Imaging the Primate Adrenal Medulla with [^{123}I] and [^{131}I] Meta-Iodobenzylguanidine: Concise Communication

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An evaluation of radioiodinated meta-iodobenzylguanidine (*m*-IBG) as an adrenomedullary imaging agent is reported in 15 rhesus monkeys. Scintiscans of the monkey adrenal medulla have been obtained with [^{123}I]- and [*m*-^{131}I]IBG at 2–6 days after injection. The imaging superiority of *m*-IBG over its positional isomer, para-iodobenzylguanidine (*p*-IBG), is documented in both dogs and monkeys. Administration of reserpine, a depletor of catecholamine stores, markedly lowers the [*m*-^{131}I]-IBG content of the dog adrenal medulla, but the adrenergic blocking agents phenoxybenzamine and propranolol have no effect. Subcellular fractionation of the dog's adrenal medullae reveals that *m*-IBG is sequestered mainly in the chromaffin storage granules. The results of this study suggest that radioiodinated *m*-IBG, previously reported to image the primate myocardium, also merits evaluation as a clinical radiopharmaceutical for the adrenal medulla.

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The marked adrenomedullary affinity for para-iodobenzylguanidine (*p*-IBG), an analog of the neuron-blocking agent guanethidine, was recently reported (*1*). The use of [*p*-^{131}I]IBG provides scintiscans of the dog adrenal medullae 3–10 days after injection (*1*). We report here a more detailed evaluation of the positional isomers of iodobenzylguanidine (Fig. 1), which reveals that [^{131}I]meta-iodobenzylguanidine (*m*-IBG) gives consistently earlier and better adrenomedullary images in the dog than [*p*-^{131}I]IBG, a result that can perhaps be linked to the greater resistance of *m*-IBG to in vivo deiodination. Since it is desirable to achieve successful adrenomedullary scintigraphy with radioiodinated *m*-IBG in nonhuman primates before embarking on a clinical evaluation, we also report the use of [^{131}I]- and [*m*-^{123}I]IBG to image the adrenal medulla of the rhesus monkey. Initial studies on the mechanism of localization in the adrenal medulla suggest that *m*-IBG is being stored in the chromaffin granules.

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MATERIALS AND METHODS

Synthesis of radioiodinated *p*-IBG and *m*-IBG. The synthesis and determination of radiochemical purity of the radiolabeled compounds used in this study were based on methods previously reported (*1*). Recent improvements, which have lowered the radiosynthesis time to 2 hr, will be reported elsewhere. The specific activities ranged from 1–5 mCi/mg. Before injection, the compounds were formulated in 5 millimol acetate buffer at pH 4.5 (specific concentration of 0.2 mCi/ml).

Tissue distribution studies. These were performed on six rhesus monkeys and four mongrel dogs. The weights and sexes are given in Table 2. Following a restraining i.m. dose of ketamine hydrochloride, monkeys were anesthetized with sodium pentobarbital and injected intravenously with 100 μCi of [*m*-^{125}I]IBG. Three or 48 hr later the animals were killed by i.v. injection of sodium pentobarbital, and duplicate samples of 11 different tissues in each monkey were weighed and counted in an autogamma counter, with corrections made for radioactive decay, background, and counter efficiency. Blood samples were obtained by cardiac puncture. To nor-

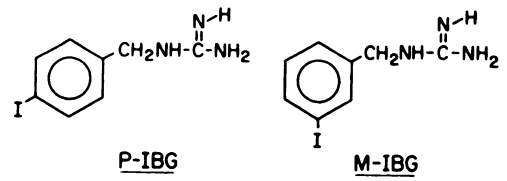

FIG. 1. Chemical structures of para-iodobenzylguanidine (*p*-IBG) and meta-iodobenzylguanidine (*m*-IBG).

malize for differences in animal weights, tissue concentrations are expressed in % kg dose/g (*2*).

The four mongrel dogs were each anesthetized with sodium pentobarbital and injected intravenously with 100 μCi of [*m*-^{125}I]IBG and killed 2 or 48 hr later by intravenous injection of an overdose of sodium pentobarbital. Duplicate samples of four different tissues were weighed and counted as described above for the rhesus monkeys.

Imaging studies. *Dogs.* Six mongrel dogs (21–34 kg) were evaluated. They were anesthetized with sodium pentobarbital and imaged posteriorly using a large-field-of-view camera fitted with a high-energy, parallel-hole collimator and interfaced to a minicomputer. Three dogs each received intravenous injections of 1.0 mCi of [*p*-^{131}I]IBG. One dog (No. 1) was imaged at 1, 3, 6, and 10 days after injection; Dog 2 was imaged at 2 and 5 days, and Dog 3 at 2 days only.

