Clinical Significance of the Solitary Functioning Adrenal Gland

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To assess the compensatory functional and anatomic changes in the remaining adrenal cortex after unilateral adrenalectomy or in the unaffected adrenal in patients with unilateral adrenal destruction by neoplasm, 17 patients with a single, functioning adrenal gland and normal indices of adrenocortical function, nine after adrenalectomy and eight with a unilateral, destructive adrenal lesion were studied with ^{131}I-6β-iodomethyl-19-norcholesterol (NP-59) scintigraphy and computed tomography. Adrenal masses with a mean (±s.d.) diameter of 2.8 ± 1.0 cm; (range 1–4 cm; 95% confidence interval (CI), 2.5–3.1 cm) were identified by computed tomography in seven of nine patients in the remaining adrenal cortex at variable times (6.1 ± 5.9 y; range 0.5–19 y) after unilateral adrenalectomy. Mean (±s.e.m.) NP-59 uptake was elevated ($p < 0.01$) in both adrenalectomy and adrenal destruction groups, mean uptake (±s.e.m.) was 0.32% ± 0.04% administered dose (95% CI, 0.24%–0.4% administered dose) as compared to normal (0.16% ± 0.05% administered dose, 95% CI, 0.06%–0.26% administered dose). The remaining adrenal cortex may be anatomically abnormal after unilateral adrenalectomy and demonstrate compensatory, increased NP-59 uptake in the presence of overall, normal adrenocortical function.

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The compensatory changes seen in endocrine organs after subtotal resection are well recognized and in the absence of exogenous hormone replacement, the remaining functioning tissues may increase their capacity to produce sufficient hormone(s) for endocrine homeostasis (*1*). Substrate accumulation by the remaining tissues increases to support a greater biosynthetic effort necessary to meet demand and glandular hormone reserve; such responses have been demonstrated for many endocrine tissues (*1–3*). These compensatory changes have been documented in the thyroid, where subtotal thyroidectomy without thyroid hormone replacement results in subsequent remnant growth, normal hormone secretion and radioiodine accumulation (*4–6*). Unfortunately, the adrenal cortex by virtue of its location deep within the retroperitoneum is accessible only through invasive or high-resolution imaging with computed tomography (CT) or angiography. However, even with finely detailed anatomic imaging, only changes in glandular contour and anatomy, such as the presence of adrenal masses or gross hyperplasia, can be appreciated with these modalities (*7–10*). The accumulation of the cholesterol analog ^{131}I-6β-iodomethyl-19-norcholesterol (NP-59) has been shown to depict adrenocortical function (*11*). Both the pattern and level of NP-59 uptake can serve as a functional map of adrenocortical tissues, and were used in the present study to document alterations in adrenal cortical function in the remaining adrenal after unilateral adrenalectomy and in the unaffected, normal adrenal gland in patients in whom the contralateral gland had been replaced by a nonfunctioning (in terms of adrenal cortical function), mass lesion.

PATIENTS AND METHODS

Seventeen patients were referred for study based upon an abnormal CT scan done for reasons other than suspected adrenal disease (10 patients), as follow-up for previously resected adrenal neoplasms (2 patients) or for the evaluation of abnormal plasma and/or urinary catecholamines (5 patients). CT was performed using both oral and intravenous contrast. Contiguous slices of 1 cm or less taken through the region of the adrenals were obtained on each patient and the scans were interpreted by experienced radiologists. In each patient, a combination of blood and urine biochemical measurements of adrenal function were performed. These included basal determination of plasma catecholamines, plasma and urinary cortisol, 17-hydroxycorticosteroids, 17-ketosteroids, and catecholamines; and plasma cortisol responses to dexamethasone and adrenocorticotrophic hormone administration. Plasma and urinary free cortisol levels were measured by radioimmunoassay (*12*) Plasma epinephrine and norepinephrine were determined by radioenzymatic methods (*13*) and 24-hr urine 17-hydroxycorticosteroids, 17-ketosteroids, catecholamines and metabolites were determined fluorometrically (*14–16*). All medications that might interfere with the scintigraphic or biochemical evaluations were omitted prior to study. Three of the

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seventeen patients described in this study have been included in previous reports dealing with the correlation of CT and ^{131}I-6β-iodomethyl-19-norcholesterol imaging in oncologic patients, and the efficacy of ^{131}I-6β-iodomethyl-19-norcholesterol scintigraphy in the evaluation of the incidentally discovered, euadrenal mass (*17,18*).

