M2 - Endocrine, Winter 2008

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<http://hdl.handle.net/2027.42/64949>
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Learning Objectives

After this lecture you should have an understanding of:

• The feedback loops regulating cortisol secretion.
• The physiologic actions of glucocorticoids (cortisol) + mineralocorticoids (aldosterone)
• The major pharmacologic uses of glucocorticoids.
• The major types of glucocorticoids.
• The major side effects of glucocorticoid therapy.
Anatomy of the adrenal glands
Histology of the Adrenal Gland

**adrenal cortex**
- Adrenal cortex:
  - zona glomerulosa (aldosterone)
  - zona fasciculata
  - zona reticularis

**adrenal medulla**
- Adrenal medulla (catecholamines)

**Histology of the Adrenal Gland**

- Capsule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Multinucleated mass of protoplasm
- Medulla
- Ganglion
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal

cortex
medulla
Steroidogenesis

glomerulosa
fasciculata
reticularis

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‘Roids: The Bottom Line

In the right amounts, steroids can be the body’s best friend....

or

in the wrong amounts, the body’s worst enemy....
In the right amounts, glucocorticoids keep:

- Your blood pressure up (maintain cardiovascular stability).
- Your blood sugar up (maintain metabolic homeostasis).
- Your disposition sunny (maintain integrity of CNS function).
- Your temperament cool (regulate response to stress).
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal
cortex
medulla
The HPA axis

Neural Stimuli

Hypothalamus

Anterior Pituitary

Adrenal

CRF

ACTH

Plasma Cortisol Concentration

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Regulation of ACTH Expression by CRH
Post-translational Processing of POMC in the Normal Pituitary

POMC = Pro-opiomelanocortin

ACTH

MSH = Melanocyte stimulating hormone

Source: Undetermined
ACTH and Steroid Biosynthesis

ACTH

CELL MEMBRANE

ADENYLATE CYCLASE

ATP  3',5' cAMP

PROTEIN KINASE

INACTIVE PROTEIN

ACTIVE PROTEIN

POLYSOME

STEREOID BIOSYNTHESIS

CHOLESTEROL ESTER

CHOLESTEROL
Secretion, Transport and Metabolism of Cortisol
Circadian Rhythm of Cortisol Secretion

Plasma Cortisol μg/100 ml

Highest in morning

Lowest in evening

Source: Undetermined
Corticosteroid Binding Globulin (CBG)

- Acidic glycoprotein MW 52,000
- Produced in liver, lung, kidney, testes
- Regulates delivery of cortisol to tissues

SHBG Grishkovskaya et al, 1999
Conditions that Affect Cortisol Metabolism

- **Increased Turnover:**
  - Thyroxine
  - Barbiturates
  - Phenytoin

- **Decreased Turnover:**
  - Liver disease

- **Increased Binding:**
  - Estrogens
Molecular Action of Glucocorticoids

Glucocorticoid receptors (GR) are transcriptional activators of a variety of gene products.
Metabolic Effects of Glucocorticoids

Prototypical Glucocorticoid = Cortisol

Glucocorticoids ≠ Insulin

Glucocorticoids effects are generally opposite those of insulin.
Glucocorticoids increase hepatic glucose output

Glucocorticoids decrease insulin sensitivity

Liver

(+)

GLUCOCORTICOIDS

(-)

MUSCLE

FAT CELL

INSULIN

Glucose

(+)

(-)
Glucocorticoid Effects on Protein Metabolism

**Insulin**

- ↑ Anabolism (storage)
- ↑ Protein synthesis
- ↓ Protein breakdown
- ↓ Amino acid release

**Glucocorticoids**

- ↑ Catabolism
- ↓ Protein synthesis
- ↑ Protein breakdown
- ↑ Amino acid release
Glucocorticoid Effects on Lipid Metabolism

**Insulin**
- ↑ Anabolism (storage)
- ↑ Lipid synthesis
- ↓ Lipolysis
- ↓ Fatty acid release

**Glucocorticoids**
- ↑ Catabolism
- ↓ Lipid synthesis
- ↑ Lipolysis
- ↑ Fatty acid release

**Redistribution of fat**
Redistribution of Fat in Glucocorticoid Excess

Central obesity seen in Cushing’s Syndrome (Glucocorticoid Excess)
Glucocorticoid Effects on Inflammatory Mediators

Glucocorticoids INHIBIT inflammation.

*Inhibit:*

1) Arachidonic acid and its metabolites (prostaglandins; leukotrienes)
2) Platelet activating factor (PAF)
3) Tumor necrosis factor (TNF)
4) Interleukin-1 (IL-1)
5) Plasminogen activator
Sites of Action of Glucocorticoids in the Responses of Leukocytes During Antigenic Challenge/Inflammation
Glucocorticoids

Clinical Uses of Glucocorticoids
Steroid Therapy: Routes of Administration

- Systemic
  - Oral
  - Parenteral
- Topical
- Inhalation
Clinical Uses of Glucocorticoids

- Replacement therapy
- Anti-inflammatory effect
- Immunosuppression
- Androgen suppression
Emily Janz, a 36-year old woman presents with a 3-year history of rheumatoid arthritis. The disease has been progressive with involvement of PIP joints in both hands, wrists, elbows and TM joints. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has not been successful.

Treatment with prednisone is begun using an alternate-day program.
A 25-year old man was walking through a field when he was stung by an insect. He developed generalized edema, dyspnea, wheezing and dizziness. He was rushed by a friend to the emergency room, where a diagnosis of anaphylactoid reaction to insect bite was made.

He received a large dose of steroids parenterally and was subsequently advised on a program to taper the steroids over the next one week.
James Allen, a 55-year old man with a history of ischemic cardiomyopathy develops increasingly severe congestive heart failure. When he becomes totally incapacitated with a life-expectancy of less than 6 mo., he is placed on the cardiac transplantation list.

