Iodine-131 Metaiodobenzylguanidine for the Locating of Suspected Pheochromocytoma: Experience in 400 Cases

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The efficacy of the newly developed pheochromocytoma-seeking radiopharmaceutical, [^{131}I]MIBG, was examined in the first 400 patients (441 studies) investigated for suspected pheochromocytoma at our institution. The results of [^{131}I]MIBG scintigraphy were classified as true positive, false positive, true negative, and false negative. Using this classification the sensitivity was found to be 78.4% in primary, sporadic pheochromocytoma, 92.4% in malignant pheochromocytoma, and 94.3% in familial pheochromocytoma giving an overall sensitivity of 87.4%. The specificity was 98.9% in primary, sporadic pheochromocytoma, 100% in malignant pheochromocytoma, and 100% in familial pheochromocytoma. The overall specificity was 98.9%. Iodine-131 MIBG scintigraphy was thus found to be a safe, noninvasive, and efficacious technique for the location of pheochromocytomas, especially for those arising from nonadrenal sites, recurring postoperatively, and exhibiting malignant metastatic disease. We find that, where available, [^{131}I]MIBG scintigraphy is the study of choice to initiate the location of suspected pheochromocytoma.

J Nucl Med 26:576–585, 1985

The clinical manifestations of pheochromocytoma are highly varied (*1–3*), but biochemical confirmation of the diagnosis is now readily possible using plasma (*4,5*) and urinary (*4,6*) catecholamine measurements. Plasma chromogranin A levels may be another useful marker for the presence of pheochromocytoma (*7,8*). Successful therapy then hinges on accurate location of all tumors thus permitting their extirpation (*1–3*).

Once a diagnosis of pheochromocytoma has been made, locating the tumor, which may be multiple, is sometimes difficult and often uncertain despite the introduction of computed tomography (*9–11*) and high resolution ultrasound (*12*). Adrenal lesions less than 2 cm in diam and some extra-adrenal lesions considerably larger than 2 cm in diam are frequently not visualized by computed tomography (*9–11*). Angiographic demonstration of tumors frequently identify adrenal lesions, but in the case of extra-adrenal lesions, this approach may be thwarted if selective injection of the feeding vessels is not possible (*13,14*). Venography with multiple sampling of venous effluent for catecholamine concentrations sometimes discloses the anatomic level of a pheochromocytoma but is both invasive and cumbersome (*11,15,16*). Any of the radiological procedures which require the injection of contrast material carry a small but appreciable risk of allergic reactions and hypertensive crisis in patients not adequately pretreated with alpha blockers (*1,13*).

The major persisting problems in tumor location are: detecting adrenal hyperplasia and small adrenal pheochromocytomas in patients with Multiple Endocrine Neoplasia (MEN) Type 2 who are at high risk for these lesions (*17*), uncovering extra-adrenal pheochromocytomas (*18*), locating residual and/or recurrent tumor at sites of previous operations where tissue planes, and

Received Sept. 12, 1984; revision accepted Feb. 27, 1985.

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vascular anatomy are disrupted and where metallic clips degrade computed tomographic images (*9*) and in the detection and delineation of spread of malignant pheochromocytoma (*19,20*).

The development of the guanethidine analog iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG), provides a safe, specific, and noninvasive technique for locating pheochromocytomas, and it has been found effective in solving many of the problems mentioned above (*21–28*). We report here our experience with 441 studies (400 cases) of suspected pheochromocytoma studied with [^{131}I]MIBG scintigraphy.

MATERIALS AND METHODS

Patient population

All patients were referred for study between June 1980 and November 1983 because of suspicion that they harbored a pheochromocytoma on the basis of hypertension and/or spells characterized by headache, sweating, palpitations, anxiety or tremor, or were at high risk because of a family history of MEN Type 2a or 2b or of neurofibromatosis. Before referral for our evaluation, the majority of patients had one or more abnormal measurement of the plasma catecholamine concentrations or urinary catecholamine or catecholamine metabolite excretion rates, these having been determined by a wide range of assay procedures and samples having been collected under a variety of circumstances.

Before scintigraphy, all patients were subjected to a detailed history with special emphasis being directed towards a history of "spells" or hypertension and of conditions known to be associated with pheochromocytoma. On physical examination, special emphasis was placed on relevant signs; pulse and blood pressure in the supine and erect positions, abdominal masses and features that might indicate an inherited tendency toward pheochromocytomas, neurofibromatosis, cafe au lait spots, goiter, and retinal angiomatosis.

For 38 patients, studies were repeated (in several cases more than once). These included: nine in which scintigraphy was performed before and after resection of pheochromocytoma; six in which scintigraphy was performed in MEN patients with evolving medullary hyperplasia; six in whom initial studies were negative but suspicion remained high; and 17 patients with positive initial scans which were repeated for confirmation.

