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Scintigraphy with I-131 MIBG as an Aid to the Treatment of Pheochromocytomas in Patients with the Multiple Endocrine Neoplasia Type 2 Syndromes

James C. Sisson, MD,* Brahm Shapiro, ChB, PhD,* and William H. Beierwaltes, MD*

We reviewed the scintigraphic images made after injections of I-131 metaiodobenzylguanidine (MIBG) or I-123 MIBG in patients with multiple endocrine neoplasia (MEN) types 2A and 2B. The information we obtained was applied to three questions about the treatment of pheochromocytoma in patients affected with these syndromes. Our first question "When should adrenal gland(s) be removed?" was not directly answered. However, adrenalectomy generally should not be contemplated unless distinct abnormalities are present in the scintigraphic images. With experience it may be possible to approximate, from the stage of pheochromocytoma depicted by scintigraphy, how many years will elapse before symptoms or hypertension will appear in the patient. The second question "Should both adrenal glands always be removed when adrenalectomy is undertaken?" was answered nega-

Pheochromocytoma is a cardinal feature of the multiple endocrine neoplasia (MEN) type 2 syndromes. Manifestations of MEN type 2A include medullary thyroid carcinoma (MTC), hyperparathyroidism and pheochromocytoma, while type 2B patients have MTC, ganglioneuromas and skeletal tissue abnormalities, and pheochromocytoma. However, pheochromocytoma does not invariably appear in every affected MEN-2 patient (1-4). In different kindreds, pheochromocytomas have been encountered as infrequently as 1/22 or 5% (5), 2/17 or 12% (6), and 2/15 or 13% (7); and as often as 18/19 or 95% (8); and in 75% of patients over 60 years of age (9).

When present, pheochromocytomas generally appear as benign tumors in both adrenal glands, and in these patients every medulla cell appears to have inherited the propensity to develop hyperplasia (10-12). Nevertheless, pheochromocytomas occasionally grow asynchronously (1,13) and a tumor may appear in only one adrenal gland (1). On the other hand, bilateral adrenal pheochromocytomas may be accompanied by paragangliomas along the aorta (4). In a few individuals, malignant change and metastases have been discovered (1,14,15), and fear of malignancy has prompted bilateral adrenalectomy even before symptoms and clear radiographic abnormalities appeared (16).

tively. In some uncommon patients, the development of pheochromocytoma in one adrenal gland may precede by decades the evolution of tumor in the other gland. If an absence of scintigraphic abnormality and a normal appearance and normal response to touch by the surgeon in one adrenal gland are observed, then an appropriate option would be to withhold removal of that gland. Our third question "Can the onset of malignancy be anticipated?" could not be answered by scintigraphic images. However, scintigraphy will reveal metastases already present and thereby will modify the therapeutic approach to the patient. Malignant change is uncommon before tumors exceed 4 cm in diameter. Earlier adrenalectomy may be indicated for members of an MEN kindred in which metastatic pheochromocytoma has already been encountered.

The varied patterns of expression make it difficult to establish indications for adrenalectomy, which is the standard treatment for patients with MEN-2A and MEN-2B. Three questions should be answered: 1) When should the adrenal gland(s) of patients with MEN-2A or MEN-2B be removed? 2) Should both adrenal glands always be removed at operation in patients with these inherited syndromes? 3) Can the onset of malignant pheochromocytoma be anticipated?

Pheochromocytomas have been accurately detected in early stages of development and in multiple locations by a scintigraphic method that uses I-131 metaiodobenzylguanidine (MIBG), an adrenergic tissue-seeking radiopharmaceutical (17-19). We reviewed the records of patients with MEN-2A and MEN-2B who had I-131 MIBG scintigraphy to find information to answer these three crucial questions.

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Methods

MEN-2A was diagnosed in individuals who exhibited either: 1) MTC or C-cell hyperplasia in the thyroid along with pheochromocytoma, or 2) MTC or C-cell hyperplasia and a family history in which a first-degree relative had MTC and at least one member of the family had pheochromocytoma or hyperparathyroidism. MEN-2B was considered to be present if a patient had typical ganglioneuromas visible on the tongue, and MTC or C-cell hyperplasia was found in the thyroid; a family history was not required.

