THE PHYSIOLOGY OF THE ADRENAL GLANDS

Sources of Chronic Stress

Mental & Emotional:

- Anger
- Worry
- Fear
- Grief
- Bitterness
- Hopelessness
- Guilt
- Depression
- Anxiety
- Job/performance demands
- Financial pressures
- Relationship conflict

Tissue Damage/Inflammation/Pain:

- Surgery
- Trauma
- Injury
- Infections
- Inhalant allergies
- Food sensitivities
- Crohn's Disease
- Colitis
- Celiac
- Arthritis
- Toxins – heavy metals, molds, chemicals

Glycemic Dysregulation:

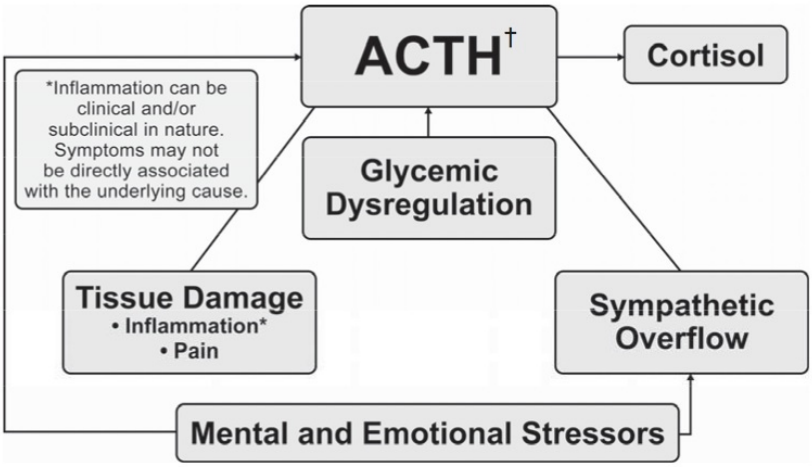
- Skipping meals
- Calorie deficit dieting
- High carbohydrate intake
- Alcoholism
- Nutritional deficiencies

Others:

- Temperature extremes
- Sleep deprivation
- Excessive exercise
- Chronic illness
- Electromagnetic fields
- Light cycle disruption (i.e. third shift work)
- Noise pollution
- Caffeine or drug abuse

Inducers of Release of ACTH Resulting in Excess Cortisol Output and Adrenal Stress

Fig. 1



†ACTH=Adrenocorticotropic Hormone

Stress-What is it?

While it may seem obvious to most, the definition of "stress" has not been easily agreed upon by biologists over the past 75 years. Does it define the necessary changes in adapting to a stressor, or the malfunction of not adapting to these same stressors? When we think of stress, we often think of negative stress, or as some would say "distress;" but positive events (wonderful surprises, passion, athletic competition) can elicit seemingly identical responses from a physiological perspective.

The scientist who, more than anyone, brought the concept of stress to the forefront is Hans Selye. His book *The Stress of Life* (1), written for the lay audience, popularized the notion of stress as the general response to a wide variety of insults. His research, mostly with rats, revealed a recurring set of physiological outcomes (hypertrophy of the adrenal gland, atrophy of the lymphatic organs, and ulcers in the stomach) when these rats were exposed to a variety of insults. He later formed what he called the general adaptation syndrome (G.A.S.) in a three-stage format:

1. The **alarm reaction**, involving increased adrenocortical secretion and activation of the sympathoadrenal system.

2. The **stage of resistance**, involving the balancing of the adrenocortical hormones' affect on water and electrolyte balance and carbohydrate metabolism. The "true adaption" to stress.

