheochromocytoma or functioning paraganglioma (extra-adrenal pheochromocytoma) was made at or before the age of 18 years were identified from our data base of patients referred to the University of Michigan Medical Center, Ann Arbor, Michigan, or the University of Munster, FRG, for evaluation with iodine 131 metaiodobenzylguanidine (^{131}I -mIBG) in the 5 years ending December 1985. (After 1985, the more widespread availability of mIBG outside these institutions resulted in a change in our referral base.) All studies were performed with the written consent of the patients or their legal guardians, according to protocols approved by the institutions' research ethics committees.

Upon referral, a history was taken and a physical examination performed with all patients, with particular attention to family history or clinical evidence of familial syndromes including MEN and neurocutaneous syndromes. Blood samples were collected for the measurement of plasma catecholamine (adrenaline and noradrenaline) levels in resting, supine, fasted patients through an indwelling intravenous cannula which had been inserted at least 30 min before sampling. Plasma catecholamines were measured by a radioenzymatic assay (Peuler and Johnson 1977). The 12- or 24-h urinary catecholamine and metanephrine (metanephrine and normetanephrine) levels were determined by a fluorimetric assay (Von Euler and Lishajko 1959), and urinary vanillylmandelic acid (VMA) levels were measured spectrophotometrically (Pisano et al. 1962).

Prior to ^{131}I -mIBG scanning, all patients received three drops of a saturated solution of potassium iodide (SSKI, 120 mg iodide) per day for 1 week starting from the day before injection to block thyroidal uptake of free radioiodide. ^{131}I -mIBG [specific activity 48 GBq (1.3 Ci)/mmol] was given by slow intravenous injection in a dose of 18.5 MBq (0.5 mCi)/1.73 m² body surface area, to a maximum dose of 37 MBq (1.0 mCi). At 24, 48 and 72 h after injection, overlapping scintigrams of the whole body were obtained using a wide field-of-view gamma-camera fitted with a high-energy,

parallel-hole collimator and interfaced to a computer. Images were acquired for 100000 counts or 20 min per view. All scans were reported by experienced observers according to criteria previously described (Nakajo et al. 1983; Shapiro et al. 1985). The location of areas of abnormal uptake was defined by using external surface markers or, when necessary, "internal markers" in the form of $^{99\text{m}}\text{Tc}$ -labelled radiopharmaceuticals or ^{201}Tl . Therapeutic doses of ^{131}I -mIBG [specific activity 300–400 GBq (8–11 Ci)/mmol], administered to patients with malignant disease unresponsive to other modalities, were based on dosimetric calculations made with a "tracer" dose of 37 MBq (1.0 mCi)/1.73 m² of body surface area and external standard sources (Shulkin et al. 1988).

Statistical comparisons were carried out using the unpaired Student's *t* test or the Mann-Whitney U test and the χ^2 test; correlations were by simple linear regression. Statistical significance was accepted at the 5% level.

Results

Among 206 patients of all ages known or subsequently proven to have pheochromocytomas or functioning paragangliomas referred to the University of Michigan or University of Munster in the period 1980–1985 for evaluation with ^{131}I -mIBG, 43 (21%) had their initial diagnoses made at the age of 18 years or younger (Fig. 1). Some of these patients have been the subjects of earlier individual case reports (Shapiro et al. 1984; Głowniak et al. 1985; Imperato-McGinley et al. 1987; Shulkin et al. 1987). The median age at initial presentation was 12.5 years (mean 13.0, range 5–18). There were 24 men (mean age at presentation \pm SD, 12.9 \pm 3.2 years) and 19 women (mean age at presentation \pm SD, 13.0 \pm 2.9 years; *P* = 0.50). The majority of patients (38, 88%) were white; 3 were black, and 2 were Hispanic. The mean age at presentation (\pm SD) of patients with adrenal tumours (13.4 \pm 2.7 years) was not significantly different from that of patients with extra-adrenal or multiple tumours (12.4 \pm 3.4 years), and that of patients with tumours which ultimately proved to be malignant (13.0 \pm 3.4 years) was similar to that of patients with benign tumours (12.9 \pm 2.4 years). The interval between diagnosis and referral to our institutions ranged from 0 to 33.5 years (median 4.0 years). The patients had been followed-up for a median period of 6 years since diagnosis (range 1–34 years). Duration of follow-up was significantly longer for patients ultimately diagnosed as having malignant tumours (1–34 years, median 10.5 years) than for those thought to have benign tumours (1–17 years, median 4.5 years; *P* = 0.004).

