The Efficacy of Iodine-123-MIBG as a Screening Test for Pheochromocytoma

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The primary objective of this study was to characterize the effectiveness of ^{123}I-metaiodobenzylguanidine (MIBG) as a screening test for pheochromocytoma in routine clinical practice. An attempt was made to determine why some tumors and some adrenal glands without pheochromocytoma minimally manifest increased uptake. **Methods:** Planar images were obtained with a standardized protocol in a diverse group of patients. The intensity of uptake in each adrenal gland was graded on a 0–3-point scale by using the intensity of activity in the liver as a reference. Follow-up data were obtained from both the patients and the referring physicians. A final diagnosis was eventually established in 120 patients who had a total of 238 adrenal glands. **Results:** There was an intramedullary pheochromocytoma in 24 of the 238 adrenal glands (10.1%). The uptake was very intense (Grade 3) in 21 of them (87.5%). The uptake was only mildly to moderately increased in the other three intra-adrenal tumors. There was no visible uptake in 148 of the 214 (69.2%) adrenals without a pheochromocytoma, but there was mildly to moderately increased activity in 66 (30.8%). There were no other features of the clinical data base which could differentiate between mildly increased uptake in a pheochromocytoma and mildly increased activity in a gland without a tumor, including the 24-hr urinary excretion of catecholamines. **Conclusions:** Since every intra- and extra-adrenal tumor was visualized, the findings suggest that ^{123}I-MIBG may be the most sensitive screening test available for diagnosing pheochromocytoma. The test results should be definitive in most patients.

Key Words: iodine-123-metaiodobenzylguanidine; pheochromocytoma; catecholamines

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Pheochromocytoma produces catecholamines (*1,2*). The symptoms of hyperautonomic nervous system dysfunction that may result can be protean (*3,4*). Making the definitive diagnosis can be difficult because several other disorders can cause similar symptoms (*2,5*). Many of these chromaffin cell tumors only periodically secrete catecholamines into the systemic circulation. The episodic nature of these catecholamine storms can make it difficult to establish definitive biochemical evidence of the disease (*2*). The demand for a more sensitive and specific test for pheochromocytoma may be increasing in clinical practice. The evidence suggests that the disease is currently underdiagnosed (*6*). More abdominal imaging procedures are being performed for other indications, and more adrenal masses are being found incidentally in patients with hypertension.

Adrenal scintigraphy with ^{131}I-metaiodobenzylguanidine (MIBG) appears to be a safe and effective procedure for localizing pheochromocytoma and ruling out metastases (*7–26*). However, its use as a primary diagnostic tool in patients without compelling biochemical evidence of the disease has been discouraged (*27,28*). The sensitivity of ^{131}I-MIBG has been reported to range from about 79% to 89% (*19*), which may not be high enough to justify the costs of using ^{131}I-MIBG as a screening test. This is essentially comparable to the sensitivity of x-ray computed tomography (CT) and magnetic resonance imaging (MRI), both of which are more readily available in most centers than ^{131}I-MIBG.

The sensitivity of ^{131}I-MIBG is limited in part by the poor image quality that can be produced with the high-energy, low-photon flux from ^{131}I. Labeling MIBG with ^{123}I instead of ^{131}I can enhance the image quality substantially (*29–34*). The radiation exposure that is associated with ^{123}I is more favorable than the dosimetry with ^{131}I. This may also increase the sensitivity of the test because 10 times more activity can be administered with the ^{123}I-labeled product than with the ^{131}I-labeled radiopharmaceutical. However, there are concerns that labeling MIBG with ^{123}I may also decrease the specificity of the test, because normal and abnormal adrenal glands without pheochromocytoma frequently take up enough ^{123}I-MIBG to be visualized (*31*). The consequences of a false-positive test are potentially grave because major surgery would presumably follow in most cases (*35–37*).

These observations have led to questions about whether MIBG should be labeled with ^{131}I or ^{123}I. A consensus has not been reached about whether ^{131}I or ^{123}I-MIBG should be used as a primary screening test or limited to a localization procedure in patients with overwhelming evidence of the disease. This study tried to address some of these issues by reviewing the performance of ^{123}I-MIBG in a conventional clinical setting.

