Iodine-131 Metaiodobenzylguanidine Scintigraphy for the Location of Neuroblastoma: Preliminary Experience in Ten Cases

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Ten patients with histologically proven neuroblastoma were studied by [^{131}I]MIBG scintigraphy. Tumor uptake of the radiopharmaceutical showed a spectrum varying from no uptake in one case, to slight uptake in two, moderate uptake in two and intense uptake in five cases. Iodine-131 MIBG scintigraphy was more effective in demonstrating the extent of neuroblastoma spread than were conventional bone scan and CT in one patient, equal to these modalities in four cases, almost equal in two cases and significantly inferior in three cases. These preliminary results suggest that [^{131}I]MIBG scintigraphy is useful in detecting the presence and delineating the distribution of neuroblastoma and may, in certain cases, have therapeutic potential.

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Among the solid, extracranial, malignant tumors in pediatric patients, the most frequent is neuroblastoma with an incidence of between one and three cases per 100,000 children per year. Only 30% of patients afflicted with neuroblastoma survive 5 yr, and survival correlates with stage of disease as well as age of patient (*1,2*). Iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) has already been widely used for detection and location of another adrenergic tumor pheochromocytoma (*3–5*), and we therefore hypothesized that this radiopharmaceutical would be helpful in diagnosing and staging of neuroblastoma. To date we applied scintigraphy using [^{131}I]MIBG to ten patients with neuroblastoma.

MATERIALS AND METHODS

The plasma concentrations of norepinephrine and epinephrine were determined in the fasted, supine and resting state by radioenzymatic assay (*6*). The overnight (12-hr) urinary excretion of catecholamines and their metabolites was determined by the technique of Von Euler and Lishajko (*7*). Iodine-131 metaiodobenzylguanidine scintigraphy was performed by previously described techniques (*4*). The administered dose of 0.5 mCi per 1.7 m^2 was given by i.v. injection over 10–20 sec. The thyroidal uptake of the dissociated [^{131}I]iodine was prevented by the administration of iodides. Multiple overlapping images including anterior and posterior views of the head, thorax, abdomen, pelvis, and upper femoral regions were obtained (*4,5*). Anatomical orientation was provided by surface markers and in selected cases by scintigraphic visualization of other organs such as kidney([^{99m}Tc]diethylenetriaminepentaacetic acid), liver and spleen ([^{99m}Tc]sulfur colloid) and skeleton ([^{99m}Tc]methylene diphosphonate [MDP]). Digitized [^{131}I]MIBG and orientation scans were superimposed by computer (*4,5*). A number of different modalities were used in various combination to delineate the patients' lesions. They included standard radiographs, intravenous pyelography, ultrasound, computed tomography, and bone marrow biopsy in various combinations in different patients. Computed tomographic (CT) scans were performed using a GE 8800 third-generation CT scanner. Studies were performed with and without the injection of contrast media. Io-

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TABLE 1
Data on Ten Patients with Pathologically Proven Neuroblastoma