Clinical features

At least one of the symptoms classically associated with catecholamine excess – namely, hypertension (34 patients, 79%), headache (19 patients, 44%) and sweating (18 patients, 42%) – were present in the majority of patients at presentation (Table 1). Hypertension was non-paroxysmal in the majority of cases, although two pa-

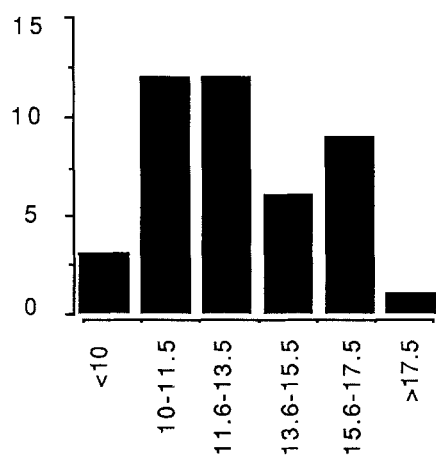


Fig. 1. Age at presentation (years)

tients presented in hypertensive crisis. The triad of hypertension, headache and sweating occurred in 10 patients (23%).

One patient presented with congestive cardiac failure due to catecholamine cardiomyopathy which resolved after successful surgery for her pheochromocytoma; she also had the triad described above. Her case is described in detail elsewhere (Imperato-McGinley et al. 1987). Four patients, all with malignant tumours, had erythrocytosis; all were hypertensive at presentation, and one is the subject of a recent case report (Shulkin et al. 1987). Four patients had neurological symptoms other than headache associated with hypertension: visual disturbance (2), encephalopathy (1) and gait disturbance (1).

Four patients had their tumours discovered incidentally. In one, a hypertensive black woman, a benign paraganglioma of the organ of Zuckerkandl was discovered at age 17 during laparotomy for an abdominal mass which proved to be a leiomyosarcoma; 9 years later, she was found to have a malignant intrathoracic paraganglioma. This patient exhibited Carney's triad. Another patient, a normotensive white man, presented at the age of 13 years with abdominal pain and an enlarging pelvic mass; laparotomy disclosed a complex pelvic lymphangiomyoma and an incidental benign pelvic paraganglioma. His catecholamine levels remained elevated postoperatively, and he was subsequently found to have an additional benign juxta-adrenal paraganglioma as well as recurrent visceral lymphangiomyomatosis. This association has not, to our knowledge, been described previously. The patient is an adopted child, and his family history is unknown. In the third patient, a large mass apparently arising from the aortic bifurcation was noted during an appendectomy; palpation of this mass resulted in a dramatic rise in blood pressure – she had not previously been known to have hypertension. The last, asymptomatic patient with bilateral adrenal pheochromocytomas was initially discovered at age 17 during biochemical screening of a kindred with Lindau–von Hippel disease; he developed skeletal and extradural metastases 19 years later.

Table 1. Clinical features

	Final diagnosis		Total
	Benign (n=17)	Malignant (n=26)	
<i>Symptoms</i>			
Hypertension	11	23	34
Headache	8	11	19
Sweating	8	10	18
Triad ^a	4	6	10
Other:	7	16	23
Polydipsia/polyuria			4
Erythrocytosis			4
Haematuria			2
Tremor			2
Visual disturbance			2
Gait disturbance			1
Encephalopathy			1
Catecholamine cardiomyopathy			1
Miscellaneous			6
<i>Delay in diagnosis (n)</i>			
Range (years)	6	3	9
	1–2	2–8	1–8
<i>Syndromes</i>			
Familial pheochromocytoma:			
Definite	–	5	5
Possible	2	1	3
MEN-2b	1 ^b	1	2
Neurofibromatosis	1	–	1
Lindau–von Hippel	1	1	2
Carney's triad	–	1	1

