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# Alterations of Iodine-131 MIBG Biodistribution in an Anephric Patient: Comparison to Normal and Impaired Renal Function

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Iodine-131 metaiodobenzylguanidine (MIBG) is an effective agent for the scintigraphic portrayal of pheochromocytomas of all types. Iodine-131 MIBG is a relatively stable radiopharmaceutical that is primarily excreted in the urine. Therefore, impaired renal function would be expected to alter [<sup>131</sup>I]MIBG pharmacokinetics which would thus affect blood levels, as well as scintigraphy. An 18-yr-old anephric male presented with hypertension and suspected pheochromocytoma. We have compared the [<sup>131</sup>I]MIBG scintigraphy and blood clearance kinetics in this anephric patient, two patients with renal insufficiency and four patients with normal renal function. The degree of renal insufficiency was directly correlated to the CPM/image (an index of whole-body retention) on all 3 days of imaging and the slower clearance of radioactivity from the blood. The relative distribution of radioactivity between the plasma and cell fractions was greatest in the patients with renal insufficiency. We therefore suggest that attention be paid to plasma creatinine levels prior to the administration of [<sup>131</sup>I]MIBG to permit accurate interpretation of scintigraphy. In addition, the effect of renal insufficiency on radiation dosimetry should be considered. It may thus be prudent to reduce the administered dose of [<sup>131</sup>I]MIBG given to anephric or renally insufficient patients to decrease radiation dose.

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Iodine-131 metaiodobenzylguanidine ([<sup>131</sup>I]MIBG) is a sympho-adrenal avid radiopharmaceutical which is safe and efficacious in the location of pheochromocytomas of all types (1,2), including primary adrenal and extraadrenal lesions (1,3,4), familial pheochromocytomas, (5,6) and metastatic disease (7).

Animal (8,9) and human (10,11,12,13) *in vivo* experiments and tissue culture studies (14-16) all suggest that [<sup>131</sup>I]MIBG enters sympho-adrenal tissue primarily by the active sodium- and energy-dependent, high affinity, low capacity "Type I" uptake mechanism (13, 16,17). There appears to be competition for uptake of MIBG and norepinephrine (14,15). In addition, both MIBG and norepinephrine also enter sympho-adrenal

tissues by a sodium-independent, low affinity, high capacity, passive diffusion mechanism (13,16,17). Following entry into the cell MIBG is sequestered in the secretory granules (8,9). The retention of the tracer in sympathetic tissues is more prolonged than that in other organs, probably because of storage in the granules. Thus, the target-to-background of most pheochromocytomas tends to increase over the 3 days of imaging (1,10). Even large pheochromocytomas seldom take up more than a few percent of the administered dose (2,3, 18). Following the administration of an *i.v.* dose of [<sup>131</sup>I]MIBG, the tracer is rapidly cleared from the blood (12,19). The majority of the [<sup>131</sup>I]MIBG is excreted unchanged in the urine, with 40-55% appearing in 1 day and 70-90% by the fifth day (3,20). A small component (4-22%) is metabolized to [<sup>131</sup>I]metaiodohippuric acid, [<sup>131</sup>I]metaiodobenzoic acid and deiodinated. The metabolites and free <sup>131</sup>I iodide appear in the urine where they can be identified by high perform-

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ance liquid chromatography (20). Therefore, impaired renal function may have significant effects upon the pharmacodynamics and biodistribution of [<sup>131</sup>I]MIBG.

To examine this hypothesis we compared [<sup>131</sup>I]MIBG scintigraphy and blood clearance kinetics in an anephric patient, two patients with renal insufficiency, and four patients with normal renal function who were referred for known or suspected pheochromocytoma.

