

Preclinical Cushing's Syndrome in Adrenal "Incidentalomas": Comparison with Adrenal Cushing's Syndrome

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ABSTRACT

Adrenal tumors are usually diagnosed by clinical symptoms of hormone excess. The increasing use of ultrasound and computed tomography results in the detection of a substantial number of incidentally discovered adrenal tumors. Most of these tumors are nonfunctional adrenocortical adenomas, but a few cases of subclinical cortisol production in "incidentalomas" have been reported. We investigated prospectively the prevalence of autonomous cortisol production in 68 patients (44 females and 24 males, aged 25–90 yr) with adrenal incidentalomas at our institution. As a screening procedure all patients with incidentalomas underwent an overnight dexamethasone suppression test (1 mg). Patients who failed to suppress serum cortisol below 140 nmol/L (5 µg/dL) underwent more comprehensive studies (prolonged dexamethasone suppression test, determination of the diurnal rhythm of cortisol secretion in saliva, and CRH stimulation test). Eight patients (12% of all patients with incidentalomas; 5 females and 3 males, aged 25–71 yr) were finally identified as having cortisol-producing tumors, and the findings in these patients were compared with those of overt Cushing's syndrome in 8 patients (8 females, aged 26–50 yr) suffering from cortisol-producing adrenal adenomas.

The tumor size of patients with cortisol-producing incidentalomas ranged from 2–5 cm. No specific signs and symptoms of hypercortisol-

ism were present, but arterial hypertension (seven of eight subjects), diffuse obesity (four of eight subjects), and noninsulin-dependent diabetes mellitus (NIDDM; two of eight subjects) were frequently observed. Baseline cortisol levels were in the normal to upper normal range, whereas baseline ACTH levels were suppressed in five of the eight patients. In none of the patients was serum cortisol suppressible by low dose or high dose dexamethasone. The ACTH and cortisol responses to CRH were normal in two, blunted in one, and suppressed in four patients. Unilateral adrenalectomy was performed in seven patients and resulted in temporary adrenal insufficiency in four of them. After surgery, improvement of arterial hypertension, a permanent weight loss in obese subjects, and a better metabolic control of NIDDM were noted in the majority of patients.

The following conclusions were reached. Incidentally diagnosed adrenal tumors with pathological cortisol secretion in otherwise clinically asymptomatic patients are more frequently observed than previously assumed. Adrenocortical insufficiency is a major risk in these patients after adrenalectomy. After surgery, hypertension, obesity, and NIDDM may improve. Patients with asymptomatic adrenal incidentalomas, therefore, should be screened for cortisol production by means of an overnight dexamethasone suppression test. (*J Clin Endocrinol Metab* 75: 826–832, 1992)

FUNCTIONAL adrenocortical tumors are usually associated with signs and symptoms of hormone excess. In contrast, nonfunctional tumors are presumed if the patients are asymptomatic, and baseline hormone levels are in the normal range. With wider application of ultrasound, computed tomography (CT), and, more recently, magnetic resonance imaging (MRI), adrenal neoplasms have been detected incidentally in increasing frequency (1–11). These so-called "incidentalomas" of the adrenal gland are usually asymptomatic and are often classified as nonfunctional tumors. However, these lesions may be truly nonfunctional or may secrete adrenocortical hormones in amounts insufficient to cause clinically apparent disease. In recent years there have been several case reports of functional adrenal nodules secreting cortisol without clinical evidence of Cushing's syndrome (12–18). Since the prevalence of autonomous glucocorticoid secretion by incidentally detected adrenal tumors is unknown, the hormonal evaluation of patients with incidentalomas is

still controversial. Recently, Ross and Aron (19) concluded that the low probability of cortisol production in adrenal incidentalomas does not justify endocrine screening procedures such as the overnight dexamethasone suppression test. However, there is growing evidence that cortisol production by asymptomatic adrenal tumors is more frequently observed than assumed until now. Hensen *et al.* (20) reported 3 cortisol-producing tumors (6%) in a series of 50 incidentalomas. More recently, in a retrospective study, 6 of 122 patients (5%) with adrenal incidentalomas were shown to harbor cortisol-producing tumors, but the study was hampered by incomplete endocrine data (21). In our series of 68 patients with asymptomatic adrenal tumors, 8 patients (12%) were subsequently found to have pathological cortisol production by their tumor. This high prevalence emphasizes the importance of a careful endocrinological evaluation in patients with adrenal incidentalomas.