For the evaluation of *m*-IBG, Dog 4 was injected intravenously with 1.3 mCi of [*m*-^{131}I]IBG and imaged at 1 and 2 days. Dogs 5 and 6 were evaluated 1 day after injections of 5.0 mCi of [*m*-^{123}I]IBG. Dog 5 was also imaged by the coded-aperture tomographic technique (*3*). Confirmation of all adrenal images was made by subsequent injection of 2 mCi of Tc-99m DTPA into the immobilized dogs without altering position. The resultant renal images were superimposed over the adrenal scans using the computer.

Monkeys. Nine animals (4.5–10.5 kg) were given a restraining i.m. dose of ketamine hydrochloride (7–15 mg/kg) and then anesthetized with i.v. sodium pentobarbital (12–25 mg/kg). Three monkeys were injected with [*p*-^{131}I]IBG (0.27–0.55 mCi), three with [*m*-^{131}I]IBG (1.0–1.3 mCi), and three with [*m*-^{123}I]IBG (1.8–2.3 mCi). Planar posterior adrenal images were obtained using a gamma camera with a high-energy, parallel-hole collimator. Confirmation of the adrenal images was done as described with dogs (1 mCi Tc-99m DTPA).

Of the three monkeys receiving [*p*-^{131}I]IBG, one (10.5 kg male) was injected with 0.53 mCi and imaged at 2 days. Six weeks later this same monkey was injected again with 0.55 mCi and scanned at 1, 2, and 7 days. A second monkey (5.0 kg female) received 0.27 mCi and was scanned at 2 days. The third animal (6.2 kg female) was injected with 0.31 mCi and imaged at 1 and 7 days.

In the case of [*m*-^{123}I]IBG, a female (4.6 kg) received 1.9 mCi and scanning experiments were performed at 2.5 hr, and 1 and 2 days. A second female (5.5 kg) was administered 2.3 mCi and imaged at 1 and 2 days. A third female (4.5 kg) received 1.8 mCi and was scanned at 2 days only.

Of the three rhesus monkeys administered [*m*-^{131}I]IBG, one (8.2 kg male) was injected with 1.1 mCi and scanned at 2, 3, and 5 days. The second monkey (10.0 kg male) received 1.3 mCi with imaging attempts following at 3 and 6 days. The final animal (8.0 kg female) was given 1.0 mCi and imaged also at 3 and 6 days.

Drug interventions. *Reserpine depletion study.* Six female mongrel dogs (11.6–19.8 kg) were each injected with 0.55 mCi of [*m*-^{131}I]IBG. Three animals received 0.05 mg/kg of reserpine* intravenously at 1 and 2 days. The three control dogs received an equal volume of reserpine vehicle at 1 and 2 days. At 3 days, all six animals were imaged as described above and then killed by intravenous injection of sodium pentobarbital. Adrenomedullary tissue was removed, weighed, and counted in an autogamma counter.

Phenoxybenzamine treatment. Three female mongrel dogs were administered oral phenoxybenzamine† (0.25 mg/kg) twice a day for 6 days. Three control animals were given placebo for 6 days. On the third day of the treatment, all six dogs were given intravenously 100 μCi of [*m*-^{125}]IBG. They were killed on the sixth day and their adrenomedullary tissue weighed and counted.

Propranolol treatment. Three female dogs were administered oral propranolol, 2.0 mg/kg twice a day for 6 days. The three control animals from the phenoxybenzamine studies also served as controls for this study. On the third day of the propranolol treatment, the dogs were given intravenously 100 μCi of [*m*-^{125}I]IBG. The three experimental animals were killed on the sixth day and their adrenomedullary tissue weighed and counted.

Subcellular distribution study. *Extraction of dog adrenal medullary tissue.* Mongrel dogs were each injected with 100 μCi of [*m*-^{125}I]IBG and killed 3 days later with an intravenous injection of sodium pentobarbital. Both adrenals were removed from each dog, weighed after removal of all fat and connective tissue, and immediately placed on ice. Since the adrenal medulla is very small and is surrounded by the much larger adrenal cortex, the adrenals were sliced in half to expose the medulla, and the medullary tissue was then removed by suction. A cold Pasteur pipet, attached to an aspirator, was gently passed over the medullary tissue. The tissue adhered to the pipet and was transferred to a 2-ml Potter–Elveheim homogenizer by rinsing the Pasteur pipet repeatedly with 1.0 ml of cold 0.30 *M* sucrose.

