Limited Significance of Asymmetric Adrenal Visualization on Dexamethasone-Suppression Scintigraphy

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To assess whether a single measurement of the adrenal uptake of 6β-[^{131}I]-iodomethylnorcholesterol (NP-59) on constant dexamethasone suppression would allow discrimination of adenoma from normal and bilateral hyperplasia, the adrenal uptake of 6β-[^{131}I]iodomethylnorcholesterol (NP-59) was determined in 50 patients with primary aldosteronism (30 adenoma, 20 hyperplasia) and in 13 with hyperandrogenism (six adenoma, seven hyperplasia). Bilateral adrenal NP-59 activity at 5 days was seen in 14 of 36 patients with adenoma (normal to adenoma ratio of ≥0.5), whereas marked asymmetric uptake of NP-59 was seen in six of 27 patients with hyperplasia (uptake ratio of ≤0.5). Thus the level of adrenal NP-59 uptake does not alone serve to distinguish either adenoma from the normal, contralateral adrenal or the adrenal glands in bilateral hyperplasia in all cases. It appears that the pattern of adrenal imaging, early unilateral or early bilateral NP-59 activity (<5 days after NP-59 on 4 mg dexamethasone), best serves to separate adrenal adenoma from bilateral hyperplasia.

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Scintigraphic localization of the adrenal cortex has provided important diagnostic information in the identification of abnormal adrenal-gland function (*1–4*). Early investigations depended upon the existence of sufficient asymmetry of adrenal iodocholesterol uptake to distinguish adenoma from hyperplasia in both primary aldosteronism (PA) and adrenal hyperandrogenism (AH) (*1,2*). In many instances, the qualitative evaluation of the adrenocortical accumulation of iodocholesterol was not sufficient to determine which adrenal if either, was "hotter" than the other (*1–3*). Modification of the procedure to include dexamethasone suppression (DS) of pituitary adrenocorticotrophic hormone (ACTH) was a further refinement in the evaluation of patients with PA and AH (*5,6*). Improved localization was reported but it was also recognized that the normal adrenal cortex would accumulate sufficient iodocholesterol to image "late" after tracer administration (*4–8*). With the introduction of 6β-[^{131}I]iodomethylnorcholesterol (NP-59), an agent demonstrating significantly greater avidity for the adrenal cortex than its predecessor, 19-iodocholesterol—earlier and better-defined images of the adrenals were obtained (*9,10*). It was also noted, however, in studies using NP-59 that the normal adrenal cortex would also image while on DS (*9–11*).

Recent studies have indicated that the magnitude of the adrenal uptake of iodocholesterol reflects the function of the adrenal cortex in patients with PA and AH (*12,13*). Measurements of adrenal uptake were used in the following study to assess whether the presence and degree of adrenal uptake asymmetry could be used to discriminate adenoma from hyperplasia while on a constant DS regimen. If successful, this would facilitate discrimination of adenoma from hyperplasia without multiple, serial imaging protocols.

MATERIALS AND METHODS

Fifty patients with PA and 13 with AH underwent DS adrenal scintigraphy. All were studied after definite

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TABLE 1
Patterns of Adrenal Imaging in Patients with Primary Aldosteronism and Adrenal Hyperandrogenism Studied 3 or 4 Days After NP-59 Injection

	Primary aldosteronism 50 cases	
Pattern of NP-59 uptake	30 adenomas	20 hyperplasia
Unilateral	30	0
Bilateral	0	20
	Adrenal hyperandrogenism 13 cases	
Pattern of NP-59 uptake	6 adenomas	7 hyperplasia
Unilateral	6	0
Bilateral	0	7

biochemical confirmation of disease had been made. In PA all patients manifested suppressed or low plasma renin activity (PRA) with concomitant elevation of urinary and/or plasma aldosterone levels (*14*). AH was established by the presence of elevated plasma concentrations of testosterone and/or dehydroepiandrosterone sulfate (DHEA-S) and urinary 17-ketosteroids, together with normal 17-hydroxycorticosteroid levels (*15*).

Plasma levels of aldosterone, PRA, testosterone, and DHEA-S were measured by radioimmunoassay (*16–19*). Urinary 17-ketosteroids and 17-hydroxycorticosteroids were measured by fluorometric methods (*20,21*).

