Functional and Scintigraphic Evaluation of the Silent Adrenal Mass

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Seven patients with unilateral and one patient with bilateral and asymmetric (R > L) incidentally discovered adrenal mass abnormalities depicted by computed tomography (CT) were studied by ^{131}I-6β-iodomethyl-19-norcholesterol (NP-59) scintigraphy. There was marked lateralization of NP-59 uptake to the side of the mass lesion in the seven patients with unilateral masses and prominent asymmetric, (R > L) bilateral uptake in the patient with bilateral masses despite the fact that there were no obvious abnormalities of adrenocortical or adrenomedullary function as determined from peripheral blood and 24-hr urinary hormone measurements. Simultaneous bilateral adrenal vein catheterization (AVC) was employed to measure the levels of hormone effluent from the adrenal cortex and medulla and in all instances the cortisol concentrations were greatest from the side of the mass lesion in those patients with unilateral masses and from the larger of the two adrenals in the patient with bilateral adrenal masses. Thus, there was congruence between the anatomic (CT) and functional (NP-59 scintigraphy and AVC) investigations that depicted asymmetry of the adrenal glands which were not associated with abnormalities of overall adrenal function or hypothalamic-pituitary-adrenal axis integrity.

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Variability of adrenal morphology is not uncommon. Results of autopsy series are in agreement with those utilizing computed tomography (CT) that estimate the incidence of endocrinologically "silent" nodules of the adrenal to occur in from 1–10% of patients (*1,2*). An increasing frequency of these nodules has been observed with advancing age, hypertension and/or thyroid disease (*3,4*). In patients without clinical evidence of adrenal dysfunction these nodules have been described as "nonfunctioning"; this based upon normal peripheral blood levels of adrenal cortical and medullary hormones, urinary hormone and metabolite excretion rates and normal hypothalamic-pituitary control of adrenal gland function (*1,5–7*). The noninvasive determination of differential adrenal gland function is possible with ^{131}I-6β-iodomethyl-19-norcholesterol (NP-59) adrenal scintigraphy (*8,9*). NP-59 uptake depicts adrenocortical glucocorticoid, mineralocorticoid and androgen secretion (*10–12*). Thus, NP-59 uptake has been shown to depict the functional status of the adrenal cortex and was used in the present study to identify asymmetric adrenal activity in those patients with adrenal nodules seen on CT examinations of the abdomen performed for reasons unrelated to suspected adrenal disease. The asymmetry of adrenal NP-59 uptake depicted by the scintiscan was related to hormonal measurements obtained by bilateral, simultaneous adrenal vein catheterization (AVC) used as an index of individual adrenal secretory activity. These data suggest that the abnormal adrenal anatomy described by CT may be characterized functionally by iodocholesterol scintigraphy, and in the context of increased NP-59 accumulation in the abnormal adrenal as compared to its anatomically normal mate these adrenal masses do indeed function and produce measurable hormones that contribute to normal peripheral hormone levels.

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MATERIALS AND METHODS

Patients were referred for study based upon the results of CT scans performed for reasons other than suspected adrenal

disease (most often unexplained abdominal pain) showing a discrete nodule or nodularity of one adrenal and the finding of normal peripheral levels of cortisol, renin activity, aldosterone, dehydroepiandrosterone sulfate (DHEA-S), epinephrine and norepinephrine. Additionally normal 24-hr urinary 17-hydroxycorticosteroids, 17-ketosteroids and vanilmandelic acid (VMA) and a normal response of cortisol to the administration of adrenocorticotrophic hormone at variable times throughout the day (a normal response is at least a twofold increase of cortisol from basal levels) and 1 mg overnight dexamethasone suppression tests (a normal response is a plasma cortisol level 0.5 μg/dl or less at 800 to 900 hr on the subsequent morning) were established in each patient (Table 1). No patient had hypertension or evidence of metastatic carcinoma and all medications that might interfere with either the biochemical or scintigraphic evaluations were discontinued prior to study. Patients were studied while on an unrestricted sodium intake.

