Iodine-131 MIBG Scintigraphy of Neuroendocrine Tumors Other than Pheochromocytoma and Neuroblastoma

Lisa Von Moll, Alexander J. McEwan, Brahm Shapiro, James C. Sisson, Milton D. Gross, Ricardo Lloyd, Edward Beals, William H. Beierwaltes, and Norman W. Thompson

Division of Nuclear Medicine, Departments of Internal Medicine, Surgery, and Pathology, University of Michigan, Ann Arbor, Michigan; Wessex Regional Department of Nuclear Medicine, Southampton General Hospital, Shirley, Southampton, England; and Veterans Administration Medical Centers, Ann Arbor, Michigan

Metaiodobenzylguanidine (MIBG) locates most pheochromocytomas and neuroblastomas. The tracer is concentrated in intracellular storage vesicles by an active process. Many other neuroendocrine tumors of the amine precursor uptake and decarboxylation (APUD) series have hormonal storage vesicles and, thus, the potential to take up [^{131}I]MIBG. A variety of neuroendocrine tumors in 57 patients were studied 1, 2, and 3 days after 0.5 mCi [^{131}I]MIBG. Views from skull to pelvis were obtained. Results of MIBG scans were compared with all available imaging modalities (including plain radiography, liver scan, ultrasound, computed tomography, and angiography) and surgical exploration. The neuroendocrine nature of the tumor was determined by histology, immunohistochemistry, electron microscopy, and the assay of appropriate biogenic amines and peptide hormones. Results were (positive/total cases): carcinoids (four of ten), nonsecreting paragangliomas (three of three), sporadic medullary carcinomas of the thyroid (MCT) (one of five), familial MCT (one of 26), chemodectomas (two of five), oat cell carcinomas (zero of four), choriocarcinoma (one of one), atypical schwannoma (with storage granules) (one of one), Merkel cell skin cancer (one of one), islet cell carcinoma (zero of one). We conclude that a wide range of neuroendocrine tumors show [^{131}I]MIBG uptake; tumors other than pheochromocytomas and neuroblastomas are less often seen scintigraphically, but in certain cases (e.g., carcinoid and nonsecreting paragangliomas) scintigraphy may be useful in depicting the extent and location of disease and may indicate therapeutic potential. Iodine-131 MIBG shows promise in the diagnosis and staging of tumors of varied types.

J Nucl Med 28:979–988, 1987

The radiopharmaceutical, iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG), has been shown to locate pheochromocytomas (*1–3*), including sporadic, benign intraadrenal (*2,4*) and extraadrenal (*2,4,5*), malignant (*6*), and familial neoplasms (*7–9*). Tracer uptake is also observed in the hyperplastic adrenal medullae of multiple endocrine neoplasia types 2a and 2b (MEN-2a, -2b). Furthermore, [^{131}I]MIBG has been used to locate and stage primary and metastatic neuroblastomas (*10–14*). The high concentrations of [^{131}I]MIBG by some malignant pheochromocytomas (*15–18*) and neuroblastomas (*1,19*) has led to the therapy of these tumors with infusions of therapeutic quantities of [^{131}I]MIBG.

Pheochromocytomas and neuroblastomas are neuroendocrine tumors derived from the sympathoadrenal system, which itself, is a component of the amine precursor uptake and decarboxylation (APUD) system (*20–22*). These neuroendocrine tumors have the common properties of containing neuroendocrine secretory granules, amine precursor uptake mechanisms and biogenic amine synthesis, storage and reuptake, as well in some tissues as peptide hormone/neuromodulator synthesis and storage (*22*). Iodine-131 MIBG enters the adrenal medullae by a specific, energy-dependent uptake mechanism ("uptake 1") in which it competes with

Received Apr. 3, 1986; revision accepted Oct. 1, 1986.

For reprints contact: B. Shapiro, PhD, Div. of Nuclear Medicine, Dept. of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI 48109.

norepinephrine, although the kinetics are not those of simple competitive inhibition (*23–26*). The majority of the [^{131}I]MIBG taken up appears to reside in the intracellular granule fraction (*27*). The uptake and retention by pheochromocytomas appears to be by a similar mechanism (*24–26*).

Because neuroendocrine tumors arising from other tissues considered to be part of the APUD system (*20–22*) appear to have similar properties, we examined the scintigraphic patterns of [^{131}I]MIBG in a variety of neuroendocrine tumors. The results give preliminary data on the possible efficacy of the technique in the location of such lesions.

MATERIALS AND METHODS

Iodine-131 MIBG scintigraphy was performed using previously described techniques (*2,4,28*). Each patient was injected intravenously with 0.5 mCi [^{131}I]MIBG and imaged 1, 2, and 3 days later using a large field-of-view gamma camera equipped with a high-energy collimator and interfaced to a dedicated minicomputer. Multiple overlapping views were obtained to examine the patient from the skull to the pelvis. Thyroidal uptake of free ^{131}I was inhibited by the administration of oral iodides begun the day before tracer injection and continued for 1 wk. The results of [^{131}I]MIBG scintigraphy were correlated with all available data including other imaging techniques (various combinations of plain radiographs, radionuclide liver scans, ultrasound, computed tomography, angiography) and surgical explorations.

Plasma epinephrine and norepinephrine concentrations were measured by the radioenzymatic technique described by Peuler and Johnson (*29*), urinary excretion rates of epinephrine, norepinephrine, metanephrine and normetanephrine, and vannillylmandelic acid by the technique of Von Euler and Lishajko (*30*), and urinary excretion of 5-hydroxyindolacetic acid (5HIAA) by the technique of Undenfriend et al. (*31*). Plasma concentrations of cortisol and the relevant peptide hormones (gastrin, insulin, calcitonin, ACTH) were determined by standard radioimmunoassays (*32,33*).

Light microscopy of resected tumors and biopsies included standard hematoxylin and eosin, and various combinations of silver stains and immunohistochemical stains to determine the neurosecretory nature of the tumor and identify its hormonal product(s) (*34,35*). In selected cases electron microscopy was used to demonstrate the presence of neurosecretory granules and to categorize their morphology (*37*).

Patients suspected of harboring neuroendocrine tumors were sought. The tumors in these patients were carcinoids (ten cases), medullary carcinoma of the thyroid (MCT; five sporadic cases and 26 cases of MEN-2 with a history of past or present medullary carcinoma of the thyroid or C-cell hyperplasia resected, recurrent or residual; not all these cases were suspected of harboring MCT at the time of study), nonsecretory paragangliomas (three cases), small cell carcinoma of the lung (four cases), chemodectomas (five cases), and one case each of pancreatic islet cell tumor, atypical schwannoma, choriocarcinoma, and Merkel cell tumor.

Diagnostic Criteria and Definitions

The diagnosis of the tumor was based on fulfillment of one of the following criteria.