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METHODS

Subjects

The original population consisted of 130 consecutive patients studied over a 45-mo interval between 1989 and 1993. They were referred by more than 80 different local physicians, none of whom were engaged in research. There were many different indications for the study. Most patients had labile hypertension or an episode of extreme hypertension that was being worked up. Some of the patients had hypertension and family histories suggestive of multiple endocrine neoplastic syndromes. There were six patients who were excluded because they were referred for the evaluation of a carcinoid disorder. One patient was excluded because she was surreptitiously taking amitryptaline at the time of study. Scans that were repeated after surgery were not considered.

A final diagnosis was established in 120 patients (53 males and 67 females, mean age 51.9 ± 14.7 yr, range 15 yr to 80 yr). The 24-hr urinary excretion of at least one catecholamine or catecholamine metabolite was elevated in 76 patients. Urine assays were not performed in 15 patients with at least one elevated plasma catecholamine level. They were normal at the time of study in 12 subjects. The values could not be recovered in the remaining 17 subjects. There were 58 patients (48.3%) who were referred because an adrenal mass had already been discovered with MRI or x-ray CT. The MIBG scan was the only imaging procedure performed in nine patients. An intra-adrenal tumor was ruled out prior to scintigraphy in the rest of the sample. Most of these patients were referred to have an extra-adrenal paraganglioma ruled out.

Radiopharmaceuticals

The pharmacological precursor, meta-iodobenzyl guanidinium sulfate, was obtained commercially (Parag Intl., Upper Darby, PA). An average of 12 mCi of sodium iodide ^{123}I was purchased separately to label each dose (Nordion Intl., Vancouver, BC). The radiochemical purity of the radioisotope was guaranteed to exceed 99.8% by the manufacturer at the time of delivery. Thin-layer chromatography demonstrated that the radiopharmaceutical purity of each dose exceeded 90%. In all, six doses failed to meet quality control standards and were discarded.

Imaging Protocol

All sympathomimmetic medicines that could potentially interfere with the uptake of MIBG were discontinued for at least five half-lives prior to the procedure. Patients were pretreated with about 10 drops of Lugol's solution in a cup of water about 1 hr before the administration of the radiopharmaceutical. About 370 MBq (10 mCi) of ^{123}I-MIBG were administered intravenously at about 3 p.m. Scans were performed the next morning after an 18-hr interval. Planar images of the whole body were acquired with a gamma camera equipped with low-energy, all-purpose, large field-of-view, parallel-hole collimators. Whole-body scans performed on dual-headed cameras were acquired for 30 min. When single-headed cameras were used, the planar images of the adrenals were acquired for a minimum of 20 min or one million counts. Most contained over two million counts. Spot views of the rest of the body were acquired for 10 min or one million counts, whichever came first. Lateral views, high-count images and ^{99m}Tc-DTPA subtraction images were ordered as necessary for localization.

Ratings of Adrenal Intensity

The intensity of MIBG uptake was qualitatively compared to the activity in the liver by two experienced observers who were unaware of the clinical circumstances surrounding each case at the time of assessment. Each independently rated the intensity of adrenal activity. A score of 0 indicated no visible adrenal uptake. A score of 1 represented mildly increased uptake that was less intense than the activity in the liver. A score of 2 (moderately increased uptake) was used to grade adrenal uptake of approximately the same intensity as the activity in the liver. A score of 3 represented intense uptake. Discrepancies between the two raters were resolved for purposes of analysis by consensus with a third observer.

Statistical Methods

The positive predictive values (PPV) were independently derived for each grade of adrenal uptake. For example, the PPV of Grade 1 uptake was calculated by dividing the number of surgically proven cases with Grade 1, intra-adrenal uptake by the total number of adrenals with Grade 1 uptake.

The population was divided into patients with and without a final diagnosis of pheochromocytoma. The subsample without pheochromocytoma was split into a group with visible adrenal uptake and a group of patients without visible adrenal uptake. Group mean values were calculated for the levels of three urinary catecholamines and two metabolites. Group means were compared with two-tailed, independent t-tests.