Catecholamine measurements

The plasma concentrations of epinephrine and norepinephrine were measured by radioenzymatic assay on samples obtained after an overnight fast, the patient having been recumbent for at least half an hour with an indwelling venous cannula in situ (*29*). The urinary excretion rates of catecholamines and catecholamine metabolites were determined on 12-hr, overnight urine samples by the technique of von Euler and Lishajko (*30*) and were expressed in μg/24 hr.

Iodine-131 MIBG scintigraphy

Iodine-131 MIBG was synthesized by the method of Wieland et al. (*31*) and had a specific activity of at least 1.8 mCi/mg and was administered by slow i.v. injection over a period of 10–20 sec in a buffered bacteriostatic saline (pH 5.5) with a specific concentration of at least 0.5 mCi/ml. The dose was 0.5 mCi/1.7 m^2 body surface area to a maximum of 0.5 mCi. The uptake of free ^{131}I by the thyroid was minimized by the administration of Lugol's solution, 40 mg/day or saturated solution of KI 120 mg/day, beginning the day before and continuing for 7 days after the administration of [^{131}I]MIBG (*23*). Using this regime, thyroidal uptake of free ^{131}I was seldom visible (<5% of cases) on the image obtained of the posterior head, neck, and upper thorax. Faint thyroid uptake of free ^{131}I could be discerned in 70% of cases in which an anterior neck view was obtained.

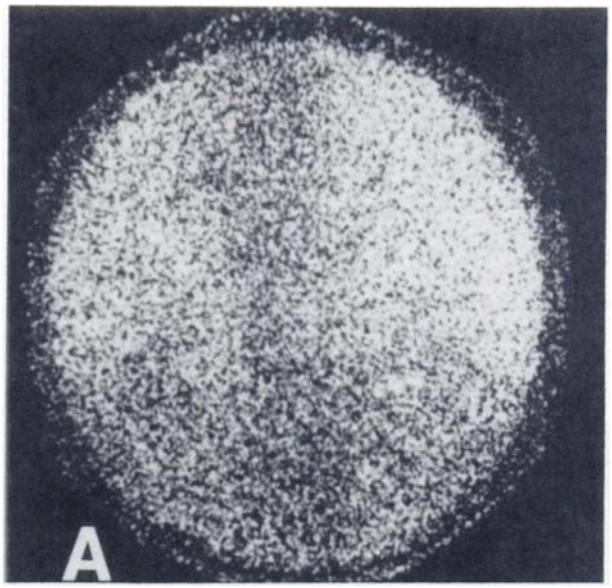
Images were obtained using a large-field-of-view gamma camera with high-energy, parallel-hole collimator and interfaced to a dedicated minicomputer. Multiple overlapping images from the skull to the urinary bladder were obtained. Images containing 100,000 counts and were displayed as analog and digitized images on film (*23*). A small number (*32*) of earlier studies were performed in which images contained 50,000 counts and were displayed on polaroid. Anatomical orientation was provided by surface markers (^{137}Ba) and in selected cases by scintigraphy of other organs; kidney by technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA); liver and spleen by sulfur colloid; myocardium by thallium-201; cardiac blood pool by ^{99m}Tc-labeled red blood cells (*23,26,28*). Studies were performed at 1 day only (three studies), 2 days only (43 studies), 3 days only (two studies), 1 and 2 days (88 studies), 1 and 3 days (five studies), 2 and 3 days (44 studies) but subsequent experience has been obtained with images at 1, 2, and 3 days (256 studies) (Total 441—Tables 2 and 3 based on these 441 studies).

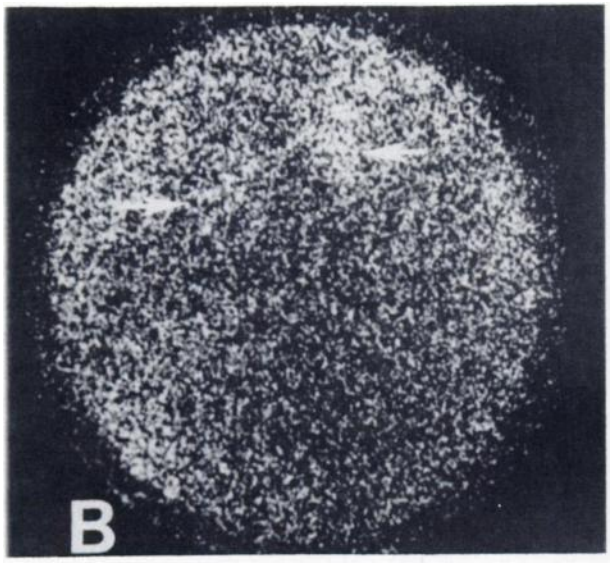
The totals of Tables 2A–C add up to more than 441 studies (451 in Table 2D) because some cases are represented more than once (e.g., both familial and malignant). The total number of patients in Table 2A–C adds up to more than 400 patients (421 in Table 2D) because certain patients were studied at different times (e.g., having a true-positive scan preoperatively and a true-negative scan following successful curative surgery).

