Remember *life* isn’t a *busy contest*. 
Functions of Cortisol

- Balances blood sugar
- Weight control
- Immune system response
- Bone turnover rate
- Stress reaction
- Sleep
- Protein synthesis
Functions of Cortisol (Cont.)

- Mood and thoughts
- Influences testosterone/estrogen ratio
- Influences DHEA/insulin ratio
- Affects pituitary/thyroid/adrenal system
- Participates with aldosterone in sodium reabsorption
- Is an anti-inflammatory
What Elevates Cortisol

- Stress
- Depression
- High progestin intake
Consider **fresh air**

God’s **prozac.**
Consequences of Elevated Cortisol

- Decreased immune system
- Increased osteoporosis risk
- Fatigue
- Irritability
- Sugar cravings
- Shakiness between meals
- Confusion
- Memory is not as sharp
Consequences of Elevated Cortisol (Cont.)

- Low energy
- Night sweats
- Binge eating
- Increased blood pressure
- Increased cholesterol
- Increased triglycerides
- Increased blood sugar
Consequences of Elevated Cortisol (Cont.)

- Increased insulin/insulin resistance
- Increased infections
- Thin skin
- Easy bruising
- Muscle weakness
- Weight gain around the middle
- Sleep disturbances
- Impaired hepatic conversion of T4 to T3
Abnormal Cortisol Levels Are Associated With

- Menopause
- CFS
- Fibromyalgia
- Depression
- Impotence
- Anorexia nervosa
- Insulin resistance/diabetes
- Generalized memory loss
- IBS
- Exacerbations of multiple sclerosis
Abnormal Cortisol Levels Are Associated With (Cont.)

- Panic disorders
- PMS
- Infertility
- Sleep disorders
- Osteoporosis
- Heart disease
- Rheumatoid arthritis
- Breast cancer
- Coronary heart disease
- Alzheimer’s disease
Adrenal Burnout (Hypoadrenalism)

- Cortisol and DHEA levels decline
Symptoms of Hypoadrenalism

- Fatigue
- Low blood pressure
- Sensitivity to light
- Insomnia
- Digestive problems
- Emotional imbalances/lack of motivation
- Hypoglycemia
- Decreased sexual interest
Symptoms of Hypoadrenalism (Cont.)

- Decreased immunity
- Lack of stamina
- Emotional paralysis
- Poor wound healing
- Alcoholism and drug addiction
- Allergies
- Unresponsive hypothyroidism (does not respond to treatment)
- Feeling of being overwhelmed
Hormones Are A Web

- If cortisol is increased, it decreases the making of progesterone and its activity.
- Cortisol competes with progesterone for common receptors.
- When cortisol is elevated, thyroid hormone is more bound and less active.
- Decreased estradiol in a woman is a stressor to her body (causes decline in function of NE, serotonin, dopamine, and acetylcholine).
Treatment of Hyperadrenalism

- Replacement of DHEA with adrenal support
- Adaptogenic herbs
- Calming herbs
- Stress reduction techniques
- If cortisol is high in the evening then add phosphatidylserine 300 mg which may be taken any time of the day.
Treatment of Hyperadrenalism (Cont.)

► Nutrients
  ◦ Vitamin C
  ◦ B vitamins
  ◦ Calcium
  ◦ Magnesium
  ◦ Zinc
  ◦ Selenium
  ◦ Copper
  ◦ Sodium
  ◦ Manganese
Treatment of Hypoadrenalism

- Stress reduction techniques
- Adaptogenic herbs
- Adrenal extracts (if adaptogenic herbs do not work)
- Calming herbs
- Licorice (cannot use if the patient has hypertension)
- Hydrocortisone
Become a pathological optimist.
Estrogen, progesterone, DHEA, and thyroid hormones are all important for the regulation of glucose in the body.