Of the patients with PA, 30 had an adenoma at subsequent operation and 20 had bilateral hyperplasia demonstrated by adrenal-vein hormone sampling. We analyzed only those cases with a confirmed diagnosis (either by surgery or catheterization) and available adrenal uptake measurements. Of the 13 patients with AH, six had androgen-secreting adrenal adenomas confirmed at surgery. The other seven constituted a control group for patients with tumoral AH; they had adrenal hyperandrogenism due to bilateral hyperfunction, proven by adrenal-vein hormone sampling.

All antihypertensive medications or other drugs known to affect adrenal NP-59 uptake were discontinued for at least a 2-wk period before the study, and spironolactone was stopped for 6 wk before NP-59 injection. After obtaining informed consent, each patient received dexamethasone, 4 mg in divided doses daily, for 7 days before the injection of 1 mCi of NP-59 (*22,24*). Lugol's solution or SSKI (2–3 drops twice daily) was given 24 hr before NP-59 injection and daily throughout the imaging intervals. Posterior and lateral scintigrams were obtained with a gamma camera interfaced to a digital minicomputer. Adrenal images were obtained at 3 or 4 and 5 days following NP-59 injection. A semi-operator-independent computer algorithm semi-independent of operator was used to estimate adrenal NP-59 radioactivity from images obtained from each patient on the fifth day after injection (*25–27*). Lateral images were obtained to assess depth and correct for attenuation of NP-59 radioactivity by overlying tissues (*25–27*). Estimations of adrenal DS-NP-59 uptake from earlier images (Days 3 or 4) were not performed, as resolution of adrenal gland activity is poor due to low target-to-background activity ratios and an accurate measurement of adrenal gland depth cannot be made at these early time intervals.

TABLE 2
Patterns of Adrenal Imaging in Patients with Primary Aldosteronism and Adrenal Hyperandrogenism Studied 5 days After NP-59 Injection

	Primary aldosteronism 50 Cases		
Pattern of NP-59 uptake	30 adenomas	20 hyperplasia	NP-59 uptake
Unilateral	22	17	Symmetric (>0.5)
Bilateral	8	3	Asymmetric (<0.5)
	Normal/adenoma ratio		
	≥0.5	<0.5	
	4	4	
	Adrenal hyperandrogenism 13 cases		
Pattern of NP-59 uptake	6 adenomas	7 hyperplasia	NP-59 uptake
Unilateral	0	4	Symmetric (>0.5)
Bilateral	6	3	Asymmetric (<0.5)
	Normal/adenoma ratio		
	>0.5	<0.5	
	1	5	