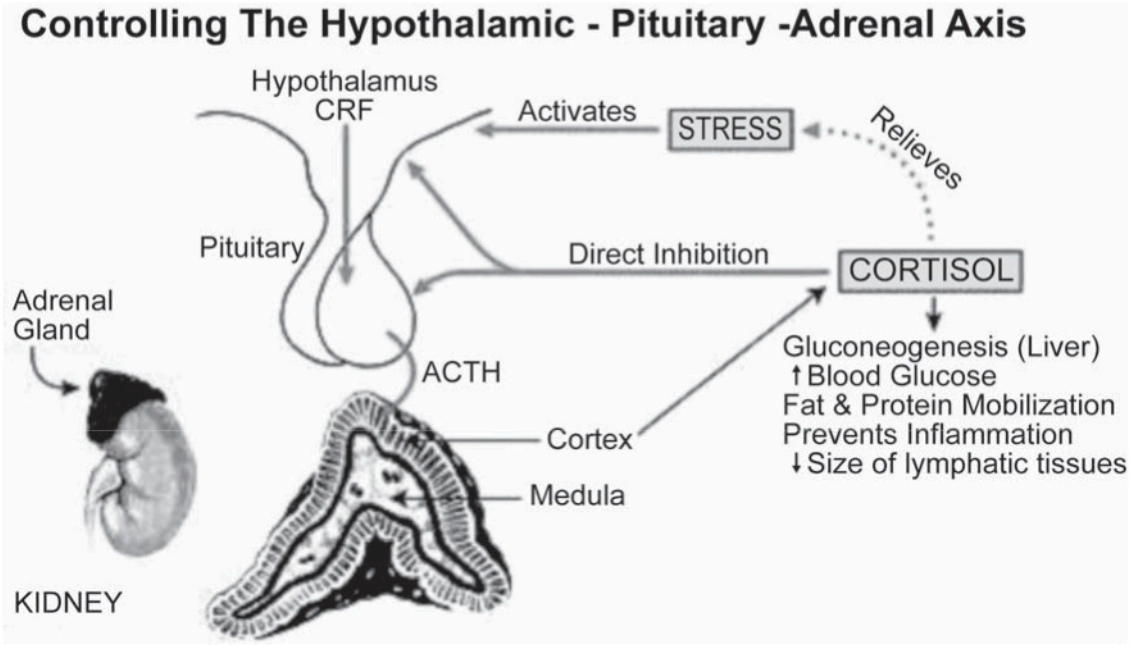
3. The **stage of exhaustion**, involving the depletion or exhaustion of the adrenal glands' ability to make corticosteroids.

We recognize that Selye has simplified a very complex set of responses and has some limitations (2). However, this three-stage model is still the most commonly used in clinically defining adrenal status and is incorporated into the ARK paradigm as the three stages: 1. Acute Adrenal Dysfunction, 2. Adrenal Fatigue, 3. Adrenal Exhaustion. Adrenal failure or Addison's disease may be considered the fourth and last stage.

Adrenal Gland

The adrenal glands are small (5 grams) glandular tissues lying atop each of the kidneys (See figure 2). Originally called suprarenal glands because of their location, they were first discovered by the anatomist Bartolomaeus Eustachius, further described by Cuvier and then later by Thomas Addison. The inner portion, called the medulla, secretes epinephrine and norepinephrine and is an extension of the sympathetic nervous system. The larger outer portion, called the cortex, is responsible for secreting various steroid hormones. From every point of view, functional, structural and developmental, the adrenal cortex and medulla can be considered two separate glands. Of the nearly 30 steroid hormones produced by the adrenal cortex, the principal ones include aldosterone (a mineralocorticoid), cortisol (a glucocorticoid) and various sex hormones and their precursors (DHEA, androstenedione). The mineralocorticoids play an essential role in regulating potassium and sodium levels and water balance. DHEA and its metabolites have diverse effects during the lifecycle of the individual.