- Estrogen lowers blood sugar in a woman.
- Testosterone decreases blood glucose in a male.
- Progesterone raises blood sugar if not balanced with estrogen.
Functions Of Insulin In The Body

► Counters the actions of adrenaline and cortisol in the body
► Helps the body repair
► Helps convert blood sugar into triglycerides
► Keeps blood glucose levels from elevating
► Plays a major role in the production of serotonin
► At normal levels increases development of muscle
Levels of Insulin

- It is important that the levels of insulin in the body not be too high or too low.
Low Insulin Levels

► Insulin is not working effectively in the body
► This is a pre-diabetes state
Symptoms of Insulin Deficiency

- Bone loss
- Depression
- Fatigue
- Insomnia
Causes of Insulin Deficiency

- Eliminating carbohydrates from the diet
- Not eating enough
- Over-exercising
Excess Insulin Is Associated With

- Acne
- Aging process accelerates
- Asthma
- Breast cancer
- Colon cancer
- Depression and mood swings
- Diabetes/insulin resistance
- Estrogen levels that are too low
- Irritable bowel syndrome
- Migraine headaches
Excess Insulin Is Associated With (Cont.)

- Heart disease
- Heartburn
- Hypercholesterolemia
- Hypertension
- Hypertriglyceridemia
- Infertility
- Insomnia
- Osteopenia/osteoporosis
- Weight gain
Causes of Excess Insulin Production

- High carbohydrate diet
- Soft drinks
- Diet pills
- Eating a low-fat diet
- Intake of trans-fats
- Elevated DHEA levels
- Excess caffeine intake
- Intake of thyroid medication that is excessive or not needed
Causes of Excess Insulin Production (Cont.)

- Excessive progesterone replacement
- Increased testosterone levels
- Insomnia
- Lack of exercise
- Low estrogen levels
- Skipping meals
- Smoking
Causes of Excess Insulin Production (Cont.)

- Hypothyroidism
- OTC meds that contain caffeine
- Stress
- Use of natural stimulants
- Use of recreational stimulants
- Using artificial sweeteners
- Yo-yo dieting
Causes of Excess Insulin Production (Cont.)

▶ Medications
  ◦ Beta blockers
  ◦ Birth control pills
  ◦ Steroids
  ◦ Thiazide diuretics
  ◦ Some antidepressants and antipsychotics
Pregnenolone

- Precursor to DHEA, estrogen, progesterone, and testosterone
- Is made from cholesterol
  - If the patients cholesterol is below 140 they may not make pregnenolone effectively
- Decreases with age
  - At age 75, most people have a 65% decline compared to age 35.
Functions of Pregnenolone

► Regulates the balance between excitation and inhibition in the nervous system
► Increases resistance to stress
► Improves energy both physically and mentally
► Enhances nerve transmission and memory
► Reduces pain and inflammation
► Blocks the production of acid-forming compounds
Functions of Pregnenolone (Cont.)

► Modulates the neurotransmitter GABA
► Helps to repair nerve damage
► Promotes mood elevation
► Improves sleep
► Modulates NMDA receptors
  ◦ Regulates pain control, learning, memory, and alertness
Causes of Low Pregnenolone Levels

- Aging process
- Eating too much saturated fat and trans-fats
- Low cholesterol levels
- Hypothyroidism
- Pituitary tumor
- Having a severe illness
  ◦ Pregnenolone will make more cortisol and less of the other hormones to help the body deal with stress.
Symptoms of Pregnenolone Deficiency

- Arthritis
- Depression
- Fatigue
- Inability to deal with stress
- Insomnia
- Lack of focus
- Memory decline
Pregnenolone Used in Treatment

► Arthritis
► Depression
► Memory loss
► Fatigue
► Moodiness
► Improves delta-wave sleep
► Prevention of memory loss
► Autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, and lupus
New Study: Use of Pregnenolone

- Pregnenolone may protect the brain from cannabis intoxication.
Elevated Pregnenolone Levels Can Cause the Following Symptoms

- Acne
- Drowsiness
- Muscle aches
- Fluid retention
- Headache
- Heart racing
- Insomnia due to overstimulation
- Irritability, anger, anxiety
Melatonin

► Made from tryptophan which is also used to make serotonin
► Is made in the pineal gland, retina, GI tract, and WBCs
► If melatonin goes up, serotonin goes down.
► If you eat too many high glycemic index carbohydrates you will make less melatonin (more serotonin is made instead).
► The body needs vitamin B to convert melatonin from tryptophan.
Functions of Melatonin

- Affects the release of sex hormones
- Aids the immune system
- Acts as an antioxidant
- Blocks estrogen from binding to receptor sites
- Decreases cortisol levels
- Helps balance the stress response
Functions of Melatonin (Cont.)

