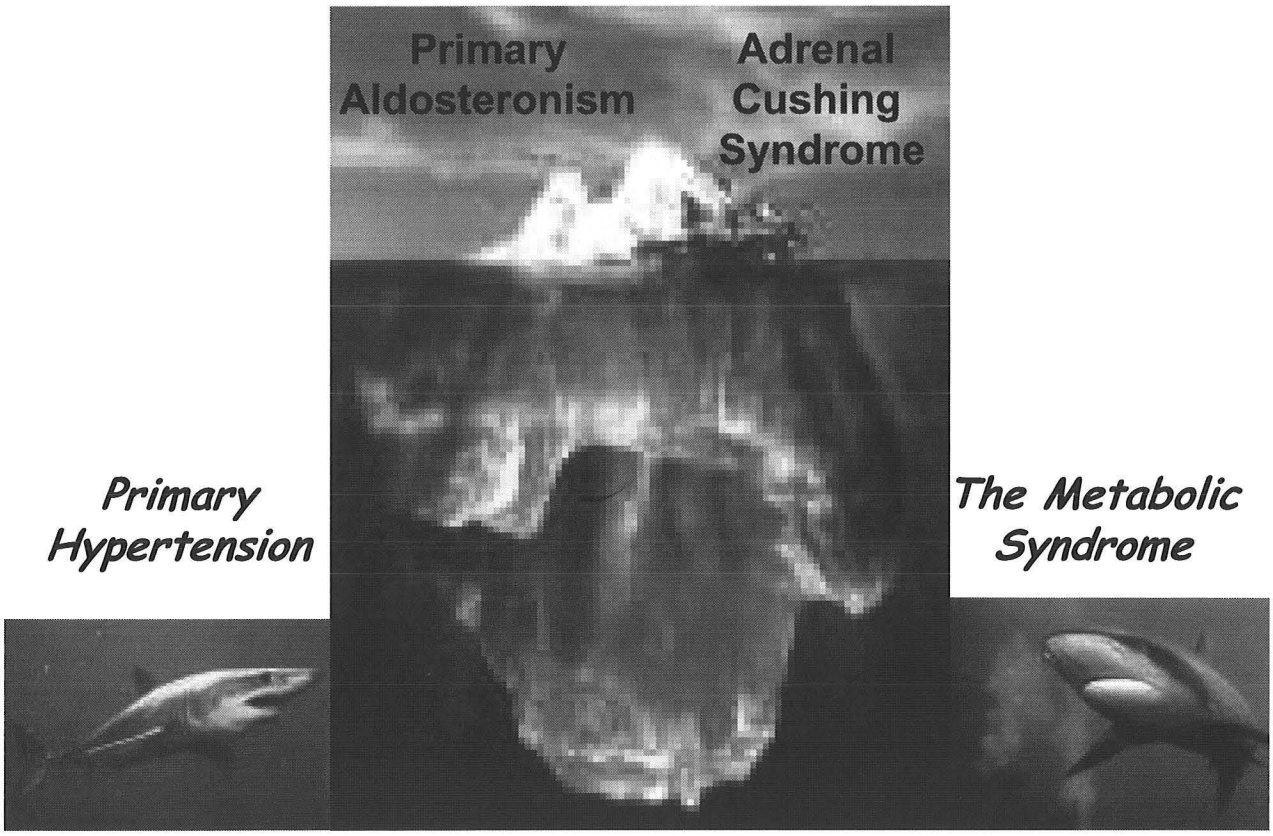
Adrenal Tumors, Diagnostic Challenges, and the Tip of the Iceberg



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This is to acknowledge that Richard J. Auchus, MD, PhD, has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Auchus will not be discussing off-label uses in his presentation.

Dr. Auchus' basic research interests include the genetics of human steroid biosynthesis and the biochemistry of steroidogenic cytochromes P450 and steroid dehydrogenases/reductases. His laboratory studies the structural basis of substrate discrimination, product distributions, and reaction mechanisms and the principles that relate enzyme structure to physiological function. His clinical research focuses on mineralocorticoid-dependent hypertension, determining diagnostic strategies and understanding genetic mechanisms of hypertension. His clinical practice focuses on pituitary, adrenal, and gonadal disorders, including endocrine hypertension and adult patients with genetic disorders of steroid biosynthesis.

Today I will discuss the following topics:

1) Primary Aldosteronism
2) Adrenal Cushing Syndrome
    For 1) and 2) above:
    The classic syndromes
    The recognition of milder cases
    The difficulties in making the diagnosis, particularly in mild cases
    Limits to pursuit of a definitive diagnosis
3) Incidental Adrenal Nodules
4) The Future of Adrenal Disorders

I will review the clinical presentations and diagnostic strategies for primary aldosteronism and cushing syndrome and then explore the evidence that some cases of primary hypertension and the metabolic syndrome—which are very common disorders—lie on one end of the spectrum of these uncommon disorders.

Primary Aldosteronism (PA)

A comprehensive analysis of primary aldosteronism is contained in the article appended to the end of this protocol (1). My key recommendations include:

•Do screen all patients with resistant hypertension (not controlled on 3 or more drugs), with spontaneous or easily provoked hypokalemia, and with hypertension and an adrenal mass.

•It is OK to screen with a "random" ARR, even when on drugs except spironolactone and eplerenone; however, β-blockers can suppress renin and vasodilators and diuretics can increase renin, leading to false-positives and false-negatives, respectively. *If the results of the screen do not match your clinical suspicion or are equivocal, screen again off as many meds as you can.*

•Beware: the units and normal range for the direct renin assay and PRA are different!

•When screening all hypertensives, most patients with a positive screen will NOT have a positive confirmatory test and even fewer will have tumors, so do NOT feel compelled to complete the evaluation if the patient is well-controlled on medical therapy.

•Do NOT be hypnotized by CT scans!! We do adrenal vein sampling here!!

Screening Procedures

1. 24 h Urine Na and K

•Procedure: Collect 24 h urine, no preservative or acid, for Na, K, Creatinine. DO NOT give K supplements or correct hypokalemia but do ensure >150 meq Na intake (usually not a problem in USA). I usually obtain a plasma K when the urine is brought to the lab.
•Criterion for positive test: A 24 h K excretion of > 30 meq (definitely > 40 meq) with a concomitant Na excretion of >150 meq in the face of a serum K of < 3.5 is reliable evidence of mineralocorticoid excess.
•Caveats: Make sure patient is not taking diuretics of K supplements!