Patient no.	Age Sex (yr)	Duration of disease	Extent of tumor			Functional data		Prior therapy	[^{131}I]MIBG Imaging‡	Correlation between [^{131}I]MIBG and others (bone scan, liver scan, CT, US, bone marrow)
			Soft tissue	Bone	Bone marrow	*Catecholamines †Plasma	Urine			
1	10/12 M	1 mo	Upper right abdomen & liver	Negative	Bone marrow invaded	—	NE = 27 E = 6 VMA = 2.0	No	1–hot rim surrounding large cold hole in abdomen	Complete correlation; at surgery tumor had large necrotic area
2	5 F	6 mo	Left and right abdomen and liver	Negative		—	NE = 49 23 E = 29 7 NM = 98 49 M = 24 45 VMA = 3.3 1.5	Chemo.	1–large area of mild diffuse uptake in abdomen	Liver metastasis seen at liver scan and US (CT not performed) not visualized. Histology of tumor was 90% ganglioneuroma with multiple small foci of neuroblastoma
3	17 F	28 mo	Neck, abdomen	Axial skeleton invaded	Bone marrow invaded	E = 125 NE = 1,675 E = 416 NE = 3,103	NE = 93 663 E = 28 321 NM = 76 27 M = 21 335 VMA = 6.5 46.4	Chemo.	2–four areas of uptake in abdomen	[^{131}I]MIBG didn't visualize bone mestastasis seen at bone scan (histology ganglio-neuroblastoma
4	1 1/12 F	5 mo	Right abdomen	Axial skeleton invaded	Bone marrow invaded	E = 382 NE = 1,004 E = 274 NE = 704	NE = 22 16 E = 6 8 NM = 101 17 M = 19 6 VMA = 1.7 1.2	No	3-increased uptake in the abdomen and in left orbit skull, lumbar spine, pelvis and both femurs	Complete correlation with bone scan and [^{131}I]MIBG showed additional lesions not otherwise suspected
5	10 M	10 mo	Right chest	Axial, skeleton femurs	Bone marrow invaded	E = 137 NE = 240	NE = 18 E = 10 NM = 44 M = 13 VMA = 1.2	Chemo.	0–no uptake	No correlation
6	3 8/12 M	Less than 1 mo	Mid abdomen & liver	Negative	Negative	E = 5,785 N = 707	NE = 62 E = 31 NM = 118 M = 7 VMA = 4.1	No	3–large area of intense uptake in abdomen corresponding in part with cold area on liver scan	Complete correlation

7	7 3/12 F	1 mo	Right abdomen	Left humerus invaded	Bone marrow invaded	E = 1,672 NE = 1,076	NE = 38 E = 26 NM = 252 M = 26 VMA = 2.6	No	3-large mass with increased uptake and photon deficient center in right abdomen	Correlation with bone & liver scan, not with bone marrow and x-ray ofleft humerus
8	23 6/12 F	6 mo	Mediastinal	Invaded shoulder and pelvis	Bone marrow invaded	NE = 3,064 E = 240	NE = 495 E = 42 M = 35 NM = 7293 VMA = 34.6	Chemo.	2-area in mediastinum and throughout axial skeleton, humerus and femurs	Correlation with bone scan except for a lesion in left distal femur. Mediastinal mass correlates with CXR and CT
9	1 5/12 M	Less than 1 mo	Left abdomen	Negative	Negative	—	NE = 12 E = 21 VMA = 1.6	No	3–excellent uptake in mass located in left upper abdominal quadrant	Complete correlation
10	9 M	24 mo		Axial skeleton–all long bones	Bone marrow invaded	E = 9,369 NE = 23,716	NE = 257 E = 89 M = 1169 NM = 436 VMA = 17.2	Chemo. & radiation	3–excellent uptake throughout skeleton	[^{131}I]MIBG showed more skeletal & marrow involvement than bone scan or radiographs

*Urine (Newborn to 3 yr):

NE–Norepinephrine (Normal < 20 μg/24 hr).
E–Epinephrine (Normal < 5 μg/24 hr).
M–Metanephrine (Normal < 65 μg/24 hr).
NM–Normetanephrine (Normal < 165 μg/24 hr).
VMA–Vanilylmandelic Acid (Normal < 1.5 μg/24 hr).

*Urine (3 to 10 yr):

NE–Norepinephrine (Normal < 60 μg/24 hr).
E–Epinephrine (Normal < 10 μg/24 hr).
M–Metanephrine (Normal < 65 μg/24 hr).
NM–Normetanephrine (Normal < 165 μg/24 hr).
VMA–Vanilylmandelic Acid (Normal < 4 μg/24 hr).