Two months later, he receives a heart and is subsequently placed on an immunosuppressive “cocktail” that includes prednisone, 5 mg daily.
A 25-year old woman comes in for evaluation of hirsutism present over the past 3 years. The hirsutism is of the androgen type and is associated with acne and irregular menses. Diagnostic studies reveal elevated serum dehydroepiandrosterone (DHEA) and testosterone levels.

She receives Dexamethasone 2.0 mg daily, for seven days and serum DHEA and testosterone levels are measured the 8th day.
Adrenocortical Hormones = Steroids

- **GLUCOCORTICOID**: Cortisol
- **MINERALOCORTICOID**: Aldosterone

Adrenal gland with cortex and medulla.
Effects of Mineralocorticoid on Renal Tubule

Prototypical mineralocorticoid = Aldosterone

Aldosterone increases sodium resorption and potassium and hydrogen ion excretion.
Prototype of Steroid Compounds

**CORTISOL (HYDROCORTISONE)**

**PREDNISOLONE**

**METHYL PREDNISOLONE**

**CORTISONE**

**PREDNISONE**

**DEXAMETHASONE**

Source: Undetermined
Steroids: Structure-function Relationships

A. Hydrocortisone  
B. Prednisone  
C. 9-α-Fluorocortisol

- Double-bond in 1,2 position increases glucocorticoid activity.
- Fluoro- group in 9-a position increases mineralocorticoid activity.
### Steroids

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anti-Inflam. potency</th>
<th>Na-Retain. potency</th>
<th>Duration of action</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>Short</td>
<td>20 mg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>Intermediate</td>
<td>5 mg</td>
</tr>
<tr>
<td>9-α-fluorocortisone</td>
<td>10</td>
<td>125</td>
<td>Short</td>
<td>*</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>Long</td>
<td>0.75 mg</td>
</tr>
</tbody>
</table>

**Glucocorticoid effects:** Dex > Prednisone > Cortisol

**Mineralocorticoids:** 9-α-fluorocortisone RULES
Glucocorticoid Therapy

Side Effects

Or

“Yes, Virginia, there can be at times ‘Too Much of a Good Thing…”"
Glucocorticoid Effects on Calcium & Bone

STEROIDS → “BRITTLE BONES”

↓ Osteoblastic activity
↓ Calcium absorption from gut.
↑ PTH secretion
↑ Osteoclastic activity
A 60 yo postmenopausal woman was seen in clinic with acute onset of mid-thoracic back pain. She had complained of back pain for the past 2 years and a 2” loss of height. She had been on Prednisone, 10-15 mg daily, for the past 5 years for chronic polymyositis. Radiographic exam of the spine shows compression deformities in several vertebral bodies.
Chronic glucocorticoid therapy may “unmask” diabetes in genetically susceptible individuals.
Glucocorticoid Effects on the Central Nervous System

- Neuronal death or atrophy
- Structures affected: Hippocampus, caudate
- Neuropsychiatric symptoms:
  - Cognitive - memory, learning
  - Mood - irritability, depression
  - Sleep - insomnia
A 42-yo woman with an exacerbation of lupus nephritis was treated with high-dose prednisone for several days. Her nephritis improved markedly; however, she became increasingly euphoric and severely agitated with paranoid ideation and confusion.

Following tapering of the steroid, she returned to her “usual self.”
Glucocorticoid therapy may increase risk of ulcers.
Complications of Chronic Exogenous Corticosteroid Use

CRH → ACTH → Cortisol → Adrenal Gland

Hypothalamus → Pituitary

(+) → (-) → (-) → (+)
Complications of Chronic Exogenous Corticosteroid Use

Exogenous Glucocorticoid

CRH

(-)

ACTH

Hypothalamus

Pituitary

↓↓ Cortisol

Adrenal Gland

Exogenous glucocorticoids suppress ACTH-stimulated cortisol secretion.
Complications of Chronic Exogenous Corticosteroid Use

Exogenous Glucocorticoid

ACTH is normally a trophic factor for the adrenals

High-dose, long-term glucocorticoid use results in adrenal atrophy from ACTH suppression

CRH

ACTH

Hypothalamus

Pituitary

↓↓ Cortisol

Adrenal Gland

(-)

(+)

High-dose, long-term glucocorticoid use results in adrenal atrophy from ACTH suppression.
Complications of Chronic Exogenous Corticosteroid Use

Exogenous Glucocorticoid → CRH → ACTH → ↓ Cortisol → ↓ Adrenal Insufficiency

CRH: Corticotropin-Releasing Hormone
ACTH: Adrenocorticotropic Hormone
Adrenal Insufficiency
Hypothalamus
Pituitary
Adrenal Gland
Recovery of Endogenous Cortisol Secretion Following Withdrawal of Exogenous Steroids

Full recovery of endogenous cortisol secretion may require up to 18 months following steroid withdrawal.
Case #1

A 45-year old woman present with a two-month history of anorexia, nausea, fatigue, dizziness when assuming the upright posture, and increased pigmentation of the skin.

A diagnosis of Addison’s disease (Cortisol and Aldosterone deficiency) is confirmed by appropriate testing.