MEN, multiple endocrine neoplasia

^a Hypertension + headache + sweating

^b Bilateral adrenal medullary hyperplasia

Pheochromocytomas were a manifestation of MEN-2b in 2 patients, Lindau–von Hippel disease in 2 (including the patient mentioned above) and neurofibromatosis in 1. Five patients – all with malignant tumours – had a definite family history of pheochromocytomas consistent with an autosomal dominant inheritance but not associated with neurocutaneous or MEN syndromes. Three additional patients (2 with benign and 1 with malignant tumours) had a possible family history, suggested by a history of hypertension and unexplained sudden death of a first-degree relative in young adulthood. Thus, at least 10 patients (23%) – and possibly up to 13 – had pheochromocytomas or functioning paragangliomas associated with an autosomal dominant, familial syndrome.

The diagnosis of pheochromocytoma was made within 1 year of presentation in the majority of patients. There was a delay in diagnosis of 1–8 years in 9 patients (14%).

Table 2. Plasma and urine biochemistry results

	Normal	Mean	Median	Minimum	Maximum	Percentage abnormal
Plasma (<i>n</i> = 37)						
Adrenaline (pg/ml)	< 100	198	96	16	1157	43
Noradrenaline (pg/ml)	< 500	7131	2661	205	54253	97
Urine (<i>n</i> = 42)						
Adrenaline (µg/24 h)	< 30	43	12	< 5	611	28
Noradrenaline (µg/24 h)	< 110	872	530	24	4493	90
Metanephrine (µg/24 h)	< 85	88	18	4	1043	21
Normetanephrine (µg/24 h)	< 165	1113	212	6	9739	57
VMA (mg/24 h)	< 7	36	24	1.7	146	79

VMA, vanillylmandelic acid

Biochemical findings

The results of plasma and urinary catecholamine and metabolite estimations are summarised in Table 2. There were no significant differences in any of these measurements between benign and malignant or between adrenal and extra-adrenal tumours. There were significant correlations between plasma and urinary noradrenaline ($r = 0.90$, $P < 0.001$), plasma adrenaline and noradrenaline ($r = 0.79$, $P < 0.001$) and urinary adrenaline and noradrenaline ($r = 0.69$, $P < 0.001$) levels. Urinary VMA and total metanephrine levels correlated weakly ($r = 0.39$, $P = 0.018$). Only 1 patient had normal plasma and urinary biochemistry results; she was a 13-year-old girl with MEN-2b and surgically proven bilateral adrenal medullary hyperplasia detected by ^{131}I -mIBG scan. No patient with abnormal urinary biochemistry data had normal plasma catecholamine levels. The 4 patients with normal urinary noradrenaline levels also had normal urinary adrenaline and metabolite levels, i.e. measurement of urinary metabolites did not improve the sensitivity of urinary catecholamine estimation. The combination of urinary VMA and normetanephrine estimations was a sensitive as measurement of urinary catecholamine excretion.

Pathology

Tumours arose in the adrenal glands in 24 patients (right adrenal in 10, left adrenal in 6, bilateral in 8); in 3 patients with bilateral adrenal tumours, the tumours were metachronous (Table 3). Nineteen patients had extra-adrenal or multiple (other than bilateral adrenal) tumours. The sites of presenting extra-adrenal tumours were periadrenal or perirenal in 6, para-aortic (including the organ of Zuckerkandl) in 6, the pelvis in 4 (including one bladder tumour), pericardiac in 1, paraspinal in 1 and multiple tumours at presentation in 1 (the patient described above). There were no significant sex differences between patients presenting with adrenal (13 men,

11 women) or extra-adrenal tumours (11 men, 8 women). Six patients with apparently solitary, benign tumours at initial operation went on to develop additional benign tumours (3 adrenal, 3 extra-adrenal), 1–16 years (median 3.3 years) later (Fig. 2).

