Penn State College of Medicine
Continuing Education

Metabolic Syndrome: Could it be Cushing's Disease?

Wednesday, April 23, 2025

Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

PennState College of Medicine

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Metabolic Syndrome: Could this be Cushing Disease?

Marie Conley Lecture on Cushing Syndrome
Penn State Medical Center
April 23, 2025

James W Findling MD
Professor of Medicine & Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin

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Disclosures

Adrenal Insufficiency:

Consultant

Diurnal (Neurocrine)

Cushing syndrome:

Investigator/Consultant

Corcept

Crinetics

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Objectives

- How should we define neoplastic hypercortisolism [(Cushing syndrome (CS)]?
- What is the incidence/prevalence of neoplastic hypercortisolism?
- Why should we diagnose CS?
- Who and how should we screen for hypercortisolism?
- How to establish the cause of hypercortisolism?
- What treatment should be offered to patients?

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December 29, 1910
MG 23 year old woman

obesity
hirsutism
hypertension
amenorrhea

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Why is the Diagnosis of Neoplastic Hypercortisolism (Cushing syndrome) the most challenging problem in endocrinology?

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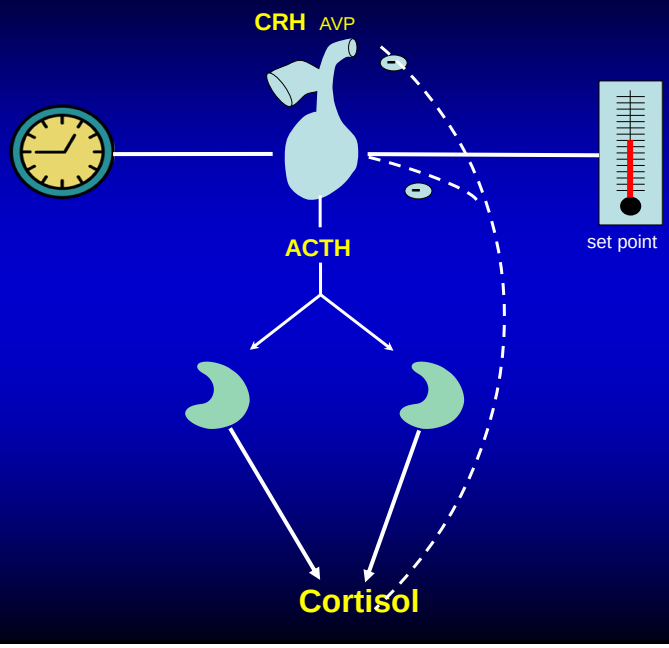
Hypothalamic-Pituitary –Adrenal (HPA) Axis



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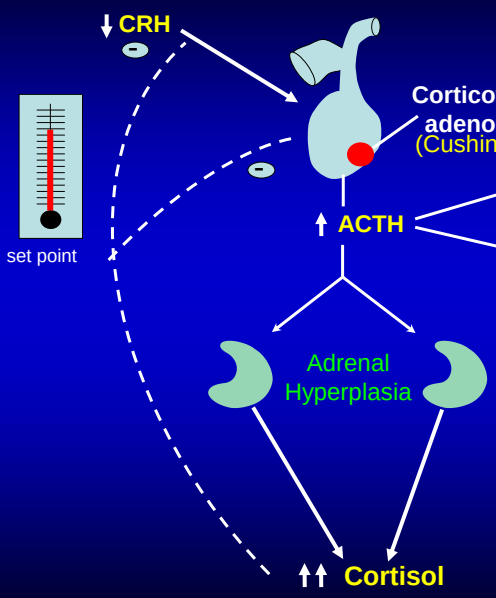
Pathophysiology: ACTH Dependent Hypercortisolism



- weight gain
- facial fullness/plethora
- Increased supraclavicular fat
- hypertension
- diabetes
- osteoporosis
- myopathy
- neuropsych disorders
- edema
- hypogonadism
- androgen excess

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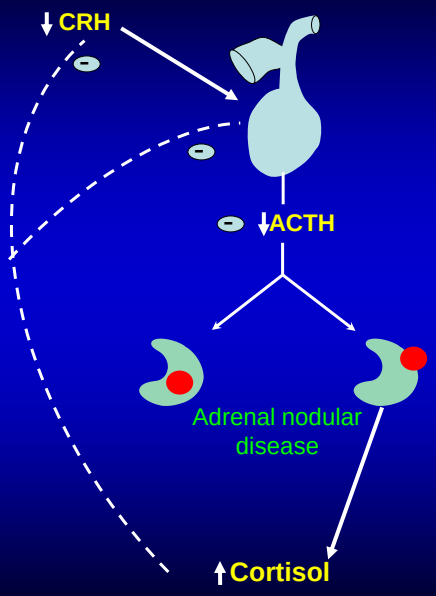
Pathophysiology: Adrenal Dependent Hypercortisolism



Clinical Features:

- Incidentally discovered
- Intermittent cortisol excess
- Hypertension
- Hyperglycemia/metabolic syndrome
- Osteoporosis
- Vertebral Compression Fx
- Very long duration, 10-40 yrs.
- **Mild Autonomous Cortisol Secretion (MACS)**