Fig. 2



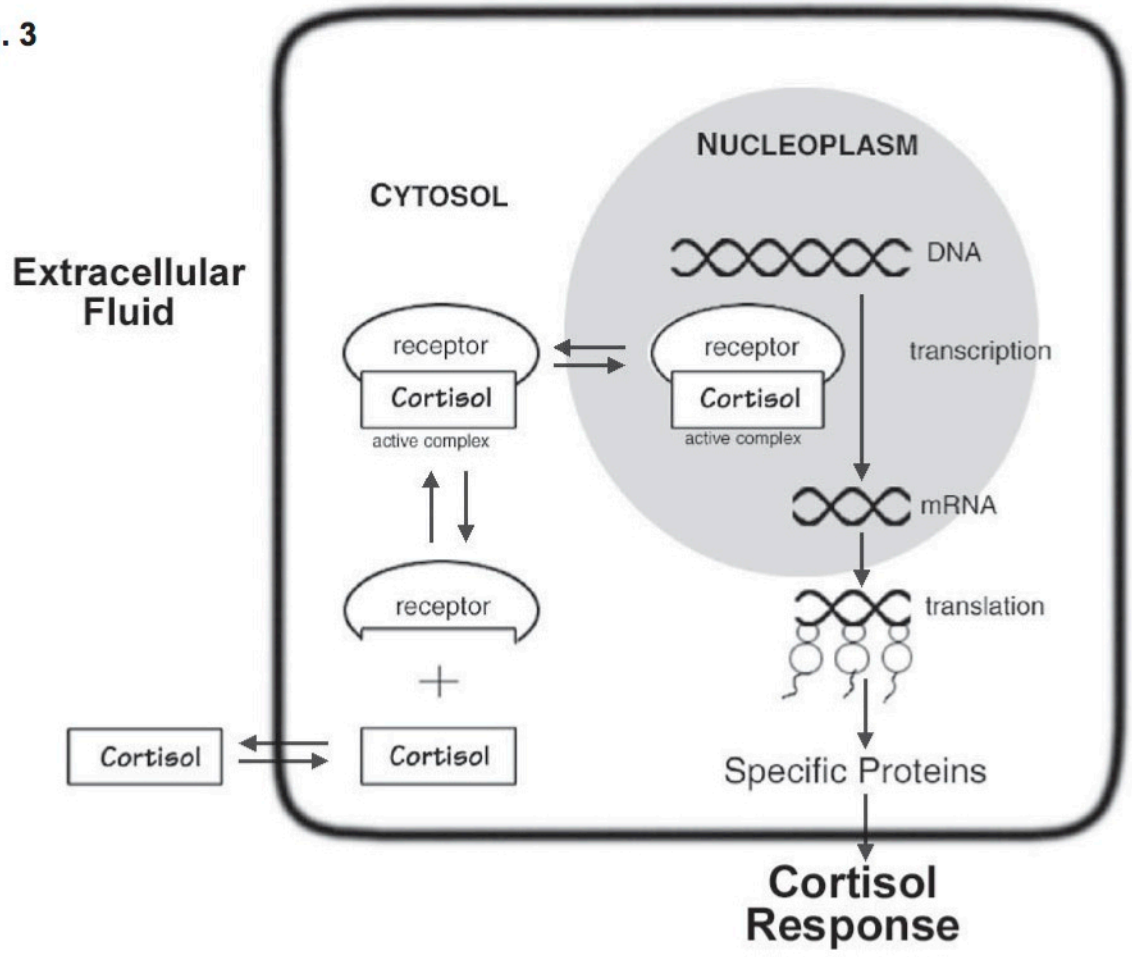
Cortisol

The synthesis and regulation of cortisol production is shown in figure 4. Cortisol is tightly regulated by feedback mechanisms in both the hypothalamus and the pituitary glands, where the original hormonal signals trigger its production. As in other systems, the hypothalamus begins the process by secreting corticotropin-releasing factor (CRF) in response to a variety of "stressors." CRF then triggers the anterior pituitary to release adrenocorticotropic hormone (ACTH) which increases the adrenal cortex secretion of cortisol. In turn, increasing cortisol levels slow down the production of both CRF and ACTH from their respective glands. This whole circuit is referred to as the hypothalamic-pituitary- adrenal (HPA) axis or system. Normal functioning of the HPA is known to have three attributes. First, when the system is unstressed there is a circadian rhythm of activity in the system. The rhythm consists of the highest cortisol levels shortly after awakening (7-8 a.m.) and progressively falling until they are lowest during the first several hours of sleeping (for normal circadian rhythm of salivary cortisol see page 15). A healthy HPA should have a circadian rhythm as well as appropriate total daily secretion of cortisol. The second function of the HPA is the various feedback loops. As mentioned previously, increasing amounts of cortisol should be able to shut down ACTH and CRF production, and hence reduce the cortisol levels. Clinically appropriate challenges with corticosteroids like dexamethasone can be used to test this feedback loop. Positive tests for pituitary and adrenal cortex functions can also performed by giving patients CRF or ACTH and measuring cortisol responses. Third, and most importantly for us, is the fact that various stressors can stimulate the HPA; and many can do so in a way that overrides both the circadian and feedback controls. It is this well-known phenomenon that allows the functional testing of the HPA system, giving us a glimpse of the effects of stress (both acute and chronic) on the health of an individual.