RESULTS

Pheochromocytoma was eventually ruled out in 75.8% (91/120) of the patients in this sample. There were 29 patients with a final diagnosis of pheochromocytoma. The disease process was confined to the adrenals in 23 (79.3%). These 23 patients had a total of 24 intra-medullary tumors, because one patient had bilateral disease. A solitary intra-adrenal pheochromocytoma was found on the left in 12 patients and a solitary tumor was found on the right in 10 (Table 1).

The grading scale that was used to rate the intensity of activity produced four discordant readings, which only differed by one grade. In a subsample of 108 adrenals, the raters agreed on the grade of uptake in 104 (96%).

Every tumor was visualized with ^{123}I-MIBG. The uptake was intensely increased (Grade 3) in 19 of the 22 unilateral, intra-adrenal tumors (Fig. 1). The only patient with bilateral disease had Grade 3 uptake on both sides, which made the total number of intra-adrenal tumors with Grade 3 uptake 21 of 24 (87.5%). The intra-adrenal tumor uptake was about as intense as the activity in the liver (Grade 2) in one patient (4.3%) with a solitary pheochromocytoma. The uptake was less intense than the liver (Grade 1) activity in the other two (8.7%) (Table 2).

There were six patients with extra-adrenal tumors, each of which corresponded to a mass on MRI or CT. Of these, five had multifocal disease. There were at least two tumors with Grade 3 uptake in four of these five patients (Fig. 2). One patient presented with Grade 3 uptake in a solitary para-aortic tumor (Fig. 3). Only one patient with extra-adrenal disease had Grade 2 uptake. No extra-adrenal tumors had Grade 1 or Grade 0 uptake. None of the patients with extra-adrenal disease had a coexisting adrenal tumor at the time of their MIBG scan. However, two of these

TABLE 1
Distribution of Pheochromocytoma

	No. of patients in group	No. of adrenal glands with pheochromocytoma	No. of adrenal glands without pheochromocytoma
Total with pheochromocytoma	29	24	32
Left pheochromocytoma	12	12	12
Right pheochromocytoma	10	10	10
Bilateral	1	2	0
Extramedullary	6	0	10
Total without pheochromocytoma	91	0	182
Total	120	24	214

patients had originally presented with intra-adrenal disease and were three or more years status postadrenalectomy.

There were a total of six extra-adrenal foci of Grade 1 activity in patients without pheochromocytoma that prompted radiographic correlation with MRI or CT. None were ever shown to represent a paraganglioma. There were three other patients with hypertension who were referred for the scan because an extra-adrenal mass on MRI or CT was suspected of being a catecholamine-secreting tumor. No MIBG activity was found in these sites. Biopsy ruled out a pheochromocytoma in two, and the disease was excluded medically in the other.

There were a total of 214 adrenal glands without pheochromocytoma in the entire sample. The 91 patients without pheochromocytoma had 182 adrenal glands without a tumor, and the 22 patients with a solitary intra-adrenal pheochromocytoma had 22 disease-free glands on the other side. The six patients with extra-adrenal pheochromocytoma only had 10 disease-free glands because two patients had a gland surgically excised several years before the study.

Of the 214 adrenal glands without a tumor, there was no visible activity at all (Grade 0) in 148 (69.1%). The uptake was Grade 1 in 62 of the 66 (93.9%) other glands without a tumor that had visibly increased activity. Grade 2 uptake was seen in the remaining four adrenals without a tumor, two of which were unilateral in two patients, and two of which were bilateral in a single subject. There were 14 patients without pheochromocytoma who had unilateral Grade 1 uptake; 21 patients without pheochromocytoma who had bilaterally symmetric, Grade 1 uptake in 42 glands; five patients with a solitary intra-adrenal pheochromocytoma who had Grade 1 activity in a disease-free gland on the contralateral side; and one patient with extra-adrenal paragangliomas who had Grade 1 activity in an uninvolved adrenal gland.

When the PPV was calculated for each grade of adrenal uptake independently (Table 2), the PPV of both Grade 0 and bilateral Grade 1 uptake was 0%. A solitary focus of Grade 1 adrenal uptake had a PPV of 9.1% (2 of 17). Grade 2 unilateral uptake had a PPV of 33% (one of three). The PPV of any solitary focus of Grade 1 or Grade 2 adrenal activity representing a pheochromocytoma was 15% (3 of 20). Grade 3 had a PPV of 100%.