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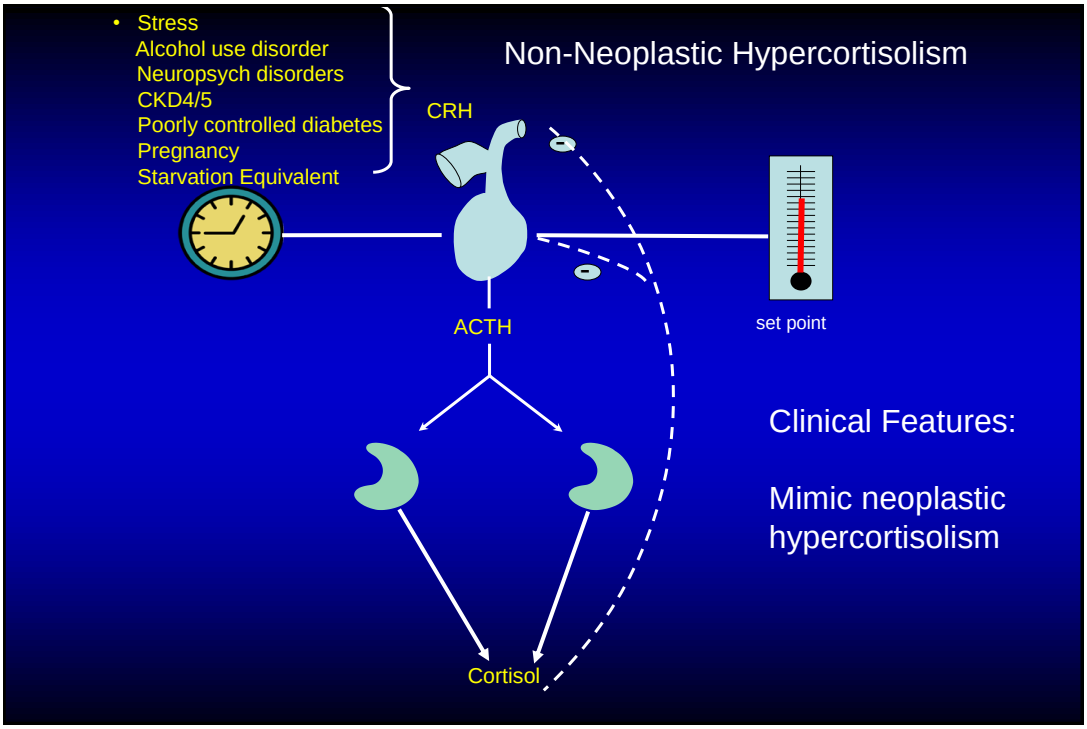
• Stress
Alcohol use disorder
Neuropsych disorders
CKD4/5
Poorly controlled diabetes
Pregnancy
Starvation Equivalent
Non-Neoplastic Hypercortisolism
CRH
ACTH
set point
Cortisol
Clinical Features:
Mimic neoplastic hypercortisolism

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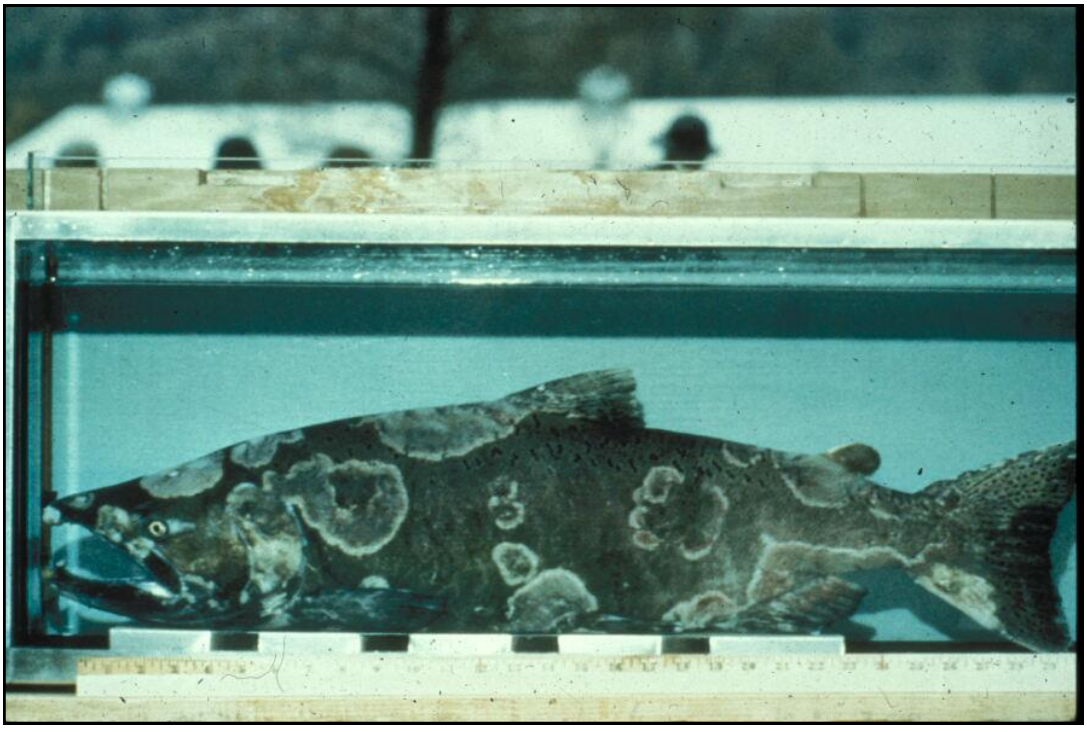

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Endogenous Hypercortisolism

Neoplastic/Pathologic	Non-neoplastic/Physiologic
ACTH secreting neoplasm	**Phenotype similar**
Pituitary (Cushing disease)	**Alcohol induced**
Ectopic	**Chronic Kidney Disease 5**
Adrenal Nodular Disease	Neuropsychiatric disorders
Adenoma/Carcinoma	**Uncontrolled diabetes**
Bilateral Nodular Disease	Pregnancy
Macronodular	Glucocorticoid resistance
Primary pigmented micronodular	Obstructive sleep apnea (severe)
	Phenotype not similar
	Starvation equivalent disorders
	Critical illness
	Eating disorders
	Relative Energy Deficiency of Sport
	And many more to be characterized

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PRIOR STUDIES OF CS INCIDENCE

- Data collected from 1955-2017
- Method of patient identification varies
  - National database vs medical records
- Definition of confirmed case varied

Author	Publication Year	Data Collection Time	Location	Patient Identification	Incidence (million-pt yr)
Lindholm	2001	1985-1995	Denmark	National Database	1.2-1.7
Arnardottir	2011	1955-2009	Iceland	National Database	1.5
Wengander	2019	2002-2017	Sweden	National Database	3.2
Etxabe	1994	1975-1992	Spain	Medical Records?	2.4
Bolland	2011	1960-2005	New Zealand	Medical Records	1.8

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METHODS

- Clinic records searched from May 1, 2017-Dec 31, 2022 from the Medical College of Wisconsin
- Identified WI residents diagnosed and treated for CS
- Diagnosis of CS was established with standard guideline-supported biochemical testing and appropriate imaging
- Patients with exogenous and non-neoplastic hypercortisolism, and those who did not undergo therapy for CS were excluded