Cortisol is best known for stimulating gluconeogenesis, and it is essential for normal glycogenolysis. Cortisol affects the heart, vasculature, blood pressure, water excretion and electrolyte balance. It mobilizes protein stores in all tissues except the liver. It mobilizes fatty acids from adipose, it is the precursor of cortisone and acts as an anti-inflammatory agent; and it is the primary hormone directing immune function. Cortisol can stimulate and inhibit gene transcription, it promotes apoptosis and it affects bone and calcium dynamics. It affects behavior, mood, neural activity and a variety of central nervous system biochemical processes. Cortisol affects the eyes, gastrointestinal tract, reproductive function and the production and clearance of other classes of hormones. The general effect of excess cortisol is usually catabolic.

Cortisol, because it is a steroid hormone, crosses the plasma membrane of cells with ease. Once in the cytoplasm, it binds to a carrier hormone and is ushered into the inner sanctum of the nucleus where it permits the transcription of DNA into an mRNA template needed for the cell to manufacture its protein products. Examples include cellular production of antibodies for the immune system, neurotransmitters for the nervous system, cellular receptors and signaling proteins and enzymes for nearly every metabolic reaction.

Fig. 3



Cortisol has been called the "death hormone" because it causes catabolism in nearly every tissue of the body if released in large amounts and for prolonged periods of time. Too little cortisol, however, can also disrupt many metabolic processes and because it is considered a necessary facilitative hormone for most every cell in the body and without it we would die. The key point to remember is too much or too little cortisol will contribute to varied symptoms and chronic health disorders.

DHEA and Adrenal Activity

While the importance of cortisol has been relatively unheralded, the virtues of DHEA (Dehydroepiandrosterone) have made headlines for the past several years. DHEA and its sulfated metabolite DHEA-S are hormones secreted by the adrenal cortex in response to pituitary ACTH production. DHEA-S is the most abundant circulating steroid hormone in humans and the most abundant product of the adrenal glands. As such, its measurement has been of interest, especially since reduced levels of both DHEA and DHEA-S are associated with aging. Some have tried to use DHEA levels to devise a method to gauge relative biological (rather than chronological) age. One study showed that DHEA-S levels were significantly lower in nursing home patients who required total care versus individuals of similar ages who are able to care for themselves (3). Another study revealed that DHEA-S levels were lower in men with at least one coronary stenosis (greater or equal than 50%) compared to those without a similar arterial narrowing. Levels of DHEA-S were also inversely related to the number of diseased coronary vessels (4). While the cause-effect relationship with DHEA has yet to be determined, DHEA levels may be a marker for age-related chronic conditions. Perhaps the most interesting connection is the relationship between DHEA levels and incidence of Chronic Fatigue Syndrome (CFS). Several studies have shown that individuals with CFS are more likely to have low levels of DHEA and DHEA-S (5,6). This is probably the result of overall HPA or adrenal suppression, felt as general fatigue, accompanied by immune system irregularities and sensitivities. DHEA-S (but not DHEA) levels also seems to be associated with patients suffering from depression (5).

Because DHEA-S is so abundant and has such a long half-life, it is rather easy to detect in saliva samples and does not have a noticeable diurnal cycle like cortisol or DHEA. For this reason it can be used in combination with a cortisol rhythm to detect HPA irregularities. The cortisol/DHEA-S ratio can be a valuable tool in determining the need for pregnenolone, DHEA and stress management treatments. Remember, only individuals with lower than average DHEA/DHEA-S levels should be given supplemental DHEA, as it is a sex steroid molecule.