For scintigraphy, the dose of I-131 MIBG (specific activity approximately 1 Ci/mmol) injected intravenously was 0.5 mCi/1.7 m², but no single dose exceeded 0.5 mCi. If the thyroid gland was present, thyroidal uptake of I-131 was inhibited by administration of a saturated solution of potassium iodide (one drop three times a day) for a week before injection of I-131 MIBG. Images were produced with a wide-field-of-view Anger camera interfaced with a high-energy parallel hole collimator. For each image, data were collected either to 100,000 counts or for 20 minutes. One patient received 10 mCi of I-123 MIBG instead of I-131 MIBG.

Results

1. When should the adrenal gland(s) of MEN-2A and MEN-2B patients be removed? Specifically, can scintigraphy provide a criterion for performing or withholding adrenalectomy?

Case 1

A 17-year-old girl is a member of a family affected by MEN-2A. Her mother had died of a pheochromocytoma crisis. At age 10 years, after a provocative test using pentagastrin had produced abnormal serum concentrations of calcitonin, a thyroidectomy was performed. C-cell hyperplasia was found. Subsequently, she has been well, taking thyroxine in replacement doses. Her heart rate and blood pressure are normal. Biochemical measurements were within normal limits (Table I).

Scintigraphy showed adrenal concentrations of I-131 MIBG (Fig. 1) that exceeded those in normal subjects (Fig. 2). Such scintigraphic results appear to reveal the earliest stage of

pheochromocytoma evolution, but computed tomography was not considered to be necessary at this time. The patient is being followed closely.

Case 2

A 14-year-old girl with characteristic ganglioneuromas and habitus of MEN-2B had an MTC tumor removed by thyroidectomy. Her blood pressure and heart rate were consistently normal. However, when she developed episodes of incoordination and, on one occasion, mild abnormalities in her plasma norepinephrine level (522 pg/ml) and urinary excretion of normetanephrine (212 microg/d), we suspected that she had surges of catecholamines.

Scintigraphy demonstrated abnormal collections of I-131 MIBG in both adrenal glands (Fig. 3). When the normal-sized glands were removed surgically, they contained only medullary hyperplasia (17). The symptoms have persisted and probably were not related to catecholamines. The scintigraphic results appear to signify a slightly more advanced stage of medullary disease than in Case 1.

Case 3

A 27-year-old man exhibited ganglioneuromas and skeletal features typical of MEN-2B. Medullary carcinoma had been incompletely excised in operations at ages 11 and 17 years. He was working regularly, and a single episode of light-headedness was his only symptom. His blood pressure was 108/60 mm Hg and heart rate 80/min. Laboratory studies showed an increase in excretion of norepinephrine and catecholamine metabolites between 1981 and 1983 (Table II).

In 1983, scintigraphy demonstrated approximately the same asymmetric abnormalities as in 1981 and indicated small pheochromocytomas of different sizes in his adrenal glands (Fig. 4). The asymmetry was confirmed by computed tomography which showed the maximum diameters of the adrenal tumors to be 2 cm on the right and 1.5 cm on the left. The recommended operation has not yet been performed.

This case exemplifies a gradual increase in secretion of catecholamines over two years by diagnosed, small pheochromocytomas. We do not know how much time is required for progression from an early stage of adrenal medullary hyperplasia without demonstrable elevation in secretion of catecholamines to a 2 cm pheochromocytoma, but it probably takes many years. We also do not know how long it takes for pheochromocytomas to increase sufficiently in size and function to cause symptoms and/or hypertension.