2. "Random" Aldosterone/Renin Ratio (PAC/PRA)

•Procedure: This should not be drawn "randomly," but the specificity is improved if you try to stimulate the renin production. Thus, obtain the specimen after 2-4 hours of upright posture on a low-Na diet. Draw the blood into a chilled EDTA tube, and have the lab spin it down and separate the plasma for prompt freezing.
•Criterion for positive test: A PAC/PRA ratio of > 35 is virtually diagnostic of hyperaldosteronism, although values > 20 are compatible with the diagnosis. The higher the aldosterone, the lower the serum K, and the higher the blood pressure (and your clinical suspicion) the more compelled one is to continue.
•Caveats: Renin activity is somewhat labile, and assays can be tricky and variable. Furthermore, the units for renin activity are ng/mL/h, and values are typically down near the lower limits of the assay (near 0.3), which means that the PAC/PRA ratio involves dividing by near zero and that a change of 0.1 can alter the interpretation. The renin should be "suppressed" at < 1 in

hyperaldosteronism. I look at the two numbers independently and like to see the PRA < 1 ng/mL/h and the PAC > 15 ng/dl (and preferably >25)..

•Direct Renin: PRA assays are cumbersome and "indirect," in that angiotensin I (generated from endogenous angiotensinogen by renin) is actually assayed. Values and normal ranges vary considerably from lab to lab, and specimen handling is critical. To avoid these inconsistencies, the Nichols Institute (Quest) developed a immunoradiometric assay for renin itself, the "direct renin" assay. Normal values are 5-13 μU/mL, with values < 5 considered "low renin" and totally suppressed being < 2. N.B.: Use of direct renin will distort the aldosterone/renin ratio if different units are not taken into account.

Confirmatory Testing

1. Saline Infusion Test

•Procedure: Simply infuse > 1.25 L of normal saline over 4 hours (most use 2 L over 4h).

•Criterion for positive test: A plasma aldosterone of > 10 ng/dL at the end of the test confirms hyperaldosteronism, and values of 5-10 are equivocal. Also measure cortisol and 18-hydroxycorticosterone (18OHB) at the end of the test for localization (see below).

•Caveats: This testing requires an endocrine testing unit or equivalent.

2. Fludrocortisone Suppression Test

•Procedure: Have the patient ingest a high sodium diet (> 100 meq/day) and take 0.2 mg fludrocortisone (Florinef) p.o. Q 12 h for 3 days; during the last day, obtain a 24 h urine for aldosterone, with a plasma aldosterone at the end of the test if possible.

•Criterion for positive test: A urine aldosterone of > 8 μg/24 h and/or a plasma aldosterone > 8.5 ng/dL are considered diagnostic.

•Caveats: It is best to obtain the 24 h urine aldosterone and sodium to assure salt-loading.

3. 24 Hour Urine Aldosterone With Salt Loading

•Procedure: Have the patient consume > 150-200 meq Na^+ (suppress the renin) and vigorously replace K^+ (because hypokalemia blunts aldosterone production). Obtain a 24 h urine (acid preservative added!!) for aldosterone and sodium (and creatinine if possible); obtain a serum potassium when the specimen is delivered.

•Criterion for positive test: An aldosterone excretion of > 14 μg/24 h with a urine Na^+ of > 150 meq/24 h is confirmatory of hyperaldosteronism. Lower aldosterone excretion rates in the face of significant hypokalemia (K^+ < 3.0) are, alas, inconclusive.

•Caveats: This test is the gold standard and is extremely informative but requires a reasonably motivated patient who can follow directions.

4. Other tests: Plasma 18-hydroxycorticosterone (18OHB) values > 50 ng/dL and for sure above 100 ng/dL are virtually diagnostic aldosteronism, but we rarely see values above 50. I suspect that the commercial assays are now more specific, and we need to re-define the diagnostic ranges. Posture studies are almost impossible to do correctly with managed care.

My favorite approach that comprehensively covers everything is shown on the next page:

The Hyperaldosteronism 5-Day Urine Collections Protocol

Off Spironolactone for 4-6 weeks
Off ACEI/ARB/Diuretics for 2 weeks
Off Whatever Else Possible for 1 week

Day 0: Stop K Supplements

Day 1: Begin First 24 h Urine

Day 2: Complete 24 h Urine for K, Cr
Serum K
Begin Salt Loading After Blood Test:
Salt Tablets (3 x 0.5-1 g) + 10-20 meq KCl TID; Liberalize Salt Intake

Day 3: Continue Salt Loading

Day 4: Continue Salt Loading
Begin Second 24 h Urine

Day 5: Complete Second 24 h Urine for Aldosterone, Na (& Cr if possible)
Plasma & Serum for Aldosterone, Renin, K, 18-hydroxycorticosterone

Localizing Studies

1. CT Scanning: Must be done with fine cuts of the adrenal BUT BEWARE—can yield inconclusive or misleading information. *Unless a > 1 cm nodule is visible on > 1 image and the contralateral gland is unequivocally normal in a young patient, AVS is recommended.*

2. Saline Infusion (as above): An aldosterone/cortisol ratio > 3 or an 18OHB/cortisol ratio >2.2 is indicative of an adenoma, fairly reliably.

3. Therapeutic Trial of Spironolactone: Most adenomas are not renin-responsive, so blockade with spironolactone is generally more successful for adenomas.

4. Adrenal Vein Sampling (AVS): The gold standard

•Procedure: Infuse 250 μg cortrosyn in 500 mL 5% dextrose at 100 mL/h beginning just prior to the procedure. Obtain 1 or 2 blood samples (slowly!!) from both adrenal veins and the IVC below the renal veins for aldosterone and cortisol (internal check of adrenal drainage). Check positions of catheters after blood draws.

•Criterion for positive test: The aldosterone/cortisol ratio for each side is calculated, and a >3:1 gradient (often > 10:1), confirms unilateral aldosterone production. In addition, the adrenal vein/IVC aldosterone and cortisol gradients should be at least 10:1 (usually > 100:1) to confirm cannulation; cortisol concentrations are normally higher in the RAV than LAV (dilution).