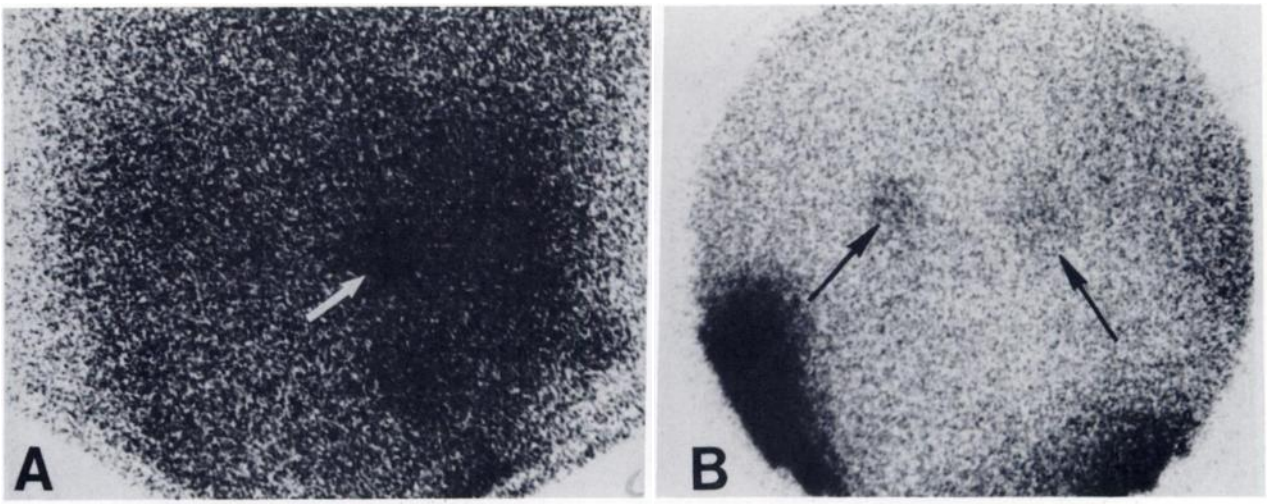

FIGURE 1
Posterior images of adrenal adenomas on Day 5 after NP-59, during 4 mg/day dexamethasone suppression. A: right-sided aldosterone-producing adenoma (arrow) is clearly visualized, without discernible left-sided adrenal activity. B: bilateral adrenal I-131 activity (arrows) is evident in this patient with left-sided adenoma (uptake 0.09%) and with contralateral "normal" adrenal uptake (0.07%). Normal-to-adenoma uptake ratio was 0.77

Imaging studies on DS were interpreted in the following manner. Unilateral adrenal visualization before the fifth day after NP-59 injection is compatible with unilateral hyperfunction or adenoma, while bilateral visualization before the fifth day is compatible with bilateral hyperfunction or hyperplasia. Normal adrenal visualization is seen at or later than the fifth day after NP-59 injection while on DS (4 mg/day for 7 days) (*24*).

RESULTS

Unilateral early imaging (<5 days after NP-59 injection) was observed in all 30 PA patients and in the six AH patients with adenoma (Table 1).

On Day 5, contralateral "normal" adrenal gland activity was evident in six of 30 PA patients and in all of the six AH patients with adenoma (Table 2 and Fig. 1).

Mean (± s.e.m.) adenoma NP-59 uptake at 5 days was 0.2 ± 0.02% in PA and 0.36 ± 0.09% in AH,