Scintigraphic studies were performed after institutional approval and with the informed consent of the patients. One millicurie of NP-59 was injected intravenously 48 hr after the administration of Lugols' or saturated potassium iodide solution to suppress the thyroidal accumulation of free ^{131}I (*19*). Adrenal scintigraphy was performed 5–7 days after NP-59 injection using methods previously described (*19*). Posterior and lateral abdominal images (50,000 counts/image) were obtained from each projection. A mild laxative (bisacodyl) was also given (10 mg daily) beginning 2 days before and on the day of imaging in most of the patients (*20*). Adrenal gland NP-59 uptake (% administered dose/gland) was measured using a semi-operator-independent computer algorithm designed specifically for this purpose (*21*). Adrenal gland uptakes were compared to normal single and combined, bilateral gland values reported previously (*22*). Statistical analyses were performed using Student's t-test and the confidence interval estimation for the binomial parameter (*23*).

RESULTS

Computed tomography was performed in nine patients after unilateral adrenalectomy as follow-up for previously treated malignancies (hypernephroma in five), previous adrenocortical disease (non-functioning cortical adenoma in 2, a nonfunctioning adrenocortical carcinoma and a pheochromocytoma (Table 1). Preoperative studies that include nephrotomography and angiography in the earlier and CT in the latter cases did not demonstrate anatomic abnormalities in the contralateral adrenal cortex (the adrenal cortex that was not removed and is the subject of this report). The mean (±s.d.) interval from adrenalectomy

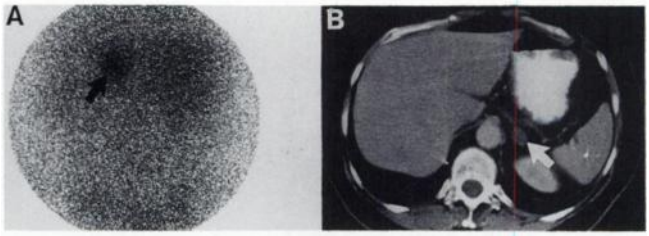

FIGURE 1. (A) Posterior NP-59 scintiscan depicts the remaining left adrenal cortex as a focal collection of ^{131}I radioactivity (arrow) in a patient nineteen years after right radical nephrectomy and adrenalectomy for hypernephroma (B) Abdominal CT identifies the left adrenal mass (arrow).

to the present study was 6.1 ± 5.9 yr (range 0.5–19 yr). In seven of these nine patients an incidental adrenal mass was discovered by CT in the remaining adrenal gland (Fig. 1). Adrenal mass diameter (mean ± s.d.) in these patients was 2.8 ± 1.0 cm (range 1–4 cm; 95% CI, 2.5–3.1 cm). An additional eight patients were studied while harboring a nonadrenocortical mass of sufficient size to cause ipsilateral adrenocortical destruction and non-visualization on an NP-59 scan (Fig. 2). The contralateral unaffected gland was considered anatomically normal by CT. This group was comprised of five patients with sporadic, unilateral pheochromocytoma, two with metastatic lung cancer and one with an adrenal cyst (Table 2). Mean (±s.d.) lesion diameter in this group was 4.7 ± 1.2 cm (range 3–7 cm; 95% CI, 4.4–5.0 cm). In the five patients with pheochromocytoma, adrenal cortical function was normal while plasma and/or urinary catecholamines were elevated (Table 2). The serum cortisol response to cortrosyn (250 μg i.v.) was also normal in the remaining three patients with unilateral, destructive adrenal lesions (Table 2). In the five patients with pheochromocytoma a thin band of

TABLE 1
Effect of Unilateral Adrenalectomy Upon Adrenal Function and NP-59 Uptake

