The Normal and Abnormal Distribution of the Adrenomedullary Imaging Agent *m*-[I-131]Iodobenzylguanidine (I-131 MIBG) in Man: Evaluation by Scintigraphy

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The scintigraphic distribution of *m*-[^{131}I]iodobenzylguanidine (I-131 MIBG), an adrenal medullary imaging agent, was studied to determine the patterns of uptake of this agent in man. The normal distribution of I-131 MIBG includes clear portrayal of the salivary glands, liver, spleen, and urinary bladder. The heart, middle and lower lung zones, and colon were less frequently or less clearly seen. The upper lung zones and kidneys were seldom visualized. The thyroid appeared only in cases of inadequate thyroidal blockade. The "normal" adrenal glands were seldom seen and faintly imaged in 2% at 24 hr after injection and in 16% at 48 hr, in patients shown not to have pheochromocytomas, whereas intra-adrenal, extra-adrenal, and malignant pheochromocytomas usually appeared as intense focal areas of I-131 MIBG uptake at 24 through 72 hr.

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The development of radiopharmaceuticals for imaging the adrenal medulla has been conducted at our medical center for the last decade (*1–8*). In 1980 the striking affinity of the radioiodinated benzylguanidines for the adrenal medulla was reported (*9*), and it was suggested that *m*-[I-131]iodobenzylguanidine (I-131 MIBG) might be a clinically useful radiopharmaceutical (*10*). This was verified in man by the visualization with I-131 MIBG of benign and malignant pheochromocytomas (*11*) and adrenal medullary hyperplasia (*12*). The normal distribution of the radiopharmaceutical, and the scintigraphic patterns observed in man both with and without catecholamine-secreting tumors, have not been described previously in detail. Since I-131 MIBG may soon be widely available, the patterns of normal and abnormal imaging—especially regarding the frequency and intensity of uptake by the normal adrenal medulla relative to that of adrenal pheochromocytoma—should be familiar to those using I-131 MIBG. In this paper we evaluate the distribution of I-131 MIBG in man as portrayed by scintigraphy and quantitated by inspection of uptake in various organs by several observers.

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MATERIALS AND METHODS

Study population and materials. We have studied the I-131 MIBG images obtained by previous methods (*11,12*) from 84 patients referred to our center for suspected pheochromocytomas between June 1980 and December 1981. I-131 MIBG scintigraphy was performed following the intravenous injection of 0.5 mCi/1.7m^2 body surface area, using a gamma camera with a high-energy, parallel-hole collimator. Images were acquired for 100,000 counts or 20 min and were obtained at 24, 48, and occasionally 72 hr after tracer injection. Posterior head and chest, posterior midabdomen, and anterior lower abdominal images provided overlapping scans from the pelvis to the base of the skull on at least one imaging occasion. Some of the early patients had images limited to the abdominal region. Thyroidal uptake of I-131 was blocked by Lugol's solution, six drops per day (40 mg iodide) or three drops of saturated solution of potassium iodide (120 mg of iodide) per day, beginning on the day before the tracer injection and continuing for at least four days afterwards.

Observation methods. Four experienced nuclear medicine physicians (MN, BS, VK, MG) independently evaluated the distribution of I-131 MIBG in various organs by means of a semiquantitative grading system

using the following scale: Grade 0 (no visible uptake), Grade 1 (uptake just visible), Grade 2 (uptake clearly visible), Grade 3 (prominent uptake), and Grade 4 (uptake yielding maximal film density). Images considered technically inadequate were not graded. Organs or sites evaluated were: the salivary glands, thyroid, heart, lungs (left and right, upper, middle, and lower zones), liver (left and right lobe), spleen, kidneys, colon, adrenal glands (left and right), urinary bladder, and any other sites showing uptake. Images were examined in random order and presented to the observers without clinical or hormonal data. The test images were examined in batches to avoid fatigue.

Data analysis. Following the grading of uptake, the medical records were reviewed for plasma epinephrine (E) and norepinephrine (NE) concentrations, and for urinary excretion rates for E, NE, metanephrine (M), normetanephrine (NM), and vanillylmandelic acid (VMA), all measured by previously described methods (*11*). The results of radiological studies (e.g., transmission computerized tomography (TCT), arteriography, and venous sampling), and of surgical explorations, were reviewed. The 84 patients (including five repeat studies) were divided into five groups.

Group I (*normal*). This consisted of 25 patients with no biochemical, radiological, or surgical evidence of pheochromocytoma. Their levels of all seven hormonal measurements were all within normal limits* (exception: two patients whose VMA measurements were omitted).

Group II (*probably normal*). This consisted of 19 patients in whom no more than two of the seven hormonal measurements were above normal limits, but not diagnostic for pheochromocytoma: plasma catecholamine concentrations less than three times the upper limit of normal; urinary catecholamines and catecholamine metabolite excretion rates less than twice the upper limit of normal). All localization techniques were negative except for one patient whose TCT scan suggested a left adrenal mass, but at surgical exploration this was revealed to be an aneurysm of the splenic artery.

Group III (*multiple endocrine neoplasia Type 2 (MEN 2) patients and their kindreds*). This consisted of two patients with MEN 2b, and nine patients with a family history of MEN 2a. Nine of the 11 patients had medullary thyroid carcinoma or C-cell hyperplasia. The remaining two patients were part of an MEN 2a kindred and apparently unaffected. These patients showed a wide range of catecholamine values. In five patients the levels of all seven hormonal values were within normal limits. In four patients, no more than two of the seven hormonal measurements were above normal limits, but not diagnostic for pheochromocytoma. In one patient with MEN 2b, three hormonal values were elevated, but none of them was diagnostic for pheochromocytoma. The remaining patient showed elevation of all hormonal values, diagnostic for pheochromocytoma. Thus this group included unaffected individuals, patients with medullary hyperplasia, and patients with pheochromocytoma.