*Urine (10 yr and above):

NE–Norepinephrine (Normal < 100 μg/24 hr).
E–Epinephrine (Normal < 20 μg/24 hr).
M–Metanephrine (Normal < 65 μg/24 hr).
NM–Normetanephrine (Normal < 165 μg/24 hr).
VMA–Vanilylmandelic Acid (Normal < 7 μg/24 hr).

†Plasma:

E–Epinephrine (Normal < 100 pg/ml).
NE–Norepinephrine (Normal < 500 pg/ml).

‡Grading of [^{131}I]MIBG uptake:

Grade 0—No uptake.
Grade 1—Minimal discernable uptake.
Grade 2—Moderate uptake (equal to that in liver).
Grade 3—Intense uptake (greater than that in liver).

dine-131 MIBG scintigrams were compared with bone scans, CT, and other imaging procedures to determine how well [^{131}I]MIBG scintigraphy delineated the extent of known disease involvement. All patients underwent skeletal survey, nine of ten had [^{99m}Tc]MDP skeletal scintigraphy and eight of ten had computed tomography (the other two patients, Cases 1 and 2, were studied by i.v. pyelography and ultrasound only). All [^{131}I]MIBG studies were performed within 1 day to 8 wk of the abovementioned investigations.

Among the 12 patients referred to our institution for [^{131}I]MIBG scintigraphy for known or suspected neuroblastoma, a total of ten patients fulfilled the histological criteria for the diagnosis of the disease. This latter group is the subject of this report.

We classified all the patients with respect to their [^{131}I]MIBG uptake intensity into the following four groups: Grade 0 no persistent uptake; grade 1 minimal, persistent, discernable uptake; grade 2 moderate, persistent uptake (equal to that in liver), and grade 3 intense, persistent uptake (greater than that in liver). Persistent uptake being defined as uptake visible at 24 and 48 hr of the tracer injection.

RESULTS

The data of the ten patients with histologically proven neuroblastoma are presented in Table 1. Some tracer uptake was seen in nine of the ten cases. Grade 1 uptake was present in two cases, grade 2 in two cases, and grade 3 in five cases.

The extent of the disease was delineated by [^{131}I]MIBG scintigraphy to a greater extent than combined conventional radiological and nuclear medicine investigations in one case, equally in four cases, almost equally (only one focus of disease amongst many being [^{131}I]MIBG negative) in two cases and to a lesser extent in three cases.

The site of the primary tumor was thoracic in two cases and abdominal in eight. Two patients presented with metastatic masses in skull and neck. In some of the patients (four cases) studied at presentation of an abdominal mass, the positive [^{131}I]MIBG scan contributed to the preoperative diagnosis of neuroblastoma in that [^{131}I]MIBG uptake by a tumor strongly suggested an adrenergic origin of the lesion.

Although two of the cases having the least [^{131}I]MIBG uptake had received extensive chemotherapy, several of those with intense uptake had received similar therapy. However, four of the five cases having grade 3 uptake had not received chemotherapy at the time of scintigraphy and four of the five with less than grade 3 uptake had received chemotherapy. Iodine-131 MIBG uptake was observed in both pure neuroblastomas and mixed neuroblastoma/ganglioneuroblastomas.

There may be a relationship between [^{131}I]MIBG uptake and the hormonal secretory characteristics of the tumor in that the three patients with grade 0 and grade 1 uptake had normal plasma and urinary catecholamines while those with grade 2 and 3 uptake had elevated plasma catecholamines and in some cases urine catecholamines in the six patients where these were measured.

Figure 1 illustrates Patient 4 in which the patient presented with an orbital mass due to metastases from an abdominal primary. Figure 2 illustrates Patient 10 with extensive bone and bone marrow metastases which were better demonstrated by [^{131}I]MIBG scintigraphy than any other modality.

DISCUSSION

Some degree of [^{131}I]MIBG uptake was observed in the lesions of nine of ten patients with pathologically proven neuroblastoma. This is in keeping with preliminary observations made in a number of single case reports (*8,9*) and small series (*10*).