•Caveats: Even the best interventional radiologists fail to cannulate the short, stubby right adrenal vein (that exits the IVC directly) in 20-25% of cases. We do 1-2 per month here (and that number is rising), and our success rate is about 85% for one procedure and 100% if the procedure is repeated.

Primary Aldosteronism in "Primary" Hypertension: The Mild Phenotype

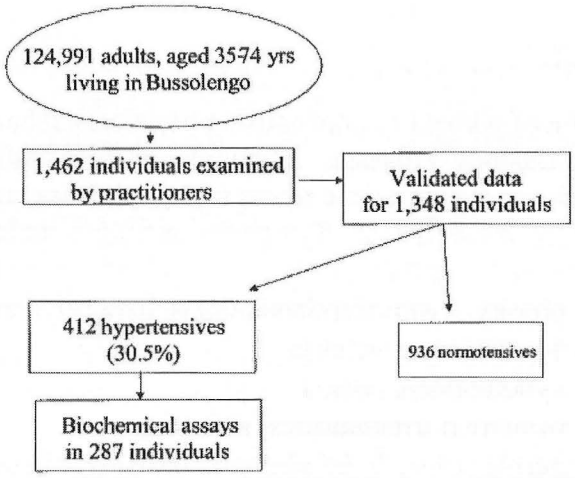
We all recognize that hyperthyroidism varies tremendously in its clinical manifestations. Thyroid storm is the extreme high end of the spectrum, and we have no difficulties making the clinical or laboratory diagnosis in this case. However, we also see cases of "subclinical" hyperthyroidism where the TSH is low/suppressed, the free thyroxine is usually normal, and the patient is asymptomatic in the classic sense—no tremor, hyperdefecation, tachycardia, etc. We seldom encounter difficulty in making this diagnosis, since the TSH assay is reliable and the circulating TSH concentration is relatively constant during the day. Of course, the milder the hyperthyroidism, the more variable are the lab data, and the more difficult the diagnosis.

Just as we recognize milder forms of hyper- and hypothyroidism, why should milder forms of adrenal disorders not also exist? The problem is that, although the feedback loops regulate most endocrine axes, the thyroid axis is a poor model for other endocrine systems. The reasons include the pulsatile secretion of most hormones, the vulnerability of these axes to other factors (stress, volume status, medications), and the variable reliability of many hormone assays, including PRA, ACTH, aldosterone, and urinary steroids.

It is clear that some type of dysregulated aldosterone production is rather common in presumed primary hypertension cases, but the incidence of surgically remediable cases remains small. There are now 14 studies measuring the ARR in various series of hypertensive subjects (2-15), most in hypertension referral clinics but 2 in primary care settings, and one in resistant hypertensives. A "high" (generally PAC/PRA > 25-35) ratio has been found in 10-40% of cases. Some studies have followed positive screens with confirmatory testing, which reduces the number to about 8%. The most recent (Bussolengo Study) with 1,348 subjects in Italy used the new direct renin assay (which they showed correlated with PRA assay). Among the 412 hypertensive subjects, an elevated ARR was found in 32% of cases, with the prevalence of high ARR increasing with age (38% in those >55 years old).

Reference	Subjects	Clinical setting	Prevalence (%)
Hiramatsu et al., 1981, Japan	348 Hypertensive patients	Hypertension unit	2.5 (APA only)
Gordon et al., 1993, Australia	52 Pharmacol. trial volunteers	Hypertension unit	12
Gordon et al., 1994, Australia	199 Hypertensive patients	Hypertension unit	8.5
Brown et al., 1996, Australia	74 Hypertensive patients	Hospital	8
Lim et al., 1999, UK	125 Hypertensive patients, GP	Primary care	14
Kreze et al., 1999, Slovachia	115 Hypertensive patients	Out-patient department	13
Mosso et al., 1999, Chile	100 Hypertensive patients	Out-patient department	10
Fardella et al., 2000, Chile	305 Hypertensive patients	Out-patient department	9.5
Loh et al., 2000, Singapore	350 Hypertensive patients	Hospital	18
Rayner et al., 2000, So. Africa	216 Hypertensive patients	Hypertension unit	32
Gallay et al., 2001, U.S.	90 Hypertensive patients	Hypertension unit	17
Schwartz et al., 2002, U.S.	505 Hypertensive patients (vol.)	Out-patient department	40
Calhoun et al., 2002, U.S.	88 Patients w/resistant HTN	Hypertension unit	20
Olivieri et al., 2004, Italy	412 Hypertensive patients	Random population sample	32

The Bussolengo Study:



Many of you are saying, "Wait a minute, how can ANY disease be THAT common??" The answer, of course, depends on how you define the disease. For example, the WHO criteria for osteoporosis is a T-score < 2.5, meaning bone density >2.5 SD below the mean for healthy young women. This means that, a priori, 65% of women age >75 have osteoporosis, ***by definition***. The problem with the Bussolengo Study is that PA was defined by an arbitrary value using a vulnerable screening test—you could say that they have a "laboratory" disease. If this type of PA is truly a disease, it should have a definable pathophysiology, a molecular and possibly genetic basis, and a natural history. Diagnosis and intervention should be designed to change the natural history. Otherwise, there is no point in making this diagnosis. We cannot afford (and certainly lack the manpower) to complete the evaluation, including CT and AVS, in 2% of the population (16).

At this time, there are no outcomes data showing that screening all hypertensives with an ARR improves hard endpoints. In addition, the criteria for positive screening aldosterone/renin ratio (ARR) tests are not known, nor are the sensitivity and specificity of the tests (probably sensitivity 75%, specificity 50%). Consequently, the wisdom of screening all hypertensives, the best subsequent actions, and the utility of completing the workup in broadly screened cases all remain unknown.

<u>Why should I care if my patient's hypertension is due to PA?</u>

Besides being an interesting academic exercise, why should we screen broadly for primary aldosteronism if most cases cannot be cured surgically? On the one hand, accumulating evidence indicates that aldosterone excess is associated with greater cardiotoxicity (17) and nephrotoxicity than other forms of hypertension. This phenomenon is easily seen in animal models and ameliorated with aldosterone antagonists (18). However, I still maintain that the patients who would benefit most from directed intervention are those who have the most severe disease and thus most likely to meet the traditional picture of PA. Nonetheless, if you never screen, you will never make the diagnosis. Finally, do not forget the potentially dramatic efficacy of even small doses of spironolactone and eplerenone, particularly in resistant hypertension, and you do not have to order labs prior to adding these drugs.