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RESULTS-INCIDENCE

- Identified 185 patients diagnosed and treated for CS
- Patients resided in 27 of the 72 WI counties
  - Representing a population of 4.5 million
    - Total WI population of 5.9 million
- Incidence of CS in WI is 7.2 cases/million population/year

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RESULTS-ETIOLOGY

- 185 total cases
- 111 (60%) adrenal Cushing's syndrome (ACS)
- 68 (36.8%) Cushing's disease (CD)
- 6 (3.2%) ectopic ACTH syndrome (EAS)

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RESULTS-INCIDENCE

- Data from the WI Hospital Association show our institution treated <50% of all patients with CS discharged from WI hospitals from 2019-2023

- **True incidence of CS in WI is at least 11-12 cases/million/year**
  - Rather than 7.2 cases/million/year

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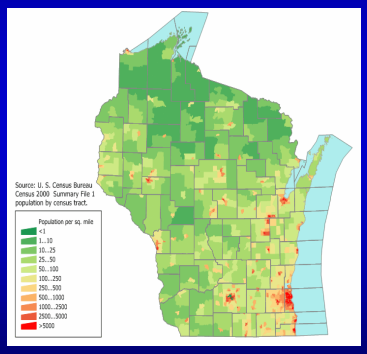
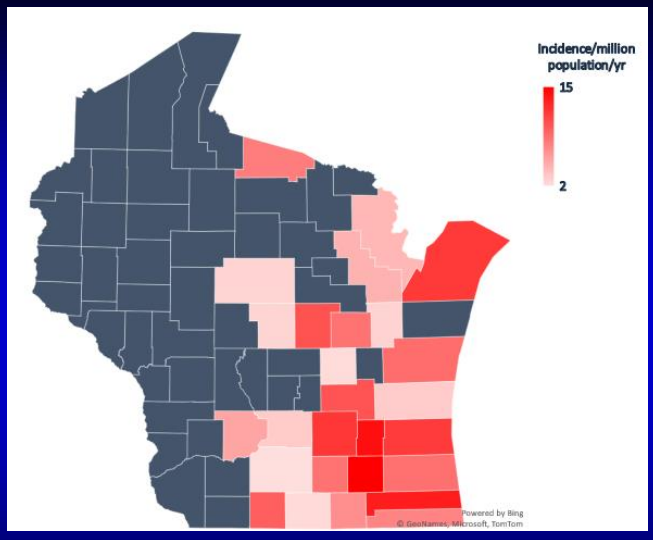
RESULTS





Incidence of Cushing Syndrome in Wisconsin 2017-2022

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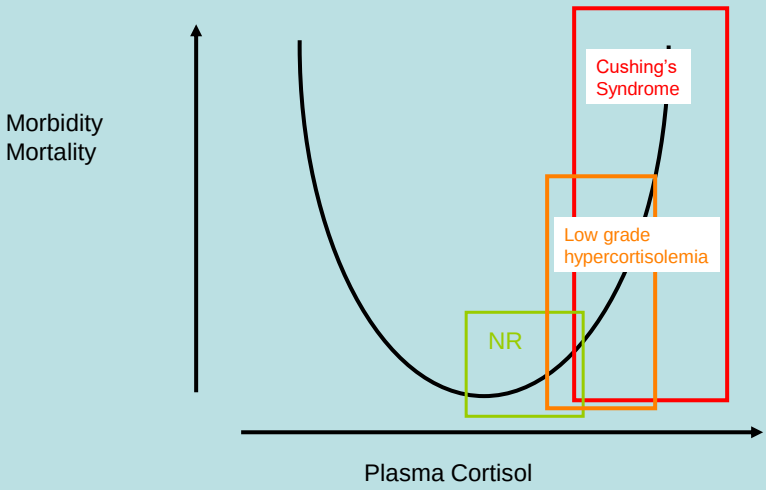
Cortisol and morbidity/mortality



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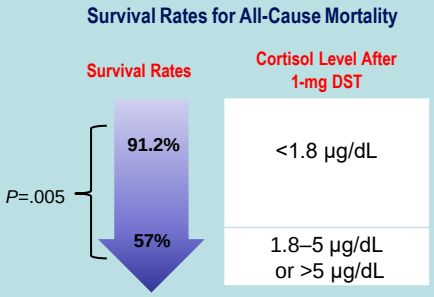
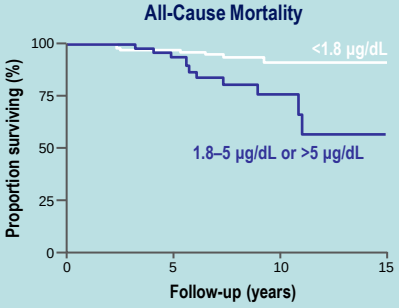
Increased Mortality and CV Events in Patients With Less Severe Hypercortisolism

Fifteen-year, retrospective, single-center study; 198 consecutive patients with adrenal adenomas





Even when clinical signs of classically described overt Cushing syndrome are not present, patients with adrenal adenomas and less severe hypercortisolism have an increased risk of mortality.

Patients with less severe hypercortisolism had a higher incidence of CVDs (*P*=.04) and increased CV mortality (*P*=.02) than patients with non-secreting adrenal adenomas

Di Dalmazi G, et al. *Lancet Diabetes Endocrinol.* 2014;2(5):396-405.

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Cushing Syndrome Who Should Be Screened?

Clinical Features

Central obesity with:

- Facial rounding with plethora
- Increased supraclavicular and dorsocervical fat
- Cutaneous wasting with ecchymoses
- Wide violaceous striae (only seen in young patients)
- Proximal myopathy
- Hirsutism (*lanugo*, terminal)
- Growth retardation (in children)

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Cushing Syndrome Who Should Be Screened?