			Adrenal mass interval			Urine (μmol/d)			Plasma			
Age	Sex	Dx	(cm)	(side)	(y)	170H‡	17KS	UFC	CORTISOL† (μmol/liter)	E (pmol/liter)	NE (pmol/liter)	NP-59 UPTAKE (%admin. dose)
54	F	HN	3	L	19	19.1	10.6	145.8	41.7	119.9	2807.3	0.58
46	F	HN	2	R	12	16.9	35.8		66.7			0.22
66	M	AD	–*	R	4	17.2	40.0	239.3	41.7	245.3	862.9	0.26
38	F	P	3.5	L	4			116.9	30.6	457.8	969.2	0.23
43	F	HN	4	L	5			151.3	47.2			0.34
67	M	HN	3	L	6	20.8	36.4		16.7			0.28
65	F	AD	3	L	0.5			137.5	27.8			0.36
69	F	ACA	–	L	3	21.3	7.0					0.30
56	M	HN	1	R	1	21.7	29.4		125.0			0.27

HN = hypernephroma; AD = adrenal adenoma; P = pheochromocytoma; and ACA = adrenocortical carcinoma.

* No mass lesions detected in remaining gland.

† After 1 mg p.o. dexamethasone at 2,000 hr and cortisol at 800 hr, normal greater than 138 μmol/liter.

‡ 17 hydroxycorticosteroids (14–29 μmol/d); 17KS = 17 ketosteroids (25–28 μmol/d); UFC = urinary free cortisol (55–276 nmol/d). E = epinephrine (0–545 pmol/liter); NE = norepinephrine (0–2955 pmol/liter).

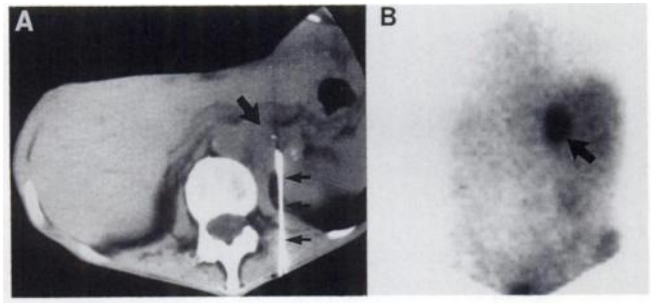

FIGURE 2. (A) CT-guided needle (small arrows) biopsy of a 5 cm left adrenal mass (large arrow) from metastatic lung carcinoma (B) Posterior NP-59 scintiscan identifies the right adrenal (arrow), no left adrenal cortical activity is seen.

cortical tissue was recognized in the excised adrenal while no gross anatomic abnormalities were noted in the contralateral gland at abdominal exploration. The diagnoses of the remaining two cases of metastatic lung cancer and an adrenal cyst were made by CT-guided adrenal biopsy.

Adrenal gland iodocholesterol uptake (mean ± s.e.m.) in the unilateral adrenalectomy and adrenal destruction groups was 0.32% ± .04% administered dose (95% CI, 0.24%–0.4% administered dose) (Fig. 3). There was no difference in NP-59 uptake between these groups (p = ns). Adrenal ^{131}I-6β-iodomethyl-19-norcholesterol uptake of both groups was elevated ($p < 0.01$) as compared to the unilateral uptake of normal subjects (0.16% ± 0.05% administered dose; 95% CI, 0.06%–0.26% administered dose), and similar (p = ns) to the total (bilateral) uptake of normal controls (Fig. 3) (*22*).