► Helps prevent cancer
► Improves mood
► Improves sleep quality
► Increases the action of benzodiazepines
► Stimulates the parathyroid gland
► Stimulates the production of growth hormone
► Cardioprotection
References


Study showed that melatonin supplementation along with estradiol replacement in women decreased oxidative stress in lab animals.

Ibid., Feng.
Melatonin and Cardioprotection

- Patients with CAD tend to have low nocturnal serum melatonin levels.
- Melatonin has been shown to reduce hypoxia and prevent reoxygenation-induced damage in patients with cardiac ischemia and ischemic stroke.
References

Melatonin and Cardioprotection

Patients who have developed adverse effects post MI were shown to have lower nocturnal melatonin levels than patients without adverse effects.

- Death
- CHF
- Recurrent MI
Melatonin and Cardioprotection (Cont.)

► Functions of melatonin in cardioprotection
  ◦ Vasodilator
  ◦ Free radical scavenger
  ◦ Inhibits oxidation of LDL-C

There is an inverse correlation between melatonin levels and CRP levels after acute MI.

Melatonin and Cardioprotection (Cont.)

- MARIA study was a prospective, randomized, double-blind, placebo-controlled trial.
- Used IV melatonin in patients following an acute MI that were having angioplasty.
  - Decreased CRP and IL-6
  - Attenuated tissue damage from reperfusion
  - Decreased V tach and V fib after reperfusion
  - Attenuated cellular and molecular damage from ischemia
Melatonin and Cardioprotection (Cont.)

Melatonin has been shown to protect cardiac myocyte mitochondria after doxorubicin use.

Study using laboratory animals showed that melatonin supplementation daily at middle age decreased abdominal fat and lowered plasma insulin to youthful levels.

Melatonin and Neurodegenerative Disease

- Studies have shown that low melatonin levels are associated with an increased risk of developing neurodegenerative diseases.
  - Ibid., Pandi-Perumal.
Melatonin and Alzheimer’s Disease

- Some symptoms of decreased melatonin are also common to patients with Alzheimer’s disease.
  - Disruption of circadian rhythm
  - Mood changes
  - Delirium
Melatonin and Alzheimer’s Disease (Cont.)

- One medical trial showed that melatonin levels in the CSF in patients over the age of 80 were \( \frac{1}{2} \) the level of younger/healthier patients.
- Patients in this study with Alzheimer’s disease had even lower levels which were \( \frac{1}{5} \) of those in young healthy people.
Melatonin and Alzheimer’s Disease (Cont.)

- Studies have shown a benefit in melatonin replacement in patients with early Alzheimer’s disease.
Melatonin and Alzheimer’s Disease (Cont.)

- Melatonin supplementation has been shown to decrease the damage caused by amyloid beta proteins and tau proteins.
References

- Ibid., Daniels.
Melatonin has also been shown to guard against the harmful effects of aluminum which has been shown to cause oxidative changes in the brain that are like Alzheimer’s disease.

◦ Ibid., Daniels.
Melatonin and Alzheimer’s Disease (Cont.)

- Studies showed that replacing melatonin in the animal model of Alzheimer’s disease reduced learning and memory deficits.
Melatonin and Alzheimer’s Disease (Cont.)

- Study in the animal module also revealed that it was important to replace melatonin before Alzheimer’s disease was clinically evident.
- In genetically predisposed mice, where melatonin was replaced early, they did not show pathological changes nor have symptoms of cognitive decline.
  - Ibid., Feng.
Melatonin and Alzheimer’s Disease (Cont.)

- Medical trials revealed that using melatonin in patients with Alzheimer’s disease they had better sleep patterns, less sundowning, and slower progression of cognitive loss.
  - Ibid., Cardinali, 2002.
Melatonin and Alzheimer’s Disease (Cont.)

- Studies have shown that supplementing with melatonin helps to protect against Alzheimer’s disease.
  - Ibid., Pandi-Perumal.
  - Ibid., Lahiri.
References

- Ibid., Feng.
Mild cognitive impairment (MCI) is impairment that precedes actual dementia.


12% of people with MCI proceed to develop dementia each year.

- Ibid., Fredericks.
Melatonin and Mild Cognitive Impairment (Cont.)