TABLE I

Biochemical Measurements of 17-year-old girl with MEN-2A (Case 1)

	Plasma (pg/ml)		Urine (µg/day)				
	Epi-nephrine	Norepi-nephrine	Epi-nephrine	Norepi-nephrine	Meta-nephrine	Normeta-nephrine	Vanillyl-mandelic Acid
Normal	(<100)	(<500)	(<30)	(<120)	(<85)	(<165)	(<7000)
	42	245	4	26	37	31	1800

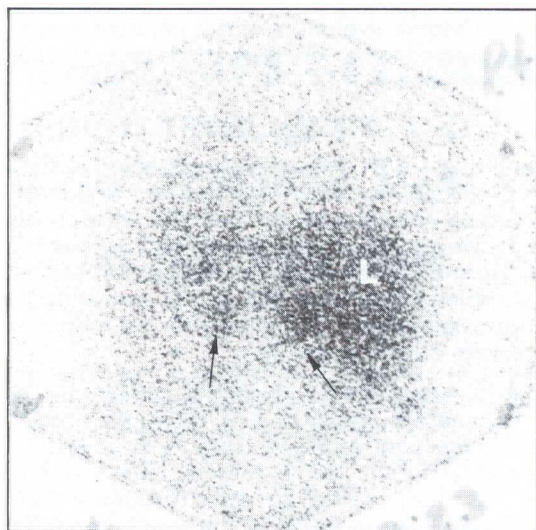


Fig. 1. Case 1.

Scintigraphic image made 72 hours after injection of I-131 MIBG. Posterior view of the abdomen. Arrows indicate regions of adrenal glands; L indicates normal liver radioactivity. A 17-year-old girl with MEN-2A who had neither clinical nor biochemical evidence of abnormality in her adrenal medullas; the image reveals collections of I-131 MIBG in her adrenal glands that are slightly beyond normal and are designated equivocal.

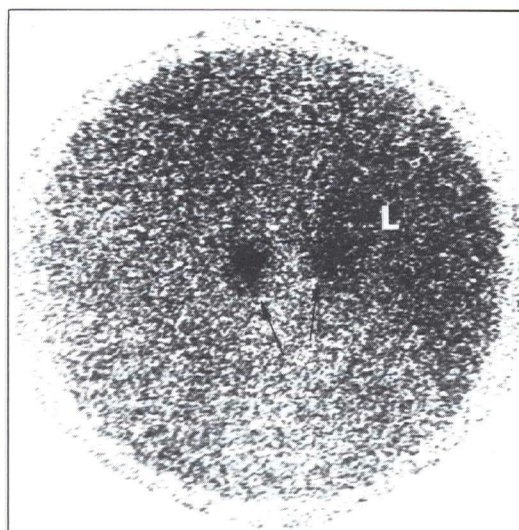


Fig. 3. Case 2.

Scintigraphic image made 48 hours after injection of I-131 MIBG. Posterior view of the abdomen. Arrows indicate regions of adrenal glands; L indicates normal liver radioactivity. A 14-year-old girl with MEN-2B who had atypical episodes probably unrelated to catecholamines and minor intermittent abnormalities in her plasma norepinephrine level and urine normetanephrine excretion rate; the concentrations of I-131 MIBG in her adrenal glands are abnormal and reflect the medullary hyperplasia found at adrenalectomy. Although this image was made at 48 hours, the relative intensity of radioactivity in the adrenal glands tends to increase between 48 and 72 hours.

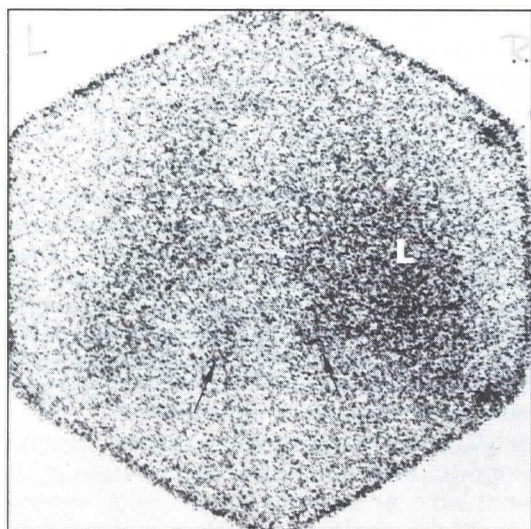


Fig. 2

Scintigraphic image made 72 hours after injection of I-131 MIBG. Posterior view of the abdomen. Arrows indicate regions of adrenal glands; L indicates normal liver radioactivity. A 50-year-old man who exhibited neither clinical nor biochemical evidence of abnormality in his adrenal medullas; the concentrations of I-131 MIBG in his adrenal glands are considered the extreme (greatest concentration) of normal.