Subcellular fractionation of the extracted dog adrenal medullary tissue. The extracted tissue was ho-

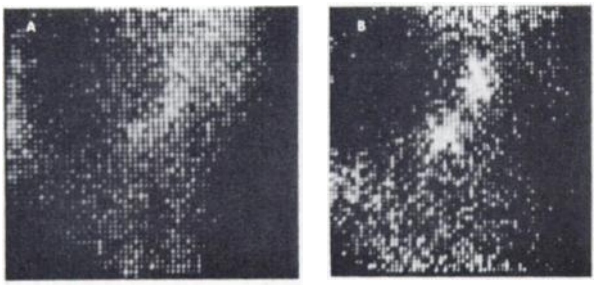

FIG. 2. Parallel-hole posterior images of the canine adrenal medullae at 2 days comparing (A) 1.0 mCi [*p*-^{131}I]IBG (22.1 kg male, Dog 2); and (B) 1.3 mCi [*m*-^{131}I]IBG (21.0 kg female, Dog 4).

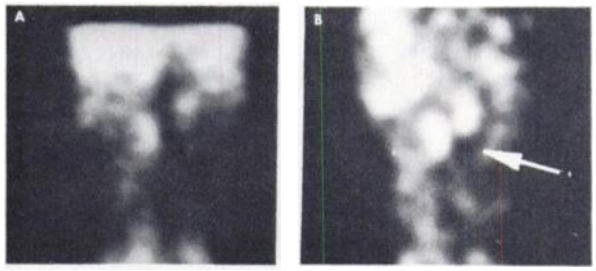

FIG. 3. Posterior images of adrenal medullae, Dog 5, 24 hr after injection of 5 mCi of [*m*-^{123}I]IBG. (A) parallel-hole image; (B) coded-aperture tomogram.

mogenized and fractionated according to a modification of the method of Bartlett and Smith (*4*). This modification, which will be described elsewhere, permitted the fractionation of a small amount of tissue. The following four fractions were obtained: Fraction A, 0–480 g; Fraction B, >100,000 g; Fraction C, 480–12,000 g; and Fraction D, 12,000–100,000 g. Fraction C, the "large granule" fraction, contains chromaffin granules, mitochondria, and lysosomes (*4*).

RESULTS

Dog adrenomedullary imaging study. [*p*-^{131}*I*]*IBG*. Dog 1, injected with [*p*-^{131}I]IBG, failed to give adrenal images at 1 day, but adrenal imaging was successful at 3, 6, and 10 days. Dog 2 gave poorly resolved adrenal images at 2 days (Fig. 2A) due to overlap of liver activity, but gave clearly delineated images at 5 days. Dog 3, scanned only at 2 days, showed a well-resolved right adrenal gland but the left adrenal was obscured by radioactivity in the region of the spleen.

[*m*-^{131}*I*]*IBG*. Posterior images of Dog 4 at 1 day revealed both adrenal medullae; activity in the region of the spleen interfered slightly with the image of the left adrenal. At 2 days, both adrenal medullae were clearly visualized (Fig. 2B). As part of the reserpine displacement study (*vide infra*), three control dogs were injected with 0.55 mCi of [*m*-^{131}I]IBG. All three gave clear adrenomedullary scintiphotos at 3 days (see Fig. 6).

[*m*-^{123}*I*]*IBG*. Planar images of Dog 5 at 1 day revealed both adrenals but the glands were not sharply delineated. A coded-aperture scintiphoto of Dog 5 at 1 day is shown in Fig. 3. Dog 6 gave clear planar images of both adrenal medullae at 1 day, although considerable activity was seen in the liver.

Tissue distribution studies. The distribution of [*m*-^{125}I]IBG in seven selected tissues of the rhesus monkey, at 3 and 48 hr after injection, is summarized in Table 1. The percentages of the injected dose sequestered by the whole adrenal glands of the six monkeys is given in Table 2, along with comparative data for four dogs. [*m*-^{125}I]IBG shows uptake in the whole adrenal of the monkey, like that obtained in dogs at early time intervals (*1*). In Table 1 the concentration ratios for adrenal medulla to nontarget organ are not high at 3 hr, but the 48-hr data, as well as the positive primate-imaging results at 2–5 days (see below), reveal that the initial concentrations of radioiodinated *m*-IBG are maintained in the adrenal medulla at longer times while the radioactivity washes out of nontarget organs.