Subjects and Methods

Patients

Eighty-two patients with asymptomatic incidentally discovered adrenal tumors were prospectively evaluated at the Medical Department

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II of the University of Cologne from 1982–1989. The majority of patients were referred from internists in private practice or medical departments of other hospitals. The adrenal tumors were discovered by ultrasound or CT of the abdomen, invariably performed for the evaluation of an unrelated disease. Patients suffering from known malignancies undergoing staging procedures ($n = 10$) and patients with questionable enlargement of the adrenals ($n = 4$) were excluded. None of the remaining 68 patients showed specific signs and symptoms of hormone excess. As a screening procedure all patients underwent an overnight, low dose dexamethasone suppression test (1 mg dexamethasone at 2300 h and determination of serum cortisol at 0900 h on the following day) and collected 24-h urine volume for measurement of catecholamines and aldosterone excretion. In addition, serum potassium levels were determined once.

Patients who failed to suppress serum cortisol to below 140 nmol/L (5 μ g/dL) after administration of 1 mg dexamethasone underwent more comprehensive biochemical testing of adrenal function (see below). The criteria used to make the diagnosis of autonomous cortisol production by the tumor (preclinical Cushing's syndrome) were as follows: 1) the patient had no overt clinical signs of Cushing's syndrome (arterial hypertension (>160/95 mm Hg), obesity (>120% of ideal weight), and noninsulin dependent diabetes mellitus (NIDDM) were not considered to be specific symptoms because they are frequently found in patients with adrenal incidentalomas); 2) the patient had no complaints directly attributable to the disease; 3) the adrenal mass was detected incidentally; 4) serum cortisol levels were repeatedly not suppressible below 90 nmol/L (3 μ g/dL) by low dose and high dose dexamethasone; and 5) the failure to suppress cortisol by dexamethasone was restored to normal by adrenalectomy, or adrenalectomy resulted in adrenal insufficiency (one patient who was ineligible for surgery did not meet this criterion).

Eight of 68 patients (12%) with adrenal incidentalomas were shown to have autonomous cortisol production by the tumor. In addition, 1 pheochromocytoma and 1 aldosteronoma were found in this series (data not shown).

Eight patients suffering from Cushing's syndrome due to unilateral adrenocortical adenomas served as a control group. These patients were treated at our institution between 1977 and 1988 and were studied retrospectively. The clinical data of all patients presented in this report are shown in Table 1.

Endocrine assessment

Adrenocortical function was assessed using routine endocrine techniques. The following tests were performed: baseline serum cortisol and ACTH were measured at 0900 h, the diurnal variation in cortisol secretion was determined by measuring salivary cortisol in 1-h intervals between 0900–2300 h (22), 24-h urine volume was collected for measurement of urinary free cortisol excretion ($n = 4$); and pituitary-adrenal suppressibility was tested by administration of dexamethasone (days 1

and 2, 3 mg at 2300 h; days 3 and 4, 2 mg, four times a day; determination of serum cortisol at 0900 h every day). The response of the pituitary-adrenal axis to exogenous CRH was assessed using human CRH (100 μ g Corticobiss, iv, at 0900 h; Bissendorf Peptide, Wedemark, Germany). In the control group (patients with adrenal Cushing's syndrome), lysine vasopressin (5 IU, iv, for 60 min) was used before 1984 ($n = 2$). A rise in cortisol concentrations greater than 120 nmol/L (4.7 μ g/dL) was considered a positive response.

Serum cortisol (Serono, Freiburg, Germany) was measured by a commercial enzyme-linked immunosorbent assay. Urinary free cortisol excretion was determined by RIA (NEN, Dreieich, Germany). Salivary cortisol was measured by RIA, as previously described (22). Plasma ACTH was determined by RIA after extraction with QUSO G₃₂ (23). The lower limit of detection was 1 pmol/L.

Radiological studies

CT scans were performed as 4- or 8-mm thick continuous slices with a Somatotom 2, Somatotom DR, or Somatotom DRH scanner (Siemens, Erlangen, Germany) before and after iv administration of contrast material.