The structural images were examined for features that might differentiate mildly increased MIBG uptake in a tumor from mildly increased MIBG activity in an adrenal gland without a pheochromocytoma. Every tumor except one that was visualized with MIBG corresponded to a mass on CT or MRI. The one exception was a 1.5 × 2-cm pheochromocytoma with Grade 3 uptake that was not visualized with either MRI or CT. Each tumor with Grade 1 or 2 activity in the three patients with pheochromocytoma, who did not have intensely increased uptake, corresponded to a mass on CT or MRI. The patient with bilateral pheochromocytoma had bilateral adrenal masses with MRI signal intensities that were characteristic of pheochromocytoma.

An adrenal mass was found with CT or MRI in 13 of the 39 patients without pheochromocytoma (33.3%) who had visibly increased adrenal activity. However, 4 of the 13 had a solitary adrenal mass on the other side of the scintigraphic focus, and six had a solitary mass associated with bilaterally symmetrical MIBG uptake. The other three patients had a structural lesion on the same side as the MIBG focus, but the appearance of the lesion was definitely characteristic of another disease process. MRI ruled out bilateral disease in all five patients with a focus of Grade 1 activity on the other side of an intramedullary pheochromocytoma with Grade 3 uptake.

The clinical database was examined for features that might differentiate mildly increased uptake in a pheochromocytoma from mildly increased activity in a gland without a tumor. No relationships were found between age or sex and the intensity of adrenal uptake in any of the patient subgroups (Table 3). The only patient with Grade 2 uptake in an extra-adrenal tumor was a large, adult male. His paragangliomas were located deep within the abdomen where soft tissue attenuation could have reduced the apparent intensity of uptake on the images. However, the three patients with Grade 1 or Grade 2 uptake in their intramedullary tumors were relatively lean. Subtraction images with DTPA indicated that the location of their tumors in the retroperitoneum was normal. The bowel activ-