1. Surgical resection or biopsy with histologic confirmation (which might include the use of silver stains, immunohistochemistry, or electron microscopy) of the nature of the lesion. This applies to primary neoplasms or recurrent or metastatic lesions. Those lesions fulfilling this criteria that also were depicted by [^{131}I]MIBG scintigraphy are defined as "definite true positive" and those not depicted as "definite false negative."

2. Radiographic depiction of a lesion strongly suggestive of tumor recurrence or metastasis in a patient in which the primary tumor was resected or biopsied and in which the nature of the primary lesion was histologically confirmed (but in which the histologic confirmation of the presumed metastasis was lacking) and in which there may be biochemical evidence of tumor marker, hormonal hypersection typical of the primary lesion (e.g., elevated calcitonin levels in MCT or elevated 5HIAA excretion rates in carcinoid). In such cases it is reasonable to assume the radiographically demonstrated lesions are derived from the proven primary and that those lesions that also were depicted by [^{131}I]MIBG scintigraphy are defined as "probable true positive" and those not depicted as "probable false negative."

3. Persistent or recurrent evidence of hormonal hypersecretion of a tumor marker following the resection of a primary tumor in which histologic confirmation was obtained but in which no recurrent or metastatic tumor can be demonstrated by conventional radiologic techniques. In such cases foci of abnormal [^{131}I]MIBG uptake are defined as "possible true positive" (unless subsequent resection of a lesion in the site is histologically proven to have arisen from the primary, in which case it is "definite true positive"). Those not depicted by [^{131}I] MIBG are defined as "possible false negative."

4. Patients in which the primary lesion has been resected and histologically shown to be a neuroendocrine tumor and in which there is no clinical, radiographic, or biochemical evidence for residual, recurrent, or metastatic disease are considered to be tumor-free and are designated as "probable true negatives." No cases in this group showed abnormal [^{131}I] MIBG uptake (this applies only to the eight cases of familial MCT with normal biochemistry and the six cases of familial MCT in which inadequate biochemistry was available).

5. In the case of nonfunctional paragangliomas the diagnosis was made on the basis of: (a) typical histology, (b) no evidence for clinical features attributable to hypercatecholaminemia, (c) normal plasma levels of norepinephrine and epinephrine and (d) normal urinary excretion rates of norepinephrine, epinephrine, and their metabolites.

RESULTS

Fifty-seven patients were studied, with a variety of different tumors; the results are summarized in Table 1 and the details of illustrative cases are provided below.

Carcinoid tumors. Ten patients with histologically proven carcinoid tumors were studied. In five patients the primary tumor site was the small bowel. Individual patients presented with a primary site in: ovary, pan-

TABLE 1
^{131}I-MIBG Scintigraphy in Neuroendocrine Tumors: Summary of Results*

Tumor type	Number of patients studied	Number of patients positive on [^{131}I] MIBG scintigraphy
Carcinoid	10	4
Paraganglioma	3	3
Chemodectoma	5	2
MCT (Sporadic)	5	1
MCT (MEN)		
Elevated calcitonins	12	1
Normal calcitonins	8	0
Unavailable calcitonins	6	0
Oat cell carcinoma	4	0
Islet cell carcinoma	1	0
Choriocarcinoma	1	1
Atypical schwannoma	1	1
Merkel cell carcinoma	1	1
Total	57	14

* A table detailing the results in the individual cases is available by writing to the authors.

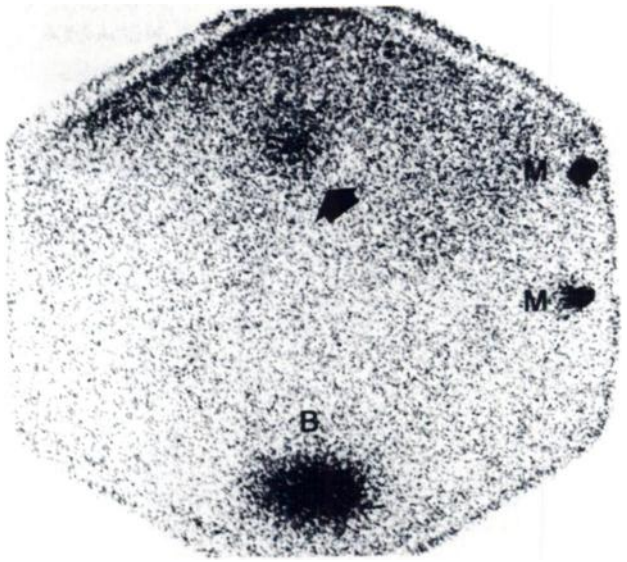

FIGURE 1
Carcinoid metastatic to mesenteric lymph nodes anterior projection of the abdomen in a study performed 72 hr after injection of 0.5 mCi [^{131}I]MIBG. Tumor is indicated by arrow. B = Normal activity in bladder; M = markers on lower costal margin and iliac crest.

creas, aryepiglottic fold, left lower lobe lung bronchus, and one with an unknown primary. All but one of the patients with the small bowel tumors had extensive liver metastases as did the one patient with aryepiglottic fold primary.

Three cases will be illustrated. The first was a 68-yr-old man who underwent small bowel resection and wedge liver resection in 1979 for carcinoid. Postoperatively, the patient did well except for frequent diarrhea until August 1984, when hematochezia prompted further investigation. CT scan revealed a 3.5-cm mesenteric mass, a presumptive lymph node metastasis, with no liver metastases demonstrated. Urinary 5HIAA was normal as may be the case in the absence of extensive liver metastases. Scintigraphy portrayed concentration of [^{131}I]MIBG in the region of the mesenteric mass (Fig. 1).

A case of small bowel carcinoid that was resected but which recurred with metastases to the liver is shown in Figure 2.

The third case involved a 59-yr-old woman who presented with Cushing's syndrome, marked hyperpigmentation, and a left lower lobe mass on chest x-ray. Investigation included the demonstration of elevated plasma cortisol and loss of diurnal variation, elevated plasma ACTH, increased excretion of urinary-free cortisol, and failure to suppress on dexamethasone. Urinary catecholamine and 5HIAA excretion rates were normal. MIBG scintigraphy was positive (Fig. 3). Bronchoscopic biopsy revealed atypical carcinoid, immunohistochemical staining was positive for 5-hydroxytryptamine, norepinephrine, ACTH, beta-MSH, MSH, beta-lipotrophin, neuron specific enolase, and chromogranin, but was negative for corticotrophin-releasing factor (CRF). The tumor was resected and the retained radioactivity in the lesion was tenfold greater than in adjacent normal lung (4 days following tracer administration). Histologic examination of paratracheal lymph nodes revealed involvement by tumor, which was not revealed by CT scan or MIBG scintigraphy.