DISCUSSION

Post-adrenalectomy compensatory changes are well recognized in the adrenal. In both acute (hours) and subacute (days) intervals after unilateral adrenalectomy, a combination of adrenocortical hypertrophy and hyperplasia have been noted (*24–26*). Early studies had suggested that adrenocorticotrophin or other pituitary/hypothalamic-derived trophic substances may be responsible for these anatomic and histologic changes, but more recent investigations with concomitant dexamethasone suppression of ACTH, in a variety of animal models did not inhibit the compensatory response after unilateral adrenalectomy (*25, 27–29*). In hypophysectomized rats compensatory adrenal changes can be blocked by the administration of aldosterone, even in the presence of adrenocorticotrophin (*25,30*). This effect of aldosterone may be related to suppression of angiotensin II and its recently described participation in the stimulation of platelet-derived (*31*) and other growth factors in the adrenal zona glomerulosa and elsewhere (*32, 33*). Others have suggested that a major stimulus for adrenal growth after unilateral adrenalectomy is neural (*34,35*). Interruption of the neural circuit by hemisection of the spinal cord has been shown to inhibit compensatory adrenal changes in animals when performed on the con-

TABLE 2
Effect of Unilateral Adrenal Destruction upon Adrenocortical Function and ^{131}I-NP-59 Uptake

					Plasma*					Urine†					NP-59 UPTAKE (in normal gland) (% admin. dose)
					Cortisol										
Age	Sex	Dx	Adrenal (cm)	AM	30	PM	E	NE	17OH	17KS	UFC	E	NE	M	VMA	
42	F	P‡	5						18.6	32.5					118.3	0.23
29	M	P	7						22.2	21.7		147.4	2,364	545	68.7	0.31
39	M	P	4	388.9	888.9							453.2	1,666.6	937.4		0.22
61	F	LCA§	5			555.6			23.9	13.1	115.5					0.46
13	F	P	4.5				899.3	43,917.2				185.6	7,304.7	16.4	123.2	0.24
30	F	P	4.7	527.8	1,388.9		534.1	39,319.2			68.8					0.27
55	M	LCA	3	777.8	1,277.8											0.25
61	F	AC**	4			333.4			21.1	18.1						0.55

* AM = 800–900 hr, 30 = plasma cortisol (nmol/liter) 30 min after 250 μg cortrosyn i.v.; PM = 1600–1800 hr, E = epinephrine (plasma 0–545 pmole/liter); and NE = norepinephrine (plasma 0–2955 pmol/liter).

† 17OH = 17-hydroxycorticosteroids (14–28 μmol/d), 17KS = 17-ketosteroids (25–88 μmol/d), UFC = urinary free cortisol (55–276 nmol/d), E = epinephrine (urine 0–109.2 nmol/d); NE = norepinephrine (urine 0–591 nmol/d); M = metanephrine (0–11 μmol/d); and VMA = vanillymandelic acid (0–35.4 μmol/d).

‡ P = pheochromocytoma.

§ LCA = lung carcinoma.

** AC = adrenal cyst.

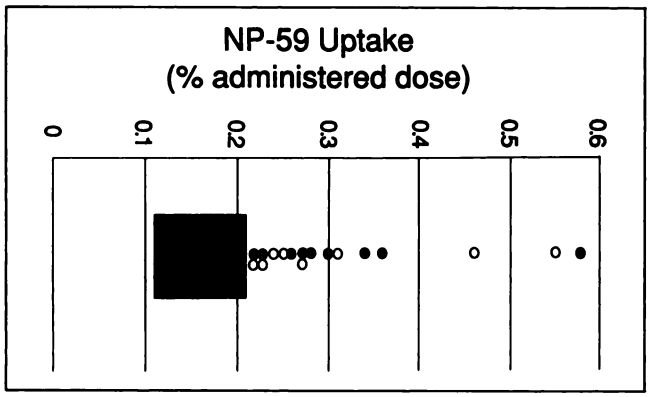

FIGURE 3. Adrenocortical NP-59 uptake in adrenalectomy (●) and adrenal destruction (○) groups compared to normal, single adrenal gland uptake ($p < 0.01$ compared to normal) (ref. 22).

tralateral side of the remaining adrenal (*24*). Unilateral, hypothalamic lesions have been shown to abolish ipsilateral, but not contralateral adrenal growth in adrenalectomized rats (*36*).