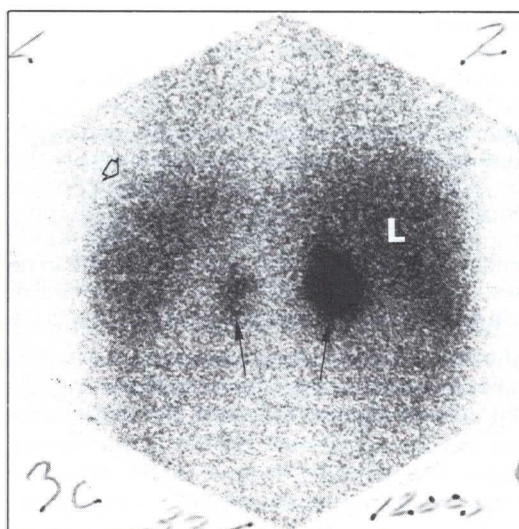


Fig. 4. Case 3.

Image made in 48 hours after injection of 10 mCi of I-123 MIBG. Arrows indicate adrenal glands; L indicates normal liver; open arrow points to normal spleen. At this time, I-123 MIBG generally reveals adrenal abnormalities only slightly better than does I-131 MIBG. This 27-year-old man with MEN-2B manifested no definite clinical features of pheochromocytoma but had moderately abnormal excretion rates of norepinephrine, metanephrine, normetanephrine, and vanillylmandelic acid. The collections of I-123 reflect small and asymmetric tumors of pheochromocytoma.

These three cases illustrate that scintigraphy with I-131 MIBG will detect abnormalities in the adrenal medulla of patients with the MEN-2 syndromes before an increase in size of the adrenal occurs or before diagnostic biochemical and clinical features of pheochromocytoma are present. However, scintigraphic abnormalities do not indicate when adrenalectomy should be done. Because scintigraphy does detect the earliest changes in the evolution of pheochromocytomas, one must have strong reasons based on other data to recommend adrenalectomy in the face of a normal scintigraphic image.

2. Should both adrenal glands always be removed at the time of operation? Specifically, if a demonstrated need to remove a pheochromocytoma in one adrenal gland is assumed, what criteria warrant removal of the other adrenal gland?

Case 4

A 40-year-old man had an MTC tumor excised six years earlier. His mother also has MTC. He experienced headaches, palpitations, and sweating for six months, but his blood pressure and heart rate between episodes were normal. Laboratory studies are listed in Table III.

Computed tomography identified a tumor in the right adrenal gland, but the left gland appeared normal. Scintigraphy showed an abnormal concentration of I-131 MIBG only in the right adrenal gland; no radiopharmaceutical was seen in the region of the left adrenal gland.

At operation, the right adrenal gland contained a pheochromocytoma weighing 46 gm. The left gland appeared slightly thickened, and touching the gland caused his blood pressure to rise. Therefore, the left adrenal gland was also excised; it weighed 10 gm and contained medullary hyperplasia and a small nodule less than 5 mm in diameter.

This case illustrates that scintigraphy may fail to demonstrate an early stage in the development of pheochromocytoma. Evaluation at the time of operation provides additional information about the contralateral adrenal medulla; an increase in either size or functional capacity may be a reason for excising this gland as well.

In our experience, asymmetry of pheochromocytomas has been common (four of seven cases, see Table IV) in patients with the MEN-2 syndromes, but asynchrony, where there is pheochromocytoma on one side and no more than nodular hyperplasia on the other, has been uncommon.

3. Can the onset of malignancy in pheochromocytoma be anticipated?

Case 5

A 26-year-old woman had neither clinical features of MEN-2B nor, on first interview, a family history of MEN-2A. Six years earlier, a thyroidectomy revealed MTC, and the presence of hypertension had led to the diagnosis of large bilateral pheochromocytomas which were removed. However, the tumor in the left adrenal gland (11x8x8 cm) was invading the pancreas and spleen, and metastases of pheochromocytoma were discovered in her liver. Hypertension was controlled by phenoxybenzamine, but computed tomography demonstrated progressive growth of the liver metastases, which were also readily demonstrated by scintigraphy (Fig. 5).

