HPA AXIS & ADRENAL DYSFUNCTION
AN EVIDENCE BASED REVIEW

Lena D. Edwards, MD, FAARM

Internal Medicine
Anti-Aging and Regenerative Medicine
OBJECTIVES OF DISCUSSION

- To discuss the role of the adrenal glands under both normal and stressful conditions
- To discuss proper function of the hypothalamic-pituitary-adrenal axis and the interrelationship to adrenal gland hormones to other hormones
- To differentiate between adrenal and HPA axis dysfunction
- To discuss proposed etiologies whereby abnormal cortisol release patterns may arise
- To review the evolution, clinical signs and symptoms, and physiological manifestations of abnormal cortisol release patterns seen in adrenal gland dysfunction
- To review the most appropriate diagnostic techniques available in order to properly treat patients with adrenal dysfunction
ADRENAL GLANDS
ADRENAL GLAND ANATOMY

**Adrenal Cortex**
- Zona Glomerulosa: Aldosterone
- Zona Fasiculata: Cortisol
- Zona Reticularis: Androgens, Pregnenolone, Progesterone

**Adrenal Medulla**
- Epinephrine (80%)
- Norepinephrine (20%)
Major Pathways in Steroid Biosynthesis

Cholesterol

Pregnenolone

17-hydroxy pregnenolone

Dehydroepiandrosterone

Progesterone

17-hydroxy progesterone

Androstenedione

Deoxycorticosterone

11-deoxycortisol

Estrone

Corticosterone

11-deoxycortisol

Testosterone

Aldosterone

Cortisol

Estradiol

Legend:
- Major progestagen
- Major mineralocorticoid
- Major glucocorticoid (species variation)
- Major gonadal estrogen
- Major gonadal androgen
ADRENAL HORMONE FUNCTIONS

- Cortisol
  - Produced only in the adrenal glands
  - Regulation of protein, carbohydrate, lipid, and nucleic acid metabolism
  - Elevates blood sugar
  - Elevates blood pressure
  - Increased protein catabolism and inhibition of protein synthesis
ADRENAL HORMONE FUNCTIONS

Cortisol
- Anti-inflammatory (cytokine suppression)
- Decreased antibody production
- Suppresses release of Growth Hormone
- Bone loss
- Increases gastric acid production
- Inhibits production of nucleic acids (except liver RNA)
- Mobilizes fatty acids
Dehydroepiandrosterone (DHEA)

- Precursor to sex hormones
- Most abundant hormone produced by adrenal cortex
- Activates endothelial nitric oxide synthase
- Directly binds to NMDA and GABA receptors in the brain
- Lowers cortisol
Dehydroepiandrosterone (DHEA)

- Anti-atherogenic
- Lowers triglycerides
- Improves insulin sensitivity
- Promotes sense of well being
- Neuroprotective
- Maintains tissue strength and repair
- Direct action on immune cells
- Promotes bone growth
ADRENAL HORMONE FUNCTIONS

- **Pregnenolone**
  - Precursor to all steroid hormones
  - Produced mainly in adrenals and brain
  - Synthesized from cholesterol
  - Blocks effects of Cortisol
  - Increases productivity and reduces stress
  - Anti-inflammatory
  - Preserves memory
    - Enhance myelinization
    - Positively influence synaptic functioning
    - Stimulates NMDA receptors
ADRENAL HORMONE FUNCTIONS

- Catecholamines
  (Epinephrine, Norepinephrine)
  + Raises blood sugar
  + Stimulates Cortisol secretion
  + Stimulates lipolysis
  + Increases heart rate
  + Increases blood flow to muscle
  + Enhances cardiac contractility

+ Decreases gastric motility
+ Vasodilation
+ Bronchodilation
+ Inhibits bladder contraction
NORMAL DIURNAL HORMONE RELEASE

[Diagram showing hormone release patterns with emphasis on stress hormones]
ADRENAL DYSFUNCTION

DEFINING APPROPRIATE TERMINOLOGY
DEFINITION OF STRESS

“Stress is a state of threatened homeostasis that is re-established by a complex repertoire of physiologic and behavioral adaptive responses of the organism....”