Some 26 patients (60%) ultimately proved to have malignant tumours. Malignancies were significantly more common among men (18) than women (8; $P = 0.028$). Fourteen (54%) of the malignancies occurred in patients who presented initially with primary adrenal tumours (bilateral in 3). Thus, malignancies were as likely to arise from adrenal (14/24, 58%) as from extra-adrenal primaries (12/19, 63%). Only 15 tumours were obviously malignant at the time of initial diagnosis; the remainder were apparently benign but developed malignant local recurrences or distant metastases 0.5–26 years after initial surgery (Fig. 2). Malignant behaviour was manifest as local spread in 23, spread to lymph nodes in 15 and distant metastases to bone in 18, lung in 8, liver in 3 and other sites in 8. Most patients with malignant tumours (24, 92%) developed multiple metastatic sites. Local recurrences of the primary tumour preceded more distant metastases in 4 patients by 2 (2 cases), 12 and 14 years. Four deaths were recorded at 2, 6, 14 and 30 years after initial presentation.

A record of the size of the presenting tumour was available for 33 patients (77%), whose tumours ranged from 1.0 to 20.0 cm in maximum diameter (median 6.0 cm; mean \pm SD, 6.0 ± 3.7 cm). There was no significant difference in size between primary adrenal (6.9 ± 4.4 cm, $n = 19$) and extra-adrenal tumours (4.8 ± 2.2 cm, $n = 14$; $P = 0.125$). However, malignant tumours were significantly larger than benign ones (7.4 ± 4.1 cm, $n = 18$ vs. 4.3 ± 2.3 cm, $n = 15$, respectively; $P = 0.015$). Fifteen of 18 malignant tumours were 5 cm or more in maximum diameter, whereas 10 of 15 benign tumours were less than 5 cm in diameter ($P < 0.01$). All 10 malignant adrenal primaries were ≥ 5 cm, while 7 of 9 benign adrenal phaeochromocytomas were < 5 cm ($P < 0.01$); benign and malignant extra-adrenal tumours were of com-

Table 3. Tumour location

Site at presentation	<i>n</i>	Apparent status at presentation	<i>n</i>	Final diagnosis	<i>n</i>	
<i>Adrenal (n=24)</i>						
Unilateral (R 11, L 8)	19	Benign	14	Unilateral adrenal, 6	6	
				Bilateral adrenal, 2		2
		Malignant	5	Unilateral adrenal, 9	9	
				Bilateral adrenal, 1		1
				Multiple, malignant		
Bilateral	5	Benign	5	Bilateral adrenal, 2	2	
				Bilateral adrenal, 3		3
<i>Extra-adrenal (n=18)</i>						
Para-aortic ^a	6	Benign	5	Extra-adrenal, benign	1	
				Multiple, benign		3
		Malignant	1	Extra-adrenal, malignant	1	
Perirenal	4	Benign	2	Extra-adrenal, benign	1	
				Multiple, benign		1
		Malignant	2	Extra-adrenal, malignant	2	
Periadrenal	2	Malignant	2	Extra-adrenal, malignant	2	
				Multiple, malignant		1
Pelvic	4	Benign	1	Multiple, benign	1	
				Malignant		3
Pericardiac	1	Benign	1	Extra-adrenal, benign	1	
Paraspinal	1	Malignant	1	Extra-adrenal, malignant	1	
Multiple	1	Malignant	1	Multiple, malignant	1	

^a Includes tumours arising in the organ of Zuckerkandl

parable size (5/8 malignant tumours ≥ 5 cm, 3/6 benign tumours < 5 cm).

There was no correlation between tumour size and plasma or urinary catecholamine or metabolite levels.