CT was performed using either a Picker model 1200SX or GE models 8800 or 9800. Patients were studied following the administration of both oral and intravenous contrast. Contiguous one cm. slices through the region of the adrenals were obtained on each patient and were interpreted by experienced radiologists. Scintigraphic studies were performed with institutional review board approval and with the informed consent of the patients. One millicurie of NP-59 was injected intravenously 48 hr after the administration of Lugol's or saturated potassium iodide solution to suppress thyroidal accumulation of free iodine-131 (^{131}I) (*13*). Adrenal imaging was performed 5 to 6 days after NP-59 injection using a gamma camera equipped with a high-energy, parallel hole collimator* interfaced to a digital minicomputer (MDS-A2). Posterior and lateral abdominal images (50,000 counts/image) were obtained on each patient. Adrenal NP-59 uptake was estimated using a depth and decay corrected semioperator-independent-computer algorithm specifically designed for this purpose (*14,15*).

Selective percutaneous catheterization of each adrenal vein was performed using a femoral approach. Correct placement of the catheters was assessed by the injection of a small amount of contrast medium. Blood was sampled simultaneously from both adrenal vein catheters and from a catheter placed in a peripheral vein. Blood samples were drawn with minimal aspiration so as not to disturb normal adrenal perfusion. During positioning catheter patency was maintained with a dilute solution of heparin (20 u/ml) in saline. Repeat injections of contrast were performed after hormone samples had been collected to reconfirm the correct position of the adrenal vein catheters.

Blood specimens were placed immediately into prechilled tubes containing glutathione and ethylenediaminetetraacetic acid (EDTA) for the measurement of epinephrine and norepinephrine, EDTA for the measurement of aldosterone and DHEA-S and into a plain tube for the measurement of serum cortisol. Plasma and serum were separated by centrifugation within 30 min. and were stored at −20°C until the biochemical analyses were performed.

Cortisol (*16*), DHEA-S (*17*), aldosterone (*18*) and plasma renin activity (*19*) were measured by radioimmunoassay. Plasma epinephrine and norepinephrine were estimated by radioenzymatic assay (*20*) and urinary 17-ketosteroids, 17-hydroxycorticosteroids (*21*), VMA (*22*), epinephrine (*22*) and norepinephrine (*22*) were measured by fluorometric methods.

Statistical analyses were performed using the paired T and the univariate Wilcoxon sign rank test.

RESULTS

CT examination of the adrenals identified nine discrete adrenal masses in eight patients that ranged from 1.5 to 5 cm in diameter. In the seven patients with unilateral adrenal masses the contralateral adrenal was considered anatomically normal by CT criteria.

NP-59 adrenal gland uptake was greater in the abnormal gland (0.26 ± 0.07 versus 0.05 ± 0.01 administered dose; mean ± s.e.m.) in all of the patients ($p <$

TABLE 1
Biochemical Indices of Adrenal Function

Patient no./age (yr)	Plasma cortisol (μg/dl)			Urinary studies				
	ACTH stimulation*		Dexamethasone suppression†	17 Hydroxy-corticosteroids	17 Keto-steroids	Aldosterone‡	Epinephrine	Norepinephrine
	0 min	30 min	(<5 μg/dl)§	(2–11 mg/d)	(9–22 μg/d)	(<20 mg/d)	(<30 μg/d)¶	(<120 μg/d)¶
1. 57 M	5.4	30.1	0.8	5.4	9.2	12.9	9	20
2. 62 M	8	20.0	5.0	9.2	12.2	7.0	35	76
3. 66 M	16	34.4	0.6	10.0	12.0	14.0	33	56
4. 67 M	4	21.3	2.1	10.5	13.0	7.0	5	33
5. 65 M	8.5	24.4	4.4	6.1	3.6	18.0	16	52
6. 58 M	3.1	21.6	0.8	11.8	12.8	6.0	9	120
7. 60 M	16.5	53.4	2.3	7.0	10.0	7.1	30	45
8. 47 M	9.7	45	3.0	10.0	15.9	12.0	12	110

* After 250 μg Cortrosyn intravenously.
† 1 mg dexamethasone orally at 2000 hr, cortisol obtained at 900 hr.
‡ Unrestricted salt intake.
§ Normal values.
¶ 99% confidence level.