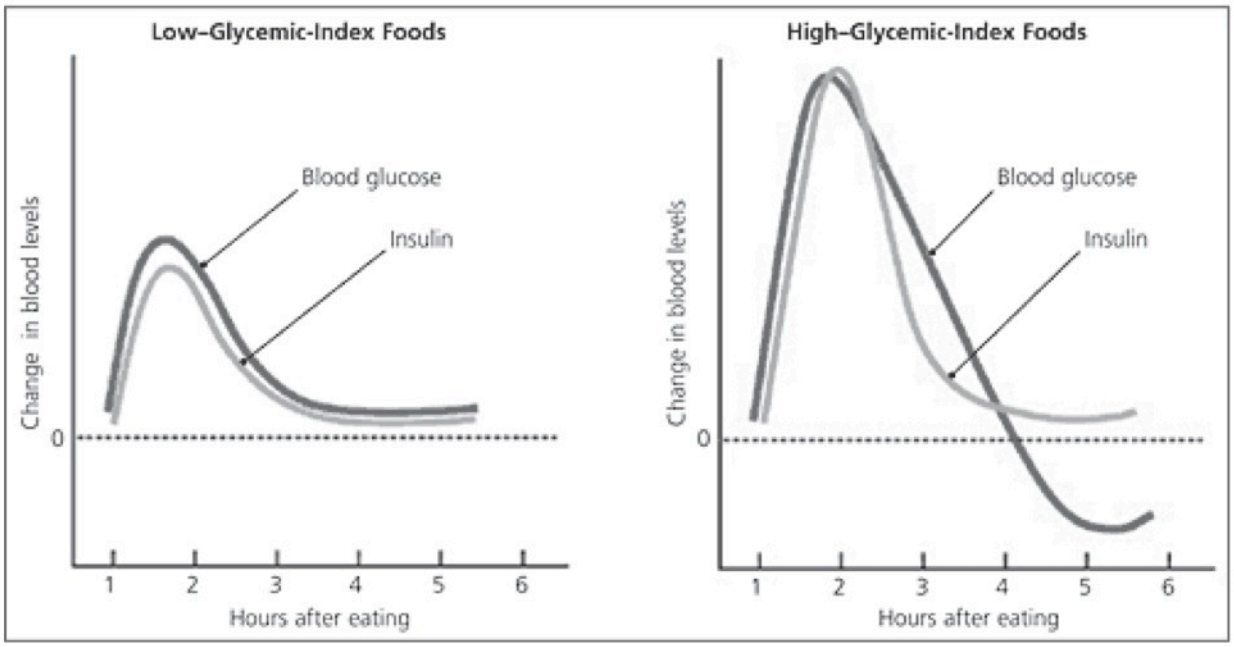
Specific Effects of Cortisol on tissues

- Together with Glucagon promotes release of glycogen from liver as glucose and stimulates gluconeogenesis to raise serum levels of glucose
- Permits release of amino acids (i.e. glutamine) from muscle tissues to be converted to glucose in the liver
- Promotes uptake and deposition of glucose by adipose tissues, especially central/trunkal adipose

- Enhances osteoclastic resorption/breakdown of calcium from the bone for release into blood stream
- Inhibits vitamin D activity in the GI tract to reduce calcium absorption
- Increases neural excitability
- Initially increases antibody production in lymph glands, eventually inhibits antibody production as lymph glands atrophy from prolonged output
- Increases levels of circulating neutrophils/polymorphonuclear cells
- Decreases numbers of circulating eosinophils and lymphocytes
- Inhibits peripheral conversion of T4 to more active T3
- Promotes peripheral conversion of T4 to reverse T3 which is a competitive antagonist to T3
- Inhibits TSH release from anterior pituitary
- Blunts/inhibits Secretory IgA production throughout mucosal tissues

The Importance of Glycemic Control

While many stressors are obvious, one of the most common and ubiquitous stressors, glycemic dysregulation, may go completely unnoticed. As mentioned previously, cortisol helps regulate blood glucose levels when they are low. **Going longer than 3-4 hours between meals will sufficiently lower blood glucose levels stimulating an ACTH response and a subsequent rise in cortisol**. As well, when individuals consume high sugar and high glycemic load meals they over-stimulate insulin production which results in radical swings of blood glucose (high to low). This will result in periods of low blood sugar, an HPA axis stressor, which will trigger cortisol production. Metabolic syndrome and insulin-resistant patients will have even more exaggerated swings in blood glucose-resulting in a constant cycle of adrenal stress.