Role of ¹³¹I-mIBG

The ¹³¹I-mIBG whole-body scan was true-positive in 33 patients (all known or subsequently proven sites of

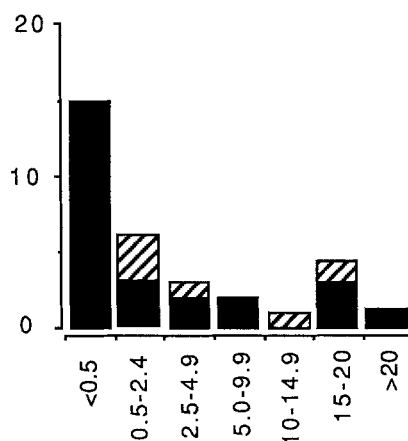


Fig. 2. Time to first metastasis (malignant tumours, black bars) or second tumour (benign tumours, hatched bars) since diagnosis (years)

Table 4. Tumour localisation by iodine 131 metaiodobenzylguanidine (¹³¹I-mibg) and computed tomography (CT) scanning

	¹³¹ I-mibg	CT ^a
True-positive	33	27
Equivocally positive ^b	3	3
False-positive	2	0
True-negative	0	2
False-negative	5	8

^a Three patients did not undergo CT scanning; 2 of these had true-positive ultrasound scans

^b Detected some, but not all, subsequently proven disease foci

disease detected) (Table 4). Three of these patients had equivocal computed tomography (CT) scan findings and 6 had false-negative CT scans. (Three patients did not undergo CT study; 2 of them had positive results on ultrasound examination). Two patients had false-negative and 2 had equivocally abnormal venous sampling studies. ¹³¹I-mIBG scanning found some, but not all, sites of disease in a further 3 patients ("equivocally positive" studies) – bone metastases were missed in 2 patients and pulmonary metastases in 1. All 3 had positive CT scans.

Five patients had false-negative ¹³¹I-mIBG scans, 3 of whom had true-positive CT scans (2 of these 3 also had positive bone scans). One of the remaining 2 patients had a cervical disease focus located by venous sampling. The 5th patient, who was asymptomatic but had developed elevated catecholamine levels 3 years after excision of a paraganglioma of the right renal hilum, defied all attempts at localisation, including venous sampling, until 4 years later when he re-presented with a metastasis in L4 and cord compression.

Finally, 2 patients had apparently false-positive ¹³¹I-mIBG scans. In 1, the scan suggested an abnormally increased right adrenal uptake in a patient who 5 years

previously had an apparently benign tumour of the organ of Zuckerkandl but persistently elevated catecholamine levels and intermittent hypertension. The CT scan was negative, and vein sampling was equivocal; the adrenals appeared normal at re-exploration. The 2nd patient developed hypertension and elevated catecholamine levels 16 years after resection of a paraganglioma of the organ of Zuckerkandl; the ^{131}I -mIBG scan suggested that abnormalities were present in the left supraclavicular and left sacroiliac regions. This was not confirmed by subsequent CT scans, but an ultrasound examination suggested the presence of tumours at the junction of the left subclavian and jugular veins and adjacent to the left ovary. Exploration of the neck and thorax were negative; the pelvis was not explored.

Eight of the patients with malignant pheochromocytomas received 1–5 therapeutic doses of ^{131}I -mIBG; the maximum total dose received was 44.6 GBq (1205 mCi). Three patients showed a partial response, 4 had no positive response (but no evidence of disease progression), and one had progressive disease and later died. ^{131}I -mIBG therapy was never curative. Two patients have also received combination chemotherapy, with a partial response in 1.

Discussion

Pheochromocytomas and functioning paragangliomas are rare tumours of childhood and adolescence. Between 1954 and 1980, there were only 3 patients with pheochromocytoma and 4 with paraganglioma recorded in the Manchester Childhood Tumour Registry (Birch 1983; Marsden 1983). This contrasts with an incidence of neuroblastoma of 168 (6.2 per million) and an overall prevalence of malignancies of 2688 (99.3 per million). Melicow (1977) reported 11 cases of childhood pheochromocytoma/paraganglioma among 100 cases studied at a single institution. In the 20-year experience of over 500 hypertensive children at the Children's Hospital Medical Center, Cincinnati, Ohio (Loggie 1985) only 4 pheochromocytomas, 1 adrenal ganglioneuroma and 1 brachial plexus paraganglioma were found. Similarly, the 20-year experience of the Toronto Hospital for Sick Children amounted to a total of 8 cases (Stringel et al. 1980), and the 30-year experience of the Mayo Clinic came to 18 cases aged 17 years or younger (Telander et al. 1985). At the Vanderbilt University Medical Center, only 2 of 69 patients with pheochromocytoma were aged 18 years or less (Scott and Halter 1984). In their complete review of the world literature to 1962, Stackpole et al. (1963) found a total of 91 cases of paediatric (symptom onset at age 15 years or younger) pheochromocytoma (including extra-adrenal tumours) and added 9 cases of their own. Hume's (1960) earlier large review had found 85 published cases. The findings of these series, as well as our own, are summarised in Table 5. All of the larger series of pheochromocytoma