Nonfunctional paragangliomas. The tumors of all three patients with this diagnosis showed [^{131}I]MIBG uptake. An illustrative case is that of a 66-yr-old woman who presented with a firm right neck mass and fatigue (Fig. 4). The lesion was thought to arise from the right lobe of the thyroid, and thyroidectomy was attempted. Due to hemorrhage only a biopsy was taken, which was initially interpreted as being a medullary carcinoma of the thyroid. After transfer to our institution, the histology was reinterpreted as a paraganglioma. Imaging of the neck revealed intense MIBG uptake (Fig. 4) and the lesion was successfully resected along with the right lobe and part of the left lobe of the thyroid, which was demonstrated to be entirely normal. This uptake was not felt to be uptake of free ^{131}I liberated by in vivo iodination as the focus was too large and lateral to be in the right lobe of the thyroid. Uptake of free ^{131}I by the thyroid would have occurred in both lobes of the demonstrably normal thyroid. The administration of stable iodides does not entirely block all ^{131}I uptake, but because only a small fraction of ^{131}I is liberated by deiodination, the thyroid uptake when visible is always faint.

Carotid body tumors. A total of five patients were studied: three patients were negative, whereas, some

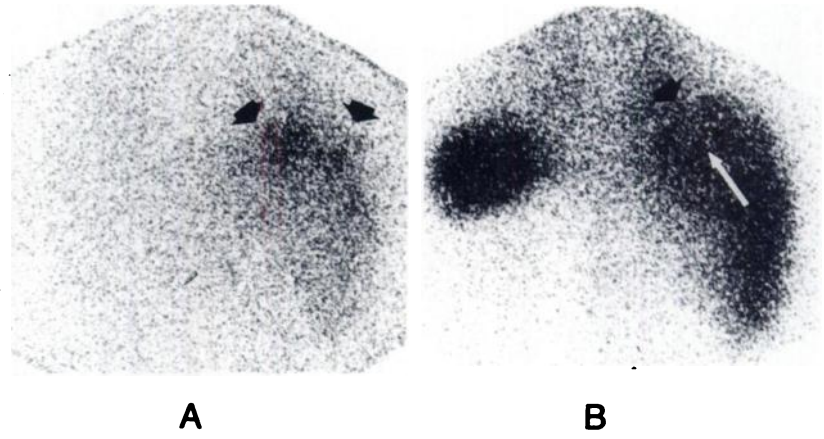

FIGURE 2
Carcinoid metastatic to the liver. A: Posterior projection of abdomen showing foci of moderately increased [^{131}I]MIBG uptake in the upper portion of the right lobe (arrow). Some normal [^{131}I]MIBG uptake is present in normal liver. Study performed 72 hr after injection of 0.5 mCi [^{131}I] MIBG. B: [^{99m}Tc]sulfur colloid liver scan (anterior projection) showing "cold" defect corresponding to area of increased [^{131}I]MIBG uptake (arrow).

uptake was observed in two patients. In one patient the tumor was secreting large amounts of norepinephrine but failed to take up [^{131}I]MIBG.

Medullary carcinoma of the thyroid. Five patients with sporadic MCT and a history of previous thyroidectomy underwent [^{131}I]MIBG scintigraphy for the presence of elevated basal calcitonin levels indicative of metastatic disease. One such patient with suspected recurrent MCT demonstrated a faint area of increased [^{131}I]MIBG uptake in the upper mediastinum (Fig. 5),

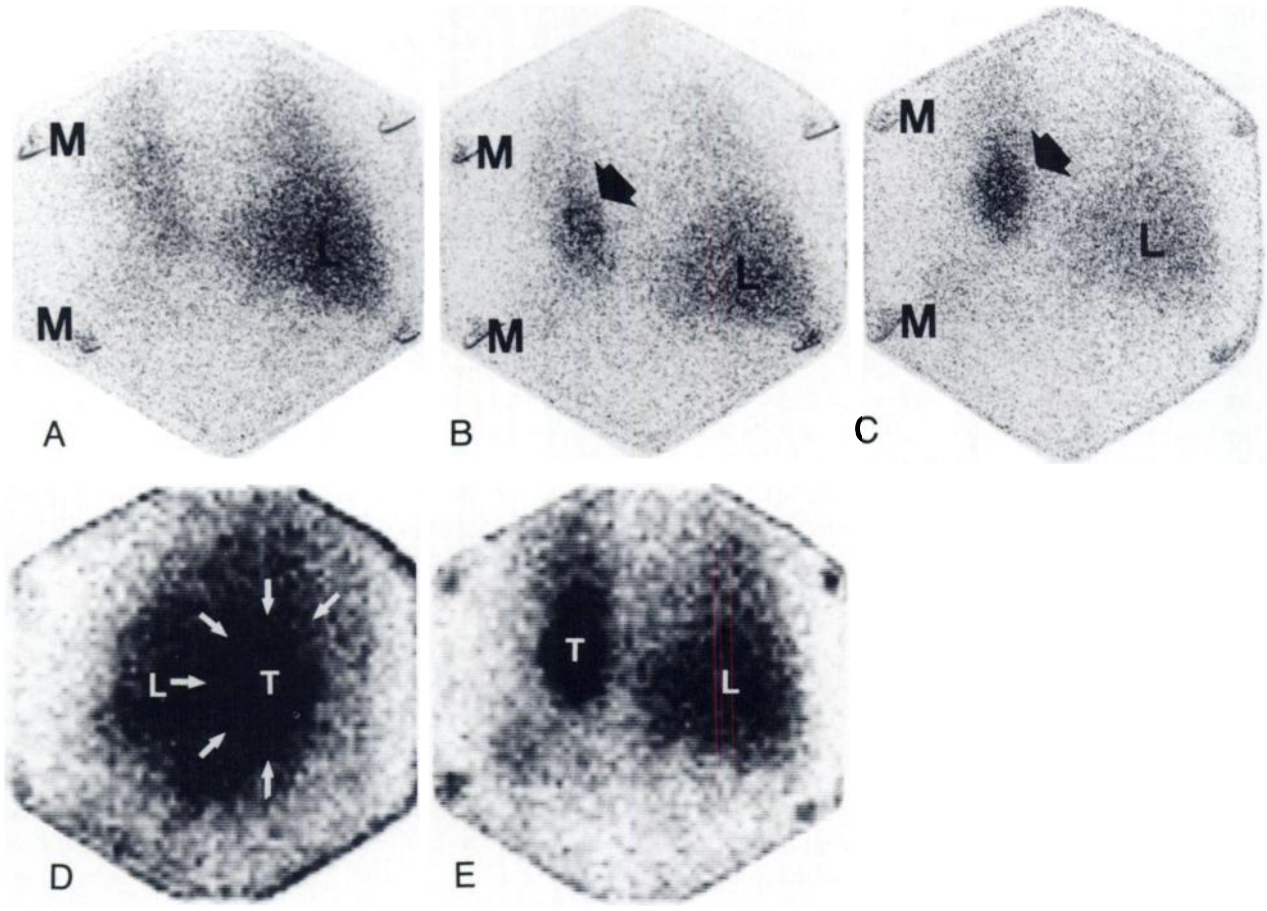

FIGURE 3
Primary pulmonary carcinoid associated with Cushing's syndrome due to ectopic ACTH secretion. Lesion in the posterior portion of the left lower lobe of the lung. Study following 0.5 mCi [^{131}I]MIBG. A: Posterior projection of chest at 24 hr; B: posterior projection of chest at 48 hr; C: posterior projection of the chest at 72 hr. [^{131}I]MIBG is not demonstrable at 24 hr and becomes increasingly obvious at 48 and 72 hr (tumor indicated by arrow, L = liver, M = surface markers); D and E: Digitized images left lateral posterior and images of the chest 72 hr after injection showing the mass (T) lying in the posterior portion of the left lower lobe; note normal liver uptake (L).