As with the uptake of [^{131}I]MIBG by malignant metastatic pheochromocytoma (*4*), the uptake of [^{131}I]MIBG in neuroblastoma shows a spectrum from no detectable activity to intense tracer uptake. The lesions of a patient may exhibit heterogenous with tracer uptake, but in other patients (e.g., Cases 2, 3, 7, and 8) uptake was uniform in all the tumors. Overall efficacy of [^{131}I]MIBG scintigraphy appears to be greater or equal to that of combined conventional radiological and nuclear medicine studies (e.g., Cases 1, 4, 6, 9, and 10) or may fail to demonstrate some (e.g., Cases 2, 3, 7, and 8) or all known foci of disease (e.g., Case 5). The changes demonstrated by skeletal scintigraphy in the metaphyses of the long bones are often symmetrical and sometimes subtle. [^{131}I]MIBG uptake resolves such difficulties and is specific for involvement by adrenergic tumor.

The correlation of [^{131}I]MIBG uptake with hormonal secretory capacity of the tumor suggests that those tumors with the greatest catecholamine secretion show best uptake. This is in keeping with the findings of other investigators (*11*). Previous therapy may reduce tracer uptake in some cases (e.g., Cases 2 and 5) but does not preclude it (e.g., Cases 8 and 10). Nevertheless, four of five cases with grade 3 uptake had been untreated. These potential influences of [^{131}I]MIBG uptake require further investigation before definitive statements can be made.

Iodine-131 MIBG scintigraphy may provide a simple, noninvasive technique to screen the entire patient for neuroblastoma deposits in a single procedure. Iodine-131 MIBG uptake by the tumor would strongly suggest a sympatho-adrenal origin of the lesion which may be useful in suggesting the nature of the tumor