### Case Report

The patient was an 18-yr-old white male with a long standing history of chronic renal failure due to urethral valves with obstructive nephropathy. At the age of 13 mo, he underwent an ileal loop urinary diversion and remained normotensive up to age 17 yr. After this time significant hypertension was documented (peak measurement 182/124 mmHg). Blood pressure control was suboptimal despite therapy with hydralazine and propranolol. Renal function continued to deteriorate and he was started on chronic hemodialysis. In preparation for possible renal transplant, bilateral nephrectomies and excision of the ileal loop were performed 3 mo following the institution of hemodialysis. During surgery there were no major changes in blood pressure, nor was there any evidence during the abdominal exploration of pheochromocytomas or paragangliomas. In the weeks following the surgery progressive and severe hypertension developed, reaching values as high as 220/150 mmHg. In seeking a cause for this accelerated hypertension, plasma catecholamines were found to be elevated (epinephrine 1800 pg/ml and 1000 pg/ml [normal < 200 pg/ml] and norepinephrine 13,000 pg/ml and 15,400 pg/ml [normal 500–2,000 pg/ml]). The assay used was a radioimmunoassay which measures both free and conjugated catecholamines. Blood pressure was then controlled by a combination of phenoxybenzamine, propranolol, and minoxidil. Abdominal and pelvic ultrasound were negative as were thoracic, abdominal, and pelvic angiography. Selective catheterization of the left adrenal artery was, however, not possible. Because of the possibility that the patient harbored a pheochromocytoma despite the negative localizing procedures, he was referred for [<sup>131</sup>I]MIBG scintigraphy. At this time he was undergoing thrice weekly hemodialysis.

When examined the patient showed evidence for growth and developmental delay, no neurofibromata, mucosal ganglioneuromata, cafe au lait spots or medullated corneal nerves. The thyroid was impalpable. Supine blood pressure was 110/70 mmHg and the pulse rate 80/min. There was grade III hypertensive retinopathy. There was a patent arteriovenous shunt in the left forearm. On the day of [<sup>131</sup>I]MIBG injection, blood urea nitrogen (BUN) was 35 mg/dl and serum creatinine was 9.1 mg/dl.

The findings in this patient were compared with two patients having mild to moderate renal insufficiency due to SLE leading to renal hypertension in one (BUN 64 mg/dl, creatinine 3.7 mg/dl) and malignant metastatic pheochromocytoma with hypertensive nephropathy in the other (BUN 28 mg/dl, creatinine 2.4 mg/dl). Comparison was also made with four patients with normal renal function. These patients were eventually shown to have metastatic neuroblastoma, sporadic malignant pheochromocytoma, multiple endocrine neoplasia type 2A with malignant pheochromocytoma, and essential

hypertension. Serum creatinines ranged from 0.8–1.3 mg/dl and BUN 12–20 mg/dl.

### MATERIALS AND METHODS

Renal function was evaluated by measuring serum creatinine and blood urea nitrogen. Standard clinical laboratory assays were used for these measurements.

The patients were injected intravenously with ~0.5 mCi [<sup>131</sup>I]MIBG. The nonradiolabeled MIBG was synthesized by the method of Wieland et al. (21), and [<sup>131</sup>I]MIBG was prepared at a specific activity of 1.5 to 2.3 Ci/mmol using an iodide exchange technique (22). Overlapping views of the head, neck, chest, abdomen, and pelvis were obtained using a large field-of-view gamma camera equipped with a high-energy, parallel-hole collimator and interfaced to a dedicated minicomputer. Images were obtained at 1, 2, and 3 days after tracer injection, each image being accumulated for 100,000 counts (1,10). Images were recorded as analog scintigrams on film and also stored in the computer for digital presentation and quantification. Orientation was provided by surface markers.

Blood was sampled for catecholamines via an indwelling needle which was left in position for at least 30 min to exclude the stress of venipuncture, the patient having been fasted overnight and remaining in the supine position. Blood was drawn into prechilled tubes containing EGTA and glutathione and kept on ice until the plasma was separated within 30 min of drawing. Samples were then frozen at –30°C until assay. Epinephrine and norepinephrine were assayed by the radioenzymatic assay of Peuler and Johnston (23).