TABLE 2
Adrenal Gland ^{131}I-6β-Iodomethylnorcholesterol Uptake (% Administered Dose)*

Patient no.	Right	Left
1	0.74	0.05
2	0.26	0.03
3	0.15	0.06
4	0.09	0.04
5	0.22	0.04
6	0.26	0.03
7	0.05	0.22
8†	0.17	0.12

* Obtained on Day 5 after NP-59 injection.
† Bilateral adrenal masses.

0.001) (Table 2). The smallest degree of asymmetry of NP-59 uptake was seen in a "nodular" adrenal and in the smallest of nodules depicted by CT (Case 4). The levels of NP-59 uptake observed in the enlarged gland were within the previously described normal range of uptake of 0.07 to 0.26% administered dose in seven of the eight cases (*23*). Accumulation of NP-59 in the contralateral, normal gland was 0.05 ± 0.01 and was less than the normal mean uptake of 0.16% administered dose ($p < 0.05$) (*23*) (Table 2). Examples of representative CT and NP-59 scans are shown in Figures 1 and 2.

Adrenal vein cortisol levels were higher from the adrenal that demonstrated the greatest accumulation of NP-59 (abnormal adrenal on CT) ($P = 0.016$) (Table 3). In three patients the secretion of cortisol from the normal adrenal appeared to be suppressed as adrenal vein cortisol levels approximated those in peripheral blood (Cases 1, 3, and 5, see Table 3) suggesting relative suppression of glucocorticoid secretion from the anatomically normal gland. Adrenal vein levels of DHEA-S and aldosterone although variable between patients were higher in the adrenal vein effluent from the abnormal gland in four (P = N.S.) and six ($P = 0.03$) of the eight cases, respectively (Table 3). Epinephrine levels were variable between individuals, but demonstrated symmetrical values from each adrenal vein which were significantly greater than peripheral plasma epinephrine values confirming successful adrenal vein catheterization (Table 3).

DISCUSSION

Studies of the "silent" or incidentally discovered adrenal mass indicate that in the majority of cases these nodules are hormonally nonfunctional, i.e., they do not produce recognizable endocrine syndromes (*1,5–7*). Although normal adrenal appearance using CT has been described, many authors have suggested that some degree of nodularity may represent a normal anatomic variability made apparent by high resolution CT (*1,2, 24–27*). The silent adrenal mass constitutes a heterogenous group of lesions and the most important issue raised with the identification of these masses is their malignant potential and the question of what constitutes an adequate evaluation sufficient to exclude a small adrenocortical carcinoma or metastasis to the adrenal (*1,5–7,28,29*). In the absence of an endocrine abnormality demonstrated by peripheral hormone analysis and dynamic testing, needle aspiration of adrenal masses under CT guidance has been suggested (*1, 30*). Although cellular material can be obtained, this is an invasive approach with an identifiable morbidity