THE FIGHT OR FLIGHT RESPONSE
Physiologic Stressors
ADRENAL STRESSORS

- Environmental Stress
- Physical Stress
- Psychological Stress
- Nutritional Stress

HPA axis & Adrenal Dysfunction
DEFINITION OF ALLOSTATIC LOAD

- The wear and tear of the body and brain resulting from chronic over activity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge.

- Allostatic load results when the HPA axis is either overworked or fails to shut off after stressful events or when normal compensatory systems over react.

TRADITIONAL MEDICAL DEFINITION OF “ADRENAL FATIGUE”

“A putative disorder in which the adrenal glands are claimed to be exhausted and unable to produce adequate quantities of hormones. “Adrenal fatigue” is a label sometimes applied to a collection of non-specific medically unexplained symptoms, but it is not a recognized medical condition. The term is used by practitioners of alternative medicine who claim adrenal fatigue to be too mild to be picked up on standard blood tests.”
“Proponents of the adrenal fatigue diagnosis claim this is a mild form of adrenal insufficiency caused by chronic stress. The unproven theory behind adrenal fatigue is that your adrenal glands are unable to keep pace with the demands of perpetual fight-or-flight arousal. As a result, they can’t produce quite enough of the hormones you need to feel good.......
“...But accepting a medically unrecognized diagnostic label from an unqualified practitioner could be worse. Unproven remedies for so-called “adrenal fatigue” may leave you feeling sicker, while a treatable condition—such as depression or fibromyalgia—continues to take its toll”.
ACTUAL DEFINITION OF ADRENAL DYSFUNCTION

The inability of the adrenal glands to produce adequate amounts of stress hormones in a normal diurnal pattern, whether primarily or secondarily, in response to allostatic load ultimately resulting in HYPOCORTISOLISM.
The age related decline in DHEA and DHEA-S production by the adrenal glands

Several clinical signs are related to the decline in DHEA secretion in aged people:
- Sarcopenia
- Osteopenia
- Atherosclerosis progression
- Impairment of cognitive and affective performances
- Deterioration of immunocompetence

These clinical conditions are further exacerbated by concomitant age related glucocorticoid excess.

“All together, these clinical signs construct the corpus of a syndrome named adrenopause.”
EVOLUTION OF ADRENAL DYSFUNCTION

Hypothalamus

Pituitary Gland

Adrenal Gland

ALLOSTATIC LOAD

HPA AXIS DYSFUNCTION

CORTISOL EXCESS

CORTISOL DEFICIENCY
Physical Effects of Chronic Stress
Reduced biosynthesis of releasing factors or hormones from hypothalamus +/- pituitary glands
Decreased or Increased target receptor sensitivity at the level of the pituitary or adrenal glands
Hippocampal atrophy (causes de-regulation of cortisol release)
Hypersecretion of secretagogue (CRH +/- ACTH) with down-regulation of target receptors on respective gland
PERIPHERAL MECHANISMS OF ADRENAL DYSFUNCTION

- Reduced adrenocortical sensitivity and reactivity
- Reduced target tissue sensitivity to glucocorticoids
- Systemic inflammation (cortistatin)
- Down regulation of adrenal ACTH receptors
- Adrenal gland atrophy
  + Scott and colleagues, 1999
  + Found patients with blunted cortisol responses to ACTH stimulation to have adrenal glands 50% smaller on CT
OTHER MECHANISMS
OF ADRENAL DYSFUNCTION

- Adrenal injury (trauma, hemorrhage, auto-immune)
- Drug toxicity (etomidate)
- Nutrient deficiency (i.e. B1, B5, Vitamin C)
- Substrate deficiency (progesterone, HDL cholesterol)
- Heavy metal toxicity
- Infection (down-regulation of cortisol production to allow appropriate immune response)
FACTORS MEDIATING DEVELOPMENT OF ADRENAL DYSFUNCTION

- Stressor characteristics
  - Duration
  - Severity
  - Exposure to previous chronic stressors
- Individual coping mechanisms
- Genetics
- Gender (female > male)
FACTORS MEDIATING DEVELOPMENT OF ADRENAL DYSFUNCTION