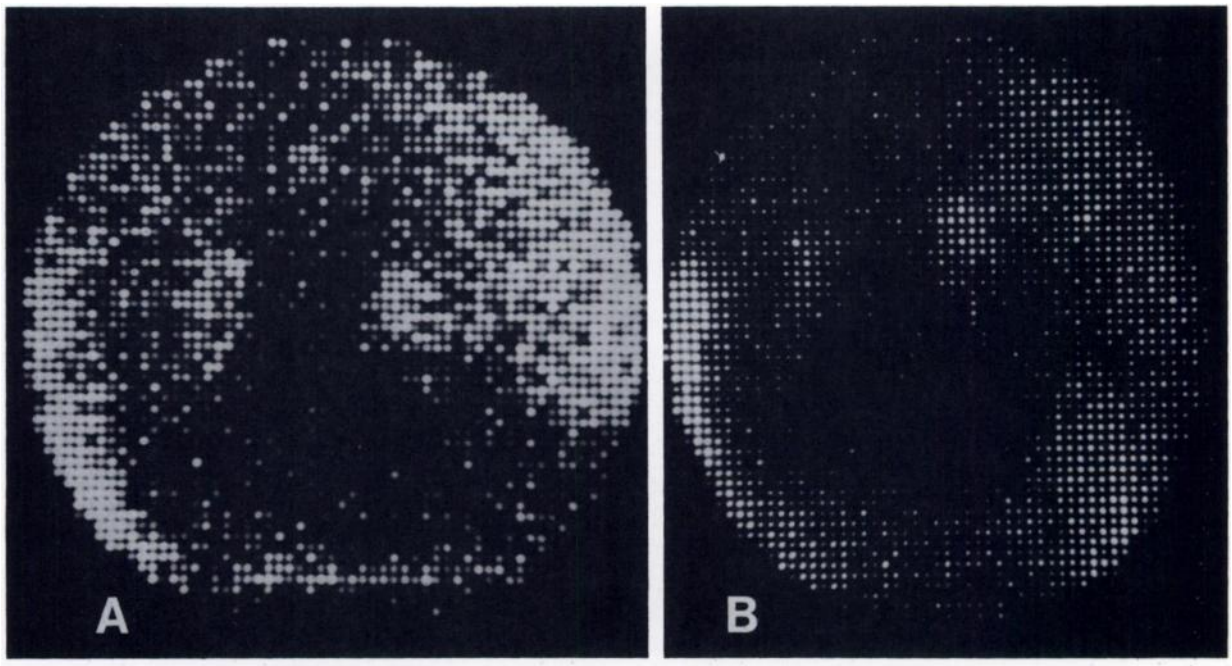

FIGURE 2
Posterior adrenal images in bilateral adrenal hyperplasia on Day 5 after NP-59, during 4 mg/day dexamethasone suppression. A: Bilateral symmetric uptake (L = 0.09, R = 0.11). B: Bilateral asymmetric uptake (L = 0.14, R = 0.28; ratio = 0.5)

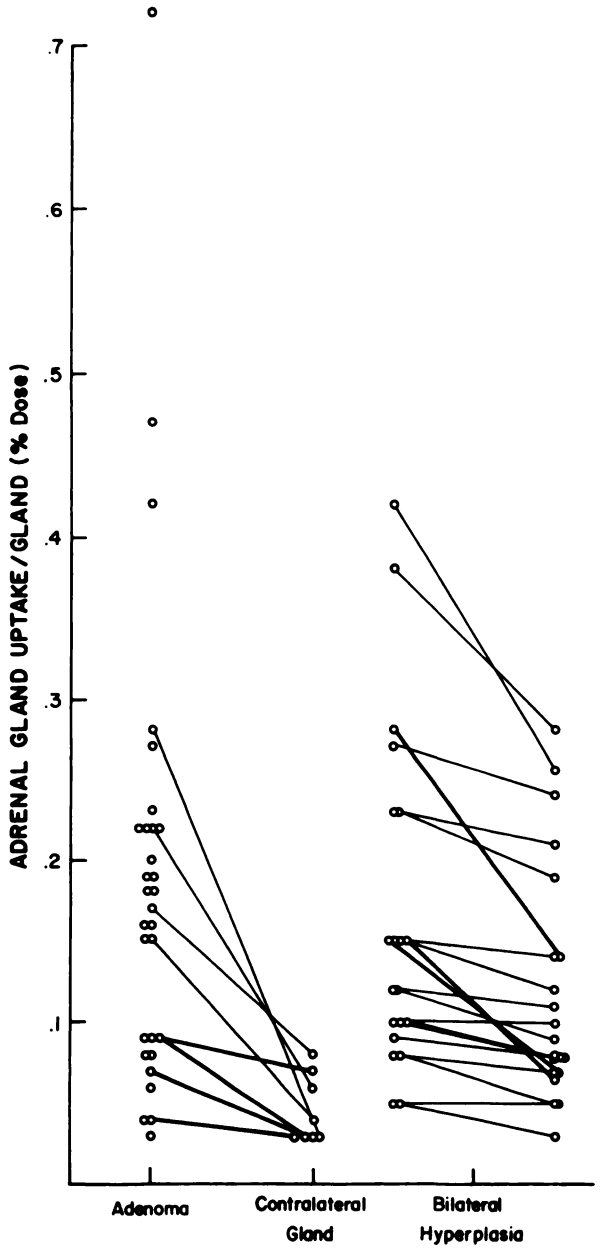

FIGURE 3
Adrenal NP-59 uptake in primary aldosteronism (4-mg DS) on Day 5 after injection. Lines connect adrenal uptakes of individual patients. Higher uptake of two adrenals is shown at left in each case. Eight of 30 patients with adenoma had bilateral adrenal visualization at Day 5, and in 4 (darkened lines) N/A ratio was ≥0.5. In three of 20 with bilateral hyperplasia (darkened lines), adrenal uptake ratios were ≤0.5