Clinical Diagnosis

- Metabolic Syndrome
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Polycystic ovary syndrome
- Hypogonadotropic Hypogonadism
  - Oligomenorrhea/amenorrhea
  - Decrease libido and impotence
- Osteoporosis
- Incidental adrenal mass

Bariatric surgery patients

Javorsky BJ, et al: Obes Surg 25:2306, 2015

Lower ext insufficiency fxs

Poonuru S, et al Osteo Internat 27:3645-3649,2016

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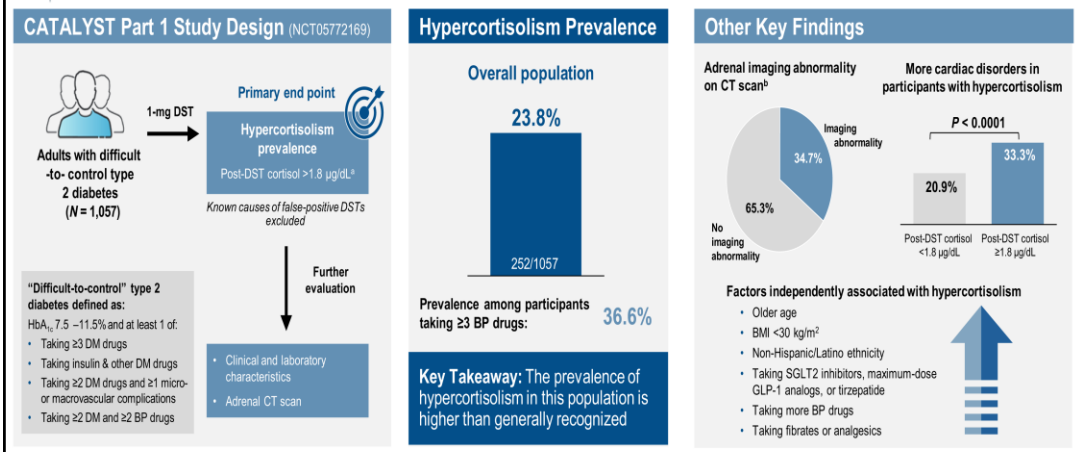
American Diabetes Association.

CATALYST
Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

Prevalence of hypercortisolism in patients with difficult-to-control type 2 diabetes



[a]With dexamethasone ≥140 ng/dL. [b]In patients with hypercortisolism. BP, blood pressure; CT, computed tomography; DM drug, glucose-lowering drug; DST, dexamethasone suppression test; GLP-1, glucagon-like peptide 1.

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Hypercortisolism is *Common* in the Metabolic Syndrome

- Steffensen, et al (2019): 384 new DM2
  Abnl DST: 22%
- Costa et al (2016): 393 DM2 w/ vascular comps
  Abnl DST: 33 %
- Catargi, et al (2003): 200 obese DM2 (A1C>8)
  Abnl DST: 26%
- Chiodini, et al (2005): 294 DM2 w/poor control
  Abnl DST: 17%

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CATALYST: Part 2

- Double-blind RCT of mifepristone v placebo for 24 weeks
- Mifepristone treatment reduced A1C by 1.47%
- Placebo reduced A1C by 0.3%
- Presence or absence of adrenal nodules did not impact the response to GR anagonist

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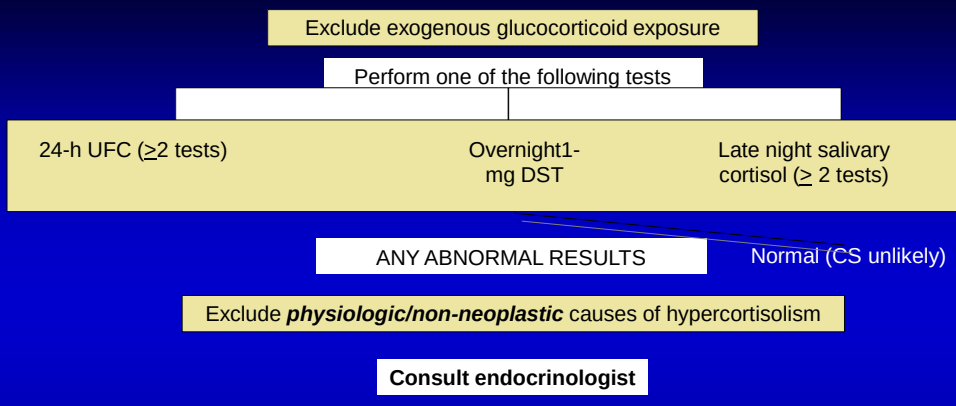
Cushing's Syndrome Suspected



Nieman LK, et al JCEM 93:1526-1540, 2008

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Overnight 1 mg DST

Pros

- Simple
- Normal range <1.8 mcg/dL
- Great sensitivity (95%)
- 60 years of clinical use
- Reproducible
- Measure post dex ACTH

Cons

- Improper execution
- Poor specificity (ie, false pos)
- Drug interference (OC)
- Rapid metabolic clearance
- Measure dex levels (>140 ng/dL)

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Late-night salivary cortisol

Pros

- Simple, widely available
- Great sensitivity for ACTH CS
- Well established normal range
- Patient convenience for multiple samples
- Stable room temperature

Cons

- Specificity (ie false positives)
  - Proximal stress
  - Pre-analytic mischief
  - Abnl sleep-wake cycle
  - Smoking/blood contamination
  - Exogenous steroids

If DST and LNSC are normal, endogenous hypercortisolism has been excluded

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Urine Free Cortisol

Pros

- Daily cortisol secretion
- 20th century gold standard
- Utilized in clinical trials
- Specificity? Good 3-4xULN
- Widely available
- Good tool for monitoring treatment outcome
- LC-MS/MS

Cons

- 0.1-0.3% daily cortisol secretion
- We're in the 21st century
- ≥2 or more collections
- Increased w/ OC (30%)
- Suboptimal sensitivity (70-75%)
- Wide day-to-day variation
- Normal range is <30 µg/24h

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Who should we screen?

Spanish Study Group: prospective study probabilistic model

Leon-Justel A, et al JCEM 2016; 101(10) 3747-3754

353 patients w/ obesity (BMI>30), DM (A1C>7), HBP (>2 drugs), PCOS

Screened with late-night salivary cortisol and 1 mg DST

219 normal studies

35 both abnl

99 discordant studies: repeat→7 both abnl

26/42 had proven CS (17 CD, 3 ectopic, 6 adrenal)

7.4% of screened patients had neoplastic hypercortisolism

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Odds Ratio (p-value):

- Osteoporosis: 4.6 (0.003)
- Dorsocervical fat: 3.3 (0.004)
- Muscle atrophy: 15.2 (<0.001)
- Obesity: 0.2 (0.01)
- Diabetes: 0.26 (0.002)

- Adrenal nodules: 25-40% have mild cortisol excess

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27 yo woman

- 3 year history of acne, 30 pound weight gain
- Oligomenorrhea; dx: PCOS (OC, spironolactone)
- No hypertension or diabetes
- Exam: BP 135/93 BMI 26.5

facial rounding with acne

Should screening for neoplastic hypercortisolism be done?