Treatment is initiated with Cortisol 25 mg. (10/10/5) and 9-α fluorocortisol 0.05 mg QD.
Corticosteroid Therapy
Considerations

- How serious is the underlying disorder?
- How long is therapy required?
- What is the anticipated effective dose range?
- Is patient predisposed to complications?
- Which preparation to use?
- Alternate day v. every day therapy.
- Program for withdrawal.
Complications with Prolonged Steroid Therapy

- Retarded longitudinal growth in children*
- GI Bleeding
- Osteoporosis*
- Diabetes*
- Cushing’s Syndrome

- Steroid myopathy
- Hypertension
- Cataracts
- Psychiatric
- Adrenal suppression*

*Complications to remember
Things to Remember if Dr. Lash put you to sleep and you’re just waking up…:

Understand:

- Feedback loops regulating cortisol secretion.
- The major physiologic actions of glucocorticoids (cortisol) and mineralocorticoids (aldosterone).
- The major pharmacologic uses of glucocorticoids.
- The major types of glucocorticoids—hydrocortisone, prednisone, dexamethasone, 9-a-fluorocortisol.
- The major side effects of glucocorticoid therapy.
Questions?
Disorders of the Adrenal Cortex

2008

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Ann Arbor, Michigan  USA
Goals/Objectives

- Remember the basic principles of the HPA axis: homeostatic control of plasma cortisol and aldosterone levels

- Remember the mechanism of action of glucocorticoids and mineralocorticoids

- Understand etiology, clinical features, differential diagnosis, evaluation and therapy of 3 classic adrenal disorders:
  - Adrenal Insufficiency
  - Cushing’s Syndrome
  - Primary Hyperaldosteronism
Which Twin is Sick????

Image of patients removed
Adrenal Glands in Medical History

Andreas Vesalius (1543)
Book Five of De Corporis Humani Fabrica in 1543

Bartholomäus Eustachius (1564)
glandulae quae renibus incumbent” in 1564
History of Adrenal

- **1716**: Académie des Sciences of Bordeaux poses the question
  "Quel est l'usage des glandes surrenales?"

- **1845**: French thesis on organs of Undetermined function
  "The adrenal cease(s) to be a secreting gland."

- **1855**: Thomas Addison monograph
  "On the constitutional and local effects of disease of the supra-renal capsules,” described 10 cases marked by "anemia . . . feebleness of the heart action . . . a peculiar change of color in the skin occurring in connection with a diseased condition of the ‘suprarenal capsules'.

- **In 1945 Nobel Prize**
  Kendall, Pfiffner, and Reichenstein first tested adrenal extracts on a patient with Addison's disease, and the response was prompt and striking.
Anatomy of the adrenal glands
Histology of the Adrenal Gland

**adrenal cortex**
- Adrenal cortex: zona glomerulosa (aldosterone)
- zona fasciculata
- zona reticularis

**adrenal medulla**
- Adrenal medulla (catecholamines)

Capule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Multinucleated mass of protoplasm

Medulla
- Ganglion

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Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal
cortex
medulla
Definition of Adrenal Insufficiency

- “inappropriately low” adrenal steroid output
  - mineralocorticoids (aldosterone)
  - glucocorticoids (cortisol)
  - sex steroids (DHEAS)
How Frequent Is Adrenal Insufficiency?

- In general, about 40-60 per million individuals have adrenal insufficiency.
- 30,000-34,000 people in U.S.
Types of Adrenal Insufficiency

- **PRIMARY**
  - CRH
  - ACTH
  - Adrenal Gland

- **SECONDARY**
  - CRH
  - ACTH
  - Pituitary

- **TERTIARY**
  - CRH
  - Hypothalamus
  - Pituitary

Cortisol

(+) Adrenal Gland

(-) Pituitary

(-) Hypothalamus
Adrenal Insufficiency

1º adrenal insufficiency
- hypothalamic CRH
- pituitary ACTH
+ adrenal cortisol
+ adrenal aldosterone

adrenal defect

2º adrenal insufficiency

2º adrenal insufficiency

hypothalamic defect
Adrenal Insufficiency: Age Dependent Prevalence

Mean age 40 yo (range 17-72 yo)
Autoimmune adrenalitis most common in all age groups

Children: consider PGA or genetic defect

Young men: adrenoleukodystrophy

Adults and elderly: glucocorticoids for non-adrenal diseases
Types of Adrenal Insufficiency

Cortisol

CRH

ACTH

Hypothalamus

Pituitary

Cortisol

Adrenal Gland

PRIMARY
PRIMARY Adrenal Insufficiency

- Autoimmune adrenalitis (PGA I or II) 80%
- Infections: TB (20% - historically), CMV, fungal
- Vascular: hemorrhage, thrombosis, arteritis
- In cancer patients: metastatic cancer to adrenals
- In young men: adrenoleukdystrophy

IMPORTANT: In PRIMARY adrenal insufficiency, the adrenals are destroyed, and ALDOSTERONE is affected as well.
Adrenal Insufficiency

Autoimmune Adrenalitis

Adrenal Tuberculosis

Image of autoimmune adrenalitis removed

Image of adrenal tuberculosis removed

Adrenal Hemorrhage

Image of adrenal hemorrhage removed

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Metastases in the Adrenal Gland

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Adrenoleukodystrophy/Adrenomyeloneuropathy

X-LINKED - ONLY IN MALES

PRESENTATION
- adrenal insufficiency (childhood)
- hypergonadotropic hypogonadism (puberty)
- spastic paraparesis/demyelination-AMN(20-30 yo) vs cerebral sclerosis-ALD (childhood)

PATHOPHYSIOLOGY: mutation in Adrenoleukodystrophy protein (ALPD)

ALPD function - peroxisomal transport protein anchors very long chain AcylCoA synthetase

DISEASE - build up of chol. esters w unbranched saturated long chain FAs

TREATMENT: Cortisol replacement
Lorenzo’s Oil helps serum level of VLCFA - but no clinical benefit in 3 yr F/U

MUST BE INCLUDED IN w/u of AI in young men and in w/u AI or hypoglycemia in infants
Primary Adrenal Insufficiency

Autoimmune adrenalitis results in **ADRENAL INSUFFICIENCY**

Autoimmune adrenalitis (and therefore its subsequent **ADRENAL INSUFFICIENCY**) can be found in specific genetic syndromes, **POLYGLANDULAR AUTOIMMUNE SYNDROMES**
Primary Adrenal Insufficiency