Group IV (*surgically proven pheochromocytoma*). This group consisted of 16 patients with pheochromocytoma (right adrenal in four and left adrenal in six). One patient had bilateral adrenal pheochromocytomas, and three had extra-adrenal pheochromocytomas (right renal hilum, neck, and mediastinum). Two patients had malignant metastatic pheochromocytomas.

Group V (*indeterminate*). Thirteen patients were included in this group, which was subdivided into: (a) Two without evidence of pheochromocytoma, in which five of the hormonal measurements were within normal limits, but in whom two urine measurements were not performed and in whom there was no radiological evidence for pheochromocytoma. (b) Nine in whom more than three hormonal values were elevated but not diagnostic for pheochromocytoma, and no localization of pheochromocytoma could be made radiologically. One of these patients showed marked elevation in urine NE, E, and VMA due to methyldopa intake. (c) Two patients in whom hormonal values were above normal in two of the seven measurements, and in whom TCT scan suggested the presence of an adrenal mass although surgical confirmation is lacking. Figure 1 shows the hormonal data for each group.

The frequency of visible uptake and the mean intensity in each organ at 24, 48, and 72 hr in each group were calculated. In addition, the distribution of intensity of adrenal visualization was plotted for each group. In Group IV this was performed separately for the tumor-bearing adrenal and the contralateral gland of the eleven patients with intra-adrenal pheochromocytomas. There was no significant interobserver variation in the grading of adrenal uptake in either normal or pheochromocytoma-bearing adrenals, nor in the uptake of extra-adrenal pheochromocytomas. In some instances, there were significant interobserver variations in the grading of intensity of uptake in liver, spleen, bladder, and upper lung fields. We felt that this resulted from the difficulty in distinguishing the left lobe of liver from spleen, or from upper and middle zones of the lung, while in the case of the bladder, this organ often lay at the edge of the field.

RESULTS

The normal distribution of I-131 MIBG (Table 1). A representative example of a normal, 48-hr series of scintigrams is shown in Fig. 2. In Group 1 the 24-hr distribution was as follows: the salivary glands, liver, spleen, and urinary bladder were usually visualized, with mean intensities ranging from 1.6 to 2.6. Much of the bladder activity is due to I-131 MIBG in the urine (see Fig. 3). The heart and lower zones of the lungs were

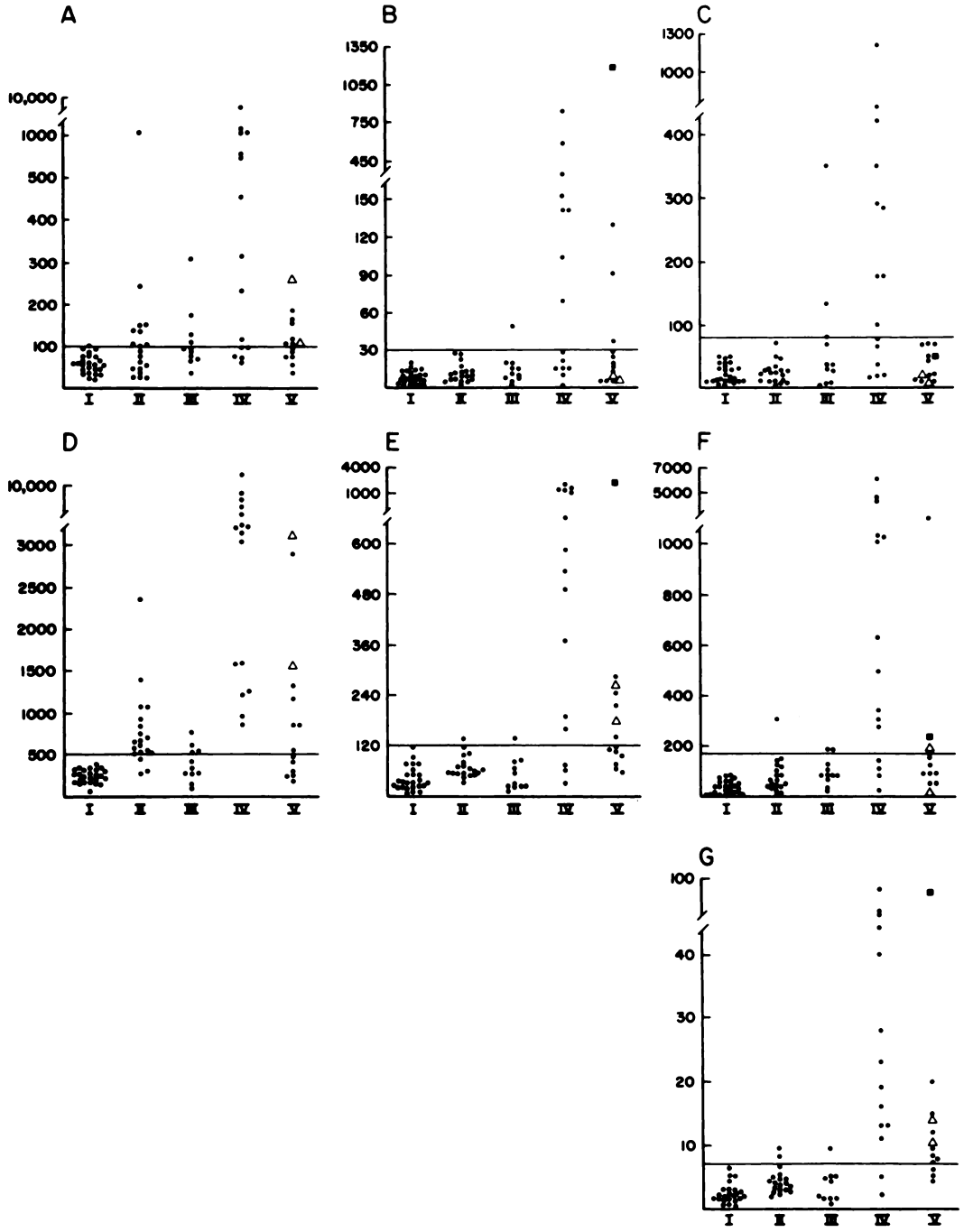

FIG. 1. Hormonal data are shown for Group I (Normal), Group II (probably normal), Group III (MEN), Group IV (pheochromocytoma), and Group V (indeterminate). Plasma concentrations (pg/ml) are given for epinephrine (A), and norepinephrine (D), and urinary excretion rates (μg/24 hr) for epinephrine (B), norepinephrine (E), metanephrine (C), normetanephrine (F), and VMA (mg/24 hr) (G). Upper limit of normal is indicated by horizontal dashed line. (△) repeat case, (■) patient on methyl dopa.