Thus, scintigraphy will detect metastases from malignant pheochromocytomas, an observation reported previously (18-20). Demonstration of metastatic disease establishes that surgical excision of the adrenal glands could not be curative. Nevertheless, the scintigraphic appearance of primary tumors indicates nothing to predict that malignancy is about to occur or that metastases would soon occur.

TABLE II
Biochemical Measurements of 27-year-old Man with MEN-2B (Case 3)

	Plasma (pg/ml)		Urine (µg/day)				
	Epi-nephrine	Norepi-nephrine	Epi-nephrine	Norepi-nephrine	Meta-nephrine	Normeta-nephrine	Vanillyl-mandelic Acid
Normal	(<100)	(<500)	(<30)	(<120)	(< 85)	(<165)	(< 7000)
1981	129	555	20	66	133	125	4600
1982	78	505	20	58	89	203	4100
1983	106	575	13	166	490	284	11600

TABLE III
Biochemical Measurements of a 40-year-old Man with MTC (Case 4)

	Plasma (pg/ml)		Urine (µg/day)				
	Epi-nephrine	Norepi-nephrine	Epi-nephrine	Norepi-nephrine	Meta-nephrine	Normeta-nephrine	Vanillyl-mandelic Acid
Normal	(<100)	(<500)	(< 30)	(<120)	(< 85)	(< 165)	(<7000)
	740	556	156	162	852	4812	8900

TABLE IV
I-131 MIBG Scintigraphy in 16 Patients* with the MEN-2 Syndromes

Syndrome	Normal	Results (No. of Patients)			
		Equivocal**	Unilateral	Abnormal	Bilateral
				Asymmetric +	Symmetric
MEN-2A	7†	2	1¶	2	1
MEN-2B	0	0		1	2§

* Patients from four kindreds of MEN-2A and three unrelated cases of MEN-2B in whom adrenal glands were in place.

** Borderline concentration of radioactivity; all were bilateral as in Case 1.

+ In each case, computed tomogram showed bilateral asymmetric tumors.

† Age range: 14-68 years; in none did catecholamine values suggest the presence of pheochromocytoma.

¶ Nodular hyperplasia on one side did not visualize; a unilateral false negative result of scintigraphy (Case 4).

§ Including Case 2: Bilateral medullary hyperplasia.