Five patients with preclinical Cushing's syndrome underwent MRI of the adrenal glands using the fast field-echo pulse sequence technique at 1.5 T (Gyroscan S 15, Philips Medical Systems, Best, The Netherlands) before and after the administration of 0.1 mmol/kg gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA, Schering, Berlin, Germany) (24).

Pathology

All surgically removed asymptomatic tumors and five of eight symptomatic cortisol-producing tumors were available for histopathological studies. Light microscopy was performed using routine staining methods of paraffin-embedded sections, including immunostaining for neuron-specific enolase and D11 as a specific marker for adrenocortical tissue (25).

Statistical analysis

The results are expressed as the mean \pm 1 sd. Statistical analysis was performed by two-tailed Wilcoxon test for unpaired data. Significance was retained for $P < 0.05$.

Results

Clinical data

Patients with preclinical Cushing's syndrome were younger than patients with nonfunctional adrenal inciden-

TABLE 1. Clinical data of patients with nonfunctional incidentalomas, cortisol-producing incidentalomas (preclinical Cushing's syndrome), and symptomatic cortisol-producing adrenal adenomas causing overt Cushing's syndrome

	Patients with incidentalomas		
	Nonfunctional	Preclinical Cushing's syndrome	Overt Cushing's syndrome
No.	58	8	8
Age (yr)	59 \pm 12 (25–90)	50 \pm 15 (25–71)	39 \pm 8 (26–50)
Sex (%)			
Male	36	37	0
Female	64	63	100
Tumor size (by CT; cm)	3.0 \pm 2.0 (1.0–15.0)	3.7 \pm 1.0 (2.0–5.0)	3.9 \pm 0.9 (2.0–4.5)
Tumor location (%)			
Left adrenal	44	37	50
Right adrenal	35	63	50
Bilateral	21		
Temporary adrenal insufficiency after adrenalectomy [no. (%)]	0/8 (0)	4/7 (57)	8/8 (100)
Duration of glucocorticoid replacement therapy (months)		17 \pm 15 (8–39; 4) ^a	19 \pm 8 (9–33; 8)

^a Range; number of subjects.

talomas but older than patients with overt adrenal Cushing's syndrome (Table 1). Female patients were more frequently observed in all three groups. Mean tumor size, determined by CT, was smaller in nonfunctional tumors than in both preclinical Cushing's syndrome and overt Cushing's syndrome. Tumor location caused no significant difference.

Specific signs and symptoms of Cushing's syndrome were absent in patients with nonfunctional adrenal incidentalomas (Table 2). In preclinical Cushing's syndrome, the majority of patients lacked classical Cushing's signs. One patient had a mild moon-face appearance, which, however, could only be identified retrospectively when this feature disappeared after adrenalectomy. Hypertension, diffuse obesity, and NIDDM were frequently observed in all patients with adrenal neoplasm.

Endocrine data

The endocrine results of the individuals with preclinical Cushing's syndrome are shown in Table 3. Biochemically, the patients exhibited different stages of hypercortisolism. Patient 1, for example, had an abnormal dexamethasone suppression test, but normal urinary free cortisol excretion, normal diurnal rhythm of salivary free cortisol, and a normal response to CRH. In contrast, patients 6–8 showed biochemical characteristics of adrenal Cushing's syndrome, with lost diurnal rhythm of cortisol secretion, elevated urinary free cortisol excretion, nonsuppressible cortisol by dexamethasone, and no response of ACTH to CRH. Apparently, the degree of hypercortisolism in preclinical Cushing's syndrome ranged from slightly abnormal to completely pathological and was indistinguishable from that in overt adrenal Cushing's syndrome in some of the patients. One may, therefore, speculate whether this spectrum represents the natural course of cortisol-producing tumors evolving toward symptomatic Cushing's syndrome.