PGA I (Polyglandular Autoimmune Syndrome I)
autosomal recessive disease- Iranian Jewish heritage starting in childhood

APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy)
autosomal recessive-Finnish heritage starting in childhood

2 of the following
- adrenal insufficiency (<15 yo)
- hypoparathyroidism (<10yo)
- chronic mucocutaneous candidiasis (<5 yo)

PLUS OFTEN
- dental enamel hypoplasia
- keratopathy/ecdodermal dystrophy

occasionally
- chronic active HepB
- malabsorption
- cholelithiosis
- juvenile onset pernicious anemia
- alopecia/vitiligo
- primary hypogonadism
- hypothyroidism
- diabetes mellitus

AIRE (AutoImmune REgulator) Nat Gen 17: 393398; 399-403
Which Twin is Sick????

Image of patients removed
Famous Names in Endocrinology

Addison’s Disease

John F. Kennedy  Jane Austin (1775-1817)
Addison’s Disease & History

1960 Presidential Debate
John F. Kennedy vs. Richard M. Nixon
Chicago, Ill., September 21, 1960
Adrenal Insufficiency

Autoimmune adrenalitis

- PGA II
  - usually in middle age females
  - adrenal insufficiency
  - hyothyroidism or diabetes mellitus
  - *uncertain genetic component
  - autosomal dominant more likely
  - HAL-B8 chromosome 6

- PGA III
  - hypothyroidism
  - other autoimmune disorder (NOT adrenal insufficiency)
Primary Adrenal Insufficiency

**SYMPTOMS**

**Cortisol**
- Fatigue
- Weakness & Malaise
- Anorexia
- Nausea and vomiting

**Aldosterone**
- Dizziness

**SIGNS**
- Proximal muscle weakness
- Orthostatic hypotension
- HYPERPIGMENTATION—Primary Al only
- HypoNa, HyperK—Primary Al only
Hypoaldosteronism
Primary Adrenal Insufficiency (ALDOSTERONE DEFECT ONLY SEEN IN PRIMARY AI not SECONDARY AI)

Aldosterone increases sodium resorption and potassium and hydrogen ion excretion.

So, with aldosterone deficiency:
Glucocorticoid Deficiency

17OHPregnenolone \rightarrow 17OHprogesterone

p450c17

3\beta\text{HSD}

DOC \rightarrow cortisol

fatigue

hypotension

hypoglycemia
DHEAS Deficiency

- **Male:** fatigue, Δ mood
- **Female:** fatigue, Δ mood, libidinal dysfunction

Chemical pathways:
- Cholesterol → pregnenolone → progesterone
- Pregnenolone → 17αOHprogrenolone → androstenedione
- 17αOHprogrenolone → DHEA → DHEAS
Adrenal Insufficiency: Hyperpigmentation

N Engl J Med
1997;337:1666.

T. Addison
“On the constitutional and local effects of disease of the suprarenal capsules” 1855

Hyperpigmentation of palmar creases

Source: Undetermined
Types of Adrenal Insufficiency

- CRH
- ACTH

Hypothalamus

Pituitary

Cortisol

SECONDARY

Adrenal Gland
Types of Adrenal Insufficiency

Adrenal Gland

Hypothalamus

Pituitary

CRH

ACTH

TERTIARY

Cortisol

(+)

(-)
Secondary & Tertiary Adrenal Insufficiency

- Vascular: Postpartum necrosis (Sheehan’s)
- Lymphocytic hypophysitis
- Infiltrative diseases: Sarcoidosis, Histiocytosis X
- Tumor compression
- Following surgery or radiation

Long term glucocorticoid treatment
Pharmacologic Dose = more than physiologic replacement
Secondary Adrenal Insufficiency

**SYMPTOMS**
- Mild malaise, fatigue
- Proximal muscle weakness

**SIGNS**
- NO hyperpigmentation
- NO orthostatic hypotension

**SIGNS & SYMPTOMS** are generally milder than with primary adrenal insufficiency due to cortisol deficiency ALONE (ie: NO ALDOSTERONE DEFICIENCY)
Adrenal Insufficiency

REMEMBER TO DIFFERENCE BETWEEN PRIMARY AI AND SECONDARY AI

PRIMARY ONLY
- hyperpigmentation (92-96%)
- HYPERkalemia (52-64%)

associated features (ie can see if PGA)
- vitiligo (4%)
- hypothyroidism (primary)
- hypogonadism (primary)

SECONDARY ONLY

associated features (ie can see if entire pit. involved)
- growth delay
  - HA
  - DI (if stalk involved)
- hypothyroidism (secondary)
- hypogonadism (secondary)
Adrenal Crisis

*hemorrhage
- thromboembolic disease
- Coagulopathy
- anticoagulant therapy
- Waterhouse-Friderichsen Syndrome
  - Neisseria meningitidis septicemia
  - Streptococcus pneumoniae
  - Pseudomonas aeruginosa
  - Staphylococcus aureus
  - Escherichia coli
  - Haemophilus influenzae
- *drugs - increase metabolism GC
  - phenytoin, phenobarbital, rifampin
- *drugs - decrease production GC
  - ketoconazole, AG, mitotane, metyrapone
- *withdrawal of exogenous glucocorticoids
If the diagnosis is missed, your patient will most likely die

- **suspect in setting of:**
  - catecholamine resistant hypotension
  - hypotension with abd pain
  - must r/o adrenal hemorrhage

- **look for:**
  - hyperpigmentation/decreased pubic hair
  - hyperkalemia
  - hyponatremia
  - hypoglycemia

If the diagnosis is missed, your patient will most likely die
SCREENING TEST:

AM CORTISOL: GOAL is to RULE OUT disease

Principle of test: Cortisol is highest in the AM allowing maximal chance of ruling out disease