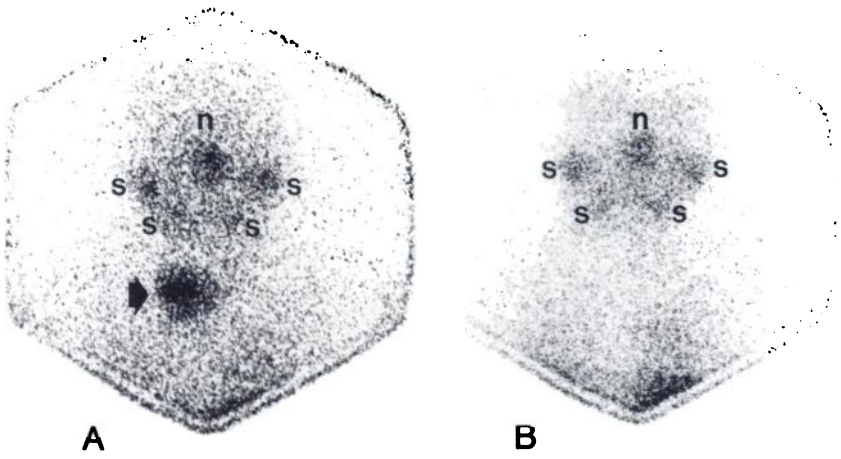

FIGURE 4
Nonfunctioning paraganglioma of the anterior neck. Iodine-131 MIBG scintigraphy 24 hr after injection of 0.5 mCi [^{131}I]MIBG, anterior projection of head and neck. A: Study preoperatively; B: study postoperatively following successful resection of the lesion. Normal uptake of [^{131}I]MIBG in salivary glands (S) and nasopharynx (n). Abnormal focus of uptake corresponding to tumor mass (large arrow).

which corresponded to an area of thallium-201– (^{201}Tl) positive uptake on a ^{201}Tl/^{99m}TcO$_4$ subtraction scan. Mediastinal exploration was performed with excision of an anterior mediastinal lymph node containing MCT. The preoperative calcitonin was 16.5 pg/ml (normal 0.06–0.31), which declined to 0.13 pg/ml postoperatively [reported previously (*38*)].

The other four patients were presumed to have metastatic disease on the basis of elevated calcitonins, but no tumor site was demonstrable by any technique.

The [^{131}I]MIBG scans of 26 patients with MEN-2a and -2b were reviewed: 25 had MCT previously resected, recurrent or residual and one C-cell hyperplasia. Of these, 12 had elevated calcitonin concentrations indicative of residual or metastatic MCT, whereas, eight had normal calcitonins and were presumed free of disease at the time of study. In six patients, calcitonin values were not available. Eight of these patients referred for [^{131}I]MIBG imaging to exclude possible pheochromocytoma before the possibility that MCT might take up [^{131}I]MIBG was recognized.

Only one of the 26 patients imaged demonstrated [^{131}I]MIBG uptake in MCT (abnormal uptake in adrenal pheochromocytomas or adrenal medullary hyper-

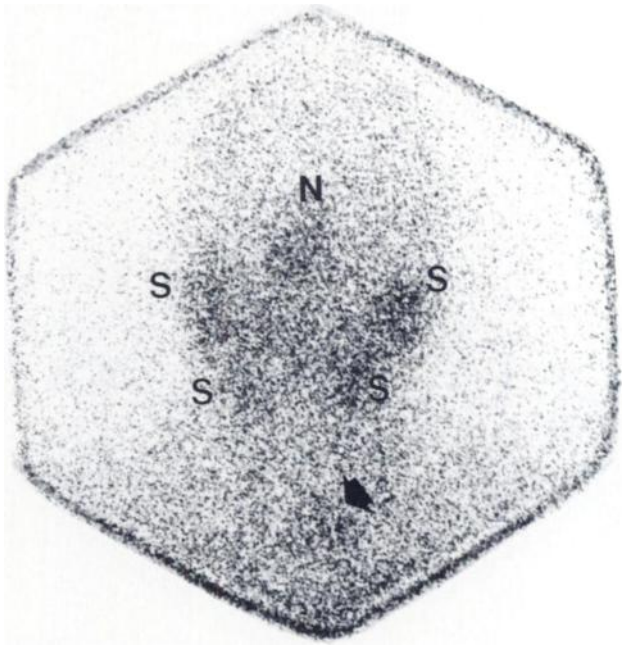

FIGURE 5
Sporadic medullary carcinoma of the thyroid following total thyroidectomy but having persistent elevation of serum calcitonin. Anterior projection of the head and neck 72 hr after injection of 0.5 mCi [^{131}I]MIBG. Normal uptake of [^{131}I]MIBG in salivary glands (S) and nasopharynx (n). Abnormal focus of uptake in superior mediastinum (arrow).

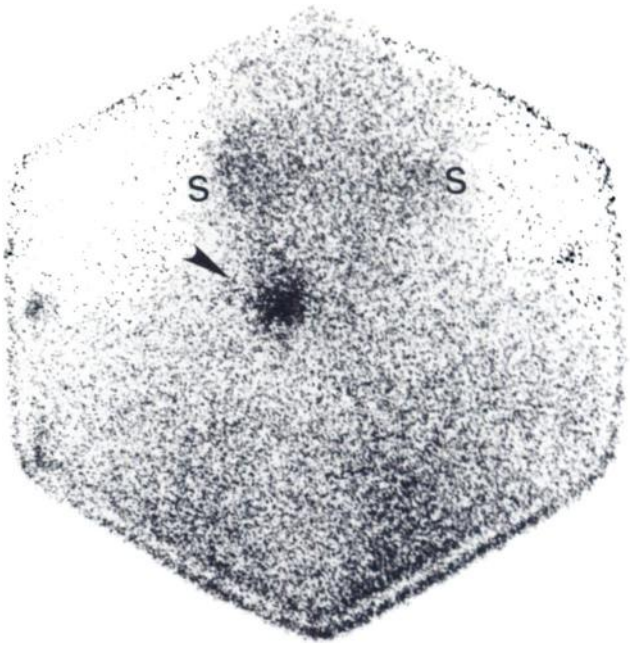

FIGURE 6
MEN-2a after total thyroidectomy but having persistent elevation of serum calcitonin. Posterior projection of the head and neck 48 hr after injection of 0.5 mCi [^{131}I]MIBG. Normal uptake of [^{131}I]MIBG in the parotid salivary glands (S) and abnormal (impalpable) focus of uptake in the neck (arrow).