Stress fx: Left femoral neck fx and rib fx

Hip Z score: -1.3

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Laboratory:

Post dex cortisol: 2.0 mcg/dL (dex 299 ng/mL)

ACTH: 67 pg/mL

UFC: 74 µg/24h

LNSC: 10.7, 6.7 nmol/L (n: <3.2)

- Caveat: BC pills may obfuscate DST and UFC

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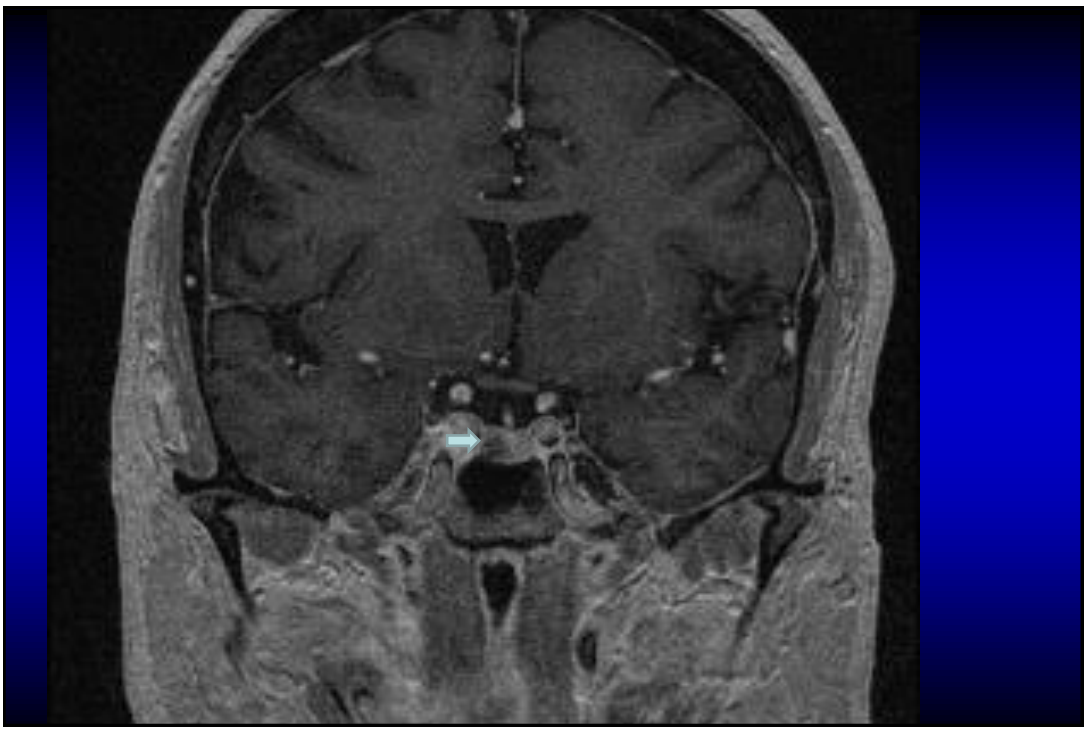

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49 yo man with Cushing syndrome referred for IPSS

- 2016: weight gain w/ increasing abd girth,
  difficulty concentrating, sleep disturbance
- 2018-21: sleep apnea, diabetes, hypertension, hypokalemia,
  easy bruising, facial rounding, striae
  low testosterone→ endocrine referral

SH: 3-4 drinks/week; non smoker

Meds: metformin, bumetanide, metolazone, KCl, pravastatin,
spironolactone, transdermal testosterone

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Examination

BP 132/78 P88 Wt 152 kg (336#) BMI 42

Cushingoid facies w/ increased supraclavicular fullness
No goiter; grossly distended abdomen w/ wide violaceous striae
2+ edema; muscle strength seemed normal
Normal mood and affect

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Laboratory/Imaging

Na 135 K 2.9 Cl 97 Bicarb 33 Ca 9.2 BUN 20 creatinine 1.4
Glucose 102 AST 70 (9-40) ALT 55 (12-64) Alk Phos 138 (38-127)
Total testosterone 33 ng/dL LH 0.1 FSH 1.5 PRL 29

Cortisol 27.7 µg/dL ACTH 36 pg/mL DHEAS 152 µg/dL

LNSC: 11.9 and 9.3 nmol/L (<3.2 nmol/L)
2 mg DST: cortisol 13.5 µg/dL
2- day DST (0.5 mg q6h): cortisol 5.1 µg/dL ACTH 2 pg/mL
UFC: 15 µg/24h

Pituitary MRI: normal
CT chest/abd/pelvis: negative

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dDAVP* Stimulation Test

	Basal	+10	+20	+30	+60
ACTH (pg/mL)	19	19	19	17	15
Cortisol (µg/dL)	21	17	16	15	

*10 mcg IV

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Phosphatidylethanol (PEth)

- Component
  Latest Ref Rng & Units *11/16/2021*
- Peth 16:0/18.1 ***402 ng/mL***
- PEth 16:0/18:1 (POPEth)
  Less than 10 ng/mL.....Not detected
  Less than 20 ng/mL.....Abstinence or light alcohol consumption
  20 - 200 ng/mL.....Moderate alcohol consumption
  Greater than 200 ng/mL.....Heavy alcohol consumption or chronic alcohol use

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Phosphatidylethanol (PEth)

PEth is known to be a direct alcohol biomarker.

PEth is incorporated into the phospholipid membrane of red blood cells and has a general half-life of 4-10 days and a window of detection of 2-4 weeks, the window of detection is longer in individuals who chronically or excessively consume alcohol.

Nguyen VL et al 2018, Alcoholism Clinical & Experimental Research.