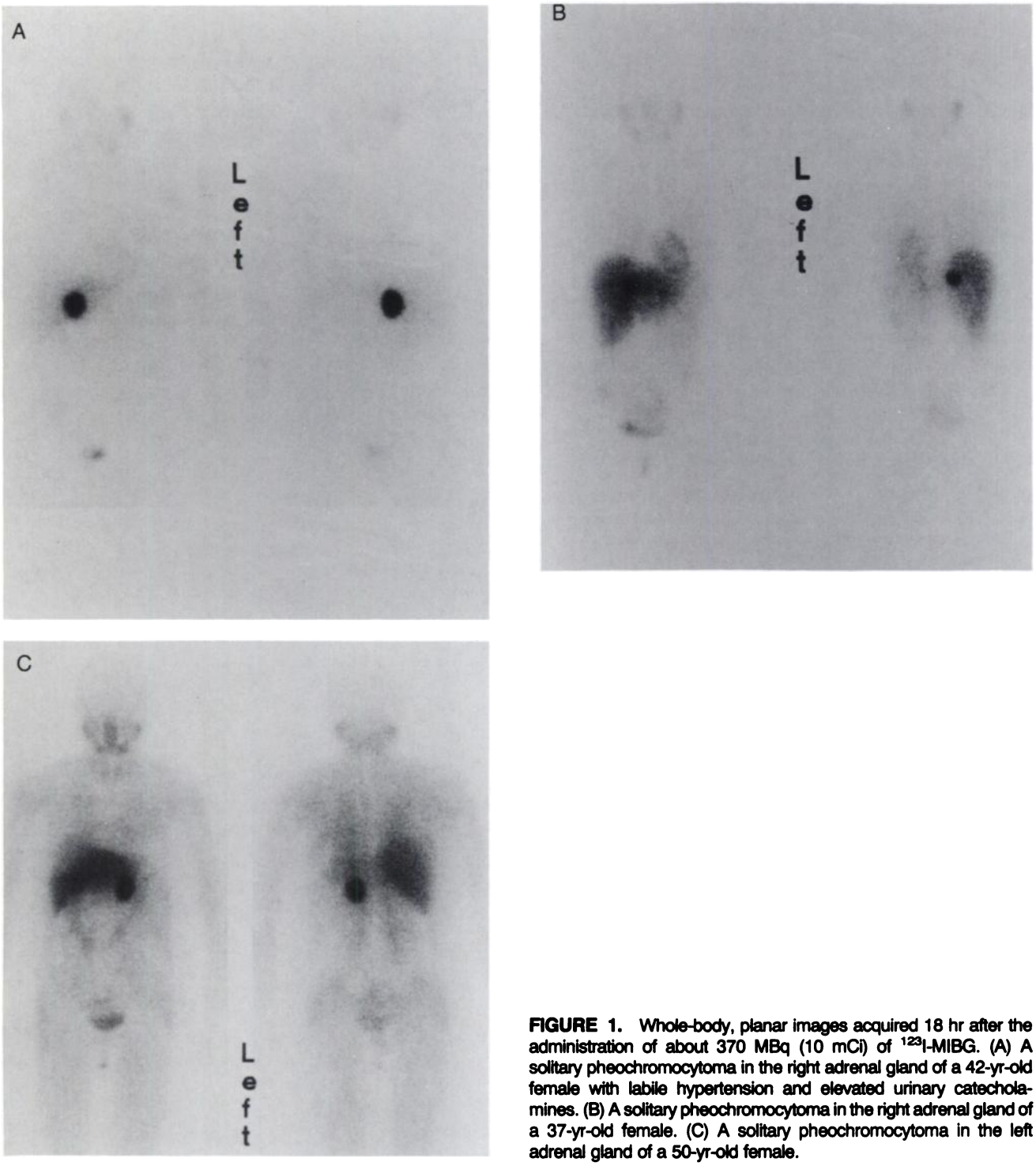

FIGURE 1. Whole-body, planar images acquired 18 hr after the administration of about 370 MBq (10 mCi) of ^{123}I-MIBG. (A) A solitary pheochromocytoma in the right adrenal gland of a 42-yr-old female with labile hypertension and elevated urinary catecholamines. (B) A solitary pheochromocytoma in the right adrenal gland of a 37-yr-old female. (C) A solitary pheochromocytoma in the left adrenal gland of a 50-yr-old female.

ity, which provided most of the contrast with the adrenal glands, was equivalent in each group.

Pre- and postsurgical measurements of tumor size indicated that the tumors with Grade 1 or 2 uptake were larger than several with Grade 3 uptake. One was 6 × 5 × 4.5 cm. The smallest was 2 × 2 × 2 cm. Postsurgical histopathology showed central necrosis in some tumors, but this did not occur in any of the tumors with less than intense uptake. There was no suggestion of anaplasticity in the tumors with less than intense uptake. However, no systematic tissue studies were performed. No measures of cellular dedifferentiation were performed and no attempts were made to measure the intracellular autometabolism of the catecholamines that were synthesized.

Urinary catecholamine levels were available in 25 of the 29 patients with pheochromocytoma, and available in 61 of the 91 patients without pheochromocytoma. The 24-hr urinary excretion of metanephrine (META), epinephrine

TABLE 2
Intensity of Adrenal Activity

Intensity of adrenal uptake	Adrenal glands with pheochromocytoma (m = 24)	Adrenal glands without pheochromocytoma (m = 214)*	PPV
Grade 0	0	148	0%
Grade 1			
Bilateral (n = 21)	0	42	0%
Asymmetric†	0	5	0%
Solitary‡ (n = 17)	2	15	13.3%
Grade 2			
Bilateral (n = 1)	0	2	0%
Unilateral (n = 3)	1	2	33%
Grade 3			
Bilateral (n = 1)	2	0	100%
Unilateral (n = 19)	19	0	100%

*Based on the sum of 182 adrenal glands in 91 patients without pheochromocytoma and 32 adrenal glands in the 29 patients with pheochromocytoma that were not involved with the disease.

†Patients with a solitary pheochromocytoma who had Grade 3 uptake in the tumor and Grade 1 uptake in the normal gland on the other side.

‡Includes one patient with extra-adrenal pheochromocytoma who had faint uptake in an uninvolved gland, 14 patients without pheochromocytoma, and 2 patients with Grade 1 uptake in a surgically proven tumor.

m = Number of adrenal glands, n = number of patients.