- Developmental factors
  - Prenatal stress
  - Childhood stress
- Personality
  - Low self esteem
  - High external control
  - Introversion
Metabolic Consequences of Chronic Stress

THE STEROIDOGENIC PATHWAY
WITH ENZYMATIC STEPS

- STRESS

Enzymatic Steps:
1. 20 α-hydroxylase, 22 hydroxylase & 20,22 desmolase
2. 3β-hydroxysteroid dehydrogenase & Δ5 - Δ4 isomerase
3. 17 α-hydroxylase
4. 17,20 desmolase (17,20-lyase)
5. 21-hydroxylase
6. 11 β-hydroxylase
7. 18-hydroxylase
8. 18-hydroxydehydrogenase
9. 17 β-hydroxysteroid dehydrogenase
10. aromatase
11. 3β-hydroxysteroid sulfotransferase
HYPERCORTISOLISM

Progression

TIME OF EACH STAGE IS HIGHLY VARIABLE

Cortisol
Pregnenolone
DHEA
Metabolic Consequences of Stress Induced Hypercortisolism
METABOLIC CONSEQUENCES OF HYPERCORTISOLISM

- Immune suppression
- Impaired thyroid function
- Decreased kidney function
- Exacerbation of skin conditions
  - Acne
  - Dermatitis
  - Psoriasis
  - Eczema
- Increased risk of cardiovascular diseases
  - Arrhythmia
  - CHF
  - MI
  - Atherosclerosis
  - HTN
Mood disorders (especially major depression)
Increased risk of neurodegenerative diseases
Osteoporosis
Dementia/memory loss
Sleep disorders
Insulin resistance → diabetes
Reproductive disorders
Premature aging
HYPERCORTISOLISM AND THE GASTROINTESTINAL TRACT

- GERD
- Irritable bowel syndrome
- Non-ulcer dyspepsia
- PUD
- Malabsorption
- Achlorhydria
- Chronic abdominal pain
HYPERCORTISOLISM AND IMMUNITY
Prolonged hypercortisolism leads to degeneration of the:

- Hippocampus – memory
- Hypothalamus – CFS, FM, Depression, PTSD
- Pre-Frontal Cortex – executive decision making
- Amygdala – emotional stability

fMRI Pathologic changes seen, some irreversible despite treatment

Effects remain after hypocortisolism has developed
Psychological stress and the risk of diabetes related autoimmunity: a review article

*Neuroimmunomodulation*, Jan 1, 2006; 13(5-6): 301-308

“Psychological stress decreases insulin sensitivity and increases insulin resistance and may hence be important in the development/onset of type I diabetes….although the biological mechanisms are still unknown.”
HYPERCORTISOLISM & DIABETES

Abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance


“In patients with glucose intolerance, cortisol secretion, although normal, is inappropriately high given enhanced central and peripheral sensitivity to glucocorticoids……thus altered cortisol action occurs not only in obesity and hypertension but also in glucose intolerance and could therefore contribute to the link between these multiple cardiovascular risk factors.”
HYPERCORTISOLISM & HEART DISEASE

- Cortisol inhibits growth hormone production
- Cortisol interferes with thyroid hormone action
- Cortisol stimulates visceral fat deposition → metabolic syndrome
- Stress promotes unhealthy habits such as smoking and over-eating which ultimately can contribute to the formation of heart disease
Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study

*Circulation*, July 19, 2005; 112(3): 332-340

“This is the first population-based prospective study that has found a specific association between cortisol:testosterone ratio and the incidence of ischemic heart disease, apparently mediated through insulin resistance……A positive linear trend was seen across quintiles of cortisol:testosterone ratio for incident ischemic heart disease.”
There are extensive data concerning stressors contributions to diverse pathophysiological changes including sudden death, myocardial infarction, myocardial ischemia, and wall motion abnormalities as well as to alterations in cardiac regulation.