Adrenal Cushing Syndrome (ACS)

The Classical Syndrome

The presentation of adrenal tumors causing hypercortisolism is generally not much different than pituitary Cushing's disease. Although classical cushing syndrome in its extreme form may manifest with the characteristic moon facies, plethora, and buffalo hump, these findings can occur in any obese patient. Symptoms and signs include:

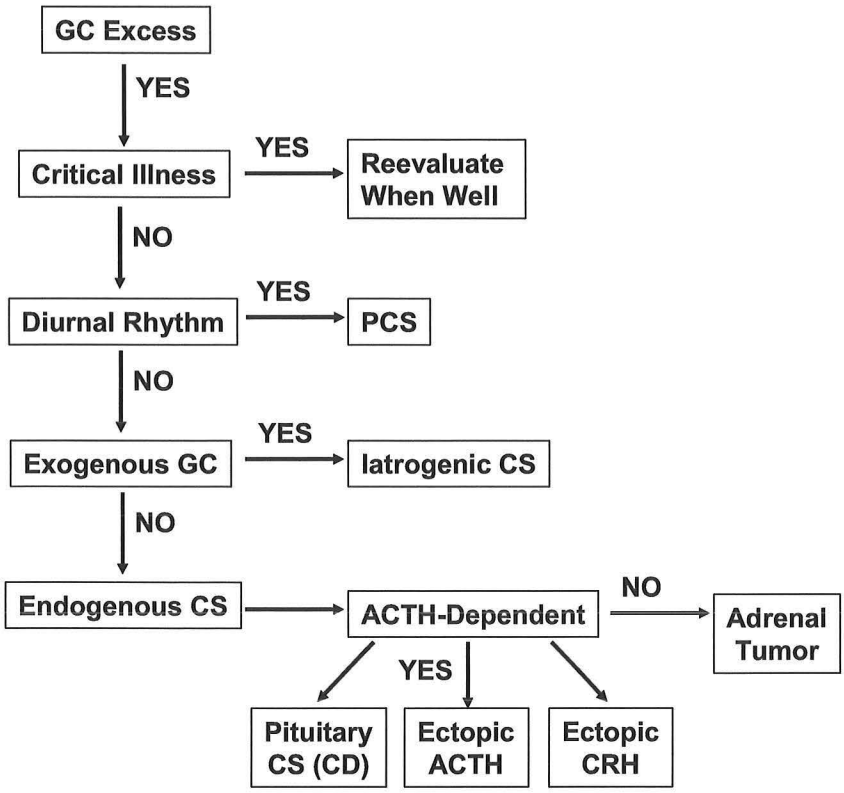
•Metabolic	obesity, hypokalemia/alkalosis, hyperglycemia, hyperlipidemia
•Psychiatric	depression, psychosis
•Cardiovascular	hypertension, edema
•Reproductive	menstrual irregularities, infertility
•Skin	purple striae, facial plethora, bruising, hirsutism, bronzing
•Muscle	proximal myopathy
•Bones	osteoporosis
•Adipose	centripetal obesity, supraclavicular and dorsocervical fat pads

The most specific signs of cushing syndrome are:

- •Wide, purple, non-blanching striae (>1 cm, "can put your finger in it")
- •Thin skin with easy bruising
- •Proximal muscle weakness
- •Osteoporosis (especially in an obese patient!!)
- •Supraclavicular fat pads

N.B.: hypertension and hypokalemia also occurs in both cushing syndrome and primary aldo.

The biochemical diagnosis of cushing syndrome in the classic, floridly affected patient is easy. A 24 h urine for free cortisol (UFC) and creatinine, assayed by tandem HPLC/MS (the standard assay at MML or Quest) is generally sufficient in the appropriate clinical context. Dexamethasone suppression testing is still good for screening but has fallen out of favor for determining the site of disease (pituitary vs ectopic ACTH vs ACS). Particularly for ACTH-dependent cushing syndrome, measures of diurnal rhythm have supplanted dexamethasone testing. The former criterion of >5 μg/dl for 1 mg DST is too high, and only <1.8 μg/dl (maybe lower) is clearly normal. In one study of 103 cases of surgically proven cushing syndrome (80 Cushing's disease, 13 ectopic ACTH, 10 ACS), the cortisol after 1 mg DST was >5 μg/dl in 18% and >2 μg/dl in 8% of the 80 patients with Cushing's disease (19)!! Serial measures of 2300-2400 saliva cortisol (reflecting the plasma free cortisol) are easily obtained as outpatients and, with a few caveats, generally exclude cushing syndrome if consistently <100 ng/dl (20, 21). Values consistently >200 ng/dl are considered abnormal, and in conjunction with an elevated UFC confirm the diagnosis. An elevated UFC with normal diurnal rhythm is found in pseudocushing states, which means that the entire axis is overactive, including the CRH neurons, due to stress, depression, alcoholism, etc. The pseudocushing state can also be excluded with the combined dex/CRH test (cortisol > 1.4 μg/dl) (22).



Thought process for cushing syndrome workup (GC = glucocorticoid; CS = Cushing syndrome; CD = Cushing's disease, PCS = pseudocushing state).

Screening Procedures

1. 24 hour Urinary Free Cortisol = UFC (and creatinine).

•Procedure: Collect a 24 hour urine, no preservative or acid.

•Criterion for positive test: UFC > 2x upper limit of normal, roughly 80 μg/24 hours.

•Caveats: Patients with early or mild Cushing syndrome can have normal or minimally elevated UFCs, especially if due to adrenal adenoma. Obesity, psychiatric diseases, critical illness, and high urine volumes can elevate the UFC value—interpretation of the test must always be based on clinical context. It is preferable to send to a lab that uses HPLC/MS methodology to measure UFC, and the normal range varies by method.