Monkey adrenomedullary images. [*p*-^{131}*I*]*IBG*. No discernible images of either adrenal were obtained from

TABLE 1. TISSUE CONCENTRATIONS* OF [*m*-^{125}I]IBG IN RHESUS MONKEY

Animal	Time (hr)	Adrenal medulla	Adrenal cortex	Liver	Kidney	Spleen	Muscle	Blood
Monkey 1	3	3.35	0.58	0.80	0.19	0.30	0.02	0.02
Monkey 2	3	3.45	0.50	0.82	0.14	0.23	0.03	0.02
Monkey 3	3	1.28	0.24	0.66	0.11	0.20	0.03	0.02
	3†	2.69	0.44	0.76	0.15	0.24	0.03	0.02
Monkey 4	48	3.37	0.05	0.08	0.02	0.06	0.01	—
Monkey 5	48	1.26	0.03	0.04	0.01	0.03	0.01	—
Monkey 6	48	2.51	0.12	0.10	0.04	0.07	0.01	—
	48†	2.38	0.07	0.07	0.02	0.05	0.01	—

* Concentrations are expressed in % kg dose/g.

† Mean values.

TABLE 2. WHOLE ADRENAL UPTAKE OF [*m*-^{125}I]IBG IN THE RHESUS MONKEY AND DOG*

Animal	Wt. (kg)	Sex	Time (hr)	Wt. of both adrenals (g)	% dose/whole adrenals	% kg dose/g adr. medulla
Monkey	9.0	F	3	0.59	0.083	3.35
Monkey	6.7	F	3	0.50	0.087	3.45
Monkey	5.8	M	3	0.54	0.040	1.28
Monkey	3.8	M	48	0.59	0.082	3.37
Monkey	3.9	M	48	0.38	0.037	1.26
Monkey	4.6	M	48	0.49	0.106	2.38
Dog	18.9	F	2	1.90	0.091	5.77
Dog	20.5	F	2	2.00	0.095	4.40
Dog	21.0	F	48	1.98	0.323	12.54
Dog	22.0	M	48	1.90	0.400	8.37

* All animals were given an intravenous dose of 100 μCi of [*m*-^{125}I]IBG.

three monkeys evaluated at 1, 2, and 7 days after injection.

[*m*-^{123}*I*]*IBG*. Figure 4 shows clear visualization of the adrenal medullae with a parallel-hole collimator 2 days after administration of 1.9 mCi of [*m*-^{123}I]IBG. Radioactivity is also noted in the gastrointestinal tract, which may in part account for the larger image size of the right adrenal medulla.

A second monkey (5.5 kg female) clearly showed the left adrenal at both 1 and 2 days after injection, but the right adrenal image was slightly obscured by radioactivity in the liver region. A third monkey (4.5 kg female) evaluated only at 2 days failed to provide images of either adrenal.

[*m*-^{131}*I*]*IBG*. Two of the three monkeys evaluated gave excellent adrenomedullary images at 3 and 5 or 6 days after injection. Images obtained with the 8.0-kg female at 3 and 6 days are shown in Fig. 5. The third monkey (10.0 kg male) did not give images of either adrenal at 3 and 6 days after injection.

Drug interventions. *Reserpine depletion study.* All three dogs injected with [*m*-^{131}I]IBG and subsequently treated with reserpine failed to give adrenal images at 3 days. In contrast, the three control dogs all provided well-defined adrenal images at 3 days. Representative scans from this experiment are given in Fig. 6.

The adrenomedullary depletion was further confirmed by direct tissue analysis of these six dogs. As detailed in Table 3, reserpine treatment resulted in approximately 90% lowering of the radioactive concentration in the adrenal medullae.

Phenoxybenzamine treatment. Dogs maintained on oral phenoxybenzamine showed no change in their adrenomedullary affinity for [*m*-^{125}I]IBG (Table 4).

Propranolol treatment. Similarly, dogs showed no change in their adrenomedullary concentration of [*m*-^{125}I]IBG (Table 4).

Subcellular distribution study. The adrenomedullary tissue extracted from two dogs, each injected with [*m*-^{125}I]IBG, was used as a representative tissue sample for the determination of the subcellular localization of *m*-IBG. As shown in Table 5, subcellular fractionation of this extract demonstrated that 53.5 ± 10.1% of [*m*-^{125}I]IBG was in the large-granule fraction. Smith and Winkler (*5*) have found that the large-granule fractions from the adrenal medullae of the ox, pig, and horse contain 63, 57, and 53%, respectively, of the catecholamines present in the original homogenates.