Although stressors trigger events, it is less clear that stress “causes the events. There is nonetheless overwhelming evidence both for the deleterious effects of stress on the heart and for the fact that vulnerability and resilience factors play a role in amplifying or dampening those effects.”
The Whitehall II study

- 10,000 patients aged 35-55
- Definite association between chronic work-related stress and coronary heart disease
- Stressed workers more prone to physical inactivity, poor diet, metabolic syndrome, and higher cortisol levels
- “Work stress may be an important determinant of coronary heart disease among working-age population”

HYPERCORTISOLISM & MOOD DISORDERS

- Borderline personality disorder
- ADHD
- Schizophrenia
- Depression
- Bipolar disorder
- Drug addiction
- Anxiety
- Autism
- Alcoholism
Future therapeutic targets in mood disorders: the glucocorticoid receptor


“A dysfunction in glucocorticoid receptors is integral to the HPA abnormalities of mood disorders. Antidepressants and mood stabilizing drugs can up regulate glucocorticoid receptors, Restoring glucocorticoid function…Drugs designed specifically to up regulate glucocorticoid receptors may be integral to future strategies in treating mood disorders.”
Subclinical hypercortisolism may be more common than is generally recognized in patients with osteoporosis in whom secondary causes of osteoporosis have been excluded (Ann Intern Med, Oct 16, 2007; 147(8): 541-8).

Osteoporosis may be the only symptom of otherwise asymptomatic cortisol excess (Recenti Prog Med, June 1, 2008; 99(6): 309-13).

The endogenous cortisol profile of healthy elderly men is a determinant of their bone mineral density and their rate of involutional bone loss (J Clin Endocrinol Metab, Sept 1, 1999; 84(9): 3058-63).
osteoporosis

- DHEA is converted into Estrone in the osteoblast which is positively regulated by glucocorticoids and Vitamin D and is important in maintaining bone mineral density after menopause (Mech Ageing Dev, Apr 30 2002; 123(8): 1107-14, Clin Calcium, Nov 1, 2003; 13(11): 1419-24)

- Among older healthy adults, daily administration of DHEA has a modest and selective beneficial effect on BMD and bone resorption in women (Osteoporos Int, May 1, 2008; 19(5): 699-707)
HYPOCORTISOLISM

TIME OF EACH STAGE IS HIGHLY VARIABLE
HYPOCORTISOLISM & IMMUNITY

- Inadequate immune cell trafficking
- Enhanced cellular immunity
- Inability to defend against pathogens
- Inadequate leukocyte trafficking
HYPOCORTISOLISM & IMMUNITY

- Elevations of immune mediators
  - Interleukins (IL-6 and 10) and TNFα
  - Prostaglandins
  - Lymphocytes
  - Natural killer cells
  - ANA antibodies
  - Thyroid antibodies
Elevated levels of cytokines have been found in patients with:
- Chronic fatigue syndrome
- Fibromyalgia
- PTSD

Breast cancer patients:
- Elevated levels of IL-6
- Flattened cortisol release patterns
- In patients with these findings, higher morbidity and mortality
HYPOCORTISOLISM IN ASTHMA & ATOPIC DISEASE

- Decreased basal adrenal activity
- Blunted adrenocortical response to CRH stimulation testing
- Attenuated cortisol responses to psychosocial stressors
Clinical correlated of DHEA associated with post-traumatic stress Disorder

*Acta Psychiatr Scan*, Sept 1, 2006; 114(3): 187-93

“The PTSD group showed significantly higher levels of DHEA as well as significantly lower cortisol:DHEA ratio, controlling for age. Regression analysis demonstrated that DHEA levels could be predicted by symptom improvement and coping, whereas the cortisol:DHEA ratio was predicted by current symptom severity. The greater symptom improvement was related to DHEA levels suggesting a role of these hormones in modulating PTSD recovery.”
HYPOCORTISOLISM &
CARDIOENDOCRINE SYSTEM

- Accelerated progression of atherosclerosis, risk of MI and CHF
- Elevated inflammatory markers
  - PAI-1
  - Fibrinogen
  - HS-CRP
- Endothelial dysfunction and hypertension
- Enhancement of insulin resistance and hyperglycemia
- Unfavorable lipoprotein profiles
Numerous studies confirm the presence of:
- low cortisol
- blunted cortisol responses to stimulation testing
- Abnormal diurnal cortisol release patterns

Some studies have shown improvement in symptoms with administration of low dose hydrocortisone treatment.
Fibromyalgia
+ Impaired ability to activate the hypothalamic pituitary portion of the HPA axis as well as the sympathoadrenal system leading to reduced corticotropin and epinephrine response to hypoglycemia (Curr Opin Rheumatol, Mar 1, 2000;12(2):113-23).