2. Overnight Dexamethasone Suppression Test

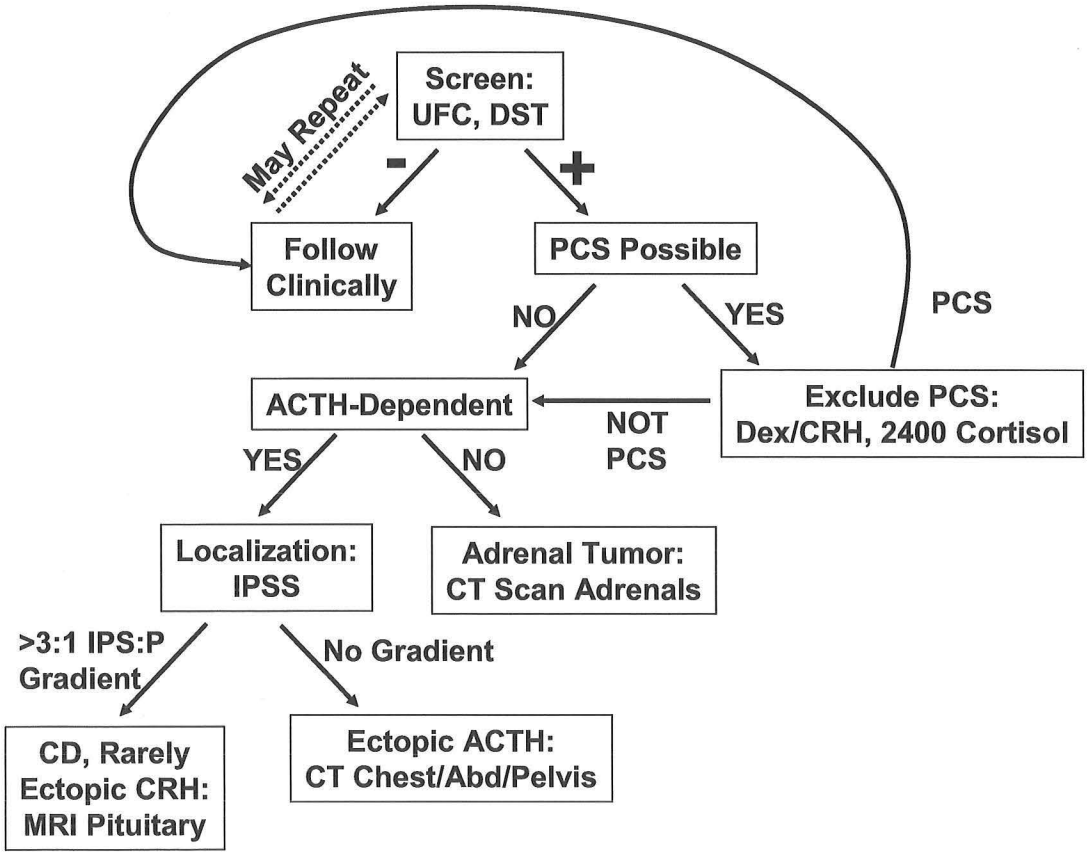
•Procedure: Give 1 mg dex PO at 2300; measure serum cortisol at 0800.

•Criterion for positive test: 0800 serum cortisol > 5 μg/dL (most suppress to < 1).

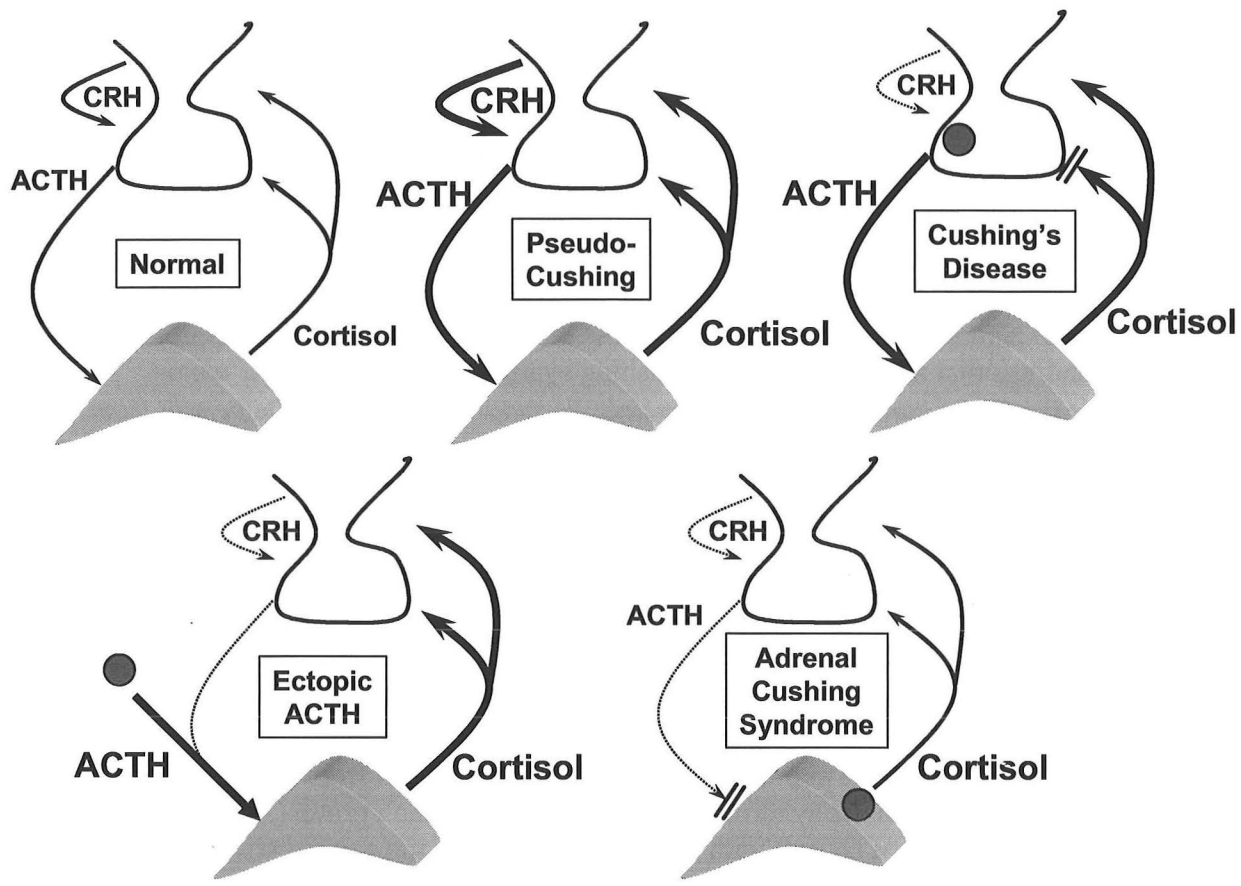
•Caveats: Some patients rapidly metabolize dex due to high CYP3A4 activity (induced by rifampin, dilantin, ephedrine [Ma Huang], phenobarbital) or undermetabolize dex due to CYP3A4 inhibitors (itraconazole and other azole antifungals, grapefruit). One can measure an 0800 dex with the cortisol, and the dex should be > 180 ng/dL. Patients with moderately functional cortical adenomas can have "normal" results but bear clinical manifestations.