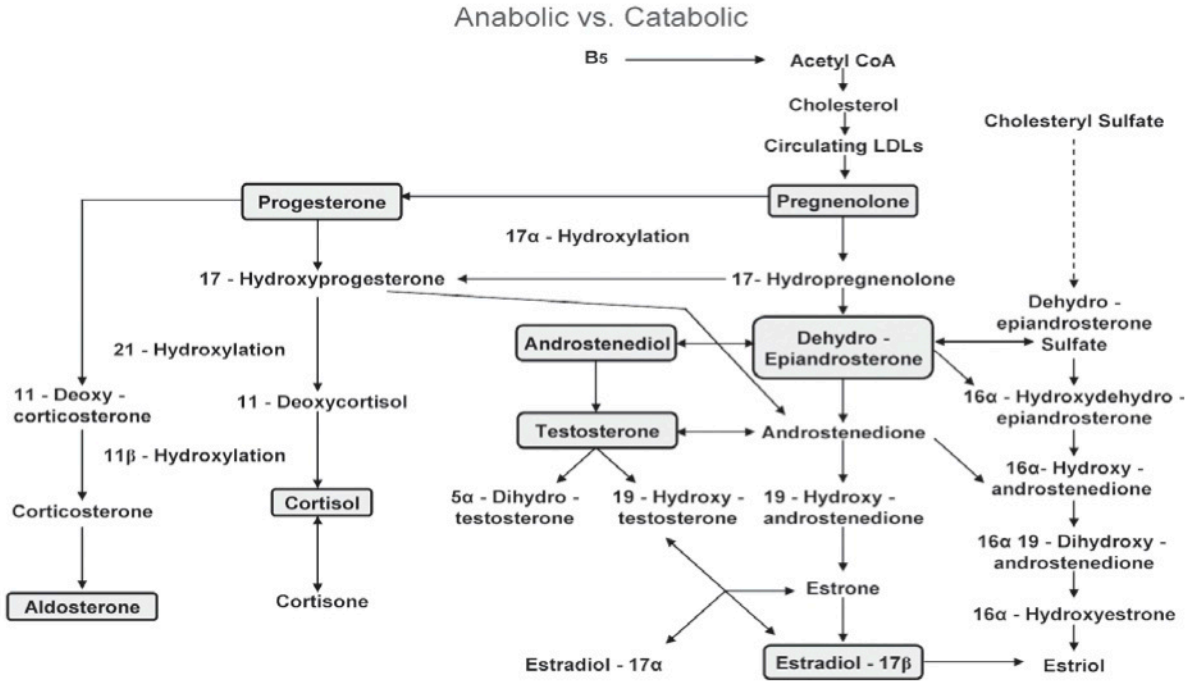
Research shows that a single meal (especially breakfast) can have a significant effect on glycemic regulation for many hours. Meals that contain protein and fat, as well as complex carbohydrates and soluble fiber will help maintain steady glucose levels, lower insulin production and prevent the need for cortisol production for glucose management. These types of meals will also result in less hunger and snacking and reduce the risk for insulin resistance.

Protocols intended to promote adrenal recovery are incomplete if they do not address the critical area of glycemic regulation. The ARK program includes Glycemic Foundation (a drink-mix, see page 53) as part of the basic package for all kits to ensure that every patient begins the process of adrenal recovery with proper glycemic regulation. It is vital that this be used along with the breakfast meal (breakfast should include protein and fat with no greater than 50% carbs) to have the most overall benefit.

Physiological/Normal Response to Stress

Cortisol enables the body to respond to various stressors through the release of stored resources within the body – glycogen to become blood sugar, bone minerals to release calcium and magnesium, glutamine from muscles to be converted to glucose, etc. As these actions of Cortisol are catabolic and create a breakdown state the body's normal response is to follow this with a release of DHEA and other anabolic hormones to help repair the effects of the catabolism. The optimal release of DHEA, human growth hormone and other anabolic hormones is during sleep.