Chronic Fatigue Syndrome
+ 2/3 of patients have adrenal hypofunction (Townsend Letter Group, 2004)
+ Impaired diurnal cortisol (Psychoneuroendocrinology, Jan 1, 2005;30(1):92-100); (Psychosom Med, April 1, 2008;70(3):298-305).
+ Reduced DHEA and DHEA-S levels (J Affect Disord, Jul 1, 1999;54(1-2):129-137).
CARDIA Study 2006

- 718 black and white middle aged men
- 6 salivary cortisol samples and coronary calcium scoring throughout one full day
- Persons with cortisol slope scores in the flattest quartile had a greater likelihood of any coronary calcium than did those in the remaining quartiles adjusted for sex-race group, age, smoking, treatment for diabetes, systolic blood pressure, triglycerides, average cortisol, and educational attainment.

HYPOCORTISOLISM & CARDIOVASCULAR DISEASE
Some studies have shown reduced adrenal secretory reserve during prolonged critical illness

Post-operative hypoadrenia is under-recognized

Due to
- Reduced adrenal gland blood flow
- Adrenal gland trauma
- Drug toxicity

Flattened cortisol curves correlate with increased morbidity and mortality

Low doses of Hydrocortisone have been found to support deficient endogenous production

ADRENAL DYSFUNCTION

CLINICAL CONSEQUENCES
Physical symptoms of stress

Here are ways in which some key body systems react.

1. NERVOUS SYSTEM
   When stressed — physically or psychologically — the body suddenly shifts its energy resources to fighting off the perceived threat. In what is known as the “fight or flight” response, the sympathetic nervous system signals the adrenal glands to release adrenaline and cortisol. These hormones make the heart beat faster, raise blood pressure, change the digestive process and boost glucose levels in the bloodstream. Once the crisis passes, body systems usually return to normal.

2. MUSCULOSKELETAL SYSTEM
   Under stress, muscles tense up. The contraction of muscles for extended periods can trigger tension headaches, migraines and various musculoskeletal conditions.

3. RESPIRATORY SYSTEM
   Stress can make you breathe harder and cause rapid breathing — or hyperventilation — which can bring on panic attacks in some people.

4. CARDIOVASCULAR SYSTEM
   Acute stress — stress that is momentary, such as being stuck in traffic — causes an increase in heart rate and stronger contractions of the heart muscle. Blood vessels that direct blood to the large muscles and to the heart dilate, increasing the amount of blood pumped to these parts of the body. Repeated episodes of acute stress can cause inflammation in the coronary arteries, thought to lead to heart attack.

5. ENDOCRINE SYSTEM
   Adrenal glands
   When the body is stressed, the brain sends signals from the hypothalamus, causing the adrenal cortex to produce cortisol and the adrenal medulla to produce epinephrine — sometimes called the “stress hormones.”

   Liver
   When cortisol and epinephrine are released, the liver produces more glucose, a blood sugar that would give you the energy for “fight or flight” in an emergency.

6. GASTROINTESTINAL SYSTEM
   Esophagus
   Stress may prompt you to eat much more or much less than you usually do. If you eat more or different foods or increase your use of tobacco or alcohol, you may experience heartburn, or acid reflux.

   Stomach
   Your stomach can react with “butterflies” or even nausea or pain. You may vomit if the stress is severe enough.

   Bowels
   Stress can affect digestion and which nutrients your intestines absorb. It can also affect how quickly food moves through your body. You may find that you have either diarrhea or constipation.

7. REPRODUCTIVE SYSTEM
   In men, excess amounts of cortisol, produced under stress, can affect the normal functioning of the reproductive system. Chronic stress can impair testosterone and sperm production and cause impotence.