- HI AM cortisol RULES OUT DISEASE
- BUT ONLY EXTREMELY LOW AM cortisol is DIAGNOSTIC

Most patients are neither EXTREMELY HI or EXTREMELY LOW and require DYNAMIC testing
Adrenal Insufficiency Diagnostic

DIAGNOSTIC TEST FOR PRIMARY ADRENAL INSUFFICIENCY:

ACTH STIMULATION TEST: GOAL is to RULE IN disease

Principle of test: ACTH stimulates steroidogenesis and secretion of cortisol - normal levels well documented

- Cortisol level after ACTH that is SUBNORMAL is DIAGNOSTIC of AI

- ACTH level that is EXTREMELY HIGH is CONSISTENT with diagnosis of PRIMARY AI but is NOT DIAGNOSTIC
The ACTH Stimulation Test

CRH \rightarrow \text{Hypothalamus} \rightarrow \text{Pituitary} \rightarrow \text{Adrenal Gland} \rightarrow \text{Cortisol}

**NORMAL**

CRH \rightarrow \text{Hypothalamus} \rightarrow \text{Pituitary} \rightarrow \text{Adrenal Gland} \rightarrow \text{Cortisol}

**ADRENAL INSUFFICIENCY**

CRH \rightarrow \text{Hypothalamus} \rightarrow \text{Pituitary} \rightarrow \text{Adrenal Gland} \rightarrow \text{Cortisol}

No or blunted increase in serum cortisol

*Synthetic ACTH (Cosyntropin)*
Adrenal Insufficiency Diagnostic

**DIAGNOSTIC TEST FOR SECONDARY ADRENAL INSUFFICIENCY:**

**INSULIN HYPOGLYCEMIA TEST:** GOAL is to RULE IN disease

Principle of test: Insulin results in hypoglycemia that is the strongest stimulus for activation of HPA axis at the level of CRH

- Cortisol level after IHT that is SUBNORMAL is DIAGNOSTIC of AI
- ACTH level after IHT that is SUBNORMAL is DIAGNOSTIC of SECONDARY AI
Diagnosis of Secondary/Tertiary Adrenal Insufficiency

The Insulin Tolerance Test

- **CRH** → **Hypothalamus**
- **Hypothalamus** → **ACTH**
- **ACTH** → **Pituitary**
- **Pituitary** → **Cortisol**
- **Cortisol** → **Adrenal Gland**
- **Adrenal Gland** → **(+)**
- **INSULIN**

Insulin-induced hypoglycemia is a powerful stimulus of the HPA axis
Therapy for Adrenal Insufficiency

Image of adrenal gland removed

Image of adrenal gland removed
Guidelines for Management

GUIDING PRINCIPLE: The more severe the stress the more cortisol patient needs.

**Acute Therapy (significant ill or Adrenal Crisis)**

- IV fluids
- IV cortisol: HI DOSE
- glucose
- treat underlying precipitating events

**Maintenance Therapy**

**Glucocorticoids**
- hydrocortisone ~ 15-25 mg/d
  - titrate to a sense of well being and physical strength
  - avoid weight gain, hypertension, hyperglycemia and osteoporosis

**Mineralocorticoids**
- fludrocortisone ~0.1 mg/d
  - titrate to salt craving and postural hypotension
  - together with serum K and upper range renin

DHEA - Do not wait for labs!!!!
# Guidelines for Management

**GUIDING PRINCIPLE:** The more severe the stress the more cortisol patient needs!

## Stress Dosing Glucocorticoids

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimally needed coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal</strong></td>
<td>no need for supplemental coverage</td>
</tr>
<tr>
<td></td>
<td>dental work</td>
</tr>
<tr>
<td></td>
<td>mild or non-febrile illness</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>25 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
</tr>
<tr>
<td></td>
<td>hernia repair</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>50-75 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
</tr>
<tr>
<td></td>
<td>rapid taper in <strong>1-2 days</strong></td>
</tr>
<tr>
<td></td>
<td>hemicolecotomy</td>
</tr>
<tr>
<td></td>
<td>significant febrile illness</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>100-150 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
</tr>
<tr>
<td></td>
<td>rapid taper in <strong>1-2 days</strong></td>
</tr>
<tr>
<td></td>
<td>cardiac surgery</td>
</tr>
<tr>
<td><strong>Critically ill</strong></td>
<td>100 mg hydrocortisone i.v. bolus followed by -</td>
</tr>
<tr>
<td></td>
<td>50-100 mg hydrocortisone i.v. q <strong>6-8 hours</strong></td>
</tr>
<tr>
<td></td>
<td>(or 0.18 mg/kg/hr)</td>
</tr>
<tr>
<td></td>
<td>0.05 mg/d fludrocortisone until shock resolves (days to weeks)</td>
</tr>
</tbody>
</table>
Discontinuing Glucocorticoids Following Long Term Suppression

GUIDING PRINCIPLE: The more glucocorticoid and the longer treated - the greater chance of long term suppression and atrophy of HPA axis

**risk of suppression**
- Low risk: Low dose, short duration or short “bursts” of glucocorticoid
- High dose and prolonged therapy (≥ 1-4 weeks) - risk is higher

**time course for recovery**
- Larger doses for prolonged periods (months - years) - recovery can take from 9 MONTHS up to 1-2 years

**need for taper**
- taper from pharmacologic to physiologic (**determined by non-adrenal disease course**)
- taper from physiologic to no treatment (**determined by adrenal suppression**)
DHEA: What is all the fuss?

- Marker of aging
  - Pharmacologic reversal of aging process

- Predictor of morbidity/mortality

- Works wonders in rodents
  - CNS, obesity, diabetes, immunity

- Preliminary studies in humans
DHEA
what is it??