visualized in about half of the cases, with the mean intensities of 0.7 and 0.8 respectively. The thyroid, colon, and the middle zones of the lungs appeared less frequently and intensely, whereas the upper zones of the lungs, kidneys, and other sites were seldom seen. The adrenal glands of Group 1 were not visualized, whereas those in Group II were visible at Grade 1 intensity in 2% of patients. The overall distribution patterns at 48 and 72 hr were similar to those at 24 hr (see Table 1), with the major differences being: (a) a decrease in the frequency and intensity of visualization of the middle and lower zones of the lungs and of the urinary bladder, and (b) a slight increase of frequency of visible uptake in the adrenals with time. Of 36 observations for each adrenal gland in nine patients at both 24 and 48 hr, adrenal visualization increased from Grade 0 to Grade 1 in 12

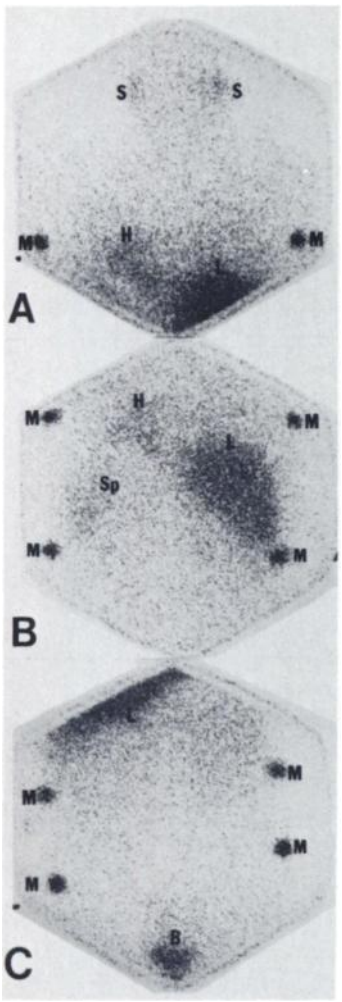

FIG. 2. Overlapping I-131 MIBG images at 48 hr in typical normal patient. A: posterior head and chest; B: posterior midabdomen; and C: anterior lower abdomen. Note accumulation of I-131 MIBG in salivary glands (S), heart (H), liver (L), spleen (SP), and urinary bladder (B). M indicates radioactive markers.

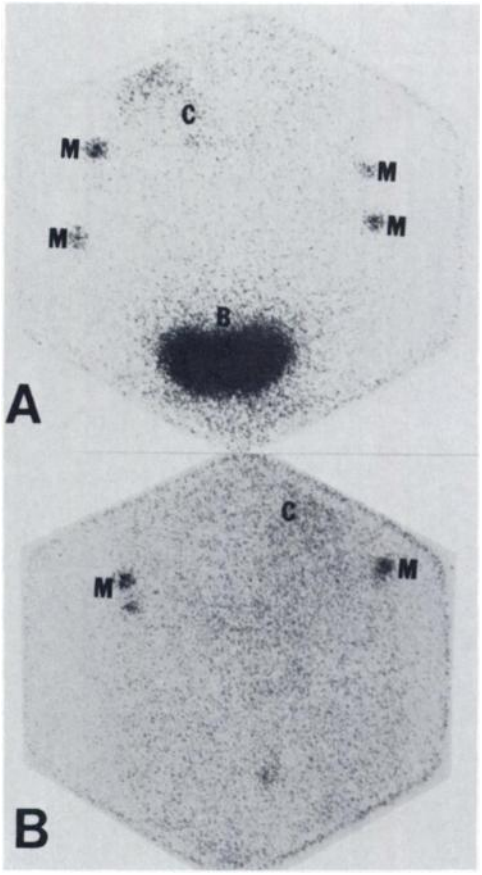

FIG. 3. A. Anterior pelvic scintigram showing prominent I-131 MIBG bladder activity (B). Colonic activity is also seen (C). B. Anterior pelvic scintigram after catheterization and drainage of bladder. Little bladder activity remains. M indicates radioactive markers.

(eight left and four right) and from Grade 0 to Grade 2 in two cases (one left and one right). Thus, approximately 20% of normal adrenals not seen at 24 hr were faintly delineated at 48 hr.

I-131 MIBG distribution in other groups (Table 1). The distribution patterns in Groups II through V were similar to Group I with the exception of: (a) much higher uptake in the adrenals of Group III (MEN patients and their kindreds) and Group IV (surgically proven pheochromocytomas) than in Groups I (normal), II (probably normal), and V (indeterminate); and (b) higher uptake in "other sites," representing extra-adrenal and metastatic pheochromocytomas in Group IV.

Adrenal uptake. Figure 4 compares the intensity of adrenal visualization between groups at 24 hr (a), 48 hr (b), and 72 hr (c). The intensity of adrenal visualization is similar in Groups I, II, and V and in the contralateral adrenal glands of Group IV; the great majority (84–100%) not being visualized (Grade 0) and in no case exceeding Grade 2. In contrast, adrenal visualization was frequent in Group III and in the tumor-bearing glands of Group IV. In Group III most of the adrenal visualization at 24 hr is Grade 1 and 2, and the adrenal pheochromocytomas of Group IV rated Grades 3 and 4. The intensity tended to increase through 48 and 72 hr. The spectrum of adrenal uptakes in Group III and Group IV are shown in Figs. 5 and 6.