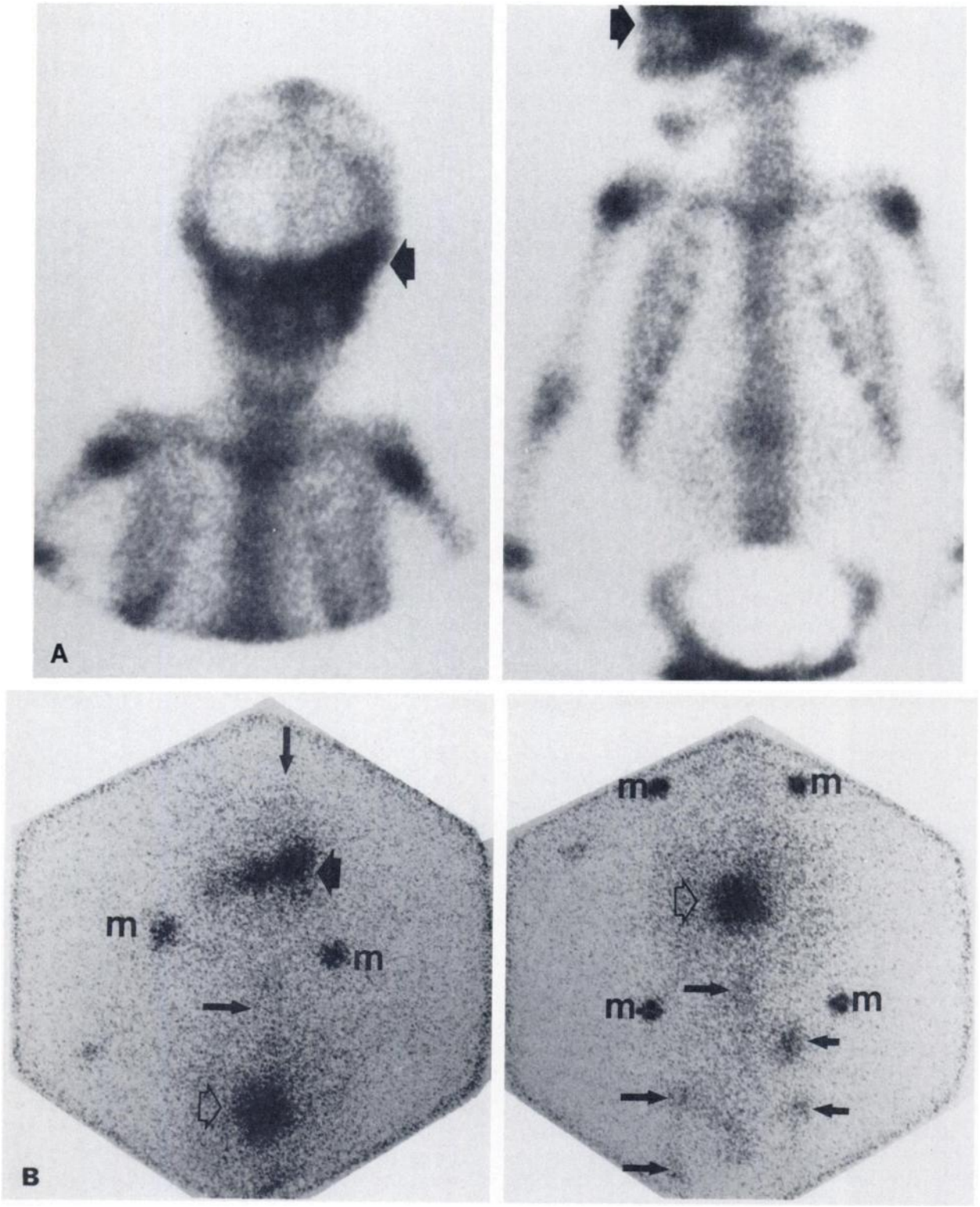

FIGURE 1

Patient 4: A: [^{99m}Tc]MDP bone scan revealing uptake in orbital metastasis (large arrow). B: [^{131}I]MIBG scan revealing uptake in orbital metastasis (large closed arrow), primary abdominal tumor (large open arrow), as well as faint abnormal uptake in the vault of the skull, thoracic and lumbar spine, pelvis and proximal femurs (small closed arrows). Markers on shoulders and iliac crests = m