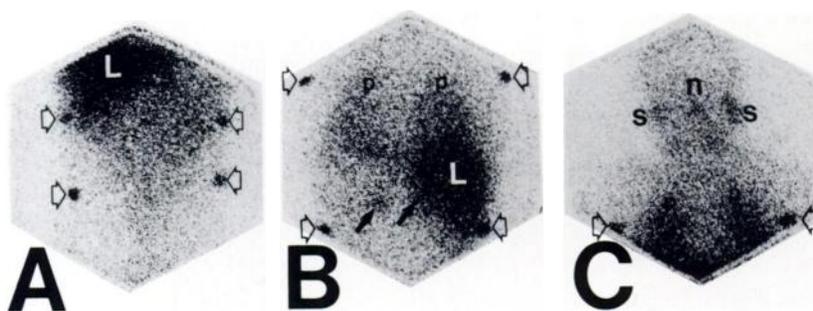
Following injection of the tracer dose of [<sup>131</sup>I]MIBG, blood samples were drawn from an indwelling cannula in the opposite arm; the patency of the cannula was maintained with heparinized saline (500 μ/ml). Samples were drawn at 2, 5, 15, 30, 50, 60, 90 min and 2, 3, 6, 24, 48, and 72 hr, and in the anephric patient, before and after two hemodialyses. Blood samples for radioactivity were drawn into tubes containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant, kept on ice until the plasma was separated from red cells in a cold centrifuge (within 40 min). Aliquots (0.5 ml) of plasma and red cells were counted in an autogamma counter and the results corrected for radioactive decay. The total activity and its distribution between plasma and red cell fractions were plotted. The data were presented in log/log format to linearize the control data and spread out the data points from the early frequent sampling phase of the study. The blood self-irradiation absorbed dose was calculated (24) from the activity measured in the serial blood samples.

### RESULTS

Figures 1 and 2 demonstrate the normal uptake of [<sup>131</sup>I]MIBG in the salivary glands, nasopharynx, liver, and spleen of the anephric patient. The lung and general backgrounds were higher than usual and the adrenal uptake more prominent than usually observed, probably as a consequence of higher and more sustained circulating levels of [<sup>131</sup>I]MIBG. Due to the anephric

### FIGURE 1

Scintigrams 24 hr after 0.5 mCi [<sup>131</sup>I] MIBG in the anephric patient. (A) anterior abdomen/pelvis. (B) Posterior chest/abdomen. (C) Anterior head/chest. The following abbreviations are used: L: liver; P: lung; S: salivary gland, N: nasopharynx, open arrows indicate surface markers. Note the increased background, especially in the lungs, the intense adrenal medullary uptake (solid arrows) and the absence of bladder activity.



state no bladder activity is seen. On the posterior views the anephric patient demonstrated a higher count rate than other subjects studied and this difference increased from Day 1 through 3 (Table 1). In the patient with moderate renal insufficiency the results were similar but with lower absolute count rates. This pattern of findings was also observed in the anterior head/neck and anterior pelvis/abdomen. These count rates are an index of whole-body tracer retention. The count rates were also higher in the patients with impaired renal function when compared to those with normal renal function despite the fact that the latter included three with intense focal uptake by various tumors.

Careful review of the patient's history, physical examination, and biochemistry led us to conclude that the anephric patient almost certainly did not harbor a pheochromocytoma. The symmetric uptake by [<sup>131</sup>I] MIBG in the adrenals can readily be explained by the alteration of [<sup>131</sup>I]MIBG kinetics and the greater amount of [<sup>131</sup>I]MIBG available for adrenal uptake.

The clearance of [<sup>131</sup>I]MIBG radioactivity from the blood of the anephric patient was most unusual in that after an initial fall (which was slower than that observed in patients with intact renal function) (Fig. 3), there was a secondary rise in the blood radioactivity. There was either no or only slight decrease in blood radioactivity following the two hemodialyses (Fig. 3). In patients with moderate and mild renal impairment the total blood activity fell more slowly than in patients with normal renal function. The correlation of blood radioactivity on Days 1, 2, and 3 with the serum creatinine was significant ( $p = 0.001$ ) (Table 2).

The distribution of radioactivity between the plasma

and red cell fractions in patients with renal failure was unusual in that a higher than normally observed fraction of the activity was present in the plasma when compared to that observed in patients with normal renal function (Fig. 4 and Table 3). This was also significantly correlated to serum creatinine (Table 2).

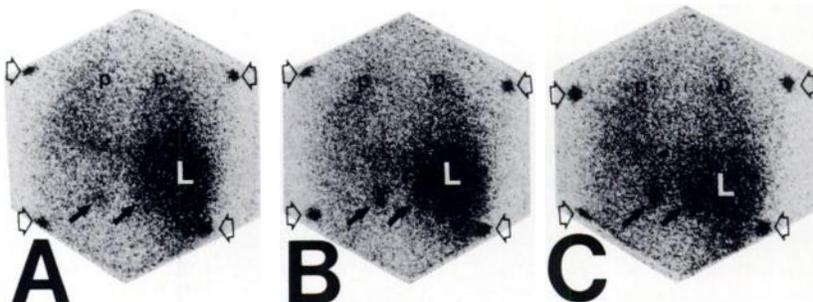
The absorbed radiation dose to the blood was calculated to be 2170 mrem in the anephric patient, 190 mrem in the patient with moderate renal insufficiency and averaged  $70 \pm 20$  mrem in the patients with normal renal function.