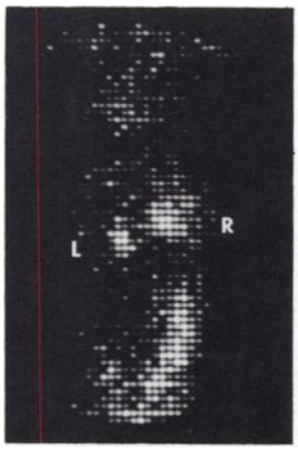

FIG. 4. Parallel-hole posterior image of adrenal medullae in monkey (4.6 kg female) 2 days after injection of 1.9 mCi [*m*-^{123}I]IBG.

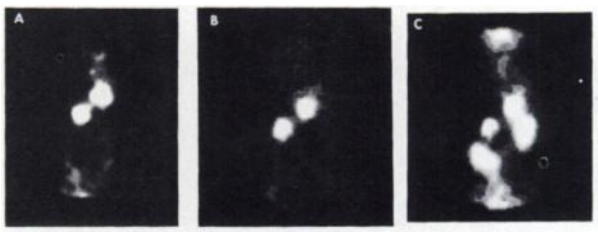

FIG. 5. Parallel-hole posterior images of adrenal medullae in monkey (8.0 kg female). (A) 3 days after injection of 1.0 mCi of [*m*-^{131}I]IBG; (B) 6 days after injection; (C) 6-day adrenal image, superimposed on kidney image (2 mCi of Tc-99m DTPA) in same monkey.

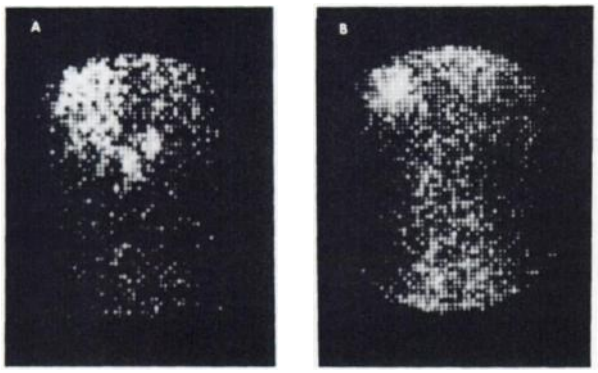

FIG. 6. Parallel-hole posterior images of dog adrenal medullae 3 days after injection of 0.55 mCi [*m*-^{131}I]IBG comparing (A) dog (19.0 kg female) receiving reserpine vehicle i.v. at 1 and 2 days after injection with (B) dog (20.3 kg female) receiving 0.05 mg/kg reserpine i.v. at 1 and 2 days after injection.

DISCUSSION

The superiority of *m*-IBG over *p*-IBG as an adrenomedullary imaging agent is not readily apparent from the tissue distribution data previously reported for dogs (*1*). The concentrations of the two isomers in the adrenal medullae were nearly identical from 0.5–192 hr and both isomers cleared from the blood at the same rapid rate. However, differences do exist between the two isomers: (a) Approximately a 50% lower concentration of radioactivity in the liver was observed with *m*-IBG at all time intervals; and (b) the thyroid radioactivity levels were at least an order of magnitude lower with *m*-IBG. The liver itself is adrenergically innervated (*6*) so the hepatic radioactivity does not necessarily represent metabolites of *p*-IBG or *m*-IBG. However, the higher liver activity accompanying *p*-IBG suggests greater metabolic breakdown of this isomer. It is known that meta-halogenated aromatics are thermodynamically more stable to dehalogenation than the ortho or para isomers (*7*), but few comparative studies of the metabolism of meta- and para-iodinated aromatics have been published (*8*). Based on the thyroid activity levels, *m*-IBG is considerably more resistant to in vivo release of radioiodine than *p*-IBG. Whether this results from different metabolic pathways for the two compounds, or merely reflects their relative in vitro stabilities, is not yet known. Regardless of their metabolic fates, the tissue distribution differences between *p*-IBG and *m*-IBG, although seemingly minor in nature, are a major factor in determining the success of adrenomedullary imaging. This point stresses the need for extremely low radioactivity concentrations in the liver and adjacent organs in order to obtain successful planar images of the adrenal medullae.

The present work raises questions of possible species

TABLE 3. EFFECT OF RESERPINE ON DOG'S ADRENOMEDULLARY UPTAKE OF [*m*-^{131}I]IBG

Treatment*	No. of dogs	Dose (mCi)	Adr. medulla conc.† at 3 days
Control	3	0.55	11.8 (19.1–7.8)
Reserpine	3	0.55	1.5 (1.6–1.5)

* Two groups of three dogs each were given either i.v. reserpine (0.05 mg/kg) or i.v. reserpine vehicle 24 and 48 hr after the [*m*-^{131}I]IBG dose, and then killed at 72 hr.