The criteria for the efficacy of [^{131}I]MIBG scintigraphy was based on the following preliminary experience (*32*).

Normal scintigraphic appearances (*32*)

In patients in whom the clinical history, examination,





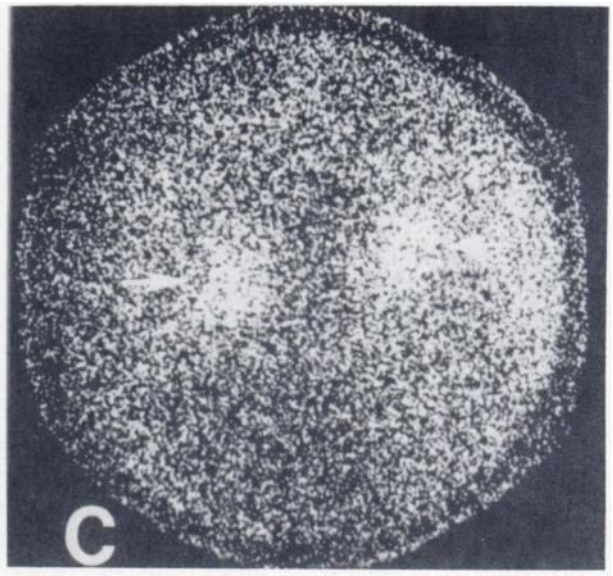


FIGURE 1
Spectrum of adrenal uptake of [^{131}I]MIBG in Multiple Endocrine Neoplasia Type 2 (MEN 2). All are posterior abdominal images obtained at 48 hr after injection. A: Patient with MEN 2a—no visible [^{131}I]MIBG adrenal uptake (Grade 0). B: Patient with MEN 2b—minimal bilateral [^{131}I]MIBG uptake (Grade 1 on left and Grade 2 on right). C: Patient with MEN 2a—prominent bilateral adrenal uptake of [^{131}I]MIBG (grade 3). Adrenal uptake indicated by arrows.

and plasma and urinary catecholamines were felt to exclude pheochromocytoma and were thus designated "normal," the scintigraphic appearances included significant uptake in the salivary glands (*33*), liver, spleen, and urinary bladder in almost all cases (*32*). Less frequent and less intense uptake was also noted in the left ventricle, lung bases, and colon. All the uptake in these organs was most prominent at 24 hr and diminished progressively thereafter to 72 hr. The thyroid uptake of free iodine was prominent in those small number of patients where blockade by the administration of iodides was inadvertently omitted. The normal adrenal medulla was not visualized at 24 hr but faint (less than liver) uptake was noted in up to 16% of patients at 48 hr and in some cases this persisted to 72 hr (*23,32*). Figure 1 portrays the range of intensity used to grade the intensity of adrenal medullary [^{131}I]MIBG uptake (*32*).

Scintigraphic appearances of pheochromocytoma

In contrast to the normal adrenal medulla, intra-adrenal pheochromocytomas manifested as intense focal uptake, often being the most intense area in the body and, in all but a very small minority, being well marked at 24 hr. Extra-adrenal or metastatic lesions manifested as focal areas of [^{131}I]MIBG uptake in sites not seen in the "normal" patients. All areas of uptake corresponding to pheochromocytomas, with only a few exceptions, became increasingly well defined between 24 and 72 hr as background activity diminished (*23,32*).

Scintigraphic appearances in patients with a genetic predisposition to pheochromocytoma

Patients from MEN Type 2a or 2b kindreds, as expected, demonstrated a spectrum of scintigraphic findings in keeping with the evolution of adrenal medullas from normal to hyperplasia to frank pheochromocytoma. The results ranged from no visible uptake through faint bilateral uptake (not distinguishable from that obtained in a minority of normal individuals) to strikingly increased symmetrical or asymmetrical bilateral uptake.

The MIBG uptake would appear to correlate with the increasing stages of adrenomedullary hyperfunction, in which at early stages biochemical indices are only minimally deranged (*22,32*). Patients with hypertension and neurofibromatosis were found in some cases to have pheochromocytomas; in all but one, these were unilateral adrenal lesions [the one exception being bilateral adrenal pheochromocytomas (*25*)]. A negative MIBG scan was also useful in other hypertensive patients with neurofibromatosis in which causes of hypertension other than pheochromocytoma (e.g., coarctation and renal artery stenosis) were present or in which mass lesions other than pheochromocytoma occurred (e.g., splenic artery aneurysm) (*25*).