Mean hormone values in patients with preclinical Cushing's syndrome and patients with overt adrenal Cushing's

TABLE 2. Signs and symptoms of Cushing's syndrome in patients with nonfunctional incidentalomas (n = 58), patients with cortisol-producing incidentalomas (preclinical Cushing's syndrome; n = 8), and patients with overt adrenal Cushing's syndrome (n = 8)

	Patients with incidentalomas		Overt Cushing's syndrome
	Nonfunctional	Cortisol-producing	
Moon-face	0	12.5 ^a	100
Central obesity	0	0	87.5
Hirsutism	5	12.5	87.5
Buffalo hump	0	0	62.5
Striae rubrae	0	0	62.5
Ekchymosis	0	0	62.5
Oligo-amenorrhoe	0	0	62.5
Psychiatric symptoms	0	0	50
Osteoporosis	0	0	37.5
Edema	11	0	25
Arterial hypertension	46	75	62.5
Diffuse obesity	36	50	12.5
NIDDM	21	25	12.5

Values given are percentages.

^a Was detected retrospectively after adrenalectomy.

TABLE 3. Endocrine findings in eight patients with preclinical Cushing's syndrome

Patient no.	Baseline cortisol (0900 h)	Baseline ACTH (0900 h)	Urinary cortisol excretion	Diurnal rhythm of cortisol in saliva	CRH test, max increase		Serum cortisol after 8 mg dexamethasone	Primary adrenal insufficiency post-op	Morphology of normal adrenal cortex	Serum cortisol after 1 mg dexamethasone postsurgery
					ACTH	Cortisol				
1	296	2.9	2.41	Normal	25.0	302	125	None	Normal	27
2	608	<1.0	1.38	Absent	4.7	121	450	None	Partially atrophic	25
3	608	2.0	ND	Absent	0.2	303	464	None	No remaining normal cortex identified	35
4	490	<1.0	ND	Absent	ND	ND	170	No surgery	No surgery	No surgery
5	174	1.6	1.21	Absent	0.0	7	221	10 months	Atrophic	ND
6	406	<1.0	ND	Absent	0.0	70	541	11 months	Atrophic	ND
7	525	<1.0	8.11	Absent	0.0	-30	735	15 months	Atrophic	ND
8	940	<1.0	ND	Absent	0.0	-191	636	37 months	No remaining normal cortex identified	ND
Normal range	140–680 nmol/L (5–25 µg/dL)	<11 pmol/L (<50 pg/mL)	<2.76 µmol/day (<100 µg/day)	°	Δ ACTH, >2.2 pmol/L (>10 pg/mL)	Δi Cortisol, >140 nmol/L (>5 µg/dL)	<90 nmol/L (<3 µg/dL)			<140 nmol/L (<5 µg/dL)

For methods, see *Subjects and Methods*. ND, Not done. To convert ACTH concentrations to picograms per ml, multiply by 4.5; to convert cortisol concentrations to micrograms per dL, multiply by 0.04.
^a See Fig. 1.

TABLE 4. Endocrine data (mean \pm SD, range) of patients with preclinical Cushing's syndrome and overt Cushing's syndrome

	Preclinical Cushing's syndrome	Overt Cushing's syndrome	Normal range
Baseline serum cortisol at 0900 h (nmol/L)	417 \pm 176 (176–756)	533 \pm 142 (459–719)	140–680
Baseline ACTH at 0900 h (pmol/L)	1.4 \pm 0.7 (<1.0–2.9)	1.1 \pm 0.3 (1–1.7)	3.7 \pm 2.2
Serum cortisol after 1 mg dexamethasone (nmol/L)	464 \pm 204 (204–815)	514 \pm 260 (88–830)	<140
Serum cortisol after 3 mg dexamethasone (nmol/L)	330 \pm 175 (100–670)	435 \pm 197 (193–691)	<140
Serum cortisol after 4 \times 2 mg dexamethasone (nmol/L)	398 \pm 175 (100–735)	503 \pm 196 (207–719)	<90
Cortisol increase in response to CRH/LVP (>120 nmol/L)	3/7	0/7	

The observed differences were not statistically significant. To convert ACTH concentrations to picograms per mL, multiply by 4.5; to convert cortisol concentrations to micrograms per dL, multiply with 0.04. LVP, lysine vasopressin. Values are the mean \pm SD; the range is in parentheses.

syndrome are shown in Table 4. Although not significantly different, we observed a tendency for ACTH levels to be higher and cortisol values to be lower in preclinical Cushing's syndrome compared to overt adrenal Cushing's syndrome.