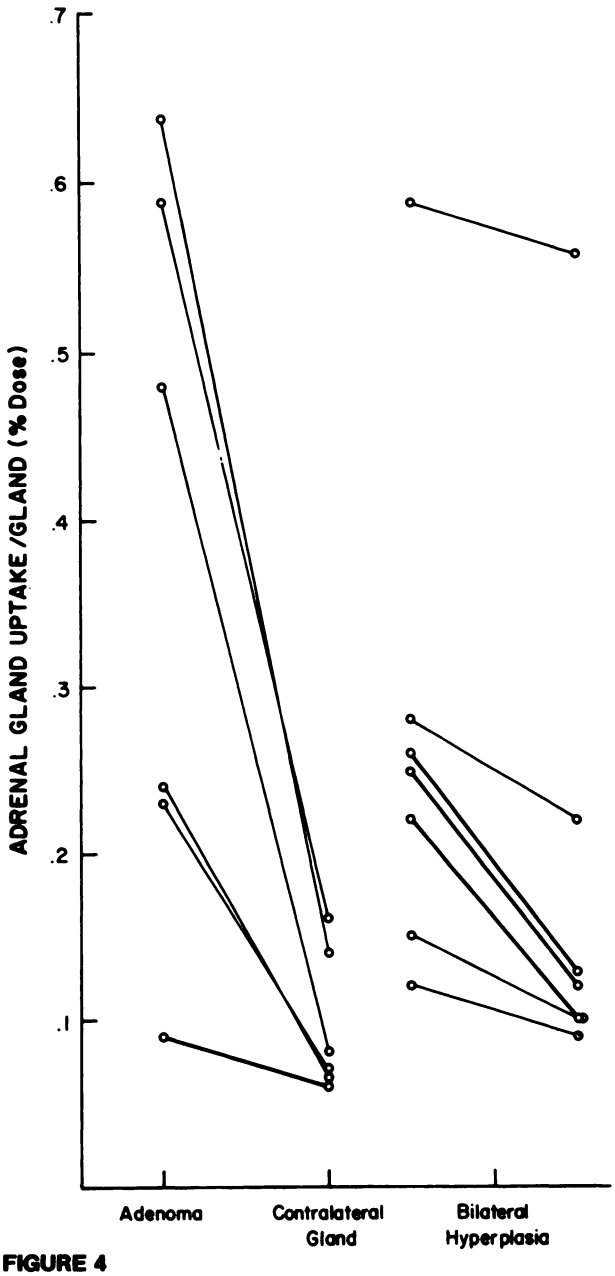

FIGURE 4
Adrenal NP-59 uptake on Day 5 (4-mg DS) in adrenal hyperandrogenism. Lines connect adrenal uptakes of individual patients. The higher uptake of two adrenals is shown at left in each case. One of six patients with adenoma (darkened line) had N/A ratio of ≥0.5. Asymmetric adrenal uptake was seen in three of seven patients with hyperplasia (darkened lines); they had uptake ratios of ≤0.5

whereas the contralateral "normal" NP-59 uptakes were 0.04 ± 0.01% and 0.09 ± 0.02% in PA and AH, respectively. Significant differences in uptake ($p < 0.01$) were seen between the adenoma and contralateral adrenal glands in both groups. Contralateral "normal" adrenal uptake was greater than 50% of that of the adenoma ($N/A \geq 0.05$) in four of the eight patients with PA and one of the six patients with AH in whom bilateral adrenal activity was discernable at 5 days after NP-59 (Figs. 3 and 4).

Bilateral early imaging (<5 days) was seen in all 20 patients with PA due to hyperplasia (Table 1 and Fig. 2). Mean 5-day NP-59 uptakes were 0.28 ± 0.04% and 0.22 ± 0.04% in the PA and AH hyperplasia groups, respectively. Marked asymmetric adrenal activity (difference 50% or greater) was seen in three of 20 with PA and three of seven with AH, all of whom demonstrated patterns of bilateral early imaging (<5 days) and had

proven bilateral adrenal hyperfunction (Table 2). In neither PA nor AH there was any significant difference in uptake between the adenoma and hyperplasia groups. Furthermore, there was no significant uptake difference between the hyperplastic gland and the "normal" contralateral adrenal in patients with adenoma from either group of PA or AH patients.

DISCUSSION

Scintigraphic localization of the adrenal glands has demonstrated a wide range of clinical utility since its introduction in the early 1970s (*23*). Studies in both PA and AH demonstrated that visual asymmetry of tracer accumulation could be used to distinguish hyperplasia from adenoma (*2,4,28*). Encouraging initial reports were later tempered as it became evident that not all studies could be reliably interpreted in this manner (*4,8,28*). The introduction of the more avid adrenal-radiopharmaceutical, 6β-[^{131}I]iodomethylnorcholesterol (NP-59) imposed a further problem, as it was recognized that, in spite of nearly complete DS of pituitary ACTH and adrenal steroid hormone secretion, there was sufficient adrenal iodocholesterol uptake for discernible, late (5 days or more) adrenal visualization (*9–11,22,24,29*).