### DISCUSSION

The elevated catecholamines are best interpreted as follows: chronic renal failure may result in elevation of catecholamines. This is usually a twofold increase above normal (25,26) and may be a consequence of decreased renal clearance and/or diminished uptake by sympathetic nerve terminals (25-27). Depleted volume status due to dialysis may result in hypovolemia (28,29) and thus provoke sympathetic neuronal discharge of catecholamines. The much higher values obtained on samples as measured by radioimmunoassay may in part be explained by the mechanisms advanced above; other contributions may result from assay interference due to substances which accumulate in uremia. Finally, there is evidence that the radioimmunoassay cross-reacts with metanephrine and normetanephrine and, as a significant fraction of these metabolites are excreted by the kidney, accumulation may occur in an anephric patient (it was unfortunately not possible to assay the patient's plasma specifically for metanephrines). As renal failure

### FIGURE 2

Posterior abdomen/chest scintigrams in the anephric patient. A: 24 hr. B: 48 hr. C: 72 hr. L: liver, P: lung uptake, open arrows indicate surface markers. Note the increased pulmonary uptake and the intense and persistent adrenal medullary uptake (solid arrows).



**TABLE 1**  
Administered Doses and Count Rates in Study Subjects

| Patient no.                    | Injected dose<br>mCi (MBq) <sup>5</sup> | Counts/min/view (posterior abdomen) <sup>†</sup> |               |               |
|--------------------------------|---|--|---------------|---------------|
|                                |   | Day 1  | Day 2         | Day 3         |
| 1 Anephric                     | 0.520 (19.24)                           | 32,154   | 29,761        | 23,696        |
| 2 Moderate renal insufficiency | 0.486 (17.98)                           | 18,348   | 13,423        | 9,588         |
| 3 Mild renal insufficiency     | 0.487 (18.02)                           | 18,484   | 10,515        | 5,467         |
| 4-7 Normal renal function*     | 0.512 ± .017 (18.94 ± .641)             | 11,258 ± (1,634)                                 | 6,199 ± 1,946 | 4,918 ± 1,266 |

<sup>†</sup> Counts uncorrected for radioactive decay.

\* Mean ± s.d.

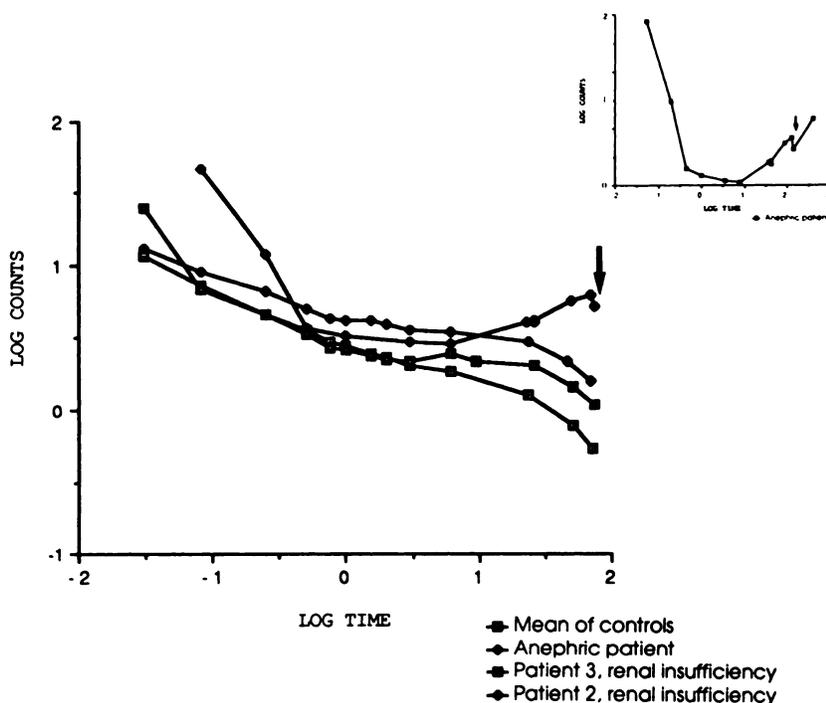
is often accompanied by hypertension resulting from a variety of mechanisms, the possibility of pheochromocytoma may be raised and the interpretation of plasma catecholamines require considerable caution (25-28).