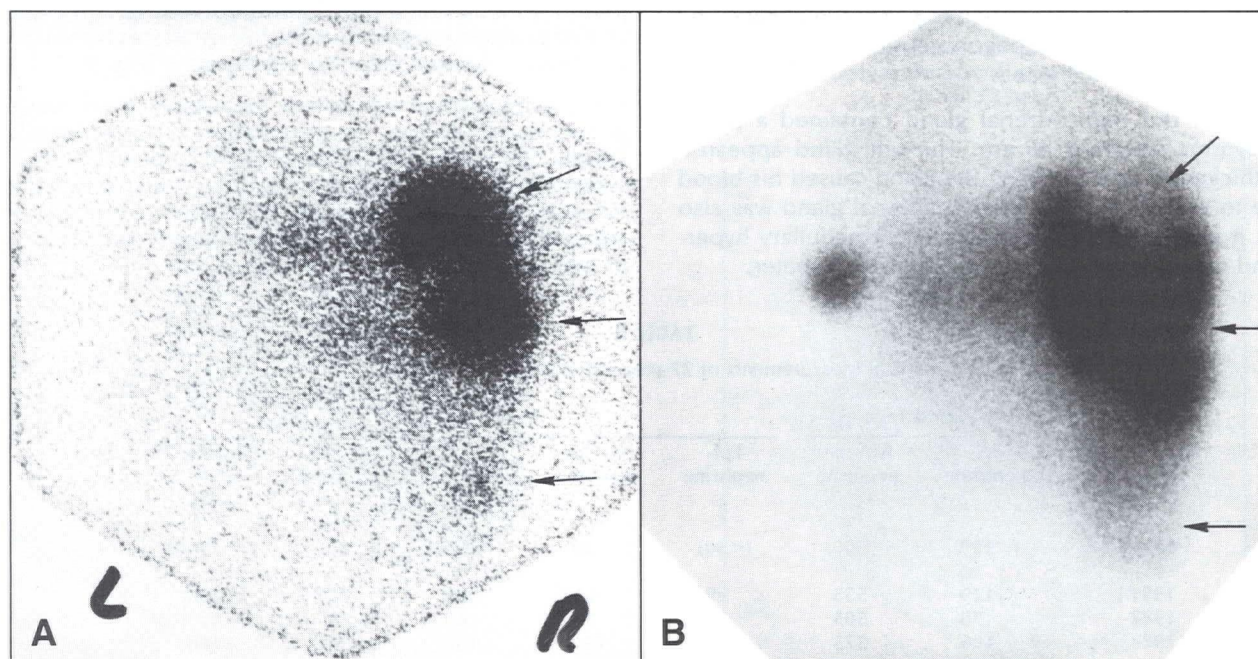


Fig. 5. Case 5.

A 26-year-old woman with MEN-2A and metastatic deposits (small, closed arrows) of pheochromocytoma after bilateral adrenalectomy. A. Image of posterior abdomen 72 hours after injection of I-131 MIBG demonstrating abnormal concentrations of radioactivity in the right lobe of the liver. B. Posterior view of the liver made with the standard liver scanning radiopharmaceutical, Tc-99m sulfur colloid, showing diminished radioactivity in the regions of metastases; this is the converse of the I-131 MIBG image in A.

Discussion

1. When should adrenal gland(s) be removed?

Although treatment of adrenocortical insufficiency, a necessary consequence of removal of both adrenal glands, is generally satisfactory, the imposition of a life-long need for medication and increased risk from stress and trauma requires careful forethought. For patients with the MEN-2 syndromes, the time at which evolving adrenal pheochromocytoma(s) should be excised cannot be answered simply. Data of several different types must be weighed.

When clinical features are absent, the risk of pheochromocytomas suddenly causing dangerous hypertension or arrhythmias (whether spontaneously or from trauma or pregnancy) relates to the rate of secretion of catecholamines and to the size of the tumors. Size probably correlates with the quantity of stored catecholamines. While adrenal glands greater than 2 cm in diameter may be worrisome, tumors up to 5 cm in diameter have not impaired health (13).

When plasma catecholamine levels consistently exceed twice the upper limits of normal, or urinary excretion rates of catecholamine or metabolites rise above 1.5 times the upper limits of normal, the danger from the tumors is appreciable. When these functional criteria are met, or when the tumors are 2 to 4 cm in diameter, surgical treatment is indicated. The onset of symptoms or hypertension attributable to pheochromocytoma make an operation imperative regardless of the size of the adrenal glands.

Scintigraphy should be used to demonstrate that functional or anatomic abnormalities have occurred in the adrenals. The method is especially valuable in establishing the presence of pheochromocytomas when other data are uncertain and in locating the abnormalities in one or both adrenal glands and/or in extra-adrenal sites. As we gain more experience in observing early stages in the evolution of pheochromocytoma, we may be able to use the method to predict how long it will be before a patient will develop symptoms and hypertension. Computed tomography is of value in displaying the size of large adrenal tumors but cannot identify the small changes in adrenal size that occur early in the development of pheochromocytomas. Moreover, it may fail to indicate extra-adrenal tumors.

2. Should both adrenal glands always be removed at the time of operation?

Because the evolution of pheochromocytomas appears to require many years, even decades, serious consideration should be given to leaving in place an adrenal gland that shows little or no evidence of pheochromocytoma. The remaining adrenal cortex would obviate the need for treatment with corticosteroids and

the infrequent but real hazards of adrenocortical insufficiency. Subtotal removal of one gland should be avoided because such pheochromocytomas have frequently recurred, and in one case, the reappearing tumor was malignant (1). Implanting fragments of the adrenal cortex has not yet proved to give either a reliable source of corticosteroids or safety from recurrent pheochromocytoma.