Uptake at other sites. Such I-131 MIBG uptake was observed in a few patients from Groups I, II, IV, and V (see Table 1). In Group I, one observation of Grade 1 intensity was noted in mid-abdomen and was interpreted as small-bowel radioactivity. In Group II, the Grades 1 and 2 uptakes that were noted by two observers in the left flank of one patient (24-hr image) might have been in the spleen. In Group IV, all but one "other areas" of focal I-131 MIBG uptake were due to the lesions of metastatic malignant pheochromocytoma (2 cases, see Fig. 7), an intrathoracic pheochromocytoma (1 case), and a displaced portion of a large cystic pheochromocytoma of the left adrenal gland (1 case). The grading of these lesions was 3 or 4 in most cases (see Table 1). One case of contamination of the lower abdomen with radioactive urine was observed. Two extra-adrenal pheochromocy-

TABLE 1. FREQUENCY OF VISIBLE UPTAKE, AND MEAN INTENSITY OF UPTAKE, IN VARIOUS ORGANS

(a) 24-hr images

Groups	Normal (14 cases) 1			Probably Normal (11 cases) 2			MEN and kindred (10 cases) 3			Proven pheochromocytoma (13 cases) 4			Indeterminate (6 cases) 5		
Organs or sites	n*	% †	m‡ ± s.d.§	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.
Salivary gland	40	98	2.3 ± 0.6	29	90	2.0 ± 1.0		—		34	85	1.9 ± 1.0	16	81	1.6 ± 1.0
Thyroid	40	23	0.4 ± 0.8	29	10	0.4 ± 0.6		—		34	26	0.6 ± 1.1	17	12	0.2 ± 0.5
Heart	44	57	0.7 ± 0.7	36	53	0.7 ± 0.7	16	50	1.2 ± 1.4	45	31	0.4 ± 0.8	18	33	0.4 ± 0.6
upper L	42	2	0.0 ± 0.2	35	6	0.1 ± 0.2	12	0	0.0 ± 0.0	44	2	0.0 ± 0.2	20	10	0.1 ± 0.3
R	42	2	0.0 ± 0.2	35	3	0.0 ± 0.2	12	0	0.0 ± 0.0	44	2	0.0 ± 0.2	20	10	0.1 ± 0.3
Lung middle L	42	24	0.3 ± 0.5	37	8	0.1 ± 0.3	12	17	0.3 ± 0.6	45	16	0.2 ± 0.4	20	30	0.3 ± 0.5
R	42	29	0.3 ± 0.5	37	8	0.1 ± 0.3	12	17	0.3 ± 0.6	45	16	0.2 ± 0.4	20	30	0.3 ± 0.5
lower L	44	68	0.8 ± 0.6	41	37	0.4 ± 0.5	15	33	0.4 ± 0.6	50	44	0.5 ± 0.5	20	60	0.7 ± 0.6
R	44	70	0.8 ± 0.6	41	37	0.4 ± 0.5	15	33	0.4 ± 0.6	50	46	0.5 ± 0.5	20	60	0.7 ± 0.6
Liver R	56	100	2.6 ± 0.6	43	100	2.5 ± 0.6	40	100	3.1 ± 0.6	62	100	2.7 ± 0.6	28	100	2.8 ± 0.8
L	56	100	1.8 ± 0.6	43	100	1.7 ± 0.7	40	100	2.4 ± 0.8	62	95	1.8 ± 0.9	28	100	1.8 ± 0.8
Spleen	56	96	1.6 ± 0.7	42	100	1.7 ± 0.6	39	97	2.0 ± 0.9	61	95	1.9 ± 0.9	28	96	1.8 ± 0.8
Kidney	55	5	0.1 ± 0.3	42	5	0.1 ± 0.2	40	8	0.2 ± 0.6	59	3	0.0 ± 0.2	28	17	0.2 ± 0.5
R	54	9	0.1 ± 0.3	41	7	0.1 ± 0.3	37	3	0.0 ± 0.2	58	2	0.0 ± 0.1	26	4	0.2 ± 0.4
Colon trans.	54	11	0.1 ± 0.3	43	9	0.1 ± 0.5	37	3	0.0 ± 0.2	58	0	0.0 ± 0.0	26	15	0.2 ± 0.5
L	55	6	0.1 ± 0.3	42	12	0.1 ± 0.3	37	0	0.0 ± 0.0	58	2	0.0 ± 0.1	26	15	0.2 ± 0.5
Adrenal L	55	0	0.0 ± 0.0	42	2	0.0 ± 0.2	40	60	1.0 ± 1.0	59	47	1.3 ± 1.6	28	7	0.2 ± 0.5
R	55	0	0.0 ± 0.0	42	2	0.0 ± 0.2	40	58	0.9 ± 0.9	60	37	1.0 ± 1.5	28	11	0.2 ± 0.6
Bladder	45	80	2.1 ± 1.4	33	94	2.8 ± 1.1	21	48	1.4 ± 1.7	43	77	2.1 ± 1.4	24	79	2.8 ± 1.5
Other sites	55	2		43	9	0.2 ± 0.8	33	0	0.0 ± 0.0	55	15	0.5 ± 1.2‖	27	4	0.1 ± 0.4

(*continued*)

TABLE 1. (*continued*)