Criteria of evaluation of efficacy of [^{131}I]MIBG scintigraphy

I. For primary pheochromocytomas (excluding members of MEN 2 kindreds)

A. True positive
   1. Abnormal [^{131}I]MIBG uptake unequivocal (if adrenal greater than grade 2) (*32*).
   2. Confirmation of the presence of a pheochromocytoma by:
      a. Histology of resected lesions, or b and c:
      b. Unequivocal depiction of a tumor by one or more radiological techniques (CT, angiography, venography with venous sampling);
      c. Plasma norepinephrine concentration >2,000 pg/ml; and
      d. Comparable abnormalities (>5 s.d. above the mean normal values) of urinary norepinephrine, normetanephrine and/or vanillylmandelic acid (VMA) excretion rates.

In a small group of patients (12 cases, 15 studies overall) the abnormal site of [^{131}I]MIBG uptake was faint and questionable in the case of foci outside the adrenal region or in the case of the adrenal medulla just above grade 2 uptake (*32*). Such cases were graded as true positive and the criteria for the confirmation of the presence of pheochromocytoma were as for IA above.

B. True negative
   1. No abnormal focus of [^{131}I]MIBG uptake and adrenal [^{131}I]MIBG uptake within normal limits (grade 2 or less) (*32*), plus
   2. The confirmation of absence of pheochromocytoma by the following:
      a. Plasma norepinephrine concentration <600 pg/ml and normal urinary excretion rates of norepinephrine, normetanephrine and/or VMA, *and* at least b or c:
      b. Normal abdominal CT scan;
      c. Noncharacteristic history.

A significant number of patients (82 cases, 83 studies overall) were classified as true negative with a somewhat lesser degree of certainty (e.g., Table 2A). Like the patients in IB above there was:

   1. No abnormal foci of [^{131}I]MIBG uptake and adrenal [^{131}I]MIBG uptake within normal limits, grade 2 or less (*32*). However,
   2. Confirmation of the probable absence of a pheochromocytoma by two or more of the following:
      a. Plasma norepinephrine concentration between 600 and 2,000 pg/ml and/or urinary excretion rates of norepinephrine, normetanephrine and/or VMA not more than borderline elevated (between 1 and 5 s.d. above mean normal values). These minimal-to-moderate biochemical abnormalities could in most cases be ascribed to the administration of drugs (e.g., phenoxybenzamine or diuretics) and/or various disease processes (e.g., congestive cardiac failure);
      b. Normal results from abdominal CT;
      c. Nonlocalizing vena caval catheterization/or angiography;
      d. Noncharacteristic history.

C. False positive
   1. Abnormal [^{131}I]MIBG uptake intense (or adrenal uptake greater than grade 2) (*32*), plus
   2. Confirmation of the absence of a pheochromocytoma at the site of [^{131}I]MIBG uptake by:
      a. Histology of the resected lesion (e.g., lesion other than pheochromocytoma or closely related tumor), or both b and c:
      b. Normal plasma norepinephrine concentrations <600 pg/ml and normal urinary excretion rates of norepinephrine, normetanephrine and/or VMA;
      c. Normal abdominal CT scan.

D. False negative
   1. No abnormal foci of [^{131}I]MIBG uptake and adrenal [^{131}I]MIBG uptake within normal limits, (less than grade 2) (*32*), plus
   2. Confirmation of the presence of a pheochromocytoma by:
      a. Histology of resected lesion or both of the following:
      b. Unequivocal visualization of the tumor(s) by one or more radiological techniques (CT, angiography, venography with venous sampling);
      c. Plasma norepinephrine concentration >2,000 pg/ml and comparable abnormalities of urinary norepinephrine, normetanephrine and/or VMA excretion rates (>5 s.d. above the mean normal values).

II. For malignant pheochromocytomas

The criteria used were as for sporadic primary pheochromocytomas, with the following additional modifications:

Iodine-131 MIBG uptake may:

a. Reveal more regions of involvement than conventional radiological techniques;
b. Reveal all the regions of involvement seen by other techniques;
c. Reveal only some of the regions seen by other techniques; or
d. Fail to be taken up by any lesions which were confirmed to be present biochemically or by other diagnostic modalities.

Parts a and b are classified as true positives. Part c is classified as true positive unless [^{131}I]MIBG failed to reveal a lesion which by the nature of its location was critical to management. In the latter instances the scan was classified as false negative even if it demonstrated the unequivocal presence of metastatic disease in other sites. Part d is classified as false negative.

III. For patients from multiple endocrine neoplasia kindreds which differed from that in the above groups in that:

a. Increased [^{131}I]MIBG uptake by the adrenals may be observed in genetically predisposed persons at a time when all plasma and urinary measurements are normal or nearly normal (*22*,*32*);
b. Patients with MEN-2 syndromes differ in their expression of pheochromocytomas only in that the early onset of hyperfunction in the adrenal medullas (hyperplasia, a precursor of pheochromocytoma) may be impossible to detect by clinical, biochemical, or radiologic information. Thus, modest increases in uptake of [^{131}I]MIBG by the adrenal medullas in patients with MEN-2a or MEN-2b may be the earliest evidence of pheochromocytoma (*22*). Such scintigraphic abnormalities were considered positive without confirmatory data from other studies. Otherwise, the criteria were the same as for patients suspected of having sporadic pheochromocytomas; and
c. In one patient having a large pheochromocytoma detected by [^{131}I]MIBG in one adrenal gland and a minute focus of pheochromocytoma in the contralateral gland not detected by [^{131}I]MIBG scintigraphy the patient was scored as both true positive and false negative (that is each lesion treated separately, as the large lesion posed an immediate problem and the small lesion a future problem).