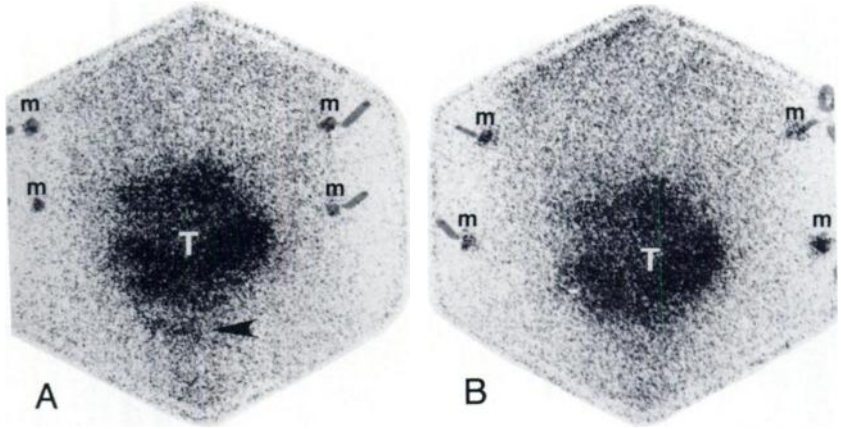

FIGURE 7
Atypical schwanoma (neurosecretory granules demonstrable by electromicroscopy). Anterior abdominal projections 48 hr after injection of 0.5 mCi [^{131}I]MIBG. A: Lesion (T) and small amount of radioactive urine present in bladder (small arrow); B: image obtained immediately following complete bladder voiding. Note that radioactivity in the region of the bladder has disappeared. M = markers on costal margin and iliac crests.

plasia was seen in the majority of those patients not previously subjected to bilateral adrenalectomy). This was a 65-yr-old woman with MEN-2a syndrome, in whom previous bilateral adrenalectomies had been performed for pheochromocytoma. Plasma and urinary catecholamines were normal and she was presumed free of pheochromocytoma. She had a history of total thyroidectomy for MCT. Since this operation there had been persistently elevated basal calcitonin values. An intense focus of [^{131}I]MIBG uptake was shown in the neck (Fig. 6).

Other tumors. No [^{131}I]MIBG uptake was observed in four cases of bronchial oat cell carcinoma and one case of pancreatic islet cell carcinoma (insulinoma) metastatic to liver. Positive images were obtained in two cases, which are not strictly classed as APUDomas. The first patient was a 68-yr-old man who presented with accelerated hypertension and headaches. Abdominal CT revealed multiple large intraabdominal masses including a left suprarenal and mesenteric mass and he was referred for evaluation as a possible pheochromocytoma. Catecholamine values in plasma and urine were normal. MIBG uptake was shown in the mesenteric mass only (Fig. 7). Exploratory laparotomy was performed and histology confirmed atypical malignant schwannoma. The lesion was most unusual in that it was demonstrated by electron microscopy to have neurosecretory granules. Commonly, schwannomas are of neural crest origin although they usually do not have APUD properties.

The second patient was a 29-yr-old woman who demonstrated uptake of MIBG in a choriocarcinoma. Hypertension, dizzy spells, and dysfunctional uterine bleeding prompted evaluation for possible pheochromocytoma. She had previously undergone a left adrenalectomy for this but no tumor was found. MIBG (Fig. 8) and abdominal CT revealed a right adrenal or renal mass. Catecholamine values were normal, whereas, human chorionic gonadotrophin levels were elevated. Histology revealed choriocarcinoma of the right kidney. The tumor was negative for chromagranin by immunohistochemical staining.

Iodine-131 MIGB uptake was demonstrated in one case of Merkel cell cancer. The patient was a 57-yr-old man who presented with a cutaneous lesion on the buttock. This was resected but 6 mo later recurrence was noted in the scar and in the ipsilateral inguinal lymph nodes (Fig. 9). Histology of the primary tumor and the biopsies of the recurrent and nodal tumor was typical of Merkel cell tumor.

DISCUSSION

Radionuclide imaging with [^{131}I]MIBG is a safe and reliable technique to screen the whole body for deposits of pheochromocytoma (*1–3, 39–42*) and neuroblastoma (*10–14*). The sensitivity is high, between 80% and 90% (*2,12*). Although some of the false-negative studies

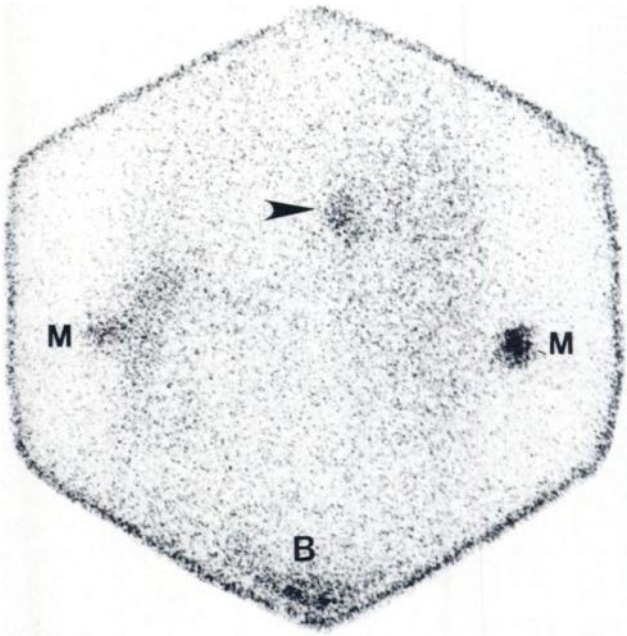

FIGURE 8
Choriocarcinoma metastatic to the adrenal gland region. Posterior projection of the abdomen 48 hr after injection of 0.5 mCi [^{131}I]MIBG showing a small focus of unusually intense tracer uptake in the region of the adrenal gland (arrow). B = Bladder, M = markers on iliac crests.