(b) 48-hr images

Groups / Organs or sites		Normal (20 cases) 1			Probably Normal (18 cases) 2			MEN and kindred (11 cases) 3			Proven pheochromocytoma (15 cases) 4			Indeterminate (13 cases) 5		
		n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.
Salivary gland		64	92	2.1 ± 0.9	40	90	2.0 ± 0.9	3	100	2.3	24	79	1.6 ± 1.0	41	98	1.8 ± 0.7
Thyroid		66	17	0.4 ± 0.9	38	8	0.1 ± 0.3	3	0	0.0	24	21	0.3 ± 0.7	43	16	0.3 ± 0.6
Heart		71	63	1.0 ± 0.9	56	29	0.4 ± 0.8	7	57	1.3 ± 1.3	44	18	0.3 ± 0.8	46	24	0.3 ± 0.5
Lung upper	L	71	4	0.0 ± 0.2	56	4	0.0 ± 0.2	4	0		41	0	0.0 ± 0.0	50	14	0.1 ± 0.4
	R	71	4	0.0 ± 0.2	56	2	0.0 ± 0.1	4	0		41	0	0.0 ± 0.0	50	14	0.1 ± 0.4
middle	L	71	14	0.2 ± 0.5	57	5	0.1 ± 0.2	4	0		42	2	0.0 ± 0.2	50	26	0.3 ± 0.5
	R	71	14	0.2 ± 0.5	57	7	0.1 ± 0.3	4	0		42	2	0.0 ± 0.2	50	26	0.3 ± 0.5
lower	L	73	48	0.6 ± 0.7	62	21	0.2 ± 0.4	7	85	0.9 ± 0.4	46	28	0.3 ± 0.5	50	58	0.7 ± 0.6
	R	73	48	0.6 ± 0.7	62	27	0.3 ± 0.5	7	85	0.9 ± 0.4	46	28	0.3 ± 0.5	50	58	0.7 ± 0.6
Liver	R	80	99	2.7 ± 0.7	70	100	2.5 ± 0.7	43	100	2.7 ± 0.8	65	97	2.2 ± 0.9	56	100	2.9 ± 0.7
	L	80	98	1.9 ± 0.8	70	97	1.7 ± 0.8	43	98	2.1 ± 0.9	65	89	1.5 ± 0.9	56	100	1.8 ± 0.8
Spleen		80	95	1.7 ± 0.8	69	96	1.6 ± 0.7	42	95	1.8 ± 0.8	64	83	1.6 ± 1.1	56	91	1.8 ± 0.9
Kidney		78	3	0.0 ± 0.3	68	1	0.0 ± 0.4	41	5	0.1 ± 0.2	62	0	0.0 ± 0.0	54	2	0.0 ± 0.1
	R	77	14	0.2 ± 0.5	70	7	0.1 ± 0.3	38	0	0.0 ± 0.0	63	16	0.3 ± 0.7	54	19	0.2 ± 0.4
Colon	trans.	77	22	0.3 ± 0.6	70	7	0.1 ± 0.3	37	0	0.0 ± 0.0	63	8	0.1 ± 0.5	54	24	0.3 ± 0.6
	L	77	31	0.5 ± 0.8	70	11	0.1 ± 0.4	37	0	0.0 ± 0.0	63	13	0.2 ± 0.6	54	35	0.4 ± 0.7
Adrenal	L	80	19	0.2 ± 0.4	70	3	0.0 ± 0.2	44	70	1.5 ± 1.2	64	52	1.3 ± 1.5	56	4	0.0 ± 0.2
	R	80	14	0.2 ± 0.5	70	1	0.0 ± 0.1	44	64	1.5 ± 1.4	64	48	1.2 ± 1.5	56	7	0.1 ± 0.3
Bladder		67	85	2.2 ± 1.3	60	75	2.4 ± 1.5	18	28	0.6 ± 1.2	49	65	1.9 ± 1.5	50	92	2.8 ± 1.2
Other sites		78	0	0.0 ± 0.0	70	3	0.1 ± 017	36	0	0.0 ± 0.0	60	23	0.7 ± 1.3¶	51	4	0.1 ± 0.4

(*continued*)

TABLE 1. (*continued*)

(c) 72-hr images

Groups	Normal (7 cases) 1			Probably Normal (7 cases) 2			MEN and kindred (2 cases) 3			Proven pheochromocytoma (6 cases) 4			Indeterminate (3 cases) 5		
Organs or sites	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.
Salivary Gland	1	100	2.0	4	0	0.0		—		2	0	0.0	3	67	0.7
Thyroid	2	0	0.0	4	100	1.3		—		2	0	0.0	3	0	0.0
Heart	19	58	1.7 ± 0.7	17	53	0.9 ± 0.9		—		4	25	0.5	4	0	0.0
upper L	9	0	0.0 ± 0.0	13	0	0.0 ± 0.0		—		3	0	0.0	4	0	0.0
R	9	0	0.0 ± 0.0	13	0	0.0 ± 0.0		—		3	0	0.0	4	0	0.0
Lung middle L	10	0	0.0 ± 0.1	13	0	0.0 ± 0.0		—		3	0	0.0	4	0	0.0
R	10	0	0.0 ± 0.0	13	0	0.0 ± 0.0		—		3	0	0.0	4	0	0.0
lower L	13	23	0.2 ± 0.4	21	24	0.2 ± 0.4		—		3	33	0.3	5	20	0.2 ± 0.5
R	13	23	0.2 ± 0.4	20	20	0.2 ± 0.4		—		3	0	0.0	5	40	0.4 ± 0.6
Liver R	28	100	2.5 ± 0.7	27	100	2.2 ± 0.7	8	100	1.7 ± 0.5	20	100	1.8 ± 0.7	11	100	2.3 ± 0.9
L	28	100	1.9 ± 0.6	27	96	1.6 ± 0.8	8	83	1.3 ± 0.8	20	95	1.3 ± 0.6	11	91	1.4 ± 0.8
Spleen	28	96	1.6 ± 0.8	27	100	1.5 ± 0.6	8	100	1.3 ± 0.5	20	75	1.3 ± 1.0	11	82	1.0 ± 0.6
Kidney	28	0	0.0 ± 0.0	27	0	0.0 ± 0.0	8	0	0.0 ± 0.0	20	5	0.1 ± 0.5	10	0	0.0 ± 0.0
R	25	12	0.1 ± 0.3	25	0	0.0 ± 0.0	8	0	0.0 ± 0.0	19	0	0.0 ± 0.0	10	0	0.0 ± 0.0
Colon trans.	26	8	0.1 ± 0.3	25	0	0.0 ± 0.0	8	0	0.0 ± 0.0	19	0	0.0 ± 0.0	10	0	0.0 ± 0.0
L	25	20	0.5 ± 1.1	25	0	0.0 ± 0.0	8	0	0.0 ± 0.0	19	0	0.0 ± 0.0	10	20	0.2 ± 0.4
Adrenal L	28	7	0.1 ± 0.4	27	4	0.0 ± 0.2	8	100	3.4 ± 0.5	20	50	1.3 ± 1.6	12	8	0.1 ± 0.3
R	28	18	0.3 ± 0.6	27	0	0.0 ± 0.0	8	100	3.4 ± 0.5	20	60	1.6 ± 1.6	12	8	0.1 ± 0.3
Bladder	19	53	1.3 ± 1.5	16	44	1.1 ± 1.5		—		11	0	0.0 ± 0.0	10	60	1.4 ± 1.4
Other sites	27	0	0.0 ± 0.0	26	0	0.0 ± 0.0	8	0	0.0 ± 0.0	19	11	0.2 ± 0.7**	10	0	0.0 ± 0.0