However, even the best assays for UFC are normal in up 25% of patients with proven cushing syndrome (23). When data are conflicting, I rely on overnight serum cortisol sampling with hourly specimens obtained, preferably from an indwelling catheter, between 2200 and 0200. Values <5 μg/dl exclude cushing's, whereas values >7.5 μg/dl are diagnostic of the disorder (24, 25). As we endeavor to diagnose patients earlier, both the clinical findings and biochemical abnormalities are less prominent, and the diagnosis becomes more challenging. Often, patients are followed with periodic basal and dynamic testing to determine progression.

Once hypercortisolism is confirmed, a plasma ACTH is obtained to distinguish ACTH-dependent (measurable, not necessarily high) from ACTH-independent (suppressed). If the ACTH is suppressed, an adrenal CT scan is obtained. If the ACTH is not suppressed, a sella MRI is obtained with/without contrast, because most ACTH-dependent cushing syndrome is pituitary Cushing's disease. If a tumor is reliably identified, particularly in a young woman, it is reasonable to proceed directly to pituitary exploration. However, the MRI is negative in half of cases, and 5-10% of normal patients have hypointensities on MRI (26). Consequently, in most cases, we will offer or recommend inferior petrosal sinus sampling (IPSS) with CRH stimulation (27). An algorithm with examples is shown below:



Simplified algorithm for Cushing syndrome workup (GC = glucocorticoid; CS = Cushing syndrome; CD = Cushing's disease, PCS = pseudocushing state).



Comparison of normal HPA axis, pseudocushing state, and three forms of cushing syndrome.

Examples of IPSS data:

Time (min)	[Cortisol] (μg/dL)	[ACTH], pg/mL LIPS	PV	RIPS
-15		419	100	573
-5		517	99	686
0		666	105	575
1		3558	102	1053
3		9362	135	3131
5	32.8	7646	189	3867
10		3644	356	2903
15	37.2	2210	386	1891
30		1146	268	963

Interpretation: Pituitary Cushig's Disease

Time (min)	[Cortisol] (μg/dL)	[ACTH], pg/mL LIPS	PV	RIPS
-15	18.6	128	117	146
-5		114	124	139
0		111	120	141
1		120	126	189
3		137	132	186
5	17.2	148	133	200
10		151	149	181
15	18.6	136	154	184
30		145	120	167

Interpretation: Ectopic ACTH Syndrome

ACS: The Mild Phenotype

Suppose that you are evaluating a 46 year-old woman with an incidentally-discovered adrenal mass (2.5 cm, benign appearance). She has hypertension on two drugs, which has been harder to control lately, mild diabetes started on metformin 3 months ago, and a 30 lb weight gain over the last 2 years. She has no bruising, myopathy, or striae, and her menses are slightly irregular. Although she has no specific findings of cushing syndrome, you screen her for cushing's and find that UFC is normal, the 1 mg DST yields a cortisol of 2 μg/dl, and the ACTH is 7 pg/ml. Thus she meets no criteria for cushing syndrome. However, as you review the data, the cortisol is not zero after dex, the ACTH is below the normal range but not suppressed, and she has soft findings that are consistent with cushing syndrome. *Is her adrenal tumor functional? Is the tumor contributing to her metabolic syndrome? Would she benefit from adrenalectomy? Do you have other patients with the metabolic syndrome who might also have adrenal tumors that make some cortisol??*

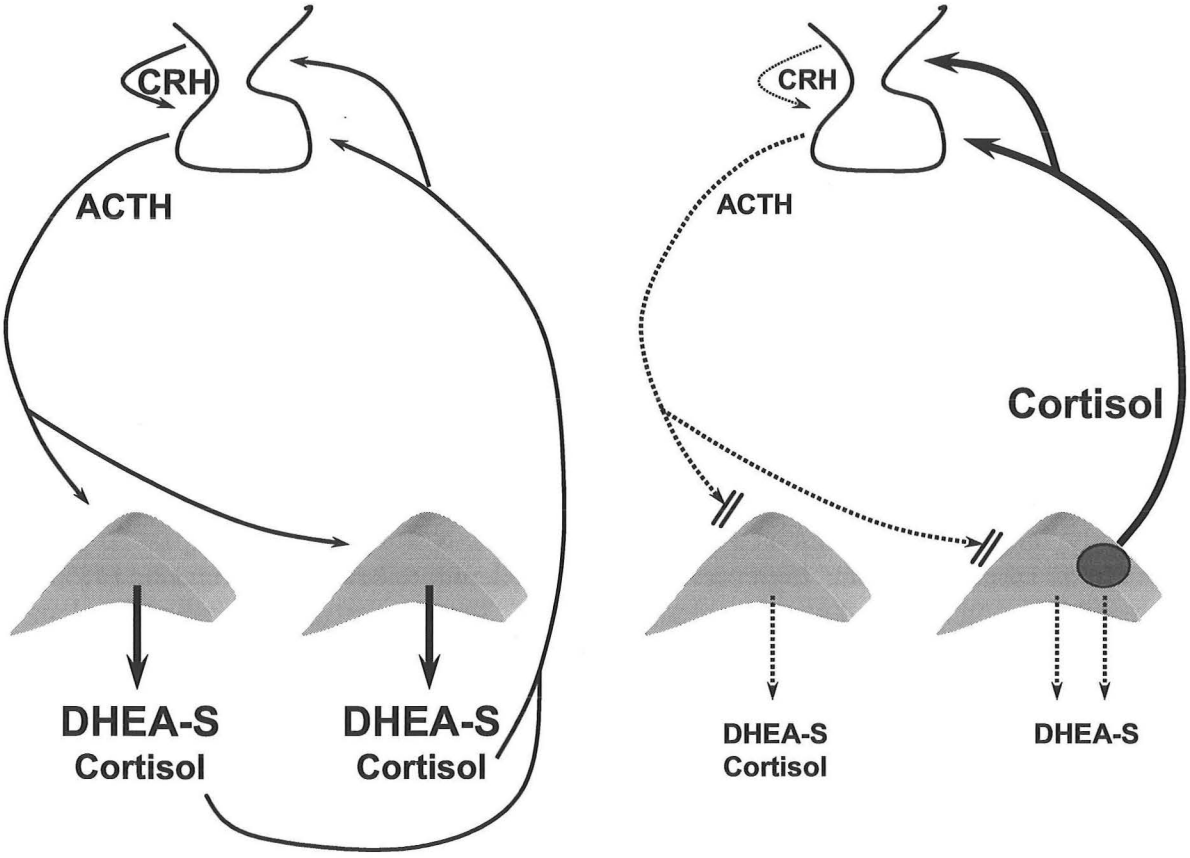
The provocative questions raised by this example (and I have seen several patients like this!) can be addressed in a few ways. First, what percentage of patients with the metabolic syndrome has functional adrenal tumors? Second, what percentage of patients with adrenal tumors have cortisol excess, either overt cushing syndrome or a milder, partial form, and what is the natural history of this process?