The diurnal rhythm of salivary free cortisol was lost in all patients with overt adrenal Cushing's syndrome and in six patients with preclinical Cushing's syndrome (Fig. 1). One patient with preclinical Cushing's syndrome had a normal diurnal rhythm of cortisol secretion.

The administration of low and high dose dexamethasone did not suppress serum cortisol concentrations in preclinical Cushing's syndrome as well as in overt Cushing's syndrome (Fig. 2). This demonstrates the autonomous nature of cortisol secretion by these tumors.

The mean response of ACTH to stimulation with CRH was suppressed in overt adrenal Cushing's syndrome, but blunted in preclinical Cushing's syndrome. In addition, mean serum cortisol concentrations after stimulation were slightly elevated in preclinical Cushing's syndrome, but not in overt Cushing's syndrome.

The preoperative CRH test was useful in identifying patients with preclinical Cushing's syndrome at risk for secondary adrenal insufficiency after adrenalectomy. In patients who showed a serum cortisol increase of at least 120 nmol/L in response to CRH, adrenocortical function remained

intact after removal of the tumor. All patients in whom serum cortisol was unresponsive to CRH suffered from adrenal insufficiency.

Radiological studies (preclinical Cushing's syndrome)

On CT images, all patients with preclinical Cushing's syndrome had lesions less than 6 cm in diameter, sharp margins, and a round shape. On plain scans, MRI showed low signal intensities on T1-weighted scans and relative signal intensities under 2.0 on T2-weighted images. The dynamic contrast-enhanced studies showed a moderate enhancement and quick wash-out in four tumors. In only one highly vasculated adenoma was enhancement stronger and wash-out slower, indicative of a malignant adrenal tumor.

Histology

Seven of eight patients with preclinical Cushing's syndrome underwent unilateral adrenalectomy. One patient suffered from advanced atherosclerosis and was ineligible for surgery. He died 5 months later due to an unrelated disease. An autopsy was not performed.

In all cases compact cell or spongiocytic adrenocortical adenomas were found. Ipsilateral atrophy of the adjacent adrenal cortex was noted in four patients and correlated well with suppressed baseline ACTH levels in these patients (Table 3). The morphology of tumors in preclinical Cushing's syndrome was similar to that in overt Cushing's syndrome. No significant differences were found in tumor size, tissue pattern, quantity of spongiocytic cells, adipose tissue, and myolipomatous foci. Upon neuron-specific enolase staining, some of the tumors in both groups showed sparse reactivity. D11 immunocytochemistry, a selective marker of adrenocortical tissue, exhibited clear reactivity of various degrees in all tumors.

Postoperative course

After adrenalectomy, four of the patients with preclinical Cushing's syndrome suffered from secondary adrenal insufficiency requiring replacement therapy. Baseline cortisol concentrations at 0900 h were below 140 nmol/L (5 μ g/dL) in

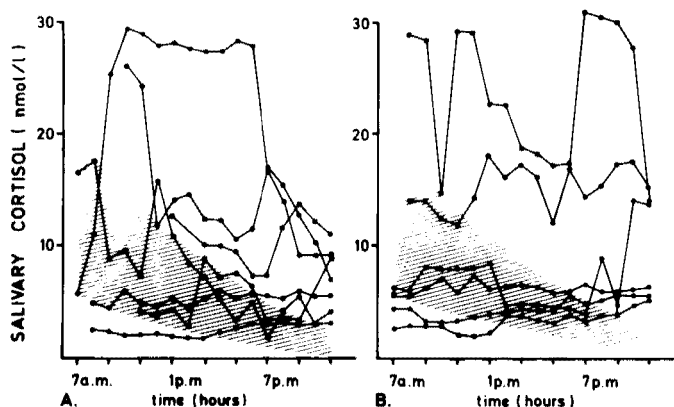


FIG. 1. Salivary cortisol concentrations between 0700–2300 h in patients with preclinical Cushing's syndrome (A) and patients with overt Cushing's syndrome (B). The shaded area represents the normal range.