Studies in normals have established the time interval of adrenal imaging during constant DS. Under pretreatment with dexamethasone (4 mg in divided doses for 7 days before NP-59 and continued through the imaging period), the normal adrenal cortex has visualized no earlier than the fifth day after iodocholesterol administration (*24*). Shorter DS regimens using higher doses of dexamethasone have resulted in earlier visualization of normal adrenal NP-59 radioactivity (*24*). Thus, the interval between NP-59 injection and normal adrenal visualization has been defined for the 4-mg DS regimen as $\geq$5 days (*24*). Adrenal NP-59 activity seen during this normal "suppression interval" is compatible with adrenal hyperfunction and the pattern of NP-59 activity defines the abnormality: bilateral visualization–hyperplasia, and unilateral visualization–adenoma (*24*). This interpretative algorithm allows for discrimination of unilateral from bilateral hyperfunction, but it is cumbersome. The absolute requirement for constant DS throughout the imaging procedures, and the multiple imaging studies that must be performed after NP-59 administration, have imposed considerable logistic difficulty in their performance (*30*).

The quantitation of adrenal NP-59 activity has allowed an in vivo functional assessment of the adrenal glands. This approach has been shown to depict abnormal function in patients with Cushing's syndrome, AH, and PA (*12,3,31*). In each instance a relationship of in vivo uptake of NP-59 to a parameter of adrenocortical hyperfunction has been described. The relationship in all cases is integrative, since the accumulation of the radiotracer by the adrenals occurs over days. DS delays the early visualization of the normal adrenal but appears to have little effect upon the visualization of the abnormal adrenal (*24,32*). Resolution of adrenal activity and calculation of NP-59 uptake is poor in DS studies, since background radioactivity remains high (*24*) and the present computer algorithms do not reliably discern early (Day 3 or Day 4) adrenal activity after NP-59 injection. Thus, estimations of uptake are not reliable from these time intervals. The 4-mg DS regimen is therefore a compromise that allows for the shortest interval on DS both before and after NP-59 injection, while providing adequate time for diagnostic imaging.

The present study was designed to examine whether the quantitative estimation of NP-59 adrenal radioactivity at a time late in the imaging process could be used to separate adenoma from normal in patients with PA and AH. This study was not designed to examine the efficacy of this technique, since patients have been selected from those with operative- or catherization-proven disease and available NP-59 uptake data. In patients with an adenoma in whom the contralateral, normal adrenal was visible at 5 days, the asymmetry criterion for normal adrenal to adenoma ratio of $\geq$0.5 was present in four of eight patients with PA and one of six with AH. In contrast, three of 20 with PA and three of seven with AH (all with adrenal hyperplasia) had sufficiently asymmetric adrenal NP-59 uptake to have been mislabeled as unilateral dysfunction. Other criteria of "significant asymmetry" can be chosen, but in the present study an unacceptable level of false diagnoses would have been made using estimates of uptake alone to separate these entities. This is as illustrated by the considerable overlap of uptakes between adenoma, the normal adrenal, and adrenal hyperplasia in PA and AH in this series (Figs. 3 and 4). Thus, the reliance upon a single measurement of adrenal NP-59 uptake, or on later imaging procedures (Day 5), as a means to discriminate unilateral from bilateral disease renders these studies no more accurate than those conducted without DS (*5,7,28,29,32,33*).

The value of DS adrenal scintigraphy is dependent upon: (a) a definite biochemical diagnosis, (b) constant DS throughout all imaging procedures, (c) removal of all medications that affect adrenal iodocholesterol uptake, and (d) imaging that is performed before the fifth day after NP-59 administration. The present study shows that adrenal uptake of NP-59 ($\geq$5 days) can be asymmetric in bilateral adrenal disease, symmetric in unilateral disease, and in the absence of early imaging procedures can lead to misdiagnosis in studies performed in patients with AH and PA.

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