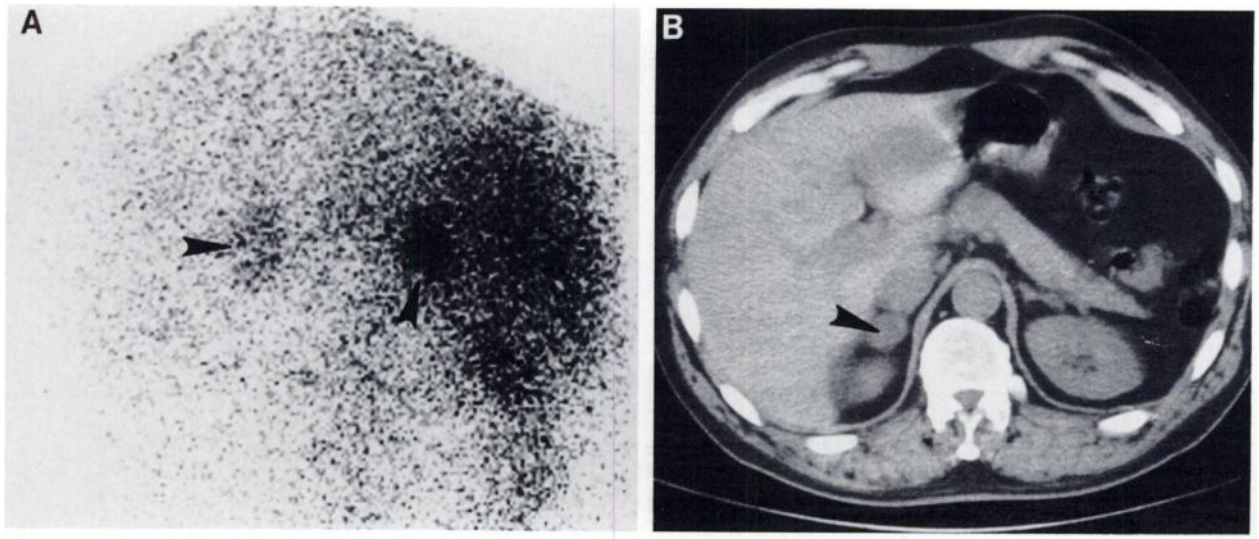

FIGURE 1
A: Posterior adrenal scintiscan 5 days after NP-59 injection (Case 2) shows marked right sided (arrow) uptake of the radiotracer with slight left adrenal radioactivity (arrow). B: Abdominal CT scan depicts the marked adrenal asymmetry, a right adrenal mass (arrow) is identified.