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Alcohol-induced Non-Neoplastic Hypercortisolism

- Described in late 1970's; now rarely reported
- Phenotype similar: obesity, diabetes, hypertension, osteoporosis
- Central activation of the HPA axis
- Biochemistry indistinguishable from neoplastic hypercortisolism and remission after alcohol discontinuation
- DDAVP does not increase ACTH/cortisol
- Careful history of alcohol use (PEth levels may be helpful)

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MCW Case Series of AIH 2014-2022

Clinical Presentation

- 8 patients (4M4F) 24-67yo
- Physical findings c/w Cushing
- 6 referred for IPSS
- 1 for pituitary surgery
- 1 for likely ectopic ACTH
- 1 persistent CS after adrenx
- None reported more than 2-3 drinks daily

Biochemical & Imaging

All patients had:
Elevations of LNSC, abnl DST
LFT elevations (AST>ALT)
ACTH >10 pg/mL

1/8 patients had elevated UFC
Absent ACTH/F to dDAVP in 5
Elevation of PEth in one
2 patients had adrenal nodule
8 mm pituitary lesion in one

Surani A, et al *Front Endocrinol (Lausanne)*. 2023 Jun 20;14:1199091.. ..

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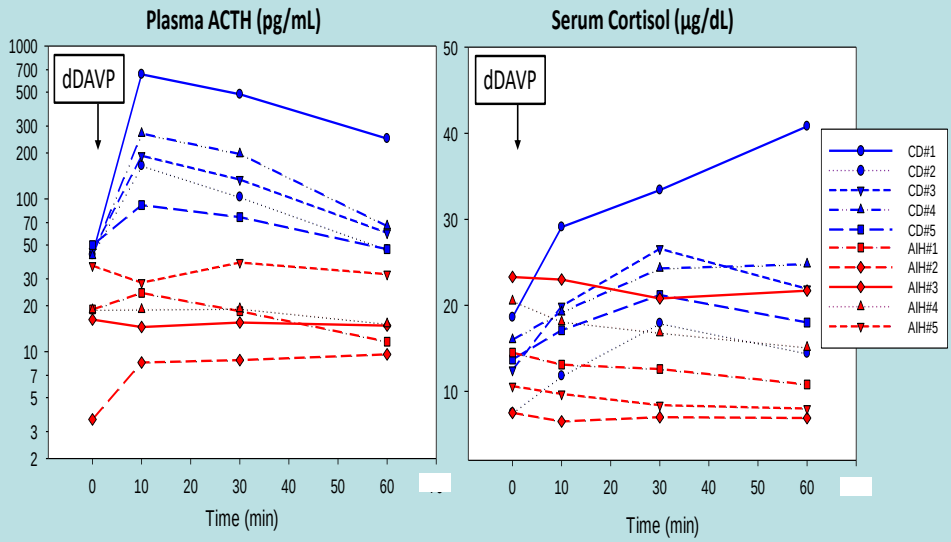
ACTH and Cortisol Response to dDAVP in Alcohol-Induced Hypercortisolism and Cushing Disease

Surani A, et al *Front Endocrinol (Lausanne)*. 2023 Jun 20;14:1199091..



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Rationale for dDAVP

- Vasopressin has 3 distinct receptors:

  V1: mediates pressor and hepatic effects
  V2: antidiuretic and hemostatic effects
  V3: pituitary ACTH secretion

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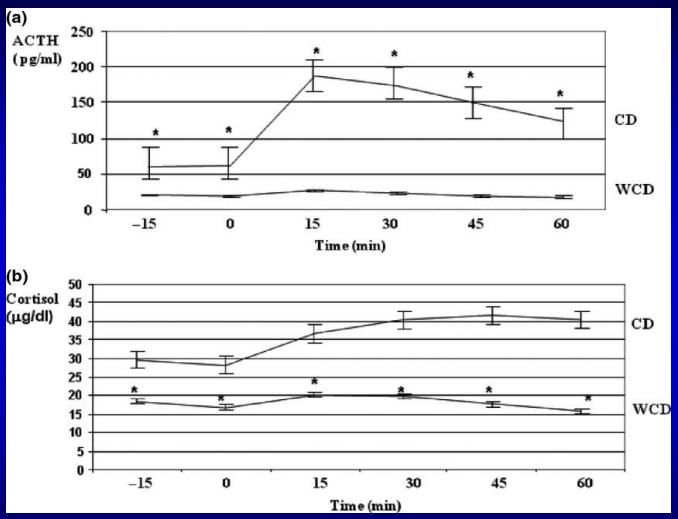
Evaluation of the DDAVP test in the diagnosis of Cushing's Disease



Cushing Disease (CD)
n=68

Without CD (WCD)
n=56

Only 2/56 had + test

Rollin, GAF, et al. Clinical Endocrinology, Volume: 82, Issue: 6, Pages: 793-800, First published: 07 November 2014, DOI: (10.1111/cen.12661)

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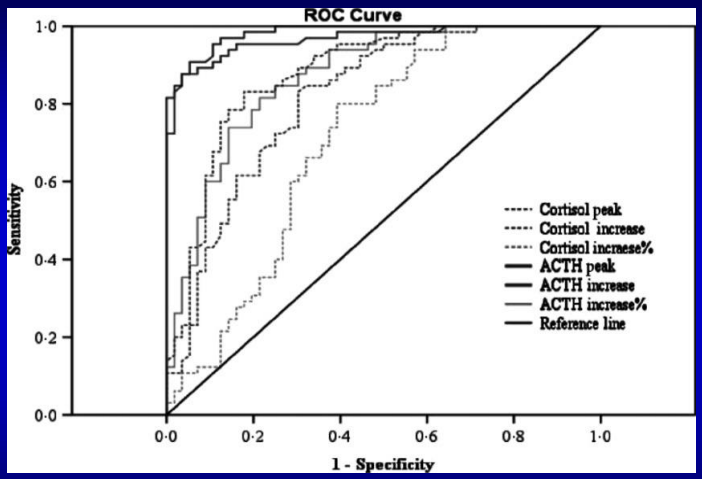
ROC curve ACTH/cortisol peak, absolute, relative increments w/ dDAVP



ACTH peak >72 pg/mL

ACTH delta >37 pg/mL

ACTH % increase 98%

Cortisol peak >28 µg/dL

Cortisol delta >7.7 µg/dL

Cortisol %increase 33.7%

Clinical Endocrinology, Volume: 82, Issue: 6, Pages: 793-800, First published: 07 November 2014, DOI: (10.1111/cen.12661)