† Concentration in % kg dose/g.

TABLE 4. EFFECT OF PHENOXYBENZAMINE AND PROPRANOLOL ON DOG'S ADRENOMEDULLARY UPTAKE OF [*m*-^{125}I]IBG

Treatment	No. of dogs	Dose (μCi)	Adr. medulla conc. at 3 days*
Control	5	100	13.0 (20.4–8.6)
Phenoxybenzamine†	3	100	13.0 (18.5–9.5)
Propranolol‡	3	100	13.2 (16.8–10.0)

* Concentration in % kg dose/g.

† Oral phenoxybenzamine (0.25 mg/kg) was given twice a day for 6 days; on Day 3 the dogs were injected with [*m*-^{125}I]IBG, then killed on day 6.

‡ Oral propranolol (2.0 mg/kg) was given twice a day for 6 days; on Day 3 the dogs were injected with [*m*-^{125}I]IBG, then killed on day 6.

TABLE 5. SUBCELLULAR DISTRIBUTION OF [*m*-^{125}I]IBG IN DOG'S ADRENAL MEDULLA*

Fraction	Description (g)	Total [*m*-^{125}I]IBG† pmol	% distribution‡
A	0–480	19.5 ± 7.1	18.9 ± 2.3
B	>100,000	15.7 ± 9.2	14.3 ± 5.3
C	480–12,000	51.6 ± 10.1	53.5 ± 10.1
D	12,000–100,000	14.3 ± 6.9	13.3 ± 3.1

* Two dogs were injected each with 100 μCi of [*m*-^{125}I]IBG and killed 3 days later by i.v. injection of sodium pentobarbital. The adrenal medulla was extracted and fractioned as described in Materials and Methods. The results are expressed as mean and standard deviation of three separate trials (six dogs total).

† Total I-125-IBG was calculated assuming the specific activity of injected compound to be 1.20 mCi/mg.

‡ Percent distribution was calculated from the total pmol of [*m*-^{125}I]IBG recovered in the four fractions.

differences in the sequestration of *m*-IBG. When calculated in % dose/organ (Table 2), the uptake of *m*-IBG in the monkey adrenal at 3 hr, though consistently lower, is nonetheless similar to that obtained in the dog. However, when the adrenomedullary uptake is determined on a concentration basis (% kg dose/g), the difference between the two species is magnified: The monkey adrenomedullary uptake is at best 3–4% at 3 and 48 hr (Table 2), whereas the canine mean adrenomedullary concentration is 5.1% at 2 hr and 10.5% at 48 hr. The total amount of catecholamines in the adrenal gland, as well as the ratio of epinephrine to norepinephrine, varies widely from species to species (*9*). West (*10*) found the combined epinephrine-to-norepinephrine concentration in the whole adrenal to be higher in the dog (1500 μg/g) than in the rhesus monkey (330 μg/g). If these values are a rough indication of the relative catecholamine storage capacities of the adrenal medullae in the two species, the higher concentrations of *m*-IBG observed in the dog adrenal medullae are understandable. The difference in catecholamine concentrations between dog and monkey appears even more pronounced in view of the higher volume ratio for adrenal cortex-to-adrenal medulla (AC:AM) found in the dog; i.e., the adrenal medulla is proportionately smaller in the dog. This latter observation is based on a direct visual comparison in our laboratory of frozen sections of the whole adrenals of the animals reported in Table 2. The extensive study by Baker (*11*) on the anatomy of the canine adrenal gland has shown that the AC:AM for the dog is approximately 5. Similar data on the rhesus monkey are not available (*12,13*). However, our observations, though limited to only twelve adrenal glands from six monkeys, reveal that the AC:AM is consistently below 3. For the sake of perspective, it should be noted that the epinephrine-norepinephrine concentration in the human adrenal gland is approximately 600 μg/g (*14*) and the AC:AM is around 9 (*15*).

Reserpine is used as a pharmacological tool to block selectively the uptake of norepinephrine into storage vesicles of adrenergic nerves (*16*). Its ability to produce long-term depletion of norepinephrine in the heart has been well documented (*17,18*). Reserpine has also been shown to cause loss of norepinephrine from the adrenal glands of the rat (*19*), cat (*20*), and rabbit (*21*). More specifically, Carlsson and coworkers have shown that reserpine inhibits the uptake of norepinephrine by chromaffin granules of the adrenal medulla (*22*). The marked depletion of the [*m*-^{131}I]IBG content of the dog adrenal medulla by reserpine reported in this work suggests that norepinephrine and *m*-IBG share a common storage mechanism in the adrenal medulla. In addition to its mechanistic implications, the reserpine depletion study may find clinical application, since this drug could possibly be administered to patients after [*m*-^{131}I]IBG imaging procedures are complete, so as to lower the radiation dose to the adrenal gland.