   In women stress can cause absent or irregular menstrual cycles or more-painful periods. It can also reduce sexual desire.
SYMPTOMS OF HYPOCORTISOLISM

- Low grade fever
- Easy fatigability
- Weakness
- Weight loss
- Muscle aches
- Abdominal pain
- Vomiting
- Hypotension
- Irritability
- Restlessness

43 symptoms overlap with Addison’s Disease

Baschetti, *CMAJ*, 2006;175(4): 386
SYMPTOMS OF HYPOCORTISOLISM IN CRITICALLY ILL PATIENTS

- General Fever (without apparent cause, not responding to antibiotics)
- Mental Weakness, fatigue, lethargy, agitation, apathy, depression without specific psychiatric disturbance, delirium, coma
- Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, abdominal or flank pain
- Hemodynamic: Unexplained circulatory instability
- Hypovolemic shock: decreased pre-load, depressed myocardial contractility, increased systemic vascular resistance
- Hyperdynamic shock (high cardiac output, decreased systemic vascular resistance)
- Laboratory (Hypoglycemia, hyponatremia, hyperkalaemia, hypercalcaemia, neutropenia, eosinophilia, hyperprolactinaemia, hypothyroidism)
SYMPTOM TRIAD OF HYPOCORTISOLISM

Chronic Fatigue Syndrome
Fibromyalgia
PTSD

Fries et al., Psychoneuroendocrinology 2005; 30: 1010-1016
POTENTIAL SYMPTOMS OF LATE ADRENAL DYSFUNCTION

- Difficulty awakening in the early morning hours
- Fatigue improves until lunch
- Mid-afternoon low energy
- Increase in energy after 6 pm
- Tired at 9-10 pm
- Second burst of energy if up at 11 pm
- Most refreshing sleep occurs between 7 and 9 am
POTENTIAL SYMPTOMS OF LATE ADRENAL DYSFUNCTION

- Intolerance to isolated carbohydrate consumption. Better if fats and proteins consumed simultaneously
- Intolerance to high potassium foods
- Salt cravings
- Sugar cravings
- Intolerance to any type of psychological or emotional stress
POTENTIAL SYMPTOMS OF LATE ADRENAL DYSFUNCTION

- Chemical Sensitivities
- Hyperventilation
- Mild constipation or diarrhea that increases under stress (IBS symptoms)
- Stress induced hypoglycemia
- Procrastination
- Lack of concern
POTENTIAL SYMPTOMS OF LATE ADRENAL DYSFUNCTION

- Mental Fatigue, confusion, poor memory
- Anxiety
- Emotionally liable
  - Tense, irritable, quick tempered, aggressive, over-reacts,
  - Feelings of isolation, alienation, withdrawal
- Reduced effectiveness in communication
- Increased use of drugs, recreational drugs, alcohol
- Increased risk taking
POTENTIAL SYMPTOMS OF LATE ADRENAL DYSFUNCTION

- Intolerance to isolated carbohydrate consumption. Feel better if fats and proteins consumed simultaneously
- Intolerance to high potassium foods,
- Salt cravings
- Sugar cravings
ADRENAL DYSFUNCTION

DIAGNOSTIC MODALITIES
Serum Cortisol
- Must been done under controlled situations
- One morning reading not useful in gauging overall adrenal function
- Results can be highly variable (Cortisol Binding Globulin)
- Numerous studies confirm the use of lab reported normal baseline or stimulated cortisol levels cannot be used to accurately rule out hypocortisolism.

Holtorf KH. *J Chr Fatigue Syn*. 2008; 14(3):1-14
DIAGNOSTIC ASSAYS

- Serum Cortisol

“It has been shown that the plasma cortisol immunoassays used by the majority of laboratories, institutions, and studies suffer from considerable inaccuracy and variance and can significantly overestimate serum cortisol levels when compared to gold standards (GC/MS, HPLC)...

This has lead to controversy, a high degree of misdiagnosis and the misclassification of patients as having normal HPA function despite significant dysfunction or severely underestimating the severity of the dysfunction.”