* n = number of observations = number of images graded for uptake in a given site or organ.

† % = percentage of observations in which uptake was graded as 1 or greater.

‡ $m = \text{mean uptake} = \dfrac{\Sigma \text{ uptake grades in images evaluated}}{\text{number of observations}}$

§ s.d. = standard deviation.

‖ = when positive, the mean grade of intensity of uptake was 3.4 ± 0.5.

¶ = when positive, the mean grade of intensity of uptake was 2.8 ± 1.1.

** = when positive, the mean grade of intensity of uptake was 3.5 ± 0.7.

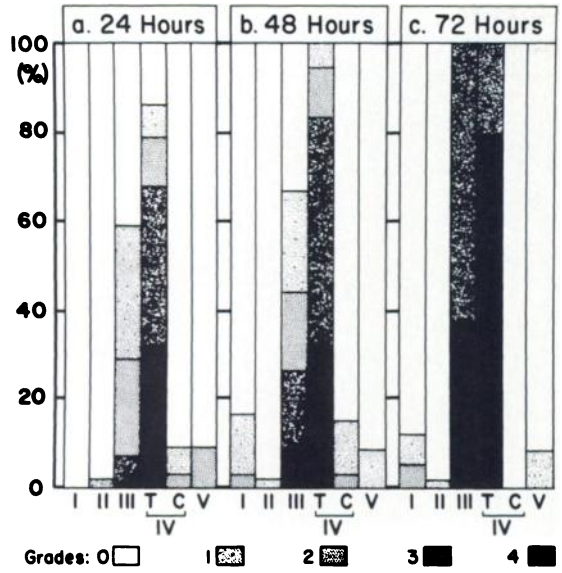

FIG. 4. Distribution of intensity of adrenal visualization in different patient groups (expressed as % of observations made at 24, 48, and 72 hr). Group I Normal; Group II Probably normal; Group III MEN two patients and their kindred; Group IV Pheochromocytoma (T = tumor-bearing gland, C = contralateral gland); Group V Indeterminate. % = number of observations in each grade × 100 ÷ total number of observations.

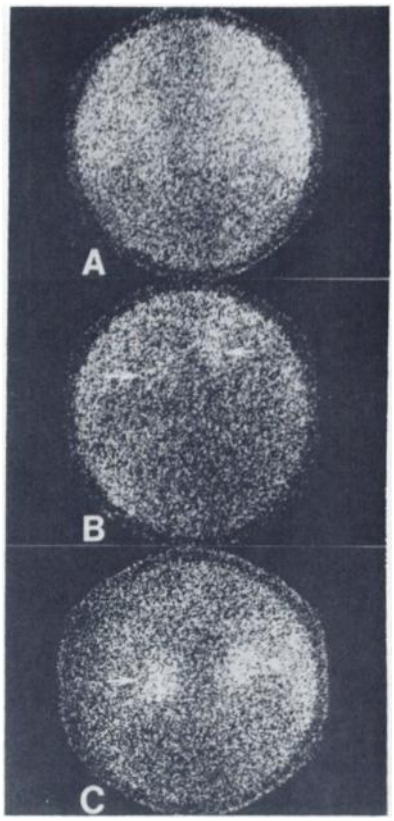

FIG. 5. Spectrum of adrenal uptake of I-131 MIBG in multiple endocrine neoplasia Type 2 (MEN 2). All are posterior abdominal images obtained at 48 hr after injection. A: patient with MEN 2a—no visible I-131 MIBG adrenal uptake (Grade 0). B: patient with MEN 2b—minimal bilateral I-131 MIBG adrenal uptake (Grade 1 on left and Grade 2 on right). C: patient with MEN 2a—prominent bilateral adrenal uptake of I-131 MIBG (Grade 3). Adrenal uptake indicated by arrows.

tomas showed no visible uptake (lesions in the right renal pelvis and right neck). In Group V, three Grade 2 spots were found in one patient in a region inferior to the spleen at 24 and 48 hr. The significance of this finding is uncertain.