Data analysis

The scans are divided into true-positive, true-negative, false-positive, and false-negative groups.

The certain "true-negative" patients, as described in the criteria for evaluation, had normal [^{131}I]MIBG scans and no radiological evidence of pheochromocytoma, but had abnormalities of catecholamine values (usually in plasma) which, although not normal, were not diagnostic of pheochromocytoma. Many of these patients have had multiple subsequent localizing procedures, yet on follow-up evaluation, as long as $3\frac{1}{2}$ yr in some cases, none has been found to have a pheochromocytoma. These minor elevations in catecholamine values above the "normal range" in this group probably reflect the fact that the "normal" range is defined for healthy adults (usually young) and does not take into account the effects of age, stress of multiple illnesses which were often present in this group, and the effects of drugs (e.g., sodium depletion due to diuretics and the administration of α adrenergic blocking drugs used for control of hypertension). The formulae used for sensitivity, specificity, and predictive accuracy are presented in Table 1.

RESULTS

No side effects were observed in any of the patients following the administration of [^{131}I]MIBG. In addition to the 400 cases presented in this publication, three studies were excluded from further evaluation because the patients were receiving tricyclic antidepressants at the time (*33*). Three patients with nonfunctioning glomus jugulare tumors and three patients with neuroblastomas were also studied but these were excluded from further consideration since in none of these cases was the possibility of pheochromocytoma seriously entertained.

The overall results of [^{131}I]MIBG scintigraphy are presented in Tables 2A–D. A number of the categories may encompass some of the cases; thus, for instance, a patient may appear under both the malignant and familial classifications.

TABLE 1
Data Analysis

Formulae Used in Analyzing Results	
1. Sensitivity	$= \frac{\text{True Positive}}{\text{True Positive + False Negative}}$
2. Specificity	$= \frac{\text{True Negative}}{\text{True Negative + False Positive}}$
3. Positive Predictive Accuracy	$= \frac{\text{True Positive}}{\text{True Positive + False Positive}}$
4. Negative Predictive Accuracy	$= \frac{\text{True Negative}}{\text{True Negative + False Negative}}$
5. Prevalence	$= \frac{\text{True Positive + False Negative}}{\text{Total Patients}}$

TABLE 2A
Results of [^{131}I]MIBG in 312 Patients with Suspected Primary Benign Pheochromocytoma

Item	True Positive	True Negative	False Negative	False Positive	Total
Suspected primary benign pheochromocytoma (excluding familial and malignant)					
a. Intra-adrenal					
Intra-unilateral	21 (23)*	0 (0)	2 (3)	2 (2)†	25 (28)
Intra-bilateral	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
b. Extra-adrenal					
Intra-abdominal	4(4)	0 (0)	2 (3)	1 (1)†	7 (8)
c. Extra-adrenal					
Extra-abdominal	8‡ (11)	0 (0)	2 (2)§	0 (0)	10 (13)
d. Unknown site¶	0 (0)	0 (0)	3 (3)	0 (0)	3 (3)
e. Suspected pheochromocytoma					
i) Not present**	0 (0)	189 (192)	0 (0)	0 (0)	189 (192)
ii) Probably not present**	0 (0)	76 (76)	0 (0)	0 (0)	76 (76)
f. Total	35 (40)	265 (268)	9 (11)	3 (3)†	312 (322)

* Number of patients (number of studies).

† Noncatecholamine-secreting retroperitoneal neuroendocrine tumor = one; adrenal metastasis of choriocarcinoma = one; unknown cause = one (possibly dilated renal pelvis).

‡ Includes one patient with Carney's triad and an extra-adrenal pheochromocytoma anterior to the arch of the aorta.

§ Catecholamine-secreting carotid body tumors = two.

¶ All patients in whom false-negative scans were obtained but in whom no localizing procedure could determine the site of the lesion are included with the primary benign group (these cases are false negative to multiple combinations of CT, angiography and venous sampling).

** All patients in whom pheochromocytomas could not be demonstrated are included with the primary benign group.

A. Primary benign pheochromocytomas: This group excludes malignant lesions, patients from MEN kindreds, patients with neurofibromatosis, Von Hipple-Lindau disease, and familial pheochromocytomas in the absence of a named syndrome. The patients in whom there is a familial predisposition to pheochromocytoma are presented in more detail under Section C of Table 2. Patients in whom pheochromocytoma was suspected but excluded or probably excluded (true negative) are presented in Section A of Table 2 (except for patients from MEN kindreds and other predisposing syndromes).