- Synthesized by adrenals only in humans and higher primates
  - obligate precursor of all sex steroids in humans

- More synthesized than all other steroids
  - up to 25 mg/day in adults
  - major secretion of fetal adrenal

- Most secreted as sulfate (DHEA-S)
  - sulfation is ONLY in ADRENAL (NOT GONAD)

- Inactive at androgen receptor

19 carbon (androstan)
$\Delta^5,3\beta$-hydroxy, 17-keto
$SO_4^-$ ester at 3$\beta$

Source: Undetermined
DHEA: How Does it Work?

- **Conversion to androgens**
  - 50 mg/d raises testosterone in females

- **Intrinsic activity of DHEA-S in brain**
  - trophic effects on cultured neurons
  - GABA, NMDA, sigma receptor-channels

- **Actions of weird metabolites**
  - concept of NEUROSTEROIDS
**Case for DHEAS**

**DHEA + DHEAS**

**major secretory products of adrenal peak in fetal life and adrenarche**

Decline throughout adult life to 20-20% by 70-80 yo

**Advertisement as ANTI-AGING drug**

In USA: FOOD SUPPLEMENT!!!!!!

**classic steroid converted to testosterone peripherally**

**neurosteroid directly binding NMDA + GABA receptors**
DHEA replacement in women with adrenal insufficiency improved overall well-being and mood, specifically depression, anxiety and both sexual interest and sexual satisfaction.

DHEA in men and women with primary adrenal insufficiency improves mood and well-being, irrespective of the patient's sex.
Adrenal Androgens

only in pts w AI who do NOT feel
“normal on replacement GC and MC”

DHEA: 25 mg po q a.m.

-may increase to 50 mg
-dictated by response and androgenic side effects
-monitor labs
  DHEAS, androstendione and free test
  LFTS and lipids at 4 + 12 w
Watch Out for Supplements

Steroids are lipophilic
Undetermined dosing
Undetermined purity

Image of Adrenal Glandular Plus Supplements removed

Image of Adrenal Cortex Complex Supplements removed

Image of Raw Adrenal Supplements removed
Congenital Adrenal Hyperplasia

- Genetic block in biosynthetic pathway for cortisol and aldosterone result in primary adrenal insufficiency.
- Decreased feedback on hypothalamus and pituitary increase CRH and ACTH.
- Increased ACTH further stimulates adrenals and results in shunting and production of precursors.
- ACTH stimulates growth (HYPERPLASIA) of adrenals.
Steroidogenesis

glomerulosa

fasciculata

reticularis

gonad periphery

DHEAS

sulfatase

DHEA

sulfotransferase

androstenediol

17\&HSD

17\&HSD

17\&HSD

17\&HSD

17\&HSD

testosterone

estradiol

estrone

aldosterone

18OHCS

18\&HSD

p450c11B2

p450c11B1

p450c11B2

18\&HSD

p450c21

DOCS

CS

DOC

Cortisol

cholesterol

sTaR

p450scc

pregnenolone

3\&HSD

progesterone

3\&HSD

17OHprogesterone

3\&HSD

p450c21

androstenedione

17OHpredrenolone

1720lyase

17,20lyase

1720lyase

17,20lyase

1720lyase

1720lyase
Steroidogenesis

glomerulosa
fasciculata
reticularis

gonad periphery

Public Domain
Wikimedia Commons
SEVERE P45c21 Deficiency in FEMALE

Image of patient removed

<table>
<thead>
<tr>
<th>AGE</th>
<th>4 1/2 yrs.</th>
<th>23 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT. AGE</td>
<td>5 yrs.</td>
<td>11 yrs.</td>
</tr>
<tr>
<td>BONE AGE</td>
<td>9 yrs.</td>
<td>ADULT</td>
</tr>
<tr>
<td>17 K.S.</td>
<td>60 mgm/24 hrs.</td>
<td>50 mgm/24 hrs</td>
</tr>
<tr>
<td>Pregnantriol</td>
<td>13.6 mgm/24 hrs.</td>
<td>—</td>
</tr>
</tbody>
</table>

results in androgen excess in utero
MILD P45c21 Deficiency in FEMALE results in androgen excess at puberty

Cliteromegaly

Beard

Hirsuitism
Important things to remember:

- Loss of function of enzyme in steroidogenesis pathway

- “Block” in pathway leads to shunting down alternate paths and abnormal build-up precursors before the block.

- Severe forms lead to virulization of females

- Milder forms (“non-classical”) may lead to hirsuitism and menstrual abnormalities in women.

- Block in pathway may result in adrenal insufficiency during times of stress.
Adrenal Excess States
Causes of hypercortisolism

- **Physiological states**
  - Pregnancy
  - Stress
  - Chronic excessive exercise
  - Malnutrition

- **Pathologic states**
  - Cushing's syndrome
  - Diabetes mellitus
  - Hyperthyroidism
  - Severe chronic disease
  - Glucocorticoid resistance
  - Psychological states
  - Anorexia nervosa
  - Panic disorder
  - Melancholic depression
  - Obsessive-compulsive disorder

- PHARMACOLOGIC USE OF GLUCOCORTICOIDS
Cushing’s Syndrome

Harvey Cushing (far left) in 1895 during his House Pupilship (internship) at Massachusetts General Hospital.