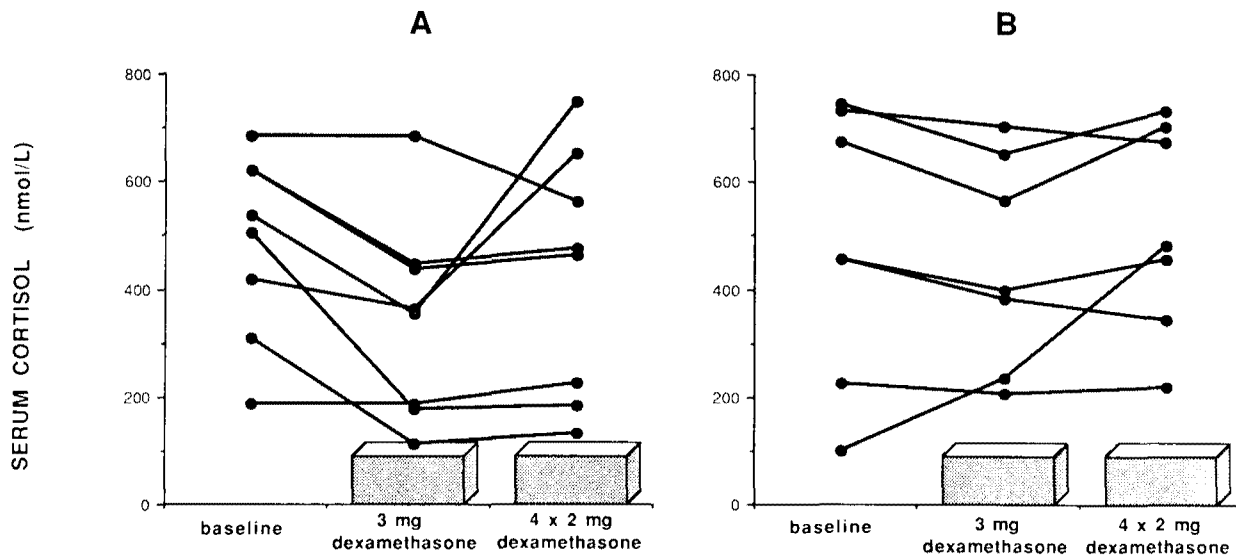


FIG. 2. Serum cortisol levels at baseline and during dexamethasone suppression. A, Patients with preclinical Cushing's syndrome. B, Patients with overt Cushing's syndrome. The shaded bars show the normal range. To convert cortisol concentrations to micrograms per dL, multiply by 0.04.

all of these patients, and did not increase above 360 nmol/L (13 μ g/dL) after stimulation with ACTH-(1-24). The patients received glucocorticoid replacement therapy for 8-39 months. Glucocorticoid therapy could not be withdrawn earlier in asymptomatic patients than in patients with overt Cushing's syndrome, of whom all suffered from adrenal insufficiency after surgery (Table 1).

In the remaining three patients with preclinical Cushing's syndrome who had normal adrenocortical function after adrenalectomy, serum cortisol was fully suppressible by low dose dexamethasone treatment, demonstrating that the lack of suppression preoperatively was due to autonomous cortisol production.

The frequency and severity of arterial hypertension, obesity, and diabetes mellitus changed considerably in patients with preclinical Cushing's syndrome after adrenalectomy (follow-up, 18-60 months; mean, 28 months).

The four obese patients reported a permanent weight loss of more than 5 kg (range up to 20 kg). Three of the hypertensive patients could reduce the antihypertensive medication, and one patient had normal blood pressure levels after adrenalectomy. Both patients with diabetes mellitus had improvement of glycemic control and could be switched to dietary treatment.

The postoperative course of patients with preclinical Cushing's syndrome shows that cortisol production by these tumors is not completely asymptomatic. Although these tumors did not secrete glucocorticoids in amounts sufficient to cause overt Cushing's syndrome, the cortisol excess to some extent caused hypertension, obesity, and diabetes mellitus.