Further evidence for the sequestration of *m*-IBG within the chromaffin storage granules has been obtained from subcellular fractionation of the dog adrenal medullae (Table 5). To our knowledge there is no information in the literature concerning the subcellular distribution of catecholamines in the canine adrenal medulla. However, the percentage of *m*-IBG found in the large-granule fraction—the one containing the chromaffin granules—is within the range of values reported for other large mammals (*5*).

Patients suffering from an adrenomedullary disease, such as pheochromocytoma, are often given α-adrenergic blocking drugs (*23*). The α-blocker controls the hypertensive episodes caused by sporadic release of large amounts of catecholamine from the tumor. Iversen and coworkers have shown that phenoxybenzamine blocks both neuronal and extraneuronal uptake of [^{3}H]norepinephrine in the isolated rat heart (*24*). A 30% lowering of the in vivo heart uptake of [^{3}H]guanethidine in the rat heart by pretreatment with phenoxybenzamine has been reported by Brodie et al. (*25*). Evidence for the possible effect of α-blockers on guanethidine or aralkylguanidine uptake in the adrenal medulla is lacking. Although unlikely based on mechanistic considerations, the possibility exists that phenoxybenzamine might at least indirectly affect the storage of *m*-IBG in the adrenal medulla or adrenomedullary tumors, thus precluding its future use with pheochromocytoma patients. However, the results in Table 4 show that *m*-IBG uptake in the dog adrenal medulla is not altered by pharmacological doses of phenoxybenzamine. The β-adrenergic blocking agent propranolol is also sometimes used in the management of tachycardia and arrhythmias in patients with pheochromocytomas (*23*). Again, however, as shown in Table 4, dogs maintained on oral propranolol did not show a change in their adrenomedullary uptake of *m*-IBG.

The fact that radioiodinated *m*-IBG failed to produce definite adrenomedullary images in two of the six monkeys evaluated should not necessarily be construed as a limitation. The tissue distribution data previously reported in dogs (*1*), and reported here in monkeys, show considerable variation in adrenomedullary uptake of *m*-IBG. Considerable intraspecies variation in amine content of the adrenal medulla has been observed in some mammals (*26–28*). Thus the focus should not be on image quality per se but on the possible underlying adrenergic physiology or pathology responsible for the observed variation in percentage uptake of *m*-IBG among individuals. If *m*-IBG is to be a dynamic indicator of norepinephrine storage in adrenergically innervated tissues then the emphasis should be on quantitation of the initial organ concentration of *m*-IBG and its subsequent rate of turnover. Factors that could possibly alter the uptake and turnover of *m*-IBG in the adrenal me-

dulla, such as plasma norepinephrine levels and various stresses, are under study.

The present paper should serve to stimulate an evaluation of the clinical utility of radioiodinated *m*-IBG as a diagnostic agent for adrenomedullary diseases. In addition, our recent use of radioiodinated *m*-IBG to image the primate heart (*29,30*) serves to stress the possible broad-spectrum application of this radiodiagnostic agent to the scintigraphic evaluation of other adrenergically innervated organs and tissues.

FOOTNOTES

* Serpasil, CIBA Geigy Corp., Summit, NJ.

† Dibenzyline, Smith, Kline and French, Philadelphia, PA.