DISCUSSION

Iodine-131 MIBG, an analog of the adrenergic blocking agent guanethidine, is thought to share the same uptake and storage mechanisms as norepinephrine (*13,14*). However, it is not metabolized by either monoamine oxidase or catechol-O-methyl transferase (*15*). In the canine adrenal, MIBG is sequestered mainly in the chromaffin storage granules (*10*). In dogs a major component of myocardial retention of I-131 MIBG may be due to sequestration within the norepinephrine storage vesicles of the adrenergic nerves of the heart (*15*). Thus, in man the scintigraphic distribution might be expected to reflect organs with adrenergic innervation, as well as in those organs that process catecholamines for excretion, such as liver and urinary bladder.

In this study, the organs most frequently and intensely visualized were: the salivary glands, liver, spleen, and urinary bladder. Of these, the salivary glands and spleen are richly innervated by sympathetic nerves (*16*). Although the salivary gland is known to accumulate free I-131 actively (as do the thyroid and stomach, *17*), there is little possibility that salivary gland visualization was due here to free I-131, since the stomach was not visualized in any patients in this study. This suggests that I-131 MIBG may be accumulated by the sympathetic nerves of the salivary gland. In mice, whole-body autoradiograms with [^{14}C]guanethidine have also revealed prominent concentration in the salivary glands (*18*). The visualization of the spleen may result from its rich sympathetic innervation. In the dog the spleen has a tissue concentration ten and 19 times that of blood at 24 and 48 hr, respectively (*9*). Despite the fact that, in animal studies, the concentration of I-125 MIBG in the liver was only 1.5 and 2 times that in blood at 24 and 48 hr (*9*), the liver was consistently visualized, probably because of its volume and vascularity. In addition, the liver is a major site for catecholamine degradation, and may be a site of I-131 MIBG uptake even though most of the drug is excreted unchanged in the urine.

Visualization of the urinary bladder results from the renal excretion of activity, 95% of which appears unchanged in the urine (*15*). In five normal subjects, the mean urinary excretion was 64% in the first 24 hr (*19*). The decreasing intensity of the bladder shadow with time reflects this excretion. In cases where pheochromocytoma in region of the bladder is suspected, imaging fol-

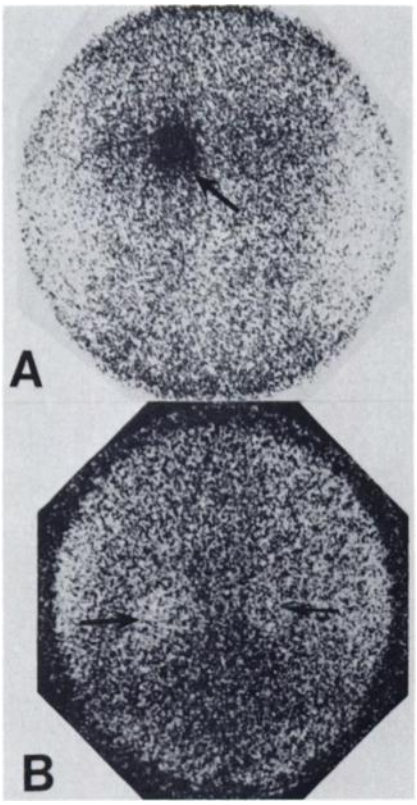

FIG. 6. A: typical intense uptake (Grade 4, arrow) at 48 hr in left-sided sporadic adrenal pheochromocytoma. B: less intense uptake (Grade 3, large arrow) in sporadic left-sided pheochromocytoma. Note faint (Grade 2) visualization of normal right adrenal, small arrow. Normality of right gland was confirmed at surgical exploration.

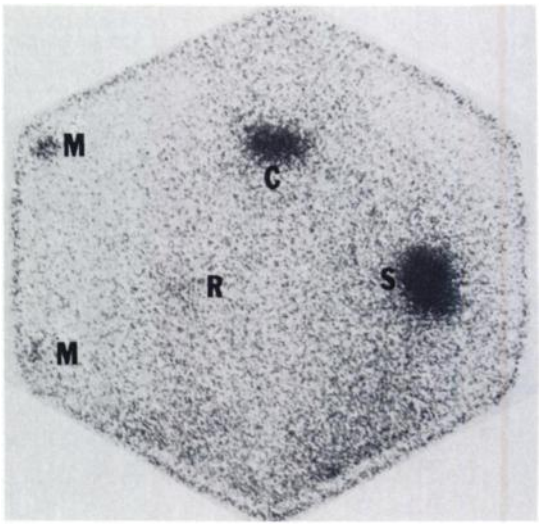

FIG. 7. Posterior image of head and chest, demonstrating malignant metastatic pheochromocytoma (arising from para-aortic *primary*) with intense (Grade 4) I-131 MIBG uptake in skeletal metastases: in fifth cervical vertebra (C) and right scapula (S), and poor uptake in anterior left rib (R). M indicates radioactive markers.

lowing catheterization may be required to reveal a lesion that may be masked by activity in the urine.

Organs less frequently and less intensely visualized in all groups were: thyroid, heart, lung, colon, and kidney. The thyroid gland was visualized only in those patients where iodide pretreatment had inadvertently been omitted.

Myocardial uptake of MIBG treated with I-131 or I-123 has been reported in both animals and man, and appears to have two components, one being nonspecific and the other a specific adrenergic neuronal concentration (*15*,*18*). Peak tissue concentrations are achieved 2 hr after injection. In the dog heart, concentrations at 24 and 48 hr were respectively 20% and 12.5% of the 2-hr level (*15*). Thus if imaging were performed at 24 and 48 hr, myocardial activity sufficient to produce images in every case would not be anticipated. Moreover, the frequency and intensity of visualization of the heart is significantly lower in Groups IV and V than in Groups I and III. Elucidation of the different factors in these groups may provide an insight into mechanisms of I-131 MIBG uptake.

The differences in frequency and intensity of visualization between the upper, middle, and lower zones of the lung perhaps reflect the relative lung volumes in these zones and the relative pulmonary vascularity.