It is well known that obesity can cause an elevated UFC and a false-positive DST. Consequently, it is perilous to screen all obese patients for cushing syndrome due to reduced specificity of he tests in this, the population who would most benefit from the diagnosis of a secondary cause of the metabolic syndrome. Nevertheless, a French group (28) screened 200 obese type 2 diabetics in poor control with the 1 mg DST, using the conservative value of 60 nmol/L (2.2 μg/dl) as cutoff for a positive screen. Not surprisingly, they had 52 positive screens (25%!!), emphasizing that this is NOT a good idea in general clinical practice. However, they performed confirmatory testing, including UFC, plasma ACTH, and diurnal rhythm assessments in 47 subjects, and they could exclude cushing syndrome in only 30 cases, leaving 17 with probable hypercortisolism. Among these, 3 cases had Cushing's disease (2 surgically proven), and 8 had adrenal tumors and low-normal ACTH. One of the 8 (3 cm tumor and concordant scan on iodocholesterol scintigraphy) had adrenal insufficiency following adrenalectomy, and his UFC was 28.5 μg, which is STONE COLD NORMAL. The other 7 cases are being followed but may have some form of hypercortisolism. It is tempting to speculate that the other 7 tumors are making moderate amounts of cortisol, not enough to completely suppress the contralateral gland but possibly enough to contribute significantly to the metabolic syndrome. Some investigators call this "Subclinical Cushing Syndrome" (SCS) (29, 30), a term that I do not like because the disease is really not "subclinical" in many cases (I prefer "mild ACS").

A similar study was conducted in Israel and found that 3/90 obese subjects with poorly controlled diabetes indeed had cushing syndrome (3%) (31). In a retrospective analysis, these same authors also found that 18% of a series of 63 patients with cushing syndrome at their institution presented with diabetes. Another study from Argentina found 1 case of Cushing's disease in 48 unselected diabetics (2%) (32). Consequently, a few percent of patients with diabetes probably have hypercortisolism of some sort, and perhaps these patients will benefit from dynamic testing and ultimately from surgery.

Recommendations for evaluating mild ACS:

•1 mg overnight DST: All I can tell you is that undetectable (<0.5 μg/dl) is truly normal, and < 1.8 is probably normal, or at least insufficient autonomy to warrant immediate action.
•Morning ACTH: Patients with overt ACS will have suppressed ACTH (<4 pg/ml), but you rarely see an ACTH <15 in a normal person, simply due to the stress of the venipuncture. Thus, values of 4-15 cannot be dismissed as "normal," especially if found on more than one occasion.
•Morning DHEA-S: ACS tumors often lack DHEA-sulfotransferase (SULT2A1), which is normally present in the zona reticularis and which enables the adrenals to export more DHEA-S than any other steroid. If the tumor makes enough cortisol to at least partially suppress ACTH production, then DHEA-S will also fall since its synthesis is also ACTH-dependent (see below).



Mechanism of low DHEA-S in mild ACS. Left, normal HPA axis, both adrenal glands make abundant DHEA-S in response to ACTH, as well as normal amounts of cortisol; feedback mechanisms are undisturbed. Right, the tumor makes moderate amounts of cortisol but little DHEA-S (dotted arrows). The cortisol from the tumor partially suppresses ACTH production, rendering the normal surrounding gland and the contralateral adrenal understimulated. Consequently, the normal adrenal tissue makes less cortisol and much less DHEA-S than usual.

The Incidental Adrenal Nodule, Mild ACS, Primary Aldosteronism, and Beyond

Mild ACS and the Incidental Adrenal Nodule

Now it is time to get serious. Just as thyroid nodules and incidental pituitary masses are common, so are incidental adrenal nodules (IANs), which are found on about 5-10% of CT scans performed for other reasons, and the prevalence increases with age. An NIH consensus conference noted that most of these tumors are nonfunctional and recommended the following screening tests (33):

•1 mg overnight DST: This is the most sensitive test for ACS. The panel gave the traditional 5 μg/dl cutoff cortisol value but did note that some experts recommend further evaluation if the cortisol is 1.8-5 μg/dl.

•Urine or plasma metanephrines: This test is used to R/O pheochromocytoma, because up to 10% of pheos are asymptomatic. In addition, 10% of pheos are malignant, and hypertensive crisis can occur if patients with occult pheos have surgery, undergo procedures, or take certain medications (i.e. beta-blockers).

•Measurement of serum potassium and aldosterone/renin ratio (ARR) if hypertensive: Note that the panel did NOT say to measure the ARR ONLY if hypertensive AND hypokalemic.

Patients with incidental adrenal nodules are an interesting group because we anticipate that ACS and PA will be enriched in this group relative to the normal population because we already know that they have an adrenal tumor. So what kind of numbers do you get when you screen this group? Pheochromocytoma is very rare, and we almost never get a positive from this group (I have seen one). However, when it comes to PA and ACS, the situation is very different.