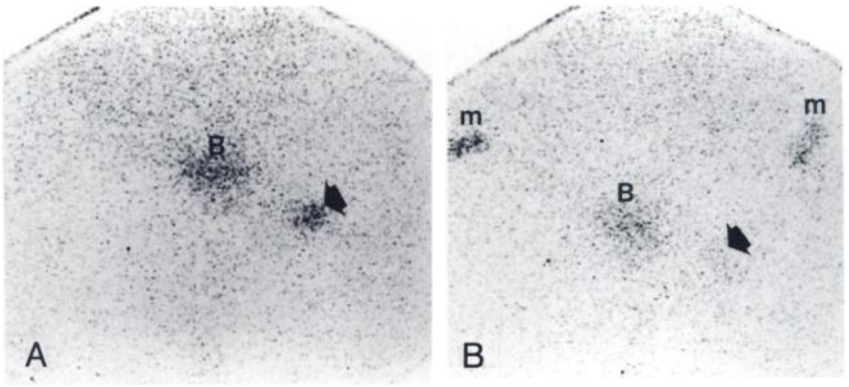

FIGURE 9
Merkel cell cancer, primary on buttock resected but abnormal [^{131}I]MIBG uptake noted in inguinal lymph nodes (arrow) 24 hr after injection of 0.5 mCi [^{131}I]MIBG on anterior projection. Panel A: Anterior projection of pelvis without surface markers. Panel B: Anterior projection of pelvis with surface radioactive markers on iliac crests. B = Bladder, M = markers on iliac crests.

can be ascribed to the unfavorable imaging characteristics of ^{131}I (*43,44*), there exist large, catecholamine-secreting tumors that are not visualized by [^{131}I]MIBG (*1,2*). This may be due to either lack of ability to concentrate MIBG or to retain it within the tumor (*26*). The specificity of MIBG scintigraphy for pheochromocytoma in early series was close to 100% (*1,2*). Subsequent demonstration of MIBG uptake by neuroblastoma has shown similar levels of specificity and sensitivity for this tumor (*13,14*). Because the clinical settings of pheochromocytoma and neuroblastoma are very different, this does not affect the clinical usefulness of [^{131}I]MIBG scintigraphy in either setting. There has been increasing evidence that MIBG uptake occurs in an even wider range of neuroendocrine tumors; these include nonsecretory paragangliomas (*45*), carcinoid tumors (*46–48*), and medullary carcinoma of the thyroid (*49,50*). Our experience confirms these observations although uptake is unpredictable. The absolute specificity of [^{131}I]MIBG for pheochromocytoma of initial studies must be modified in the light of the wider spectrum of tumors that have been shown to take up [^{131}I]MIBG. This requires that the clinical and biochemical features of the case be taken into account even more than in the past.

In the case of carcinoid tumors, we observed four of ten cases, which is similar to the finding of Fisher et al. (*46,47*) and Blinder et al. (*48*) who, using [^{99m}Tc]sulfur colloid/[^{131}I]MIBG subtraction scintigraphy, visualized five of nine cases; and Hoefnagel et al. (*51*) who visualized one of three cases. This case showed such an intense MIBG uptake that therapy with a large dose of [^{131}I]MIBG was attempted (*51*).

Nonfunctional Paragangliomas

Extra-adrenal sympathetic tissue (which is widely distributed from the base of the skull to the pelvic floor) may give rise to tumors, which, when they secrete catecholamines, are termed extra-adrenal pheochromocytomas or functional paragangliomas. Those lesions that do not show evidence for catecholamine secretion are called nonsecreting or nonfunctional paragangliomas. Three such patients were studied and had normal plasma and urinary epinephrine and norepinephrine and urinary catecholamine metabolites and 5HIAA. The case illustrated in Figure 4 is remarkably similar to that of Smit et al. (*45*) and our experience demonstrates that the majority (>80%) (*1,2,12*) of tumors of the pheochromocytoma, paragangliomas, neuroblastoma, and ganglioneuroblastoma family are able to concentrate MIBG (*1–3,10–12*) and that this uptake is independent of whether or not they actively synthesize and secrete catecholamines. Carotid body tumors (chemodectomas) are a specialized type of paragangliomas that may or may not secrete catecholamines. Of five cases, two were positive, in keeping with Jakubowski et al., who report a positive scan in a case of chemodectoma (*52*).

Our results on MCT are similar to those of Hoefnagel et al. (*51*), who observed one of seven cases to be positive with [^{131}I]MIBG. This one case of Hoefnagel et al., however, showed intense and prolonged tracer uptake and was treated with large doses of [^{131}I]MIBG (*52*). The frequency with which MCT takes up MIBG, in our hands, has been low (one of five sporadic, and one of 26 familial, or one of 12 if only those cases with elevated calcitonin are considered to have tumor) and is at variance with the Japanese experience (*49,50*) in which all of four cases of MCT in MEN-2 demonstrated uptake.

We believe the demonstration of tracer uptake in the inguinal metastases of a Merkel cell cancer is the first report in this disease. This tumor is believed to arise from the specialized sensory receptor cells in the skin (often in the hair follicles) and were first described in the nose of a mole. Electron microscopy reveals these cells to contain dense core neurosecretory granules (*53*). The tumors are malignant with a tendency to metastasize to regional lymph nodes and subsequently to the lung and bone (*53*). The other specialized cutaneous neural crest tumor, malignant melanoma, was not studied as part of this series but Hoefnagel reports that, of the five cases he studied, all have been negative (*51*).

From these results it can be seen that a range of

neuroendocrine tumors other than pheochromocytoma and neuroblastoma are capable of accumulating [^{131}I] MIBG. However, this capacity appears most frequently in the neural crest derivatives giving rise to the sympathoadrenal system. Even in pheochromocytomas, however, uptake is variable when a comparison is made between tumors from patients who do not appear to differ in demographic, clinical, pathologic, and biochemical features (*1,2,6*). Moreover, within a given patient there appears also to be heterogeneity of uptake among lesions (*1,2,6*). In neuroblastoma, there is a weak correlation between intensity of tracer uptake and the secretory capacity of the tumor (*12*). Thus, it is clear that the ability of a tumor to take up MIBG may be independent of that tissue's ability to secrete catecholamines. Many neuroendocrine tumors have the potential to synthesize and secrete biogenic amines or peptide hormones, but this is not necessarily expressed in all instances. In the review of data derived from the cases in this study, there is no obvious relationship to [^{131}I]MIBG uptake to catecholamine secretory capacity. Biogenic amine synthesis pathways may be preserved but the specific type 1 uptake mechanism on which MIBG concentration depends may be lost, and vice versa (*54,55*). Many derivatives of the neural crest show type 1 uptake in early embryonic development, which is subsequently lost. Derepression of this function may occur in tumors of this origin (*54,55*). Neoplastic transformation of neuroendocrine cells with chromosomal aberrations and gene derepression can result in a variable outcome. Alterations at any point from uptake mechanisms to product formation to storage and secretory capabilities may occur. MIBG uptake may fail at the cellular membrane, or the intracytoplasmic, extragranular handling of MIBG or in granular storage and release may be abnormal. Very recently, Tobes et al. (*56*) examined cells from pheochromocytomas that had variable uptake of MIBG scintigraphically in vivo and studied in vitro, the rate of uptake and secretion of labeled norepinephrine and [^{125}I]MIBG. Tumors exhibiting faint images in vivo gave rise to cells that in vitro had relatively rapid uptake but also rapid secretion compared with cells from tumors that had excellent uptake in vivo. This suggests that rates of secretion may be at least one explanation of the heterogeneity of uptake noted.