(EPI), norepinephrine (NE), and VMA was significantly higher in the group of patients with pheochromocytoma than in the group without pheochromocytoma (e.g., META $p = 0.002$; EPI $p = 0.019$; NE $p = 0.0506$). However, there were no observable differences between the excretion rates in patients with pheochromocytoma who had Grade 1 or 2 uptake and patients with pheochromocytoma who had Grade 3 uptake. The mean urinary excretion of catecholamines in patients without pheochromocytoma who had visibly increased adrenal uptake was essentially the same as the mean in patients without pheochromocytoma who had no uptake. There was a substantial amount of overlap between the catecholamine levels in patients with and without pheochromocytoma. The 24-hr urinary excretion of metanephrine was normal in 4/25 patients with pheochromocytoma (16%). The excretion of epinephrine was only abnormal in 7/22 (31.8%). The 24-hr urinary level of norepinephrine was elevated in 14/22 (63.6%). The dopamine levels were above the normal limit in 11/22 (50%), and the excretion of VMA was increased in 8 (34.8%). There were two patients with completely normal urinary and plasma catecholamine levels (6.9%) and five patients with only one elevated value (17.2%). This value was less than two times normal in 4 of these 5 patients. On the other hand, at least one urinary catecholamine level was elevated in 53/61 patients without pheochromocytoma (86.9%).

DISCUSSION

The results of this study indicate that adrenal scintigraphy with ^{123}I-labeled MIBG can be used in conventional imaging facilities much like any other routine procedure. In this sample, a diagnosis could be made with confidence in most cases by acquiring a single set of delayed images and reviewing the films without any special processing or quantification. The grading system that was used to rate intensity was easy to apply with good (104/108) inter-rater reliability.

The findings suggest that ^{123}I-labeled MIBG is probably the most sensitive imaging procedure that is currently available for diagnosing pheochromocytoma. Every known tumor in this sample was visualized. The problem was specificity. Grade 3 uptake had a PPV of 100% in this clinical setting, but a sensitivity of only 87.5%. This would have been about the same as the sensitivity of 79%–89% that has been reported for the ^{131}I-labeled product (*19*).

By using any visibly increased activity as the criterion for a positive test, the scan was able to pick up the remaining cases. Although about 30% (66/214) of the adrenals without pheochromocytoma was visualized, bilaterally symmetrical Grade 1 or 2 activity accounted for most of these cases and never represented bilateral pheochromocytoma. Only about 15% (20/120) of the patients in the total sample had a solitary focus of Grade 1 or Grade 2 activity, which carried a 15% (3/20) chance of representing an intraadrenal tumor. Correlative anatomical imaging was able to confirm or rule out disease in every patient who had a focus of Grade 1 or Grade 2 activity. The findings suggest that if any visibly increased activity is used as the threshold for a

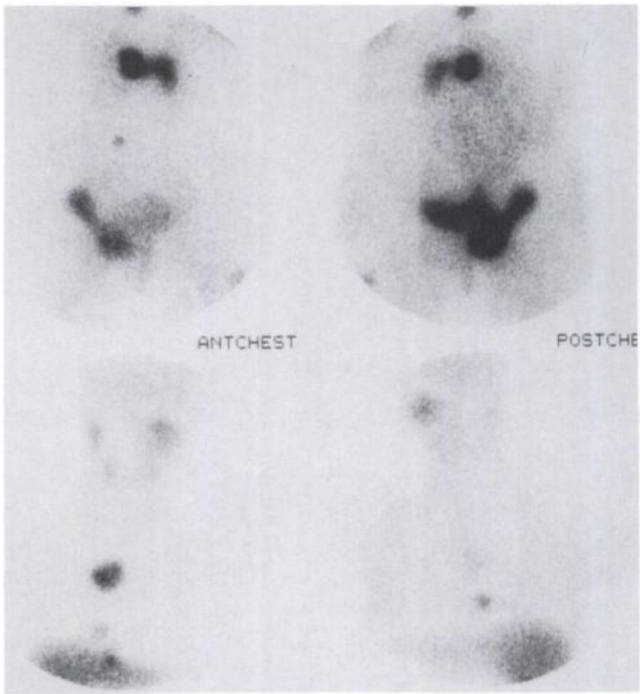

FIGURE 2. Iodine-123-MIBG images of a 39-yr-old female with an established 12-yr history of multiple endocrine neoplasms who presented with hip and sternal pain. Her scan shows significant uptake in metastatic lesions to the mediastinum, abdomen and paravertebral area.