The intra-adrenal pheochromocytoma patients totaled 23 cases of which 12 were right-sided, nine left-sided and two bilateral. The abdominal extra-adrenal lesions consisted of five pararenal lesions (two false negative and three true positive), one para-adrenal lesion and one para-aortic lesion (organ of Zuckerkandl). There were eight primary paracardiac extra-abdominal lesions (six occurring from the cardiac atria, one from the aorticopulmonary window and one from the arch of the aorta).

In patients in whom benign, recurrent pheochromocytoma was present, [^{131}I]MIBG scintigraphy was successful in seven and falsely negative in four.

B. Malignant pheochromocytomas are presented in Section B of Table 2 and are divided into sporadic and familial subgroups. (Note that sensitivity is higher for these patients than for those with sporadic pheochromocytomas.)

C. The patients from families with a predisposition to pheochromocytoma (vide supra) are presented in Section C of Table 2 and are divided into MEN, neuro-

TABLE 2B
Results of [^{131}I]MIBG in 53 Patients Suspected of Having Malignant Pheochromocytoma

Item	True Positive	True Negative	False Negative	False Positive	Total
Malignant pheochromocytoma					
a. Sporadic	39 (53)*	0 (0)	4 (4)	0 (0)	43 (57)
b. Familial†	8 (8)	1 (1)‡	1 (1)	0 (0)	10 (10)
c. Total	47 (61)	1 (1)	5 (5)	0 (0)	53 (67)

* Number of patient (number of studies).

† MEN 2 = three; Neurofibromatosis = one; VonHipple-Lindau = two; Familial in the absence of obvious syndrome = two.

‡ Negative following resection (image was positive preoperatively). Only evidence for malignancy and residual tumor was microscopic metastases noted in adjacent lymph nodes removed at surgery; at present this patient is free of disease by all criteria but subject to ongoing follow-up.

TABLE 2C
Results of [^{131}I]MIBG in 56 Patients with a Familial Predisposition to Pheochromocytoma

Item	True Positive*	True Negative	False Negative	False Positive	Total
Familial tendency to pheochromocytoma (includes malignant)					
a) MEN‡	20 (23)†	15 (16)	2 (2)†	0 (0)	37 (41)‡
b) Neurofibromatosis	5 (5)§	9 (10)¶	0 (0)	0 (0)	14 (15)
c) Other**	4 (5)‡‡	1 (1)‡‡	0 (0)	0 (0)	5 (6)
d) Total	29 (33)	25 (27)	2 (2)	0 (0)	56 (62)

Number of patients (number of studies).

* Positive for pheochromocytoma or medullary hyperplasia.

† One patient had large lesion in one adrenal which posed the immediate problem and which was detected while there was another small focus of pheochromocytoma in the contralateral adrenal which would have posed a future problem and this case has been classified as true positive for the large lesion and false negative for the other. Malignant in three cases.

‡ 37 patients studied—several had more than one study (e.g., true positive preoperatively followed by true negative following bilateral adrenalectomy; or equivocal positive evolving to true positive with the passage of time).

§ One bilateral and one malignant case.

¶ Includes a postoperative scan in a patient with bilateral adrenal pheochromocytoma.

** Von Hipple-Lindau and familial pheochromocytoma in the absence of an obvious syndrome.

†† One patient with Von Hipple-Lindau (malignant), three patients with familial pheochromocytomas unassociated with a syndrome (two right renal hilum, one of which was malignant) and one from the bladder (which was also malignant).

‡‡ One patient with Von Hipple-Lindau.

fibromatosis and others (seven of the patients with malignant lesions also appear in Section B). The MEN patients differed from those in Section A in that many were completely or nearly asymptomatic when studied. The MEN patients were also less symptomatic than the other familial cases studied.

There were a total of 37 patients from MEN 2 kindreds. Two patients were unaffected members of a MEN 2a kindred and were true negative by scintigraphy as were 11 scans performed on affected patients following successful bilateral adrenalectomy. A number of patients had more than one scan; e.g., a patient whose scan was true positive but had a true negative scan following successful bilateral adrenalectomy. Three patients (all MEN 2a) had malignant metastatic pheochromocytoma.

DISCUSSION

We have shown the new radiopharmaceutical, [^{131}I]MIBG, to be a safe and efficacious means of locating a wide range of pheochromocytoma (*21–28*). This experience has been verified by a number of independent investigators (*34–37*). In a substantial number (22% of cases with pheochromocytoma) of patients, conventional imaging techniques had failed to locate the lesions which were revealed by scintigraphy. This was especially true in cases of recurrent disease for whom surgical clips and surgical distortion of normal tissue planes rendered CT suboptimal (*24*). Also, for middle mediastinal tumors (*27,28*) and in some malignant metastatic disease, [^{131}I]MIBG scintigraphy proved more sensitive than conventional x-ray or scintigraphic procedures (*26*). The patients having false-negative scintigrams had lesions which were somewhat more frequently extra-adrenal abdominal (e.g., para renal) in location but did not differ significantly in biochemical or histological characteristics from lesions in similar sites which were well demonstrated by scintigraphy.