in childhood and adolescence thus far have emphasised the preponderance of affected males, the predominance of sustained rather than paroxysmal hypertension, the propensity for bilateral adrenal, extra-adrenal and multiple tumours and the possibility of familial occurrence.

It is obvious from Table 5 that the present series has an unusually high prevalence of malignant tumours; this is, at least in part, a reflection of referral bias, inasmuch as more "difficult" cases with suspected extra-adrenal or multi-focal (either metastatic malignant or multiple benign) disease were more likely to have been referred for tumour localisation with ^{131}I -mIBG whole-body scintigraphy (see below). Nonetheless, it should be recalled that only 15 (35%) of our patients were thought to have malignant tumours at the time of diagnosis (Table 3); the malignant potential of the tumours in the remaining 11 patients only became evident after a sometimes protracted follow-up. Similarly, 21 patients (49%) had apparently solitary, benign tumours at presentation (14 adrenal, 7 extra-adrenal), but 6 of these (29%) subsequently went on to develop additional benign tumours. The importance of (indefinite) follow-up of children or adolescents with pheochromocytoma, in order to detect the later development of multi-focal or metastatic disease, has been emphasized by others (Stackpole et al. 1963; Kaufman et al. 1983). Scott and Halter (1984) have extended this recommendation to include all patients with pheochromocytomas, since 5 of their 9 patients (aged 31–61 years) with malignant tumours were thought initially to have benign tumours but developed recurrent and/or metastatic disease 1–6 years after initial surgery. In a review of the early University of Michigan experience with ^{131}I -mIBG, Beierwaltes (1987) estimated the cumulative incidence of detection of metastases of malignant pheochromocytoma to be 5%/year for the first 9 years and 0.6%/year subsequently; metastases were present at diagnosis in only 47% of patients with malignant pheochromocytoma. In the present series, since the duration of follow-up for patients with a "final" diagnosis of benign tumour was significantly shorter than for those with malignant tumours, it may be anticipated that the ultimate prevalence of malignancy will be even higher.

The patient's age at presentation or diagnosis, the clinical presentation (with the possible exception of erythrocytosis or the presence of unequivocal metastases), the biochemical findings and the location of the tumour with which the patient presented were not predictive of a subsequent malignant course. Men were found more commonly among patients with malignant tumours, and indeed male predominance appears to be a feature of most series of childhood pheochromocytoma (Table 5), although the sex difference overall in the present series was not statistically significant. Large primary tumour size (≥ 5 cm) was significantly associated with malignancy, at least for adrenal tumours. Medeiros et al. (1985) also found malignant adrenal pheochromocytomas to be significantly larger than benign tumours, and Scott

Table 5. Comparison of present series with literature

	Hume 1960	Stackpole et al. 1963	Melicow 1977	Kaufman et al. 1983 (Telander et al. 1985) ^a	Scott and Halter 1984	Present study
No. of cases	85	100	11	16 (18)	8	43
Male:female	52:31	68:32	7:4	"2:1"	7:1	24:19
Sustained hypertension	64/69 93%	— 88%	—	9/12 75%	4/8 50%	32/34 94%
<i>Tumor location</i>						
Solitary adrenal	36/76 47%	— 49%	5 45%	6 38% (33%)	6 75%	15 ^d 35%
Bilateral adrenal	18/76 24%	— 20%	1 9%	3 19% (17%)	1 12%	8 ^d 19%
Solitary extra-adrenal	11/76 14%	— 19%	2 18%	4 25% (33%)	—	12 ^d 28%
Multiple	11/76 14%	— 12%	3 27%	3 19% (17%)	1 12%	8 ^d 19%
Malignant	3/85 3.5%	n.s. ^b	1 9%	1 6% (17%)	1 12%	26 60%
<i>Syndromes</i>						
Familial pheochromocytoma	7	2/9 ^c	3	2	—	5
Neurofibromatosis	1	—	1	—	—	1
Lindau-von Hippel	—	—	—	—	2	2
MEN-2a	—	—	—	2	2	—
MEN-2b	—	—	—	1	—	2
Carney's triad	—	—	—	—	—	1