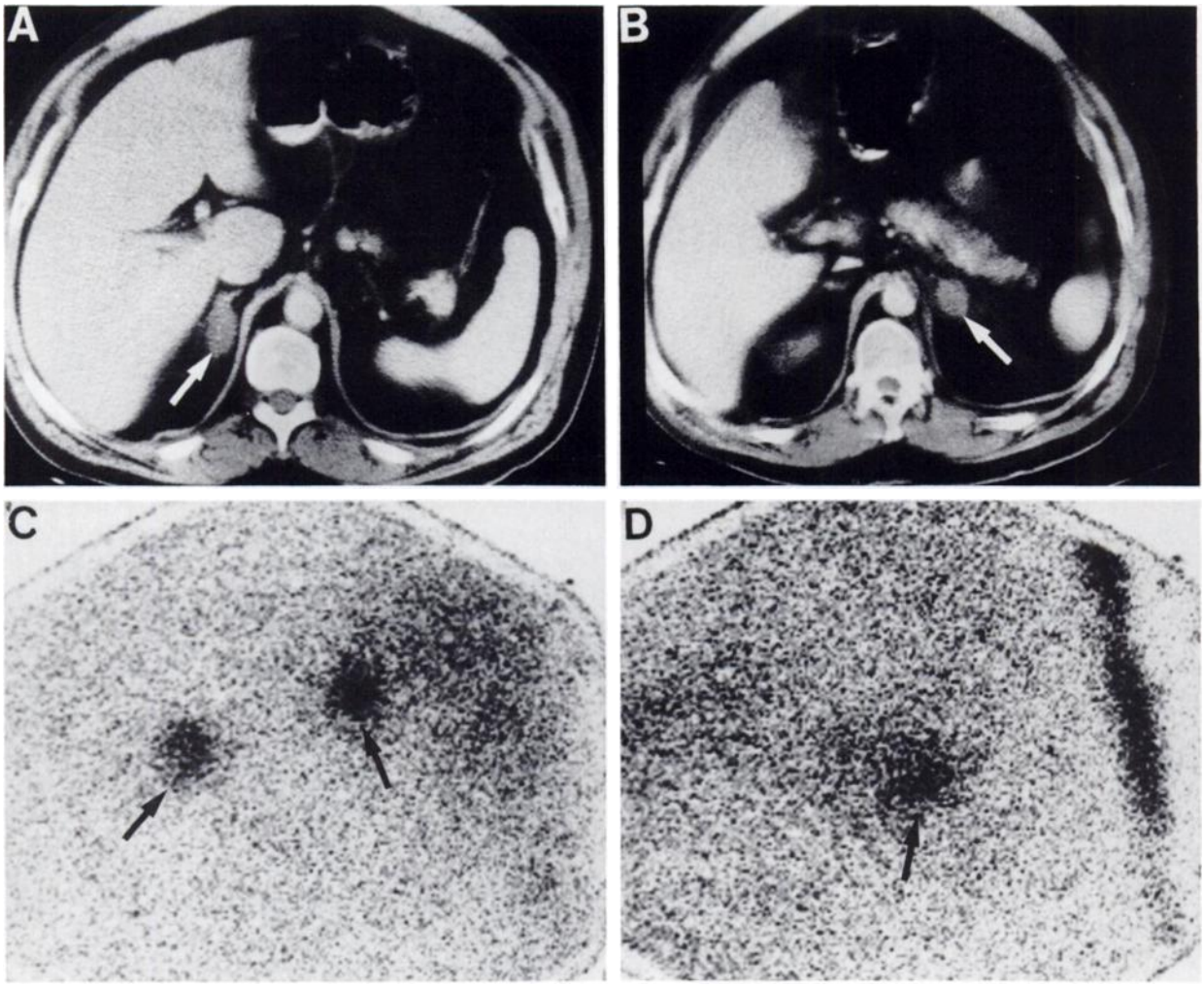

FIGURE 2
A, B: Sequential, 1 cm, CT scans of the abdomen of a patient with bilateral adrenal masses (Case 8) (arrows). C, D: Posterior (C) and left lateral (D) adrenal scintiscans 5 days after NP-59 injection shows bilateral and asymmetric uptake.

and frequently aspirated cells are not sufficient to discern malignant changes by present cytologic techniques (*30,31*).

Peripheral hormone analysis is of limited value as it identifies only those masses which exhibit obvious abnormal function sufficient to perturb normal pituitary-adrenal axis integrity. A mass, the secretory capacity of which functions within a given patient's normal hormonal requirements would thus be indistinguishable from one that was "nonfunctioning" in the hormonal sense. Such a lesion may cause a relative suppression of hormone secretion (complete or partial) from the

TABLE 3
Simultaneous Adrenal Vein Hormone Sampling

Adrenal mass		Cortisol (μg/dl)			DHEA-S (ng/dl)			Aldosterone (ng/dl)			Epinephrine (pg/ml)		
(cm)	(side)	R	L	P	R	L	P	R	L	P	R	L	P
1. 3 × 2	(R)	45	6.8	5.4	369	235	29	346	217	24.0	5,230	6,125	56
2. 2 × 2	(R)	70	33	8.0	288	460	271	2,630	2,560	25.4	32,143	43,418	45
3. 2.5 × 2.5	(R)	27	4.7	3.9	477	257	118	217	76.6	25.7	57,003	59,930	75
4. "Nodular"	(R)	245	53	16	2,000	2,196	154	223	49.7	6.4	3,887	3,500	22
5. 3 × 4	(R)	19.8	8.1	8.5	670	630	570	210	250	4.3	1,544	1,856	48
6. 2 × 2	(R)	181.2	150.1	3.1	210	300	76	2,743	2,255	21.7	51,905	53,817	57
7. 3 × 3	(L)	31.5	54.3	16.5	87	155	138	894	520	36.0	10,000	11,300	376
8. 2 × 3 2 × 2	(R) (L)	236	142	9.7	942	1,010	482	103	372	14.5	10,235	8036	392

normal adrenal in the presence of normal peripheral hormone levels.

The uptake of iodocholesterol by the adrenal cortex has been shown to depict the functional status of the adrenal glands. In Cushing's syndrome, primary aldosteronism, and adrenal hyperandrogenism, the level of NP-59 accumulation has been shown to distinguish unilateral from bilateral disease and to correlate with urinary levels of free cortisol, aldosterone and 17-ketosteroids, respectively (*10–12*). Noninvasive differential adrenal function analysis using NP-59 uptake is thus possible using the scintigraphic approach. Further characterization of the functional status of adrenal masses might be derived from the comparison of baseline and dexamethasone suppressed NP-59 scans. Although in the present series a normal response of peripheral plasma cortisol levels to dexamethasone suppression was present in the eight patients studied and normal dexamethasone suppression scintiscans would be anticipated in this group.