Cushing HW. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bulletin of the Johns Hopkins Hospital. 1932;50:137-95

His research on the pituitary body gained him an international reputation, and he was the first to ascribe to pituitary malfunction a type of obesity of the face and trunk now known as Cushing's disease, or Cushing's syndrome.
Cushing’s Syndrome

- All types of Cushing’s Syndrome
  - HI CORTISOL (urine and serum)
  - Absent circadian rhythm

- Adrenal Cushing’s syndrome is autonomous and therefore has LOW ACTH
- Only ACTH-dependent Cushing’s (by definition) has HI ACTH
Cushing’s Syndrome

ACTH independent Cushing’s

<table>
<thead>
<tr>
<th>adrenal Cushing’s</th>
<th>pituitary ACTH Cushing’s</th>
<th>ectopic ACTH Cushing’s</th>
<th>ectopic CRH Cushing’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>- hypothalamic CRH</td>
<td>- pituitary ACTH</td>
<td>- ectopic ACTH</td>
<td>- ectopic CRH</td>
</tr>
<tr>
<td>+ adrenal cortisol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACTH dependent Cushing’s

<table>
<thead>
<tr>
<th>adrenal defect</th>
<th>pituitary defect</th>
<th>ectopic defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ adrenal cortisol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cushing’s Syndrome

Exogenous GC administration

Endogenous hypercortisolism

ACTH-dependent

ACTH-independent

Pituitary adenoma

Ectopic ACTH (CRH) syndrome

Adrenal adenoma

Adrenal carcinoma
Cushing’s Syndrome

- ACTH-dependent Cushing’s Syndrome
  - pituitary adenoma-ACTH (60%)
  - Ectopic hormone (10%)
    - ACTH
    - CRH

all result in bilateral adrenal hyperplasia
Types of Cushing’s Syndrome

Cushing’s Disease ("pituitary Cushings"): hypercortisolism from a pituitary adenoma

Hypothalamus

Pituitary

CRH

ACTH

PITUITARY ADENOMA

(+)

(-)

Cortisol

Adrenal Gland

HARVEY

Public Domain
Normal Pituitary
Pituitary Cushing’s DISEASE

normal

Source: Undetermined

Cushing’s disease

Source: Undetermined
Ectopic Cushing’s

Hypercortisolism from Ectopic production of ACTH or CRH by tumor.

Causes
- Bronchial carcinoid
- Oat cell carcinoma
- Thymic carcinoid
- Pheochromocytoma
- Medullary thyroid ca

Small (Oat) cell ca of lung

Images of oat cell in lung removed
Cushing’s Syndrome

- ACTH-independent Cushing’s Syndrome
  - adrenal cortical neoplasm
    - adenoma
    - carcinoma
  - primary adrenal hyperplasia
Adrenal Cushing’s

Adrenal Causes: Hypercortisolism from a adrenal adenoma or carcinoma

Because ACTH is suppressed, the rest of the adrenal and contralateral gland are atrophied.

Adrenal adenoma or carcinoma
Cushing’s Syndrome

**CLINICAL MANIFESTATIONS of CORTISOL EXCESS**

- increased protein catabolism = striae, bruising, delayed wound healing, muscle wasting
- increased glucose production = DM
- redistribution of fat = truncal obesity
- bone breakdown = osteoporosis
- facilitation of catechol synthesis = hypertension
- anti-inflammatory = opportunistic infections
- Inhibition of HPG axis = amenorrhea, impotence
- CNS effects (limbic/hippocampus) = depression and memory difficulties

**ACTH dependent ONLY**
- Pigmentation (MSH)

**ACTH dependent or Mixed Adrenal**
- Androgen excess
  - Terminal hair hirsuitism
  - Acne
  - Irregular menses
  - Balding
Cushing’s Syndrome

- Physical examination:
  - adiposity
  - moon face, plethora
  - (pseudo-) gynecomastia
  - striae

Image of patient with striae on arms removed

Image of patient with moon face / plethora removed
Cushing’s Syndrome

- Acanthosis nigricans
- Purple striae

Image of patient with acanthosis nigricans on armpit removed

Image of patient with striae on abdomen removed

Image of patient with striae on abdomen removed
Cushing‘s Syndrome

- Myopathy
  - Proximal muscle wasting
- Osteoporosis
- Oligo-Amenorrhea/Impotence
- Psychiatric Symptoms
  - depression, mania (Steroid psychoses)
ACTH-Dependent Pituitary Cushing’s Disease

- Symptoms due to pituitary mass
  - bitemporal hemianopsia
  - pituitary insufficiency
  - HA
Cushing's Syndrome: Diagnosis

- **Diagnosis**
  - First diagnose **CORTISOL EXCESS**
    - elevated 24 hr urine cortisol < 100 mg/24 hr
  - Then diagnose **PATHOLOGIC CORTISOL EXCESS**
    - r/o physiologic causes which suppress normally with low-dose DEX (Cort < 5 mg/dl)

- **ACTH dependent or NOT**
  - Measure ACTH level
    - if DETECTABLE > 9 pg/ml - must be ACTH dependent
    - (if NOT DETECTABLE < 9 pg/ml - must be ACTH independent)
Cushing’s Syndrome: Low-dose DEX suppression

Low-dose Dex will suppress ACTH secretion in:
- normal patients
- physiologic hypercortisolism (stress)

Low-dose Dex will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma or ectopic ACTH producing tumors)
- ACTH independent Cushing’s syndrome (adrenal tumors)
Cushing‘s Syndrome: Diagnosis

- **Diagnosis**
  - First diagnose CORTISOL EXCESS
    - elevated 24 hr urine cortisol < 100 mg/24 hr
  - Then diagnose PATHOLOGIC CORTISOL EXCESS
    - r/o physiologic causes which suppress normally with low-dose DEX (Cort < 5 mg/dl)

- ACTH dependent or NOT
  - Measure ACTH level
    - if DETECTABLE > 9 pg/ml - must be ACTH dependent
    - (if NOT DETECTABLE < 9 pg/ml - must be ACTH independent)
ACTH-DEPENDENT Cushing’s Syndrome

Is it pituitary or ectopic????