- Studies showed that patients that supplemented with melatonin (3–24 mg) for 15–60 months did much better on cognitive tests.
  - Ibid., Cardinali, 2010.
  - Ibid., Cardinali, 2012.
Lab trials have shown that melatonin replacement increases SIRT1 which is a longevity protein. SIRT1 is activated by caloric restriction.

Melatonin and Parkinson’s Disease

- Melatonin replacement has been shown to decrease the risk of developing Parkinson’s disease.
  - Ibid. Pandi-Perumal.
  - Ibid., Wang.
  - Ibid., Ayer.
  - Ibid., Ma.
Melatonin and Parkinson’s Disease (Cont.)

- Animal trials have shown that melatonin can prevent and to some extent may even help reverse the motor and behavior changes that are associated with Parkinson’s disease.
Melatonin and Parkinson’s Disease (Cont.)

- In Parkinson’s disease there is an accumulation of a protein called alpha-synuclein.
Melatonin and Parkinson’s Disease (Cont.)

- In animal studies melatonin supplementation has been shown to prevent the production of alpha-synuclein in brain cells.
- Melatonin supplementation also attacks alpha-synuclein and makes it more available to be removed by the body.
  - Ibid., Ono.
Lab study showed that melatonin can reverse the inflammatory changes that occur in Parkinson’s disease.

Melatonin and Parkinson’s Disease (Cont.)

- Animal trial showed that melatonin helps to restore the normal activity of a key enzyme that is involved in the synthesis of dopamine.
  - Ibid., Cardinali, 2002.
Melatonin and Parkinson’s Disease (Cont.)

- In lab studies melatonin supplementation was shown to increase the survival of dopamine-producing cells.
  - Ibid., Niranjan.
  - Ibid., Ma.
  - Ibid., Borah.
Melatonin and CVA

- If the patient has a low melatonin level they have an increased risk of developing a stroke.
- The odds rise more than 2% for every 1 pg/mL decline in melatonin.
Melatonin and CVA (Cont.)

- In patients with a calcified pineal gland (where melatonin is produced) the risk of developing a CVA is increased by 35%.
Melatonin and CVA (Cont.)

- Melatonin supplementation has been shown to shrink the size of an infarct area in a patient’s with acute CVA.
- This may be due to melatonin’s ability to neutralize free radical production.
  - Ibid. Pandi-Perumal.
  - Ibid., Lahiri.
  - Ibid., Feng.
  - Ibid., Niranjan.
  - Ibid., Ma.
Reference

Melatonin and CVA (Cont.)

- Melatonin may also decrease the risk of CVA by significantly lowering cholesterol and also decreasing blood pressure.
Melatonin and CVA (Cont.)

- Melatonin supplementation in lab animals decreased the damage after stroke and decreased seizure occurrence.
Melatonin and CVA (Cont.)

- Melatonin has been shown to increase plasticity of neurons after CVA.
In animal studies, melatonin reduced the damage caused by stroke by decreasing the activation of “protein-melting” enzymes.


In animal trials of experimentally induced stroke, melatonin supplementation had the following effects.

- Tightened the blood–brain barrier
- Reduced tissue swelling
- Prevented hemorrhagic transformation
  - Ibid., Reiter.
  - Ibid., Hung.
  - Ibid., Jang.
Supplementation with melatonin has been shown to minimize the brain swelling and dysfunction after a closed head injury.

- Ibid., Pandi-Perumal.
- Ibid., Lahiri.
- Ibid., Feng.
- Ibid., Niranjan.
- Ibid., Ma.
- Ibid., Reiter.
Melatonin and CHI/TBI (Cont.)

- Melatonin supplementation has been shown to help protect the brain in the case of traumatic brain injury.
Melatonin and CHI/TBI (Cont.)

- Studies done on lab animals have shown that giving melatonin after a TBI had the following results.
  - Maintained the integrity of the blood–brain barrier
  - Prevents dangerous brain swelling in the hours and days after the injury
  - Shrinks the size of the bruised and injured tissue
    - Ibid., Ismailoglu.
Melatonin and CHI/TBI (Cont.)