Discussion

With wider application of ultrasound, CT, and MRI, incidental adrenal tumors have been detected with increasing frequency (1-11). It is estimated that in approximately 0.6-

2% of all abdominal CTs clinically unsuspected adrenal tumors are discovered (19). The majority of these tumors have been shown to represent stable or slowly growing adrenocortical adrenal adenomas, whereas metastases from occult malignancies, adrenomyelolipomas, pheochromocytomas, and adrenocortical carcinomas are rarely found. As far as endocrine studies have been undertaken, most of the lesions have been shown to be nonfunctional. However, some of the patients had asymptomatic pheochromocytomas (3, 4, 10) or asymptomatic aldosterone-producing tumors (25). In addition, there have been several reports of incidentally detected cortisol-secreting adrenal tumors in otherwise healthy subjects (12-19). This entity, therefore, has been termed pre-Cushing's syndrome, subclinical Cushing's syndrome, or preclinical Cushing's syndrome. We report here the clinical, biochemical, and radiological data of 8 patients with this syndrome, who represent 12% of our series of 68 prospectively studied patients with an incidentally discovered adrenal mass.

The prevalence of cortisol-producing tumors has been unexpectedly high in our series, accounting for 12% of all adrenal incidentalomas. This may be explained by the fact that careful endocrine studies are frequently not undertaken in these patients. However, recently there have been two reports on preclinical Cushing's syndrome in adrenal incidentalomas (20, 25). Hensen *et al.* (20) found cortisol-producing adenomas in 6% of all incidentally detected adrenal tumors, whereas McLeod *et al.* (21) reported a 5% prevalence cortisol-producing tumors in 122 patients with incidentalomas. Seemingly, cortisol production by adrenal tumors is more frequently found than assumed until now when thorough endocrine procedures are undertaken in these patients.

Autonomous glucocorticoid secretion without signs and symptoms of Cushing's syndrome seems to have some analogy to the more commonly recognized thyroid nodule. In the latter instance, a thyroid adenoma autonomously secretes

thyroid hormones. The surrounding normal thyroid gland may be incompletely (warm nodule) or completely (hot nodule) suppressed. Hyperthyroidism, however, develops in only 20% of patients. This outcome is more likely when the adenoma exceeds 3 cm in diameter. The clinical course of autonomous cortisol-secreting tumors in patients with preclinical Cushing's syndrome is not known. However, tumor size seems to be of minor importance in this entity. Comparison of the tumor size in our series showed that the mean diameter did not differ in preclinical Cushing's syndrome and overt Cushing's syndrome.

Comparison of the biochemical features of preclinical Cushing's syndrome with those of overt Cushing's syndrome showed clear differences in the clinical and biochemical characteristics of these entities, although the observed differences were not statistically significant due to the limited number of patients. However, the hypercortisolism tended to be of lesser degree in preclinical Cushing's syndrome compared to overt Cushing's syndrome. Baseline cortisol levels were slightly lower in these patients, and plasma ACTH levels were higher than those in patients with overt Cushing's syndrome. In none of the patients with Cushing's syndrome did ACTH and cortisol levels respond to stimulation with CRH or lysine vasopressin, whereas three of seven patients with preclinical Cushing's syndrome showed a rise in ACTH and cortisol levels. Complete suppression of the pituitary-adrenal axis, resulting in adrenocortical insufficiency after adrenalectomy, was evident in all patients with overt Cushing's syndrome, but in only four of seven patients with preclinical Cushing's syndrome. These data support the concept that cortisol-producing tumors in adrenal incidentalomas secrete glucocorticoids in amounts insufficient to cause overt Cushing's syndrome.

As a group, the endocrine findings in patients with preclinical Cushing's syndrome were heterogenous. This may be explained by variable amounts and variable duration of cortisol secretion by the tumor probably initially results in blunting of the diurnal variation and a lack of suppression of cortisol by dexamethasone. As ACTH is suppressed to low levels, the CRH test becomes progressively abnormal. Finally, excretion of urinary cortisol exceeds the normal range.

Our results show that the best screening test for preclinical Cushing's syndrome in patients with an incidentally discovered mass is the low dose dexamethasone test, which was abnormal in all of our patients. These results are in agreement with the reported cases in the literature, which all showed an abnormal response to dexamethasone (14, 16–18, 20, 21). In contrast, urinary cortisol excretion was normal in three of four of our patients tested. Six of nine patients previously reported also showed normal 24-h urinary cortisol levels. Therefore, urinary cortisol is not a sensitive indicator of hypercortisolism in these patients. Determination of diurnal cortisol secretion is also of limited value in the evaluation of these patients. It is not a practical out-patient test, and the results may be difficult to interpret if the cortisol production rate is low and evening cortisol levels are only slightly elevated.