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REFERENCES

1. WIELAND DM, WU JL, BROWN LE, et al: Radiolabeled adrenergic neuron blocking agents: Adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 21:349-353, 1980
2. KIRSCHNER AS, ICE RD, BEIERWALTES WH: Reply. *J Nucl Med* 16:248-249, 1975 (Letter to the Editor)
3. ROGERS WL, KORAL KF, MAYANS R, et al: Coded-aperture imaging of the heart. *J Nucl Med* 21:371-378, 1980
4. BARTLETT SF, SMITH AD: Adrenal chromaffin granules: Isolation and disassembly. *Meth Enzymol* 31:379-389, 1974
5. SMITH AD, WINKLER H: A simple method for the isolation of adrenal chromaffin granules on a large scale. *Biochem J* 103:480-482, 1967
6. ANTON AH, SAYRE DF: The distribution of dopamine and dopa in various animals and a method for their determination in diverse biological material. *J Pharmacol Exp Ther* 145: 326-336, 1964
7. BRAENDLIN HP, MCBEE ET: Halogenation. In *Friedel-Crafts and Related Reactions*. Vol. III, Pt. 2, Olah GA, Ed. New York, Interscience, 1964, pp 1517-1593
8. SHUM YY: Metabolism of iodo-compounds. Ph.D. Thesis, University of Michigan, 1977, pp 1-29
9. HOLZBAUER M, SHARMAN DF: The distribution of catecholamines in vertebrates. In *Handbook of Experimental Pharmacology*. Vol. XXXIII, *Catecholamines*. Blaschko H, Muscholl E, Eds. New York, Springer-Verlag, 1972, pp 120-185
10. WEST GB: The comparative pharmacology of the suprarenal medulla. *Quart Rev Biol* 30:116-137, 1955
11. BAKER DD: Studies of the suprarenal glands of dogs. I. Comparison of the weights of suprarenal glands of mature and immature male and female dogs. *Am J Anat* 60:231-252, 1937
12. INAY M, RUCH TC, FINAN S, et al: The endocrine weights of primates. *Endocrinology* 27:58-67, 1940
13. KENNARD MA, WILLNER MD: Findings in 216 routine autopsies of *Macaca mulatta*. *Endocrinology* 28:955-966, 1941
14. GOODALL McC: Studies of adrenaline and noradrenaline in mammalian heart and suprarenals. *Acta Physiol Scand* 24: Suppl 85, 7-51, 1951
15. QUINAN C, BERGER AA: Observations on human adrenals with especial reference to the relative weight of the normal medulla. *Ann Intern Med* 6:1180-1192, 1933
16. MAXWELL RA, FERRIS RM, BURCSU JE: Structural requirements for inhibition of noradrenaline uptake by phenethylamine derivatives, desipramine, cocaine, and other compounds. In *The Mechanism of Neuronal and Extraneuronal Transport of Catecholamines*. Paton DM, Ed. Raven Press, New York, 1976, pp 95-153
17. CHIDSEY CA, BRAUNWALD E, MORROW AG, et al: Myocardial norepinephrine concentration in man. Effects of reserpine and of congestive heart failure. *N Engl J Med* 269:653-658, 1963
18. CAMPOS HA, SHIDEMAN FE: Subcellular distribution of catecholamines in the dog heart. Effects of reserpine and norepinephrine administration. *Int J Neuropharmacol* 1: 13-22, 1962
19. CALLINGHAM BA, MANN M: Depletion and replacement of the adrenaline and noradrenaline contents of the rat adrenal gland following treatment with reserpine. *Br J Pharmacol* 18:138-149, 1962
20. HOLZBAUER M, VOGT M: Depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat. *J Neurochem* 1:8-11, 1956
21. TAKETOMO Y, SHORE PA, TOMICH EG, et al: Studies on the mechanism of reserpine-induced epinephrine release and hyperglycemia. *J Pharmacol Exp Ther* 119:188, 1957 (abst)
22. CARLSSON A, HILLARP NA, WALDECK B: Analysis of the Mg^{++}-ATP dependent storage mechanism in the amine granules of the adrenal medulla. *Acta Physiol Scand* 59(215):5-38, 1963
23. MANGER WM, GIFFORD RW, JR: *Pheochromocytoma*. New York, Springer-Verlag, 1977, pp 307-311
24. IVERSEN LL, SALT PH, WILSON HA: Inhibition of catecholamine uptake in the isolated rat heart by haloalkylamines related to phenoxybenzamine. *Br J Pharmacol* 46:647-657, 1972
25. BRODIE BB, CHANG CC, COSTA E: On the mechanism of action of guanethidine and bretylium. *Br J Pharmacol* 25: 171-178, 1965
26. MCKINNEY TD, BALDWIN DM, GILES RH, JR: Effects of differential grouping on adrenal catecholamines in the cottontail rabbit. *Physiol Zool* 43:55-59, 1970
27. BUTTERWORTH KR, MANN M: The percentage of noradrenaline in the adrenal glands of litter-mate cats. *J Physiol (Lond)* 162:473-484, 1962
28. VON EULER US: Chromaffin cell hormones. In *Comparative Endocrinology*. Vol. 2, von Euler US, Heller H, Eds. New York, Academic Press, 1963 pp 258-290
29. WIELAND DM, BROWN LE, ROGERS WL, et al: Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 22:22-31, 1981
30. KLINE RC, SWANSON DP, WIELAND DM, et al: Myocardial imaging in man with ^{123}I-meta-iodobenzylguanidine. *J Nucl Med* 22:129-132, 1981