There are no morphologic or biochemical studies of adrenal activity and growth and/or anterior pituitary or hypothalamic function in intact animals maintained either on or off chronic adrenocortical suppression after unilateral adrenalectomy. The present investigation examined a more chronic, post adrenalectomy condition, where the shortest interval of study after operation was six months, and where replacement adrenal steroids were not given (Table 1). In all but two of the post-adrenalectomy group adrenal masses were noted. Whether the formation of adrenal masses represents a chronic tissue response to adrenalectomy mediated by angiotensin II and/or other growth factors cannot be established in the present study, but the high proportion, seven of nine patients with discrete adrenal masses, is suggestive of such an effect. The participation of the renin-angiotensin system cannot unfortunately be assessed in these cases as an evaluation of aldosterone and its secretogogues was not performed. The level of NP-59 uptake in the remaining adrenal in the adrenalectomy group was related to neither the size of the adrenal mass nor the interval after operation, albeit the sample size is small.

The normal remaining adrenal of the adrenal destruction group represents the result of progressive, and in some cases, rapid loss of functioning contralateral cortex in one adrenal gland. Like adrenalectomy, this situation should also result in a compensatory response(s) of the contralateral gland with increased size, function and substrate (NP-59) accumulation. That stress due to the primary non-adenocortical lesion (for example, a pheochromocytoma or other neoplastic process) was not a factor in the compensatory response of these patients is suggested by the lack of a difference in NP-59 uptake between the adrenalectomy versus the adrenal destruction groups. Furthermore, the non-adrenalectomized patients with unilateral adrenal destruction consistently exhibited normal anatomy of the unaffected gland by CT. It is not surprising that in the unaffected gland, small hypertrophic and/or hyperplastic changes might not be appreciated by multi, thin slice, high resolution CT at an early time where functional changes in that gland manifested as increased ^{131}I-6β-iodomethyl-19-norcholesterol (substrate) uptake would be detected by scintigraphy.

We used adrenal non-visualization on the ^{131}I-NP-59 scintiscan as a means to identify the absence of unilateral adrenocortical function. The rationale for this approach is drawn from our previous studies which have demonstrated the efficacy of scintigraphy in identifying the sources of abnormal adrenal function (*37–40*). Although we cannot be assured of complete functional obliteration of the affected adrenal in the group with destructive lesions, given the absence of discernible NP-59 uptake, the contribution to circulating hormones from this gland must be very small. The uptake of ^{131}I-NP-59 has been used to characterize physiological changes of adrenal cortical function in both man and animals (*41,42*). Furthermore, the patterns of iodocholesterol accumulation can be used to discern differential adrenal function in the context of overall normal hormone secretion in patients harboring incidentally discovered, adrenal masses (*43–45*). That a second pheochromocytoma occurring in the remaining adrenal at a remote time after the removal of a primary lesion would be an alternative explanation for an intraadrenal mass lesion and must be a diagnostic consideration in the evaluation of these particular patients. However, in our series the presence of normal biochemistry and increased adrenocortical iodocholesterol accumulation makes this a most unlikely possibility, as a pheochromocytoma would be depicted as a cortical defect or space occupying adrenal lesion on iodocholesterol scintigraphy (*46*).

In the present study we believe that the increased uptake of iodocholesterol in these remaining, intact adrenals reflects the integrated effect of compensatory process(es) triggered by contralateral adrenalectomy or unilateral adrenal destruction. Mean adrenocortical NP-59 uptake is significantly elevated over that of the normal single gland and in some instances exceeds normal total (right + left) adrenocortical NP-59 uptake (*22*). Thus, not only can anatomic changes after unilateral adrenalectomy be appreciated, but chronic functional changes can also be documented in the remaining adrenocortical tissues after adrenalectomy or unilateral adrenal destruction by neoplasm in man.

The consequences of prolonged replacement therapy with gluco- and/or mineralocorticoids are well defined. These may include symptoms and signs of glucocorticoid excess or deficiency following abrupt cessation of therapy. Most important is the suppression of the hypothalamic-pituitary-adrenal axis with its attendant risks during medical or surgical emergencies. Viewed in this context, the current work suggests that after adrenalectomy the de-

creased "adrenal reserve" of the solitary functioning adrenal gland has no effect upon either basal adrenal function or the response to stress (ACTH challenge). Therapy with gluco-or mineralocorticoids would not therefore be indicated in these patients. The anatomic distortion (adrenal masses) developing in the remaining adrenal cortex after unilateral adrenalectomy, poses interesting mechanistic and etiologic questions that remain unanswered at this point, but based upon the present study appear to be of little pathologic significance.