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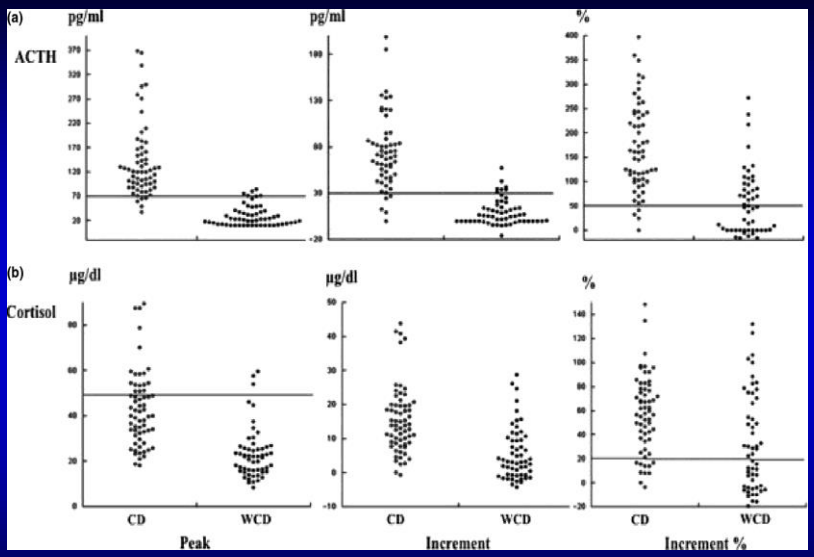

Clinical Endocrinology, Volume: 82, Issue: 6, Pages: 793-800, First published: 07 November 2014, DOI: (10.1111/cen.12661)

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- **Study should begin before 9:00 AM**
- **Indwelling IV catheter inserted, then wait 10 minutes before the first blood draw**
- **Measurements at each study timepoint:**
  - **Plasma ACTH and serum cortisol**
  - **Blood pressure and pulse rate**
- **After baseline blood draw, infuse desmopressin acetate)[a] 10 mcg (2.5 mL) IV over 60 seconds followed by a 2-mL saline flush**
- **Draw blood samples for plasma ACTH and cortisol at −15 minutes, 0 minutes (baseline), +10, +20, +30, +45, and +60 minutes**
- **Interpretation: positive response:**
  - **Increase in plasma ACTH above baseline >30 pg/mL[b] or peak ACTH >70 pg/mL**
  - **Increase in serum cortisol[c] >6 mcg/dL or peak >18 mcg/dL**

- *a* Side effects may include flushing, increased respiratory rate, hypotension (rare); if hypotension occurs immediately notify physician. Hypotension may result in a false positive test. **Patients should restrict fluid intake to 40 ounces (1.2 L) for the next 24 hours.**
- *b* Percentage increase over baseline is used by some (ranging from 35% to 150%)
- *c* Percentage increase over baseline is used by some (ranging from 20% to 40%). Cortisol cutoffs depend on the assay method used [129].

MCW dDAVP Study Protocol

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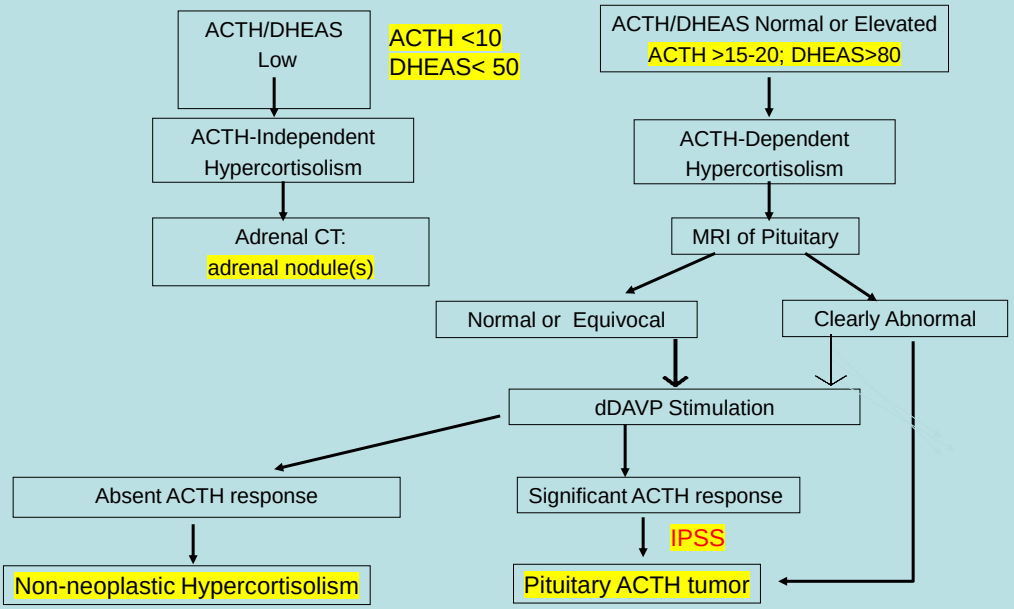
Hypercortisolism: Differential Diagnosis

Measure Plasma ACTH/DHEAS



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Treatment options:
Cushing Disease

CRH

Pituitary gland

Dopamine agonists
Cabergoline
Somatostatin analogs
****Pasireotide**

Pituitary surgery
<--Radiotherapy

ACTH

Atumelnant (Phase 2)

Adrenal glands

BLA

Ketoconazole
Metyrapone
Mitotane
Etomidate
****Osilodrostat**
****Levoketoconazole**

Cortisol

****Mifepristone**

Receptors on target tissues throughout body

****FDA approved**

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51 yo woman with osteoporosis (multiple VCFs) and severe hypertension with bilateral adrenal nodules

LNSC 5.6 nM
DST: cortisol 3.3 ug/dL
ACTH 6
UFC 12 ug/24h

Resolution of HBP s/p adrenal surgery

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May 2000
25 yo Hypertension, weight gain

Elevated UFC,
Normal Dex-CRH Test
Dx: Pseudo-CS

June 2006

LNSC 5.3. 6.8
UFC 165 µg/24h
DST: F=6.2 µg/dL
ACTH: 91 pg/mL

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21 yo nurse with new onset hypertension; normal exam