As anticipated by the data on the metabolic clearance of [<sup>131</sup>I]MIBG (12,19,20) renal insufficiency markedly altered the biodistribution and kinetics of the radiopharmaceutical. The anephric patient demonstrated slow [<sup>131</sup>I]MIBG clearance with persistently high count rates on all images obtained at 24, 48, and 72 hr and slower clearance of radioactivity from the blood in the immediate postinjection period (to 6 hr). This is in contrast with data from the four subjects with normal renal function, and with previously published clearance rates (10,19,20). The anephric patient was dialyzed on two occasions following the injection of [<sup>131</sup>I]MIBG. On the first there was no change in the blood levels of radioactivity and on the second only a slight fall. Despite the fact that [<sup>131</sup>I]MIBG is a relatively small molecule it was not cleared by dialysis; the tracer may be

associated with serum proteins or other components (a significant fraction was within the red blood cells).

Iodine-131 MIBG uptake by tissues appears to have two components; namely, specific type 1 uptake by sympatho-adrenal tissue and nonspecific passive uptake into tissues such as the lung. The type 1 uptake and subsequent granule storage tends to be prolonged, while the nonspecific uptake is of shorter duration (13,17). The mobilization of [<sup>131</sup>I]MIBG from sites of nonspecific uptake (in the absence of a renal route of excretion) may account for the rising blood radioactivity of the anephric patient. This was not observed in patients with adequate renal function presumably due to the rapid urinary excretion of [<sup>131</sup>I]MIBG and its metabolites. Whole-body retention and blood radioactivity clearance were closely related to renal function as gauged by serum creatinine levels (Table 2).

The distribution of [<sup>131</sup>I]MIBG activity between the plasma and red cells in the anephric patient and patients with renal insufficiency was unusual in that a relatively



**FIGURE 3**  
Total blood radioactivity (log counts) plotted against log time (hr) for the anephric patient, the patients with impaired renal function and the mean values for the patients with normal renal function (controls). The inset shows the data for the anephric patient extended to 192 hr postinjection. Note the values for the anephric patient and Patient 2 who had moderate renal impairment are higher than the controls at all time points. A secondary rise is present in the anephric patient. The arrows indicate the time of hemodialysis which resulted in a small fall in blood radioactivity.

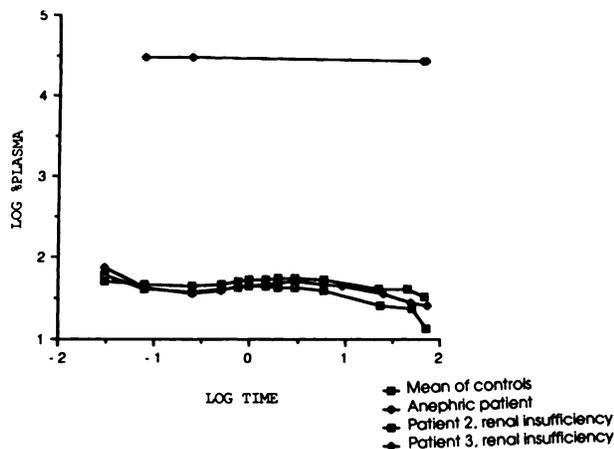
**TABLE 2**  
 Linear Correlation Coefficients Between Parameters of Renal Function (Creatine + BUN) and Blood Clearance, Plasma to Cell Distribution, and Counts per Image\*