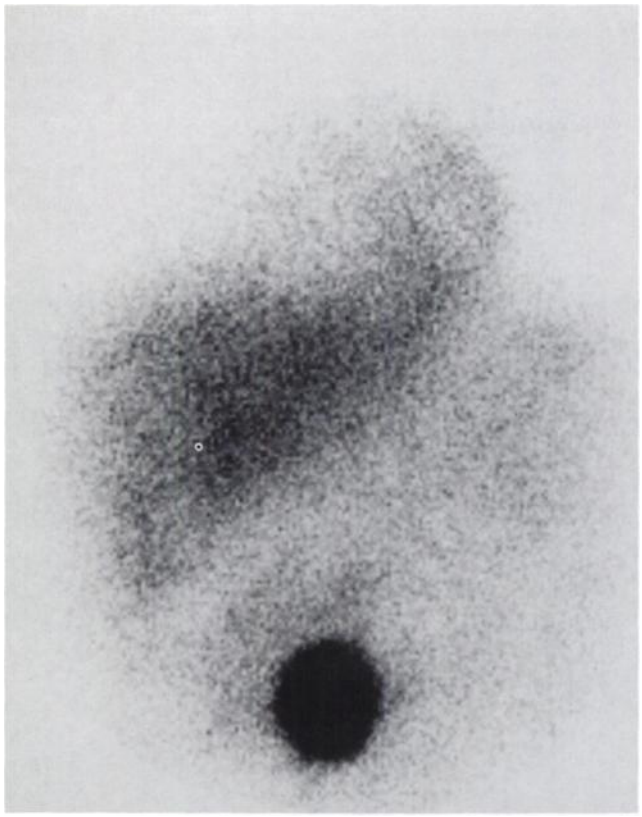

FIGURE 3. A region of intense ^{123}I-MIBG uptake in the mid-abdomen is shown. Postsurgical histopathology proved the mass was a para-aortic pheochromocytoma. The patient is a 46-yr-old female with persistent hypertension. The sum of her urinary excretion of epinephrine and norepinephrine was moderately elevated at 172 μg/24 hr.

positive test, correlative anatomical imaging can effectively correct any false-positives that result.

No other clinical variables were found that could increase the positive or negative predictive value of Grade 1 or Grade 2 uptake. The 24-hr urinary excretion rates of most catecholamines were statistically higher in the group of patients with pheochromocytoma than in the group of patients without pheochromocytoma who had mildly increased adrenal uptake. However, this seems to have been clinically meaningless because there was a substantial amount of overlap between the two groups. Abnormal catecholamine levels were never documented in two patients with pheochromocytoma despite repeated assays. These findings are consistent with the observation that there are many causes of hypercatecholaminemia (*2,5*) and 40% of all pheochromocytomas only secrete catecholamines periodically (*3*). This suggests that adrenal scintigraphy may still be indicated as a screening test for pheochromocytoma in some patients without biochemical proof of the disease.

Adrenal CT or MRI was not an effective means of screening for pheochromocytoma in more than 20% of the patients with the disease in this sample because their tumors were all extramedullary. In some populations of patients, the percentage of extra-adrenal tumors has been even higher (*38*). Since a negative adrenal CT or MRI scan cannot rule out an extra-adrenal tumor, and because an MIBG scan is still useful for ruling out multifocal disease after a CT or MRI has demonstrated an intra-adrenal tumor, it seems logical to consider using MIBG scintigraphy as the initial screening procedure for pheochromocytoma in most cases. The ^{123}I-labeled product appears to be exquisitely sensitive. A negative scan should obviate the need for any further imaging in most patients without pheochromocytoma, and a positive scan can be used to focus the correlation with anatomical imaging on specific areas of abnormally increased uptake.

TABLE 3
Demographics

	With pheochromocytoma	Without pheochromocytoma
Males	10	43
Females	19	48
Age	46.6	53.6
Range	28–80	15–76

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