Should patients with preclinical Cushing's syndrome undergo adrenalectomy? At the moment this question remains to be answered. Charbonnel *et al.* (14) reported a patient with an asymptomatic cortisol-producing tumor who initially refused surgery. The patient remained in good health for 5 yr, at which time he finally agreed to undergo adrenalectomy. This case demonstrates that the natural course of asymptomatic cortisol-producing adenomas can be stable. Apparently, preclinical Cushing's syndrome may not necessarily evolve toward overt Cushing's syndrome. However, Hensen *et al.* (26) reported a similar patient in whom after 1 yr a mild form of overt Cushing's syndrome (striae and buffalo hump) developed (26). This case shows that preclinical Cushing's syndrome can progress to Cushing's syndrome. Therefore, it may be argued that adrenalectomy is generally required in these patients to avoid morbidity from Cushing's syndrome. The hypothetical concept of tumorigenesis of cortisol-producing tumors is summarized in Fig. 3.

Additional reasons for surgery may be seen in the improvement of arterial hypertension, obesity, and diabetes mellitus that was observed in our patients after adrenalectomy. Although the tumors did not secrete glucocorticoids in amounts sufficient to cause overt Cushing's syndrome, the cortisol excess was not completely asymptomatic and apparently resulted to some extent in hypertension, weight gain, and diabetes mellitus. In patients with accelerated arterial hypertension and obesity, therefore, we recommend adrenalectomy as the treatment of choice. Completely asymptomatic

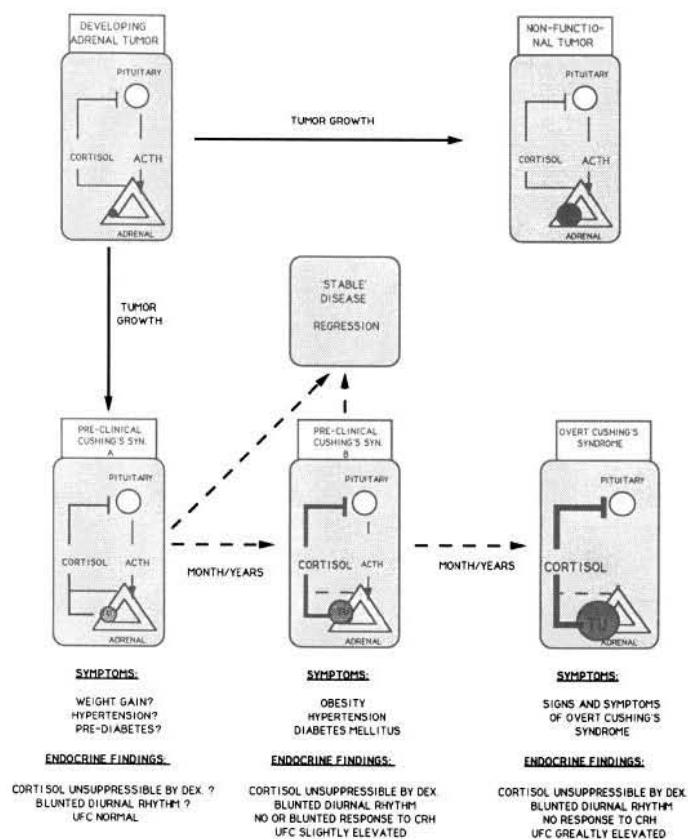


FIG. 3. Hypothetical model of the tumorigenesis of cortisol-producing tumors.

patients and very old patients may be treated conservatively, but close follow-up studies are then indicated.

In summary, we report the series of eight patients with asymptomatic cortisol-producing adrenal adenomas. These tumors represent 12% of a series of 68 patients with incidentally discovered adrenal tumors. Because the natural course of preclinical Cushing's syndrome is not known yet, we recommend adrenalectomy as the treatment of choice only in young patients and patients with arterial hypertension, weight gain, or newly recognized diabetes mellitus. In addition, adrenalectomy should be performed if tumor size (>6 cm) and contrast-enhanced MR images rise the suspicion of an adrenocortical carcinoma.

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