High spatial resolution CT is useful in depicting the anatomic configuration of the adrenals (*24–27,32,33*). Normal patterns of anatomy can be distinguished from abnormal with a high degree of efficacy (*23–25,32,33*). However, in the absence of discernible biochemical dysfunction to suggest disease or other evidence to raise suspicion of malignancy, the findings of anatomic asymmetry or nodularity are ambiguous and include numerous possible pathological entities (*34*). Size alone has been suggested as a criterion for surgical extirpation regardless of normal peripheral hormone levels (*1,5*). This approach has some merit as the probability of malignancy has been shown to rise with increasing lesional diameter (>5 cm) (*1*). However, this approach would ignore or delay a direct evaluation of smaller lesions (2–3 cm in diameter) in the absence of biochemical or clinical stigmata of adrenal disease. Such lesions have been referred to as "non-functional" in the sense of overall adrenal hormonal secretion, but individual adrenal gland function has not yet been considered in their evaluation.

The presence and degree of adrenal function is suggested by the measurable NP-59 accumulation depicted by in vivo scintigraphic imaging. Thus, in the absence of discernible NP-59 uptake in an enlarged adrenal gland seen on CT would suggest a hypofunctional or destructive lesion (e.g., carcinoma or metastasis) while discernible uptake would predict function (e.g., adenoma) (*35*). Furthermore, adrenal medullary activity in the patients studied was normal and the presence of NP-59 uptake is most compatible with adrenocortical activity, as abnormal adrenal anatomy due to a medullary lesion of significant size would result in a "cold" defect on the NP-59 scintiscan (*36*). The CT and scintiscan are thus complementary in the information obtained from each and can be used in tandem to characterize the asymmetrical anatomic and functional status of the adrenals.

This study was not designed to test the hypothesis that NP-59 uptake would predict the later development of functional abnormalities or malignancy in the case of the incidentally discovered adrenal mass (*37*); continued evaluation and follow-up will be necessary to support such contentions. Furthermore, this study did not seek unusual steroid hormone precursors or metabolites to explain the presence of the abnormal anatomic and functional findings nor was it possible to separate the venous hormone effluent of the "mass" from the ipsilateral, normal adrenal cortex (*1,38*). Our study does however, confirm that in the absence of clinical or biochemical evidence for adrenal endocrine hyperfunction and in the presence of a solitary adrenal mass there may in some patients be overall asymmetric, differential adrenal activity that can be characterized by NP-59 scintigraphy.

Simultaneous adrenal vein hormone sampling was a critical component to ensure that the variable secretion of ACTH secondary to spontaneous or stress-related secretory surges would not adversely influence the comparability of individual adrenal vein cortisol measurements. In addition to the findings of asymmetric hormone output of glucocorticoids, a similar but less marked asymmetry of androgen and mineralocorticoids secretion suggests that these masses may be composed of functioning elements of all three cortical zones and may represent a localized "functional" hyperplasia. Differences in the hormone levels from the abnormal versus normal adrenal are small, but in the case of cortisol and aldosterone are significant and outside the error of variability of their measurement. The smaller number of patients with asymmetrical secretion of androgens may be due to decreased secretion of DHEA with age (*39*) and in the case of aldosterone the result of uncontrolled sodium intake at the time of study.

Our findings in these selected cases of adrenal masses suggest a condition analogous to that of the nodular euthyroid (nontoxic) goiter with partial suppression of normal tissues characterized scintigraphically as heterogeneous foci of increased tracer accumulation (function) in the context of overall normal hormone secretion (*40*). These cases are thus examples of an "adrenal goiter". Long-term follow-up of these patients particularly those in whom the cortisol levels from the normal gland approximated peripheral values will be important to determine if the initial anatomic and functional asymmetry may evolve into autonomous and excessive adrenal hormone secretion with the development of clinically apparent adrenal disease.

NOTE

* Ohio Nuclear model 110.

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