Uptake of MIBG by the occasional tumor not belonging to the APUD series (*57,58*) remains difficult to explain. It is important to study a wide range of tumors including more APUDomas, as well as non-APUDoma tumors, to establish the sensitivity and specificity of [^{131}I]MIBG scintigraphy and, perhaps, to gain insight into the mechanisms by which [^{131}I]MIBG concentrates tumors.

Tumors manifesting high [^{131}I]MIBG uptake and prolonged retention may be suitable for treatment by means of therapeutic doses of [^{131}I]MIBG (*15,16, 18,19*). Two cases of nonpheochromocytoma/neuroblastoma neuroendocrine tumors have been treated in this fashion (*51*) but the results of the therapy are not yet described. No case in our present series met the criteria for [^{131}I]MIBG therapy; namely, a neoplasm not susceptible to treatment by means of conventional surgical, radio-, and chemotherapeutic techniques and high [^{131}I]MIBG uptake and prolonged retention. Such cases may occur and in that event therapy may then be warranted.

In conclusion, we have found that a variety of neuroendocrine tumors take up [^{131}I]MIBG and that the sensitivity of the technique is variable in different tumor types. In those tumors (e.g., nonfunctioning paragangliomas and possibly carcinoids) where imaging is frequent, routine imaging for the locating of lesions and determining the extent of disease spread is justified. The study of an even wider variety of neuroendocrine tumors may provide further insight into mechanisms of [^{131}I]MIBG uptake and retention.

ACKNOWLEDGMENTS

This work was supported in part by the following grants: NIAMDD 5P60 AM-20575, NIAMDD R01 AM-21477, NCI T32 CA 09015, DHEW 3M01 RR 00042-22-CLR, the Veterans Administration Research Service and the Nuclear Medicine Research Fund.

A.M. is the recipient of a British Nuclear Medicine Society Traveling Fellowship and B.S. is the recipient of a National Institutes of Health Clinical Associate Physician Award.

The authors thank Joanne Boldt for expert secretarial assistance and all those physicians who referred patients for study, especially Drs. A. I. Vinik and M. Orringer.

REFERENCES

1. McEwan AJ, Shapiro B, Sisson JC, et al. Radioiodobenzylguanidine for the scintigraphic location and therapy of adrenergic tumors. *Semin Nucl Med* 1985; 15:132–153.
2. Shapiro B, Copp JE, Sisson JC, et al. 131-I-metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases (441 studies). *J Nucl Med* 1985; 26:576–585.
3. Anonymous. Clinical value of adrenomedullary scintigraphy with ^{131}I-MIBG [Editorial]. *Nucl Compact* 1983; 14:318.
4. Sisson JC, Frager MS, Valk TW, et al. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 1981; 305:12–17.
5. Shapiro B, Sisson JC, Kalff V, et al. The location of middle mediastinal pheochromocytomas. *J Thoracic Cardiovasc Surg* 1984; 87:814–820.
6. Shapiro B, Sisson JC, Lloyd R, et al. Malignant pheochromocytoma: clinical, biochemical and scintigraphic characterization. *Clin Endocrinol* 1984; 20:189–203.
7. Valk TW, Frager MS, Gross MD, et al. Spectrum of