CONCLUSION

Compensatory anatomic and functional changes can be depicted in the remaining adrenal cortex after adrenalectomy. These changes appear to have little effect upon adrenocortical function, but when accompanied by significant alterations of adrenal contour or the development of an adrenal mass then it may require further diagnostic evaluation.

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FIRST IMPRESSIONS

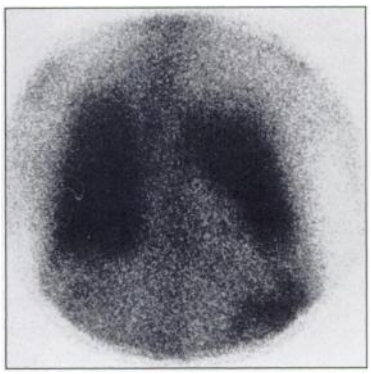

FIGURE 1. Gallium scan 48 hr postinjection shows intense lung activity and absent liver activity.

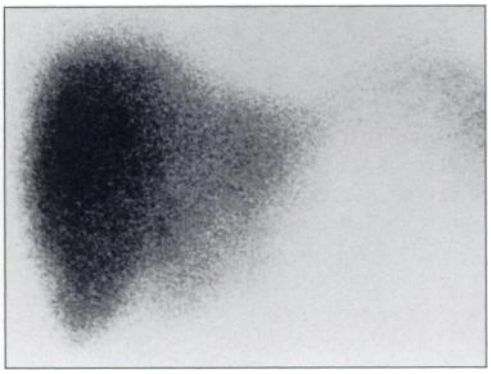

FIGURE 2. Normal liver-spleen scan with ^{99m}Tc-sulfur colloid.

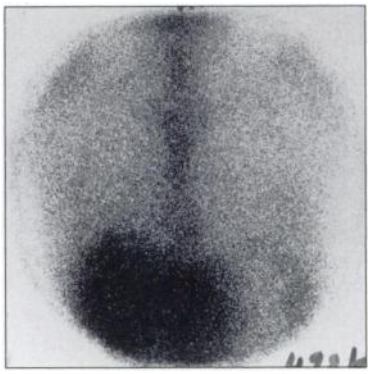

FIGURE 3. Gallium scan 7 wk after the initial scan shows normal liver uptake and absent lung activity.

Case Report: Hepatopulmonary Steal in PCP

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A gallium scan was performed on a 49-yr-old male HIV-positive patient admitted with fever, weight loss and respiratory distress that required intubation. The chest x-ray showed diffuse interstitial infiltration and his sputum was positive for PCP. The gallium scan (48 hr postinjection) showed massive uniform lung uptake bilaterally and nonvisualization of the liver (Fig. 1). All standard lab test results were unremarkable except for mild elevation of liver function values. A liver-spleen scan with ^{99m}Tc-sulfur colloid (Fig. 2) and a hepatobiliary scan with ^{99m}Tc-Mebrofenin® were found to be normal. The patient was treated with Pentamidine and Septra, which induced a dramatic clinical improvement. A follow-up gallium scan performed after 6 wk showed no lung uptake and normal liver activity (Fig. 3).

DISCUSSION

Absent or faint liver activity on gallium scans has been ascribed to hemochromatosis and other causes of serum iron elevation that block the binding sites. Other reduction in gallium uptake includes competitive uptake by tumor or inflammatory sites *(1)*, prior administration of scandium *(2–4)*, lymphangiographic contrast agents *(5)*, radiation exposure and chemotherapeutic agents *(6–8)* and, recently, gandolinum contrast for MRI *(9)*.

In this patient, no significant liver pathology or hematologic abnormalities were demonstrated throughout the hospital course nor did he receive any chemotherapeutic or contrast agents. Consequently, the poor liver uptake was ascribed to a "steal" phenomenon by the acutely inflamed lungs.

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