- **High dose** DEX SUPPRESSION TEST
  - Pituitary Cushing’s may suppress to **high dose** DEX
  - Ectopic NEVER suppresses to **high dose** DEX

- **Inferior Petrosal sinus Sampling**
  - Pituitary Cushing’s - find HI ACTH near pituitary and low in the periphery
  - Ectopic Cushing’s - find HI ACTH in the periphery and low near pituitary

- **IMAGE the pituitary**
Cushing’s Syndrome: High-dose DEX suppression

High-dose DEX will suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma)

High-dose DEX will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (ectopic tumors)

Most pituitary adenomas that secrete ACTH can still be inhibited by REALLY REALLY HIGH glucocorticoids (i.e., more that produced their diseased HPA axis).

Therefore, high-dose dexamethasone will NOT suppress ACTH from ectopic tumors.

Diagram:
- Hypothalamus
- Pituitary
- Adrenal Gland
- CRH
- ACTH
- Cortisol
- (+)
- (-)
Cushing’s Syndrome: Diagnosis

Bone Diagram:

Most ectopic ACTH-producing tumors secrete ACTH independently from regulation by glucocorticoids. Therefore, high-dose dexamethasone will NOT suppress ACTH from ectopic tumors.

High-dose Dex will suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma)

High-dose Dex will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (ectopic tumors)
Imaging in Cushing Syndrome

- **ADRENAL CT findings**
  - adrenals small = ?
  - one adrenal large and 1 small =?
  - Both adrenals large=?

- **Pit MRI findings**
  - Mass or no mass
    (some pituitary corticotrope tumors are too small to be seen on MRI)

- **Search for ectopic ACTH or CRH producing tumor**
  - Lung: Bronchial Carcinoid and SCC 50%
  - Thymic Carcinoid (epithelial thymoma) 10%
  - Pancreatic Islet Cell Tumor 10%
  - Pleochromocytoma 10%
  - Abdominal Carcinoids 5%
  - Medullary Thyroid Carcinoma 5%
Cushing’s Syndrome Treatment

- **adrenal adenoma**
  - resection
  - cortisol replacement
  - if not curative
    - XRT
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole

- **pituitary adenoma**
  - transphenoidal resection (TSR)
  - cortisol replacement
  - if not curative
    - XRT
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole

- **Ectopic ACTH or CRH**
  - Find the tumor!!!!!!!!!!!
  - if not curative
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole
Cushing’s Syndrome

before treatment

after treatment
Cushing’s Syndrome

dogs
Ferrets
horses
Conn JW. Primary aldosteronism, a new clinical syndrome. J Lab Clin Med. 1955;45:3-17
Primary Aldosteronism

- **Clinical Presentation**
  - Manifestations of HYPOKALEMIA and HTN
    - LOW K
      - neuromuscular
        - paresthesias
        - weakness
        - tetany
    - Renal
      - Polyuria
      - Carbohydrate
        - abnormal GTT
    - HTN usually not malignant
      - early in disease may have HTN with NORMAL K
Causes of Hyperaldosteronism

Definition: syndrome of inappropriate excessive secretion of aldosterone by adrenal gland

An increase in aldosterone ACTION can theoretically result from ANY defect in RAA pathway

- LOW IVV (real or perceived by kidney in renal artery stenosis)
- JGA renin tumor
- ACE polymorphisms
- overproduction of AII by renal tumors
- ADRENAL overproduction of ALDO
- constitutive MR or Na channel
**Primary Aldosteronism**

**primary hyperaldosteronism (HI ALDO/LOW RENIN)**
- ZG Aldo tumor 70%
- ZG Aldo hyperplasia 30%

- **rare/rare/rare**
  - Congenital adrenal hyperplasia <1%
    - (p450c11β, p450c17)
  - ACE polymorphisms <1%
  - All overproduction <1%

**secondary hyperaldosteronism (HI ALDO/HI RENIN)**
- JGA renin tumor <1%
- renal artery stenosis <1%

**apparent mineralocorticoid excess (LOW ALDO/LOW RENIN) (downstream of ALDO)**
- constitutively active MR <1%
- Na/K/H channel <1%
- licorice <1%
Consider in patients with:

- New HTN
- HTN with LOW K

EVEN THOUGH it only accounts for 0.5% of all HTN

BECAUSE- IF YOU NEVER THINK OF THIS--
---YOU WILL NEVER FIND IT!!!
Primary Aldosteronism

- **Work-Up**
  - R/O other causes of LOW K
    - LOW intake (diet)
    - HI output
      - N/V/D
      - Diuretic use with loops + thiazides
  - 24 h Urine ALDO
    - If LOW- pt does not have PRIMARY ALDO
    - IF HI (>10 ug/day)
      - check RENIN level (suppressed < 1 ng/ml/hr)
        - If RENIN HI ----JGA renin tumor or RAS
        - If RENIN LOW---- PRIMARY HYPERALDO
  - IF NECESSARY (ie AMBIGUOUS) Volume expand to see if can suppress RAA
    - If can suppress --essential HTN
Adrenal Zona Glomerulosa Adenoma

Image of Adrenal gland removed
Primary Aldosteronism

- **IMAGING and TREATMENT**
  - **CT scan**
    - Adenoma
      - unilateral ADX
    - NO adenoma
      - selective venous cath to measure ALDO rt vs lt
  - If unilateral elevation-small adenoma
  - If no lateralization-bilateral hyperplasia
  - Medical trt with spironolactone or amiloride
  - bilateral ADX
Adrenocortical Carcinoma

- Larger adrenal mass
  - High probability NOT benign if >5 cm in diameter
  - Development of Cushingoid features usually very rapid (several months rather than years)
  - Often associated with elevated DHEA-sulfate and virulization

Image of Adrenal gland removed
Remember:

Endocrine disorders are NOT diagnosed by means of imagining studies. Biochemical confirmation must come first before imagining is performed.
“Even our destiny is determined by our endocrine glands.”

Albert Einstein