The source(s) of colonic radioactivity appearing after injection of I-131 MIBG are not clear. Twenty-four-hr fecal collections obtained in two subjects contained 0.06% and 1.68% of the injected dose of I-123 MIBG (*18*). In a study of guanethidine distribution in the rat, an appreciable fraction of an intravenous dose of guanethidine (8% in 18 hr) was excreted in the feces due to biliary excretion, pancreatic excretion, and direct passage across the gastrointestinal epithelium (*20*). I-131 MIBG, an analog of guanethidine, may also be similarly excreted. Another possible route is the ingestion of saliva, in which we have confirmed radioactivity from I-131 MIBG. Visualization of the kidneys seldom occurred at 24 hr or later, which is a reflection of the rapid renal clearance of I-131 MIBG.

The striking discrepancy between Groups I, II, and V on the one hand and Groups III and IV on the other was in the uptake in the adrenal glands and other sites. In Group I, the normal adrenal glands were never visualized at 24 hr. Approximately 20% of these changed to positive at 48 hr. This is probably due to higher tissue-to-blood ratios at 48 hr (*9*). Normal adrenal glands, when seen at all, were always faint (less than Grade 2). This is in contrast to the reports of Wieland et al. (*10*), in which the normal adrenals of dogs and rhesus monkeys were imaged with I-131 MIBG. This may be explained by the administered dose/kg body weight of I-131 MIBG, the average value being 7 μCi in man, whereas 60 μCi was administered in dog and 130 μCi in monkeys. The human adrenal also has considerably more overlying tissue. Such dose-dependent scintigraphic densities have

TABLE 2. FREQUENCY OF VISIBLE UPTAKE, AND MEAN INTENSITY OF UPTAKE, IN ADRENAL GLANDS OF GROUP 3 (MEN PATIENTS AND THEIR KINDRED)

Biochemical diagnosis		"Normal" (5 pts)			"Probably normal" (4 pts)			"Possible pheochromocytoma" (2 pts)		
Imaging time	Side of adrenal	n	%	m ± s.d.	n	%	m ± s.d.	n	%	m ± s.d.
24 hr	L	20	70	1.3 ± 0.9	12	50	0.5 ± 0.5	8	50	1.1 ± 1.3
	R	20	60	1.3 ± 0.9	12	50	0.5 ± 0.5	8	63	1.3 ± 1.1
48 hr	L	20	65	0.9 ± 0.9	16	63	0.8 ± 0.8	8	100	2.5 ± 1.4
	R	20	60	1.3 ± 1.3	16	50	0.7 ± 0.8	8	100	3.5 ± 0.5
72 hr	L	4	100	3.0		—		4	100	3.8
	R	4	100	3.0		—		4	100	3.8

n = number of observations of the adrenal glands.

% = percentage of observations in which uptake was graded as 1 or greater.

$$m = \text{mean uptake} = \frac{\Sigma \text{ uptake grades in images evaluated}}{\text{number of observations}}.$$

s.d. = standard deviation.

been observed in the detection of iodine-avid tissue in patients with thyroid cancer using I-131 (*21*).

In Group III (MEN 2 and their kindred) catecholamine measurements showed a wide spectrum of abnormalities, overlapping the normal range. The adrenals, however, showed frequency and intensity of visualization quite different from those in Groups I, II, and V, with faint visualization occurring at 24 hr in most cases becoming increasingly more intense until 72 hr. Table 2 shows the results of adrenal visualization of the patients in Group III when divided into three subgroups according to biochemical criteria as defined in the methods section. The "normal" subgroup corresponds to Group I and the "probably normal" subgroup to Group II. The striking discrepancies in adrenal uptake between Group I and the "normal" subgroup, and between Group II and the "probably normal" subgroup, are obvious at all imaging times (also see Table 1). The "possible pheochromocytoma" group has an even higher frequency and intensity of visible uptake than the normal and probably-normal groups at 48 hr. This probably reflects the spectrum of increasing function and size of the medulla in MEN 2, from normal to medullary hyperplasia to frank pheochromocytoma (*12*,*22*). Thus, definite (greater than Grade 2) bilateral adrenal visualization was observed in a patient with normal catecholamine measurements and few symptoms, who underwent bilateral adrenalectomy that revealed medullary hyperplasia. I-131 MIBG thus appears valuable in the evaluation of patients with MEN 2 and their kindreds, even in the absence of symptoms of hypercatecholaminemia and normal or borderline hormonal and/or TCT findings.

The normal adrenal is seldom visualized (less than 20%, and then always less than Grade 2), in contrast to the frequent and usually more intense uptake observed in adrenal medullary hyperplasia and pheochromocytoma. The faint uptake may overlap normal and abnormal adrenal glands (see Figs. 4–6). In those cases where faint uptake (Grade 1 or 2) is present, this must be interpreted in the light of the plasma and urinary catecholamine measurements and the genetic background of the patient. In addition, comparison is necessary with other diagnostic modalities such as TCT, which may be helpful in ambiguous cases. Although two extra-adrenal pheochromocytomas were missed in this particular series, I-131 MIBG imaging is especially valuable in detecting extra-adrenal pheochromocytomas (*23*,*24*) and metastatic lesions from malignant pheochromocytoma (*24*,*25*). In this context, any foci of I-131 MIBG uptake other than in those organs described above must be considered as possible sites of ectopic or metastatic pheochromocytoma. In this series of patients, I-131 MIBG detected pheochromocytomas in 14/16 cases (80%). More detailed evaluation of the sensitivity and specificity of the technique is being studied.

FOOTNOTES

* Plasma E ≤ 100 pg/ml, plasma NE ≤ 500 pg/ml, urinary E ≤ 30 μg/24 hr, urinary NE ≤ 120 μg/24 hr, urinary M ≤ 80 μg/24 hr, urinary NM ≤ 165 μg/24 hr and urinary VMA ≤ 7 mg/24 hr.

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