An Italian consortium has been performing detailed biochemical testing and, more importantly, long-term follow up on a large series of patients with IANs for the past 20 years. In a series of 50 cases, they found high prevalences of moderate-to-severe hypertension (48%), diabetes (24%), and impaired glucose tolerance (12%). These investigators studied basal and dynamic hormone profiles in this cohort and found low ACTH, low DHEA-S, and high cortisol after dexamethasone (2 mg overnight test) (34). SCS, defined as 2 or more abnormal test results, was found in a staggering 24% of patients; note that the UFC was almost always normal.

Of the 12 SCS subjects so identified, 5 opted for adrenalectomy, and 3 developed clinical or biochemical adrenal insufficiency postoperatively. After surgery, 3 hypertensive subjects became normotensive without medications, and antidiabetic treatments could be reduced in 3 cases. Of the 13 subjects who failed to meet criteria for SCS but had surgery due to tumor size, 4 developed clinical or biochemical adrenal insufficiency, and half reduced or stopped antihypertensive or antidiabetic medications. I should note that these cases tended to have large (>2.5 cm) tumors; nonetheless, these data suggest that IAN subjects with hypertension or the metabolic syndrome have a high prevalence of hypercortisolism, even if they do not have outright cushing syndrome. This same group has shown an that patients with IANs have poor cardiovascular risk profiles (35).

Suppose testing is normal—does this mean that no further evaluation is required? Another study from Italy endeavored to define predictive factors for tumor progression (36). Of

75 subjects with asymptomatic IANs, no patients developed malignancy during 2-10 years of follow-up (median 4 years). However, 9 showed mass enlargement, with appearance of a new mass in the contralateral gland in 2. Adrenal hyperfunction developed in 6 cases, including 2 cases of overt ACS, 3 cases of SCS, and 1 pheochromocytoma. The estimated cumulative risk of developing mass enlargement and hyperfunction were 8% and 4%, respectively, after 1 yr, 18% and 9.5% after 5 yr, and 22.8% and 9.5% after 10 yr. Abnormal endocrine testing at diagnosis was the only risk factor identified for mass enlargement, whereas mass >3 cm and unilateral radiocholesterol uptake was predictive of adrenal hyperfunction. These data suggest that 10-20% of subjects will experience progression of the mass that warrants consideration of surgery.

Data of this type have been replicated in a study from Turkey. Of 70 patients with IANs, SCS was diagnosed in 4 (6%) (37). Low ACTH, low DHEA-S, and high cortisol after dexamethasone (3 mg) was again found in the SCS subjects, but ACTH was suppressed in only one case. The cortisol after dexamethasone was >3 μg/dl in all 4 cases and >18 μg/dl in 3, indicating more severe disease in this cohort than in the Italian study. In the Turkish series, higher UFC and higher midnight cortisols were found in the SCS cases (not surprising, as these cases had significant hypercortisolism); however, an elevated UFC was found only in 1 subject.

Primary Aldosteronism and the Incidental Adrenal Nodule

What about PA in IAN patients?? A group in Pisa screened 125 NORMOKALEMIC subjects with IANs, of whom 90 were hypertensive, as well as 82 primary hypertensives, using the ARR. False-positive ARRs (based on normal suppression tests) were found in 4 primary hypertensives and 2 patients with IANs. However, PA was confirmed in 5 of 8 patients with a high ARR, an IAN, and hypertension (6%) (38). Thus normokalemia does not exclude PA, particularly in patients with an IAN, and the diagnosis of PA should be considered in all patients with an IAN and hypertension.

Other Types of Adrenal Tumors and Adrenal Dysfunction

Now think outside the box. Why does a tumor have to make just aldosterone or just cortisol? What about other mineralocorticoids like 11-deoxycorticosterone (DOC) or glucocorticoids like corticosterone? DOC-producing tumors causing hypertension were described many years ago (39), yet this steroid rarely enters our differential diagnosis. Furthermore, genetic disorders such as 17-hydroxylase deficiency can cause DOC excess (40, 41), and milder forms of DOC excess not mediated by tumors might masquerade as low-renin hypertension. Consider the fact that even the most liberal estimates propose that aldosterone overproduction accounts for only 10-20% hypertension; however, up to 60-80% of hypertensives can be controlled with the mineralocorticoid antagonist eplerenone (42). The discrepancy between the broad clinical response to eplerenone and the prevalence of PA suggests that other mineralocorticoids might drive the hypertension in many cases. What about mixtures of steroids? Indeed, tumors that make both aldosterone and cortisol have been described (43), and these are particularly troublesome for two reasons. First, co-secretion of cortisol can complicate the interpretation of AVS data. Second, undiagnosed cortisol co-secretion can cause adrenal insufficiency following adrenalectomy, as has been reported with unilateral adrenalectomy for presumed non-functioning adrenal masses, despite preoperative endocrine evaluation (44).

The Future of Adrenal Disorders

There is no question that adrenal hyperfunction is under-diagnosed. The main two impediments to this field, in my view, are that we do not know how to make the diagnosis with certainty in all cases, and we do not know whether it is beneficial or cost-effective to make the diagnosis in all cases. We need better diagnostic algorithms and criteria for diagnosing milder forms of glucocorticoid and mineralocorticoid excess. We need outcomes data that determine whether patients benefit from detailed evaluation, tailored therapy, and surgical management in milder cases. We also need to consider contributions from other mineralocorticoids and glucocorticoids such as DOC and corticosterone, which are not routinely considered because the assays are not routinely available. Finally, what is this entity of non-tumor mediated primary aldosteronism? Is it really hyperplasia of the adrenal glands, or is this a mixture of genetic and acquired conditions in which aldosterone production continues despite the suppression of renin? I believe that urine steroid profiling using GC/MS will help, because this technology allows measurement of multiple hormones and their metabolites and identification of patterns of dysregulated steroid synthesis (45). However, this methodology must be used with dynamic testing and comprehensive clinical trials to arrive at some better answers. Finally, alas, I do not believe that we will ever be able to come to firm answers in all cases, which is what makes the field of adrenal endocrinology so challenging and frustrating yet also fascinating and rewarding.

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