However, it is controversial whether unilateral adrenalectomy for pheochromocytoma is ever proper therapy for a patient with MEN-2A or MEN-2B. Lips, et al (4) and Thompson (21) have advocated bilateral adrenalectomy for nearly all patients with MEN-2 syndromes who develop pheochromocytoma. Tibblin, et al (13) reported that leaving slightly or moderately enlarged (less than 5 cm in diameter) contralateral glands in place is associated with an average of 7.4 symptom-free years. Harrison (22) proposes an individualized approach to the problem, expressing the hope that more information will allow us to predict accurately the behavior of pheochromocytomas. We must remain aware that the progression of events in the adrenal medulla varies from kindred to kindred.

Nevertheless, it probably takes many years for a health-threatening pheochromocytoma to develop from a normally functioning adrenal medulla. When a patient with pheochromocytoma in one adrenal gland has a contralateral gland which appears to be normal by scintigraphy (ie, not more than equivocal increase in concentration of I-131 MIBG) and to the exploring surgeon, unilateral adrenalectomy and excision of any extra-adrenal tumors may lead to freedom from pheochromocytoma for more than 10 years. Less time will be required for a more advanced tumor (eg, 2 cm diameter with slight elevation of catecholamines) to progress to the point of damaging the patient's health. Of course, the preference of the patient, informed of the risks and uncertainties, should prevail in the decision about unilateral versus bilateral adrenalectomy.

3. Can the onset of malignancy be anticipated?

Table V was constructed from a review of the literature (23,24) to give perspective to the risk of malignant change in pheochromocytomas. In an unofficial poll of those attending this workshop, the occurrence of malignancy was reported to be unusual but not rare. The reported malignant pheochromocytomas were large, the smallest being 55 gm. The risk of malignancy may be greater in certain families; three of the 10 malignant cases had a relative who also had malignant pheochromocytoma. Another patient was reported (25,26) to have malignant pheochromocytoma, but the histology of the thyroid neoplasm was papillary carcinoma; this case may not have had MEN-2A or MEN-2B. Metastases from pheochromocytoma do not occur frequently and need not be anticipated at all unless the primary tumor

is large. However, special concern should be given to tumors larger than 4 cm in maximum diameter which, as a sphere, would weigh more than 34 gm. If malignant pheochromocytomas have occurred in a kindred, even small tumors of an affected family member should be removed. Scintigraphy does not anticipate malignancy, but I-131 MIBG images can indicate that metastases are already present.

Acknowledgments

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TABLE V

Malignant Change (Metastases) in Pheochromocytomas in the MEN-2 Syndromes
Relationship of Size of Primary Tumor(s)

Source and Reference	No. of Patients with Excised Pheochromocytoma Malignant/Total	Age at Operation	Sex	Largest Tumor		Death
				Diameter (cm)	Weight (gm)	
1. Mayo Clinic (1)	4/19	18*†	F	5	55	No
		28†	F	12	318	No
		29	F	13	480	Yes +
		23§	F	12	145	Yes +
2. MD Anderson Hospital (14)	2/8	53	F		210	Yes
		38	F		250	Yes
3. Maimonides Medical Center, NY (15)	Single case	49	M	19		Yes +
4. University of Michigan**	3/14	21	F	11	368	No
		27	M		64	No
		58	F	7		No

* This patient was also reported elsewhere (23,24).

† Familial occurrence of malignancy. The two at Mayo Clinic were sisters. Our patient at the University of Michigan has a great-uncle who died of metastatic pheochromocytoma (courtesy of Dr. Stephen McDonald, Wright-Patterson AFB).

+ Death from pheochromocytoma.

§ MEN-2B.

** These three patients were referred for possible treatment of malignant pheochromocytoma with I-131 MIBG.

A case in Kingston, Ontario also had a large malignant pheochromocytoma: 1722 g (personal communication from W.R. Ghent).

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