- In other medical studies in the laboratory, melatonin supplementation reduced the mortality rate after a burst aneurysm.
  - Ibid., Ayer.
  - Ibid., Wang.
Melatonin

- In Europe, melatonin is considered a medication by the European Medicines Agency.
Causes of Melatonin Deficiency

- Alcohol
- Caffeine
- Electromagnetic fields
- Tobacco
- Numerous medications including benzodiazepines
Benzodiazepines and Melatonin Suppression

- Study showed that a single dose of 2 mg alprazolam at 9 pm suppressed melatonin levels all night long and even at 7 am the next morning.
A medical trial showed that patients that used benzodiazepines at any time in their life had a 50% greater risk for developing dementia than people that did not use benzodiazepines.

Benzodiazepines and Melatonin Suppression (Cont.)

- Another study showed that for patients with benzodiazepine dependence, the risk of probable cognitive impairment was more than quintupled.
Symptoms of Excess Melatonin

- Daytime sleepiness/fatigue
- Depression
- Headaches
- Increase in cortisol which can lead to fat storage
- Intense dreaming/nightmares
- Suppression of serotonin which increases carbohydrate cravings
Causes of Excess Melatonin Production

► Foods
  ◦ Bananas
  ◦ Barley
  ◦ Cherries
  ◦ Ginger
  ◦ Oats
  ◦ Rice
  ◦ Sweet corn
  ◦ Tomatoes
  ◦ Walnuts
Causes of Excess Melatonin Production (Cont.)

- Exercise
- St. John’s wort
- Taking melatonin as a supplement
- Medications
  - Clorgyline
  - Desipramine
  - Fluvoxamine
  - Thorazine
  - Tranylcypromine
Who Should Not Take Melatonin?

- Use with caution in patients with an autoimmune disease since it can stimulate the immune system
- Pregnant or breast-feeding women
- Patients taking steroids
- Use with caution in patients that are depressed
- Do not use if patient has lymphoma or leukemia
Measurement of Hormones

- Blood
- Saliva
- Urine
# A Guide to Steroid Hormone Testing in Different Body Fluids with Different Routes of Hormone Administration

<table>
<thead>
<tr>
<th>Type of Body Fluid</th>
<th>None Endogenous Steroids</th>
<th>Oral Steroids</th>
<th>Topical Gels/Creams Steroids</th>
<th>Vaginal Steroids</th>
<th>Troche/Sublingual Steroids</th>
<th>Transdermal Patch Occluded</th>
<th>Pellet/IM Steroids</th>
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<tbody>
<tr>
<td>Serum</td>
<td>Yes</td>
<td>Yes (1)</td>
<td>No (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Saliva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (3)</td>
<td>Yes</td>
<td>No (4)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urine</td>
<td>Yes</td>
<td>Yes (1)</td>
<td>No (2)</td>
<td>No (4)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (1)</td>
</tr>
<tr>
<td>DBS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

1) Overestimation: Metabolites likely to interfere with immunoassays  
2) Underestimation: Hormone levels not reflective of tissue uptake  
3) Overestimation: Requires range adjustment  
4) Overestimation: Direct contamination of body fluid (saliva/urine)  
5) Overestimation: Direct contamination of capillary blood if ungloved hands used to apply topical hormones < 2 days prior to collection
Reference

Potential Problem with Testing Testosterone Levels in Individuals of Asian Origin

Due to deletion polymorphisms in glucuronidation pathways for testosterone, some ethnic groups (prevalence > 80% in Asians) will have “apparent” low testosterone levels in urine, but normal levels in serum, saliva, and capillary blood. This could lead to a misdiagnosis of androgen deficiency and consequent inappropriate androgen supplementation.

Epi-Testosterone, the epimer of testosterone, is normal in Asians due to a different enzyme that glucuronidates Epi-Testosterone.

When testing urine for testosterone, Epi-testosterone should always be run in concert to avoid “false-low” testosterone results.
Reference

Normal: $T = \text{Epi-T}$

T-Therapy: $T > \text{Epi-T}$

UGT2B17 del/del: $T < \text{Epi-T}$
Summary

► All of the hormones in the body are designed to work together.
► If one is altered, or deficient, it will affect the actions of all of the other hormones.
► Consequently, bio-identical, compounded, customized hormone replacement is the only way to achieve this balance.
► One size does not fit all.
Obtaining CE/CME Credit

If you would like to receive continuing education credit for this activity, please visit:
http://pcca.cds.pesgce.com