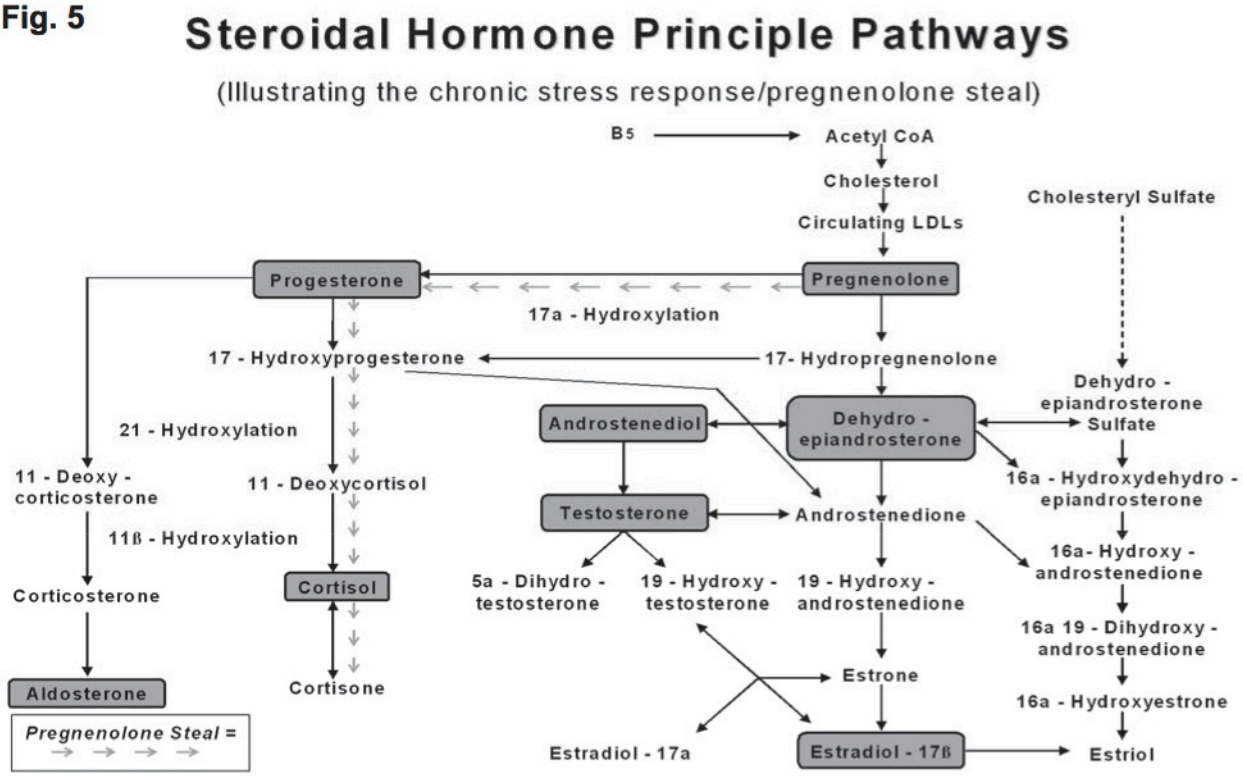
Fig. 4 Steroidal Hormone Principle Pathways



Maladaptive Response/Pregnenolone Steal

When chronic stress demands on the body accumulate and exceed the response capability of the adrenals there is a predictable maladaptation to this prolonged stress that initially manifests as lowered DHEA release. This happens because all available precursor hormones (e.g. Pregnenolone and Progesterone) are undergoing conversion to Cortisol in an attempt to keep up with the continued demands perceived by the hypothalamus and the release of ACTH from the anterior pituitary. This maladaptation to chronic stress is referred to as Cortisol escape or Pregnenolone steal. When this drop in DHEA occurs there is insufficient repair and recovery from catabolism , accelerating the aging process.