Holtorf KH. *J Chr Fatigue Syn*. 2008; 14(3):1-14
Serum Cortisol

- Immunoassays *overestimate* serum cortisol levels by an average of 70% resulting in misclassification of 44-56% of patients.

- Degree of overestimation of some assays
  - Bayer Advia Centuar: 35%
  - Abbott TDx: 79%
  - DPC Immulite 2000: 95%

Urine Cortisol

- Does not allow evaluation of individual cortisol fluctuations throughout the day
- Decreased sensitivity due to wide individual variations in cortisol excretion over 24 hours
- Largest study done (121 patients) on this testing modality showed urine cortisol underestimated cortisol levels in 30% of patients (Cleare et al. *Am J Psychiatry*. 2001;158:641-3)
DIAGNOSTIC ASSAYS

- Urine Cortisol
  - Lacks sensitivity
  - If used during stimulation testing, can give normal or not significantly reduced results in patients with demonstrated HPA axis dysfunction.
  - Cannot provide information on cortisol release patterns.

Salivary Cortisol

- Useful tool in assessing both baseline and post-stimulation levels of cortisol

“Salivary testing offers a noninvasive, stress free alternative to plasma and serum testing of hormones. Although saliva has not yet become a mainstream sample source for hormone analysis, it has proven to be reliable and, in some cases, even superior to other body fluids”.

Salivary Cortisol

“Based on its remarkable reproducibility, easy non-invasive nature, and at least similar diagnostic performance, salivary cortisol appears to be a preferable alternative to 24 hour urine free cortisol as a first line screening test.”

Salivary Cortisol

“Salivary cortisol measurements are simple to obtain, easy to measure in most labs, and provide an indirect yet reliable and practical assessment of the serum free cortisol concentrations during critical illnesses...Measurements of salivary cortisol can serve as a surrogate marker for the free cortisol in the circulation.”

Salivary Cortisol

- Endocrine Society Clinical Practice Guidelines (May, 2008) recommend the use of midnight salivary cortisol testing as an appropriate screening test for Cushing’s Disease.
- Salivary cortisol measurements
  - Practical and accurate
  - Useful in determining intermittent changes in cortisol secretion over long periods of time
  - Non-invasive
  - Stress-free
  - Real-time
NORMAL CORTISOL RELEASE PATTERN

morning  | noon  | evening | night
---------|-------|---------|-------
9         | 8     | 7       | 6     |
CASE ILLUSTRATION II

The graph shows a comparison of data points across different times of the day: morning, noon, evening, and night. The yellow line indicates a decrease in values from morning to night, while the brown line shows a less significant variation. The graph illustrates a trend that peaks in the morning and decreases towards the night.
DIAGNOSTIC ASSAYS:
SALIVARY CORTISOL PATTERNS MATTER

- Common abnormal patterns
  - Elevated
  - Depressed
  - Mixed
- Morning cortisol level most pertinent in assessing adrenal sensitivity and capacity
CASE ILLUSTRATION III

Graph showing the comparison between patient and control groups throughout the day.

- **Patient** line starts at 8 in the morning and decreases to 1 by night.
- **Control** line starts at 9 in the morning and decreases to 2 by night.

Time points: morning, noon, evening, night.
DIAGNOSTIC ASSAYS: SALIVARY CORTISOL PATTERNS MATTER

- Flattening of the cortisol curve
  - Most predictive of adrenal dysfunction
  - Most well studied
  - Hypocortisolism induces:
    - Intensified immune vigilance
    - IL-6 elevation
    - Fatigue
DIAGNOSTIC ASSAYS:
SALIVARY CORTISOL PATTERNS MATTER

- Flattened cortisol curve
- Metastases and early mortality breast cancer
- Worsened glucose control
- Early CHF and MI in atherosclerosis
DIAGNOSTIC ASSAYS:
SALIVARY CORTISOL PATTERNS MATTER

- High morning cortisol
- Flattened cortisol curve
- ACTH stimulation yields sub-optimal cortisol elevation

- Retained adrenal capacity and sensitivity
- Adrenal dysfunction
- Suboptimal adrenal capacity but not production