LNSC 8.2 nM
DST: cortisol 4.6 ug/dL
UFC: 57 ug/24hr
ACTH 64 pg/mL

Pituitary Cushing's

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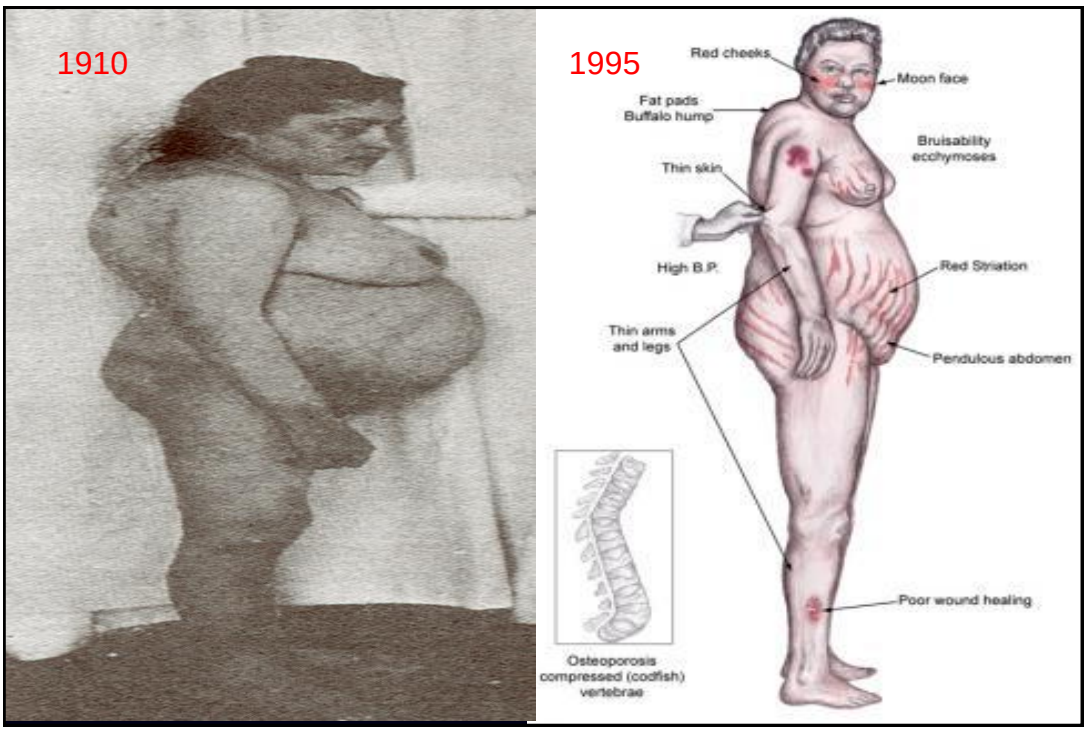

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Summary

1) Cushing syndrome is a caricature of the state of glucocorticoid excess that has clouded our diagnostic evaluation for over 60 years.

2) Neoplastic hypercortisolism is MUCH more common than previously thought and is associated with significant CV morbidity and mortality

3) Neoplastic hypercortisolism should be considered in patients with clinical history and physical features, metabolic syndrome, osteoporosis, and adrenal nodules

4) Diagnostic screening for hypercortisolism should focus on LNSC and DST

5) Non-neoplastic hypercortisolism may be clinically indistinguishable from neoplastic hypercortisolism and the DDAVP stimulation test provides reasonable discrimination

6) Effective surgical and medical therapy of neoplastic hypercortisolism is associated with significant improvement in morbidity and mortality

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His eyes, how they twinkled! His dimples, how merry!
His cheeks were like roses, his nose like a cherry; . . .

He had a broad face and a round little belly
That shook, when he laughed, like a bowl full of jelly.
He was chubby and plump - a right jolly old elf:
And I laughed when I saw him, in spite of myself;

-Clement Clarke Moore 1779-1863

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Conclusion

If you have never missed the diagnosis of Cushing syndrome or been humbled by trying to establish its cause, you should refer all your patients with suspected hypercortisolism to someone who has.

J. Findling 1997

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1910: seen by Dr. Cushing w/hypertension, amenorrhea

Subtemporal decompression for relief of low-grade hydrocephalus

1933: Weight loss, no overt features of hypercortisolism; normal menses

1958: expired; death certificate—ASHD and no mention of CS; no autopsy

Spontaneous remission? Why?

Auto-infarction of pituitary tumor

Ectopic ACTH

PPNAD (Carney) ?spontaneous remission

1920-1933 Alcohol prohibition in US

Psychosis often reported in MG

Carney JA. 1995; *Am J Surg Path* 19(1):100-108

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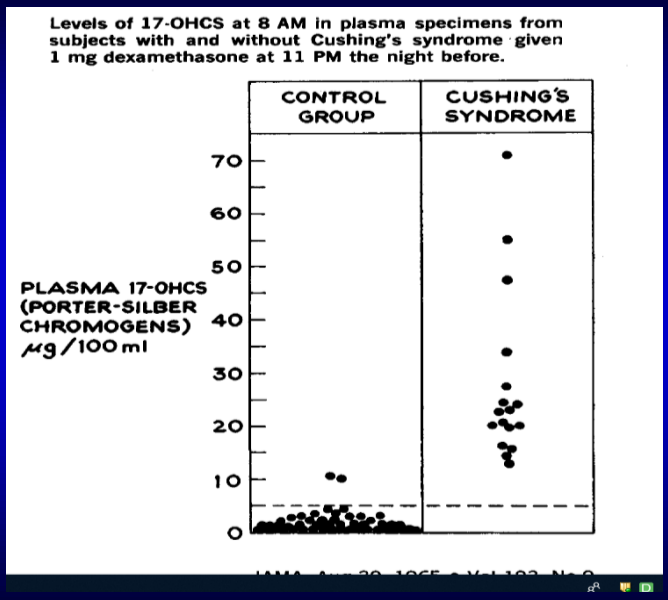
Overnight 1 mg Dexamethasone Suppression Test



Pavlatos,F, Smilo RP, Forsham PH JAMA; 1965 193:96-99

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