pheochromocytoma in multiple endocrine neoplasia: a scintigraphic portrayal using ^{131}I-metaiodobenzylguanidine. *Ann Intern Med* 1981; 94:762–767.
8. Sisson JC, Shapiro B, Beierwaltes WH. Scintigraphy with I-131 MIBG as an aid to the treatment of pheochromocytomas in patients with the MEN-2 syndromes. *Henry Ford Med J* 1984; 32:254–261.
9. Kalff V, Shapiro B, Lloyd R, et al. The spectrum of pheochromocytoma in hypertensive patients with neurofibromatosis. *Arch Int Med* 1982; 142:2092–2098.
10. Treuner J, Feine U, Niethammer D, et al. Scintigraphic imaging of neuroblastoma with ^{131}I metaiodobenzylguanidine. *Lancet* 1984; i:333–334.
11. Kimmig B, Brandeis WE, Eisenhut M, et al. Scintigraphy of neuroblastoma with ^{131}I-MIBG. *J Nucl Med* 1984; 25:773–775.
12. Geatti O, Shapiro B, Sisson JC, et al. ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy for the localization of neuroblastoma: preliminary experience in 10 cases. *J Nucl Med* 1985; 26:736–742.
13. Shapiro B, Geatti O, Sisson JC, et al. Diagnosis of therapy of neuroblastoma (neuro) ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG). European Nuclear Medicine Congress, London, England, September 3–6 [Abstract C3:23]. *Nucl Med Comm* 1985; 6:555.
14. Munkner T. ^{131}I-metaiodobenzylguanidine scintigraphy of neuroblastoma. *Semin Nucl Med* 1985; 15:154–160.
15. Sisson JC, Shapiro B, Beierwaltes WH, et al. Treatment of malignant pheochromocytoma with a new radiopharmaceutical. *Trans Assoc Am Phys* 1983; 96:209–217.
16. Sisson JC, Shapiro B, Beierwaltes WH, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. *J Nucl Med* 1984; 25:197–206.
17. Sisson JC, Shapiro B, Glowniak JV, et al. ^{131}I-Metaiodobenzylguanidine treatment of malignant pheochromocytoma [Abstract]. *J Nucl Med* 1984; 26:P72.
18. Vetter H, Fischer M, Muller Reusing R, et al. ^{131}I-MIBG in the treatment of malignant pheochromocytomas. *Lancet* 1983; i:107.
19. Shen S-W, Sisson JC, Hutchinson R, et al. The progressive and diffuse nature of neuroblastoma: Treatment with I-131 metaiodobenzylguanidine (I-131-MIBG) [Abstract]. *J Nucl Med* 1985; 16:P75.
20. Pearse AGE. The APUD cell concept and its implications in pathology. In: Pathology annual 1974. New York: Appleton-Century Crofts, 1974:27–41.
21. Pearse AGE. Peptides in brain and intestine. *Nature* 1976; 262:92–94.
22. Gould VE, Memoli V, Chejfec G, Johannessen JV. The APUD cell system and its neoplasms: observations on the significance and limitations of the concept. *Surg Clin N Am* 1979; 59:93–107.
23. Jacques S, Tobes MC, Sisson JC, et al. Comparison of the sodium dependency of uptake of meta-iodobenzylguanidine and norepinephrine into cultured bovine adrenomedullary cells. *Molec Pharmacol* 1984; 26:539–546.
24. Jacques S, Tobes MC, Sisson JC, et al. Mechanism of uptake of norepinephrine and metaiodobenzylguanidine into cultured human pheochromocytoma cells [Abstract]. *J Nucl Med* 1984; 25:P122.
25. Tobes MC, Jacques S, Wieland DM, et al. Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985; 26:897–907.
26. Tobes MC, Jacques S, Lloyd RV, et al. Comparison of the in vitro pharmacodynamics of meta-iodobenzylguanidine (MIBG) to the in vivo scintigraphy. European Nuclear Medicine Congress, London, England, September 3–6, 1985.
27. Wieland DM, Brown LE, Tobes MC, et al. Imaging the primate adrenal medulla with ^{123}I and ^{131}I metaiodobenzylguanidine: concise communication. *J Nucl Med* 1981; 22:358–364.
28. Nakajo M, Shapiro B, Copp J, et al. The normal and abnormal distribution of the adrenomedullary imaging agent m[I-131] iodobenzylguanidine (131-I-MIBG) in man: evaluation by scintigraphy. *J Nucl Med* 1983; 24:672–682.
29. Peuler JD, Johnson GA. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 1971; 21:625–636.
30. von Euler US, Lishajko F. The estimation of catecholamines in urine. *Acta Physiol Scand* 1959; 45:122–132.
31. Undenfriend S, Titus E, Weissbach H. The identification of 5-hydroxy-3-indole acetic acid in normal urine and a method for its assay. *J Biol Chem* 1955; 216:499–505.
32. Foster LB, Dunn RT. Single-antibody technique for radioimmunoassay of cortisol in unextracted serum or plasma. *Clin Chem* 1974; 20:365–368.
33. Berson SA, Yalow RS. Radioimmuno-assay in gastroenterology. *Gastroenterology* 1972; 62:1061–1084.
34. Grimelius L, Wilander E. Silver stains in the study of endocrine cells of the gut and pancreas. *Invest Cell Pathol* 1980; 3:3–12.
35. Sternberger LA. Immunocytochemistry. New York: John Wiley and Sons, 1979:104.
36. Wilson BS, Lloyd RV. Detection of chromogranin in neuroendocrine cells with a monoclonal antibody. *Am J Pathol* 1984; 115:458–468.
37. Johannessen JV. Electron microscopy in human medicine. In: Endocrine organs, Vol 10. New York: McGraw-Hill, 1981.
38. Arnstein NB, Juni JE, Sisson JC, et al. Recurrent medullary carcinoma of the thyroid demonstrated by thallium 201 scintigraphy. *J Nucl Med* 1986; 27:1564–1568.
39. Fischer M, Vetter W, Winterberg B, et al. Scintigraphic localization of phaeochromocytoma. *Clin Endocrinol* 1984; 20:17–22.
40. Brown ML, Sheps SG, Sizemore G. MIBG in the evaluation of suspected phaeochromocytoma: Mayo Clinic experience [Abstract]. *J Nucl Med* 1984; 25:P 94.
41. Baulieu JL, Guilloteau C, Canbon C, et al. MIBG scintigraphy: a one-year experience [Abstract]. *J Nucl Med* 1984; 25:P111.
42. Ackery DM, Tippett P, Condon B, et al. New approach to the localization of phaeochromocytoma: imaging with ^{131}I-MIBG. *Br Med J* 1984; 288:1587–1591.
43. Lynn MD, Shapiro B, Sisson JC, et al. Portrayal of pheochromocytoma and normal human adrenal medulla by 123-I-metaiodobenzylguanidine (123-I-MIBG). *J Nucl Med* 1984; 25:436–440.
44. Lynn MD, Shapiro B, Sisson JC, et al. Pheochromocytomas and normal adrenal medulla: improved visualization with ^{123}I-MIBG scintigraphy. *Radiology* 1985; 156:789–792.
45. Smit AJ, Van Essen LH, Hollenca H, et al. ^{131}I MIBG

uptake in a non-secreting paraganglioma. *J Nucl Med* 1984; 25:984–986.
46. Fischer M, Kamanabroo D, Sanderkamp H, et al. Scintigraphic imaging of carcinoid tumors with ^{131}I MIBG. *Lancet* 1984; i:165.
47. Fischer M, Kamanabroo D. Scintigraphic imaging of carcinoid tumors. 32nd Annual Meeting of the Society of Nuclear Medicine, Houston, Texas, June 2–5 [Abstract]. *J Nucl Med* 1985; 26:P17.
48. Blinder RA, Feldman JM, Coleman RE. ^{131}I-MIBG imaging of carcinoid tumors. 32nd Annual Meeting of the Society of Nuclear Medicine, Houston, Texas, June 2–5 [Abstract]. *J Nucl Med* 1985; 26:P17.
49. Endo K, Shiomi K, Kasagi K, et al. Imaging of medullary carcinoma of the thyroid with ^{131}I-MIBG. *Lancet* 1984; ii:233.
50. Endo K, Koizumi M, Sakahara J, et al. Uptake of ^{131}I-MIBG by medullary thyroid cancer. 32nd Annual Meeting of the Society of Nuclear Medicine, Houston, Texas, June 2–5 [Abstract]. *J Nucl Med* 1985;26:P92.
51. Hoefnagel CA, DeKraker J, Marcuse HR, et al. Detection and treatment of neural crest tumors using I-131-meta-iodobenzylguanidine [Abstract]. *Eur J Nucl Med* 1985; 11:A17.
52. Jakubowski W, Feltynowski T, Januszewicz W, et al. 131-I-meta-iodobenzylguanidine in localization and treatment of pheochromocytoma [Abstract]. *Nucl Med Comm* 1985; 6:586.
53. Sibley RK, Rosal J, Foucar E, et al. Neuroendocrine (Merkel cell) carcinoma of the skin: a histological and ultrastructural study of 2 cases. *Am J Surg Pathol* 1980; 4:211–221.
54. Black IB. Stages of neurotransmitter development in autonomic neurons. *Science* 1982; 215:1198–1204.
55. Jonakait GM, Wolf J, Cochard P, et al. Selective loss of noradrenergic phenotypic characters in neuroblasts of the rat embryo. *Proc Natl Acad Sci USA* 1979; 76:4683–4686.
56. Tobes MC, Jacques S, Lloyd RV, et al. Comparison of the in-vitro pharmacodynamics of meta-iodobenzylguanidine (MIBG) to the in-vivo scintigraphy [Abstract]. *Nucl Med Comm* 1985; 6:585.
57. Sinzinger H, Renner F, Grannegger S. 131-I-MIBG imaging of carcinoids and APUDomas [Abstract]. *Eur J Nucl Med* 1985; 11:A17.
58. Shapiro B, Fischer M. Summary of the proceedings of a workshop on 131-I-metaiodobenzylguanidine held at Schloss Wilkinghege, Munster, September 27, 1984. *Nucl Med Comm* 1985; 6:179–186.