| Renal function test | [ <sup>131</sup> I]MIBG parameter          | Coefficient of correlation <sup>†</sup> | Significance (p) |
|---------------------|--|---|------------------|
| 1 Creatinine        | Counts/posterior abdomen view/min<br>Day 1 | 0.978                                   | <0.001           |
| 2 Creatinine        | Counts/posterior abdomen view/min<br>Day 2 | 0.992                                   | <0.001           |
| 3 Creatinine        | Counts/posterior abdomen view/min<br>Day 3 | 0.984                                   | <0.001           |
| 4 BUN               | Counts/posterior abdomen view/min<br>Day 1 | 0.046                                   | N.S.             |
| 5 BUN               | Counts/posterior abdomen view/min<br>Day 2 | 0.473                                   | N.S.             |
| 6 BUN               | Counts/posterior abdomen view/min<br>Day 3 | 0.411                                   | N.S.             |
| 7 Creatinine        | Blood activity<br>Day 1                    | 0.944                                   | 0.001            |
| 8 Creatinine        | Blood activity<br>Day 2                    | 0.981                                   | <0.001           |
| 9 Creatinine        | Blood activity<br>Day 3                    | 0.974                                   | <0.001           |
| 10 BUN              | Blood activity<br>Day 1                    | 0.693                                   | N.S.             |
| 11 BUN              | Blood activity<br>Day 2                    | 0.457                                   | N.S.             |
| 12 BUN              | Blood activity<br>Day 3                    | 0.364                                   | N.S.             |
| 13 Creatinine       | % Radioactivity in plasma<br>Day 3         | 0.991                                   | <0.001           |
| 14 BUN              | % Radioactivity in plasma<br>Day 3         | 0.419                                   | N.S.             |

\* Counts per image being an index for whole-body retention of tracer.

† Linear correlation coefficient derived from the plotting of data from all seven patients.

large proportion was present in the plasma fraction relative to the red cell fraction (30,31). This may be due, in part, to the anemia and low hematocrit of patients in renal failure, but alterations in red cell



**FIGURE 4**  
 The log % plasma radioactivity plotted against log time (hr) for the anephric patient, the patients with impaired renal function and the mean values for the patients with normal renal function (controls). Note the % plasma activity is greatest in the anephric patient. For patients with moderate and mild renal insufficiency the values are only slightly greater than controls.

membranes or intracellular components cannot as yet be excluded. This may make available a larger amount of MIBG for uptake in other tissues (e.g., the adrenal medullae).

The prominent uptake by the normal adrenal medullae of the anephric patient may have resulted from the higher levels of tracer presented to these organs. High doses of [<sup>131</sup>I]MIBG (5mCi) or [<sup>123</sup>I]MIBG will clearly depict normal adrenal medullae with normal renal function (18,32). The high blood levels of [<sup>131</sup>I]MIBG and its slow clearance from the circulation in renal insufficiency thus results in adrenal depiction similar to that achieved by the administration of larger doses of [<sup>131</sup>I]MIBG in patients with normal renal func-

**TABLE 3**  
 Distribution of Activity Between Plasma and Red Cells (Day 3)

| Patient no.                            | % Distribution |             |
|--|----------------|-------------|
|  | Plasma         | Cells       |
| 1 Anephric                             | 88.66          | 11.34       |
| 2 Moderate renal insufficiency         | 32.43          | 67.57       |
| 3 Mild renal insufficiency             | 25.30          | 74.70       |
| 4-7 Normal renal function <sup>†</sup> | 15.54 ± 3.9    | 84.46 ± 3.9 |

<sup>†</sup> Mean ± s.d.

tion. The slow clearance of background activity may make delayed imaging, beyond the usual 72 hr, helpful in revealing subtle lesions in patients with renal insufficiency. In the anephric patient there did not appear to be an increase in the colonic route of excretion. Influences on the scintigraphic findings need to be considered in the interpretation of the images in the face of renal insufficiency.

The altered clearance of [<sup>131</sup>I]MIBG in the anephric state and in renal insufficiency results in an increased absorbed radiation dose to the blood (33). Although increased dosimetry was only calculated for the blood the whole-body and other organ radiation exposure (including the gonads) would also undoubtedly be increased as is evidenced by the increased count rates observed in these subjects. It may thus be prudent to reduce the administered dose of [<sup>131</sup>I]MIBG given to anephric or renally insufficient patients. The use of [<sup>123</sup>I]MIBG might also help to reduce absorbed radiation doses (32).

## CONCLUSION

The study of [<sup>131</sup>I]MIBG biodistribution in an anephric patient and two patients with renal insufficiency has provided an "experiment of nature" which has elucidated aspects of [<sup>131</sup>I]MIBG metabolism which might not otherwise have been possible. The alteration in biodistribution in the face of renal disease must be considered in the interpretation of [<sup>131</sup>I]MIBG scintigraphy and in the radiation dosimetry.

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