^a Two additional cases reported in Telander et al. 1985. Numbers in parentheses include these 2 cases

^b Not specified

^c Two of the authors' 9 additional cases were siblings

^d Final diagnosis

and Halter (1984) noted that all their malignant tumours were ≥ 6 cm in diameter.

Because of the nature of the present series, no meaningful estimate can be made of the sensitivity or specificity of the diagnostic or localising procedures used. Nevertheless, it may fairly be concluded (Table 2) that plasma and urinary noradrenaline estimations are the most useful diagnostic biochemical measurements; neither urinary metanephrine levels nor urinary VMA levels in isolation were as frequently positive as plasma or urinary catecholamine (specifically, noradrenaline) levels. These findings are somewhat at odds with the recent Mayo Clinic data in children (Kaufman et al. 1983) but consistent with those of Bravo and Gifford (1984) for pheochromocytomas in general.

An iodinated aralkylguanidine, mIBG is structurally similar to guanethidine and noradrenaline and is taken up into the adrenal medulla and similar tissue by the neuronal catecholamine reuptake mechanism and is stored in catecholamine storage vesicles (Wieland et al. 1981). Its application in the localisation of pheochromocytomas, paragangliomas, neuroblastomas and other tumours of putative neural crest origin has been the sub-

ject of several recent reviews (Shapiro et al. 1985, 1989; McEwan et al. 1985; Mauer and Mastrangelo 1987; Shapiro and Sisson 1988). The overall accuracy of mIBG scintigraphy for tumour localisation in the present series is comparable with that recorded elsewhere in the literature. The false-negative rate for CT scanning (20%) was higher than that for mIBG scanning (12%). Whole-body scanning with mIBG has been shown to be superior to CT scanning for the localisation of extra-adrenal, multifocal and metastatic malignant pheochromocytomas and paragangliomas (reviewed in McEwan et al. 1985; Shapiro et al. 1989).

The somewhat disappointing results of ¹³¹I-mIBG therapy in this group of patients is consistent with our overall experience in 28 patients with malignant pheochromocytomas (Shapiro and Sisson 1988), at least 8 of whom showed partial objective responses (5 of these subsequently relapsed), 10 had stable disease, and 10 suffered from progressive disease. The results of ¹³¹I-mIBG therapy for neuroblastoma are a little better (Mauer and Mastrangelo 1987; Shapiro and Sisson 1988; Shapiro et al. 1989), possibly reflecting the relatively greater radiosensitivity of neuroblastomas.

In conclusion, pheochromocytomas and functioning paragangliomas are rare tumours of childhood and adolescence. Unlike their adult counterparts, affected children present more commonly with sustained rather than paroxysmal hypertension and more usually have bilateral adrenal, extra-adrenal or multi-focal tumours. The prevalence of malignant tumours has probably been underestimated in the past. The need for lifelong follow-up is underscored since patient and tumour characteristics at presentation (other than primary tumour size ≥ 5 cm for adrenal tumours) are poor predictors of the later development of multi-centric or malignant disease. The usual biochemical tests (particularly plasma and urinary catecholamine levels) appear to be as diagnostically reliable as in the adult population. Whole-body scintigraphy with ^{131}I -mIBG is an efficacious, non-invasive, localising procedure, particularly for extra-adrenal, multi-focal or metastatic malignant tumours. ^{131}I -mIBG therapy has a limited role but may be considered as a palliative measure when alternatives have failed.

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