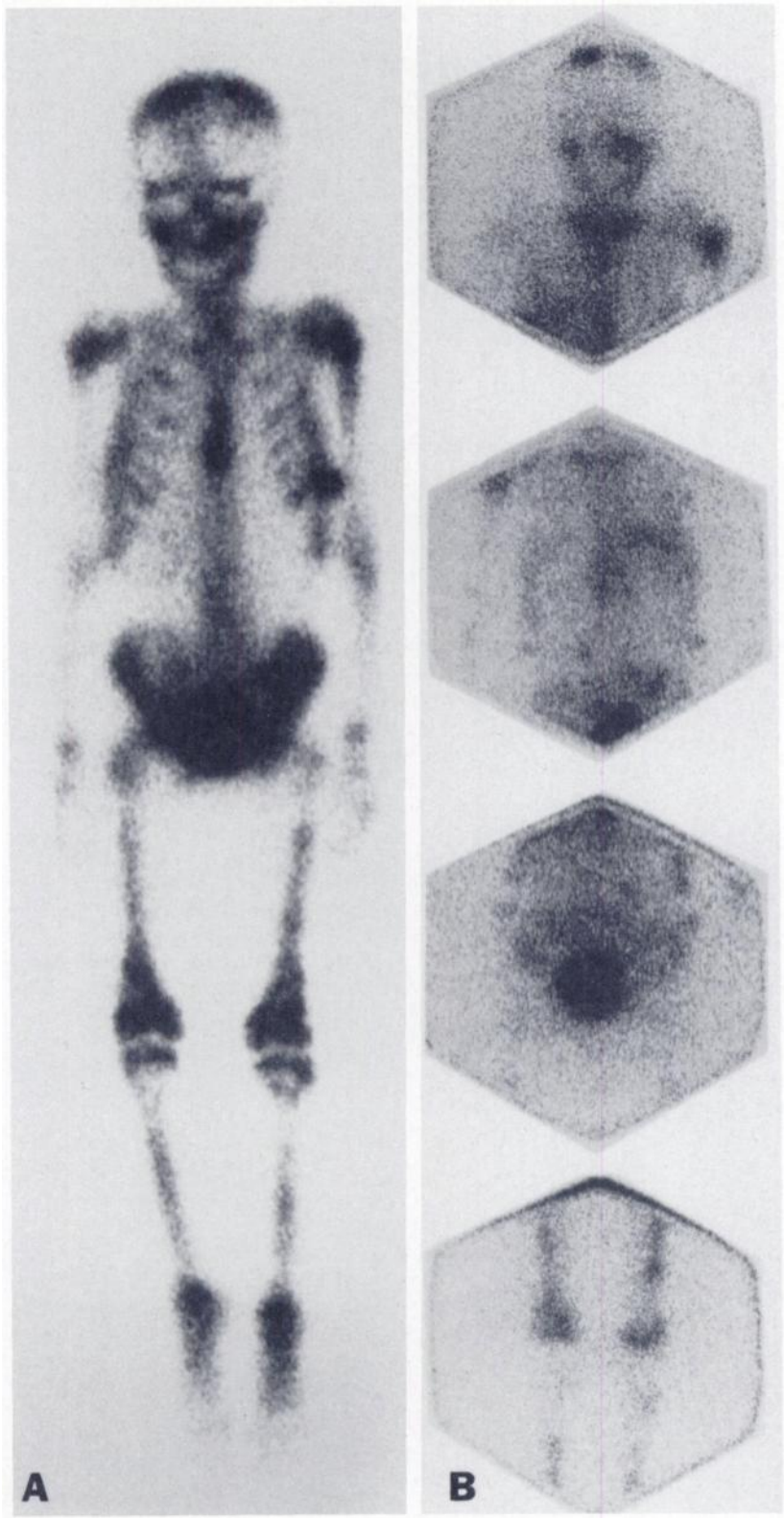

FIGURE 2
Patient 10: A: [^{99m}Tc]MDP bone scan showing multiple skeletal tumor deposits. B: [^{131}I]MIBG scan revealing extensive skeletal and bone marrow deposits to a greater extent than [^{99m}Tc]MDP scan

prior to surgical biopsy as occurred in two of our patients. Children presenting with an undetectable abdominal tumor and/or metastases may be spared exploratory surgery if in vivo demonstration of the adrenergic origin of the lesion can be demonstrated. Iodine-131 MIBG scintigraphy may also have a role in the assessment of disease response in patients following chemotherapy (*10*). This would require that treatment be demonstrated not only to reduce [^{131}I]MIBG uptake but also to correlate with objective evidence of tumor

shrinkage, cell necrosis or extirpation of tumor tissue. Studies in this area are presently ongoing.

The intense uptake of [^{131}I]MIBG by the tumor deposits in some patients, also observed by others (*9–11*), lays the foundation for the potential use of [^{131}I]MIBG as a therapeutic agent for neuroblastoma. Such therapy has already been performed for selected malignant pheochromocytomas (*12,13*). Those patients who demonstrate high initial tracer uptake in all known sites of disease and prolonged (effective $t_{1/2}$ of 1.5 days or greater) retention by the tumors would be the most suitable for such therapy. Such quantitative studies to determine the amount of tumor uptake and retention of [^{131}I]MIBG that are necessary for the utilization of [^{131}I]MIBG as a therapeutic agent are presently in progress. Neuroblastoma tends to be relatively radiosensitive (as compared to pheochromocytoma) and may respond to as little as 2,000 rad (*1,14*).

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