Comparison of our findings with [^{131}I]MIBG scintigraphy and other imaging modalities is difficult. The patient population was in many cases preselected so that patients in which conventional modalities failed are over represented (note the large proportion of malignant and extra-adrenal lesions). Certainly in the abdomen and especially in the adrenal glands, CT is highly efficacious (*9,10,38*) with sensitivity and specificity exceeding 90%. In the case of sporadic intra-adrenal lesions, [^{131}I]MIBG scintigraphy is probably no better than CT. The scintigraphic approach appears to be superior in the case of extra-adrenal, recurrent, and malignant lesions (*21,23–28,38*).

The uptake of [^{131}I]MIBG by pheochromocytoma is quite variable ranging from no detectable activity (hence the false-negative scans) through minimal uptake to intense uptake (true positive). These patterns of uptake occur in tumors which are apparently indistinguishable from each other in terms of location, histology, and measurements of plasma catecholamine concentrations and urinary catecholamine and catecholamine metabolite excretion. The uptake of [^{131}I]MIBG by sympathetic tissue is believed to be due to active uptake by the so-called Type I catecholamine uptake mechanism and subsequent storage in catecholamine storage grannules (*31*). Such an uptake and storage mechanism may not always parallel the synthesis and secretion of catechol-

TABLE 3
Data Analysis (Based on Number of Studies Performed)*

A. Suspected primary benign pheochromocytoma (excluding familial and malignant)	
Sensitivity	78.4%
Specificity	98.9%
Positive Predictive Accuracy	93.0%
Negative Predictive Accuracy	96.1%
Prevalence	15.8%
B. Malignant pheochromocytoma (sporadic and familial)	
Sensitivity	92.4%
Specificity	100.0%
Positive Predictive Accuracy	100.0%
Negative Predictive Accuracy	16.7%
Prevalence	98.5%
C. Familial (including MEN)	
Sensitivity	94.3%
Specificity	100.0%
Positive Predictive Accuracy	100.0%
Negative Predictive Accuracy	93.1%
Prevalence	56.5%
D. MEN alone	
Sensitivity	92.0%
Specificity	100.0%
Positive Predictive Accuracy	100.0%
Negative Predictive Accuracy	88.9%
Prevalence	60.9%

* Prevalence in respective subgroups A to D.

amines. Indeed there is now evidence that [^{131}I]MIBG uptake may occur in a range of neuroendocrine tumors, including neuroblastoma (*39,40*), carcinoid tumors (*41*), and nonsecreting paragangliomas (*42*). We have found that in all cases thus far examined, tumors which have taken up [^{131}I]MIBG demonstrated positive immunohistochemical staining for chromogranin A. The presence of this material is a marker for the neuroendocrine nature of the tumors (*7,8*) and the relationship of plasma chromogranin A levels to tumor uptake of pheochromocytoma remains to be explored.

We suggest that, where available, [^{131}I]MIBG scintigraphy is the best initial procedure for locating pheochromocytomas (*43*). CT and angiography may provide better anatomical resolution but are not well suited for screening the entire body and should be reserved for confirmation and detailed delineation of anatomical relations in cases with a positive scan or to search for suspected tumors where, despite a negative [^{131}I]MIBG scan, the level of suspicion remains high (*38*). Even in cases where an anatomical abnormality has been demonstrated by radiological means, [^{131}I]MIBG scintigraphy may still be useful in disclosing unsuspected metastatic or multicentric disease or in excluding this unusual but by no means rare occurrence (*26,28*).

Iodine-131 MIBG is relatively inexpensive and has a 2-wk shelf life. The unfavorable dosimetric characteristics of ^{131}I, however, limit the dose to 0.5 mCi in most instances (and no more than 1.0 mCi in exceptional circumstances). In the face of a negative [^{123}I]MIBG scan in a patient with very strong clinical and biochemical evidence of a pheochromocytoma, [^{123}I]MIBG might be usefully employed. Ten millicuries of [^{123}I]MIBG have a radiation dosimetry similar to that of 0.5 mCi [^{131}I]MIBG and provide a greatly increased useful photon flux (*44*). Where [^{131}I]MIBG is not available and the referral of the patient is impractical, CT (first of the adrenal area and then the remainder of the abdomen, the pelvis, chest, and neck) is the investigation most likely to be successful. If CT fails to locate the lesion, venous sampling would provide an invasive alternative approach.

Neither [^{131}I]MIBG scintigraphy nor any other imaging procedure should be an initial screening test for diagnosis of pheochromocytoma and patients selected for study should be those in whom there is a reasonable suspicion of pheochromocytoma based on the presence of (a) labile, severe, or uncontrolled hypertension and/or spells manifested by headache, palpitations, sweating, or abdominal pain; and/or (b) basal plasma norepinephrine > 600 pg/ml, epinephrine > 150 pg/ml and/or persistent urinary excretion rates for catecholamines that are greater than 3 s.d. above the mean for normal subjects; but also in (c) patients in whom there is historical, clinical, or laboratory evidence for syndromes in which pheochromocytomas occur with increased frequency (MEN 2a or 2b, neurofibromatosis and Von Hipple-Lindau disease) but who manifest only minor symptoms and/or intermittent or borderline laboratory abnormalities for pheochromocytoma.

Even when such criteria are applied, a substantial number of patients not suffering from pheochromocytoma will inevitably be imaged. In our hands, when the biochemical tests for catecholamines (blood obtained when the patient was fasting and recumbent, assayed by the radioenzymatic method, and urine obtained overnight under unstressed conditions) gave normal or borderline results in patients, the vast majority would exhibit negative [^{131}I]MIBG scans. Most of these patients were referred because of abnormal biochemical data when these were obtained under less rigorous conditions. In our experience, patients with symptoms not typical of pheochromocytoma and with normal catecholamine values never harbored pheochromocytomas.

The initial suggestion that [^{131}I]MIBG was taken up exclusively by pheochromocytomas (*21,22*) must be tempered by (a) the fact that in the present series, two nonpheochromocytoma tumors were imaged; and (b) the reports of [^{131}I]MIBG uptake in neuroblastomas (*39,40*), carcinoid tumors (*41*), and nonfunctioning paragangliomas (*42*). Iodine-131 might be better described as a neuroendocrine or APUDoma-seeking radiopharmaceutical. This should be recognized when

TABLE 4
Summary of Overall Result at University of Michigan and Comparison with Other Series

	TP*	FP†	TN‡	FN§	Total	Reference
¶Michigan (overall)	111	3	291	16	421	—
Southampton	21	1	21	3	46	34
Mayo Clinic	15	1	22	4	42	36
Tours	8	1	17	1	27	37
(Combined German experience)	56	1	126	8	191	35

* TP = True Positive.
† FP = False Positive.
‡ TN = True Negative.
§ FN = False Negative.
¶ Based on number of cases studied (Table 2D).

	Number	Sens*	Spec†	Neg‡ PDA	Post§ PDA	Prevalence	Reference
¶Michigan (overall)	421	87.4	98.9	94.8	97.4	30.2	—
Southampton	46	88	95	88	95	52	34
Mayo Clinic	42	79	96	85	94	45	36
Tours	27	89	94	94	89	33	37
(Combined German experience)	191	88	99	94	98	34	35

* Sens = Sensitivity.
† Spec = Specificity.
‡ Neg PDA = Negative Predictive Accuracy.
§ Post PDA = Positive Predictive Accuracy.
¶ Based on number of cases studied (Table 2D).

interpreting the scintigraphic images in the light of a given patient's catecholamine values.

Those cases in which we demonstrated slight to moderate biochemical abnormalities (insufficient for the unequivocal diagnosis of pheochromocytoma) and in whom the [^{131}I]MIBG scan was negative and defined as "pheochromocytoma probably not present" present a major uncertainty; they are the subject of an ongoing investigation by means of clinical and biochemical follow-up and in some cases [^{123}I]MIBG scintigraphy (*44*), CT, and whole-body venous sampling. To date, with up to 3½ yr follow-up in certain cases, no histologically proven pheochromocytomas have come to light in this group.

CONCLUSION

Scintigraphy with the new radiopharmaceutical [^{131}I]MIBG permits a safe and efficacious means of locating the majority of a wide range of pheochromocytomas and may have a role in the investigation of other neuroendocrine tumors.

ACKNOWLEDGMENTS

Presented in part at the European Nuclear Medicine Congress, Helsinki, August 14, 1984. Supported in part by the following grants: NIAMDD 5P60 AM 20575, NCI 09015, DHEW 3M01 RR00042-22 S1 CLR, NIH R01 AM 21477, R01 FD-01257, and the Nuclear Medicine Research Fund. B.S. is the recipient of an NIH Clinical Associate Physician Award (DHEW 3MO1 RR00042-22S1 CLR).

The authors wish to thank those physicians who referred patients for study as well as the fellows, house officers, technicians, and nursing staff of the Division of Nuclear Medicine and the Clinical Research Center who made this possible; Dr. Thomas Mangner and Holly Anderson-Davis for the manufacture of [^{131}I]MIBG; the Phoenix Memorial Laboratory for the use of their radiochemistry facilities; and Ms. J. Boldt for typing the manuscript.

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