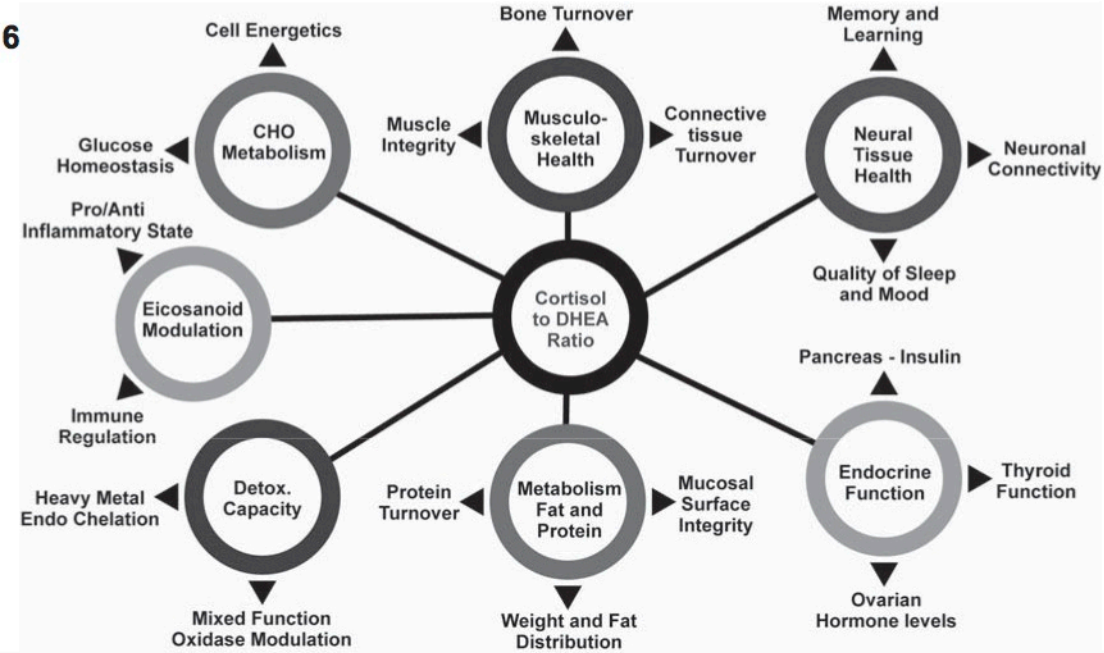
Fig. 5



Symptoms/Conditions Associated with Increased Cortisol to DHEA Ratio

- Carbohydrate Metabolism:
  - Hypoglycemia
  - Chronic Fatigue – impaired ATP production
- Musculoskeletal health:
  - Osteoporosis/Osteopenia – increased bone resorption
  - Renal calculi – increased calcium oxalate stone formation
  - Muscle wasting – increased catabolic release of amino acids
  - Weakened ligamentous/cartilaginous tissues
- Neural Tissue Health:
  - Depression/Anxiety – increased turnover of neurotransmitters
  - Insomnia – sleep initiation & maintenance
  - Mood swings/Irritability – increased neural excitability
  - Poor learning and short term memory
- Eicosanoid Modulation:
  - Chronic Inflammation – poor control of pro-inflammatory cytokines, prostaglandins, eicosanoids
  - Pain Syndromes – Fibromyalgia, headaches, arthritis, polymyalgia etc.
  - Poor wound healing
  - Easy bruising/vascular fragility
  - Immune dysfunction – impaired lymphocyte activity
- Liver Detoxification:
  - Heavy Metal Toxicity – reduced endochelation
  - Poor Antioxidant control – reduced methylation and sulfation reactions
- Endocrine Function:
  - Hypothyroidism – lowered TSH and T4 to T3 conversion secondary to prolonged catabolism
  - Premenstrual Syndrome – reduced contribution of progesterone from adrenals
  - Infertility – luteal phase deficit of progesterone
  - Severe menopause
  - Insulin Resistance – poor insulin receptor sensitivity
- Metabolism of Fat and Protein:
  - Trunkal obesity – increased uptake of glucose in central adipose cells
  - Increased Mucosal Permeability – weakened mucosal tissue integrity

Fig. 6



Overview

The Adrenal Stress Profile is a salivary test easily performed at home or at work, and mailed directly to the lab. Four saliva samples are taken throughout the course of a patient's typical day so that the cortisol circadian rhythm can be determined. Two of these samples provide an average DHEA-S value. This profile, along with the questionnaire provided (see appendix) and the patient history, can help identify the stage of adrenal exhaustion and give an accurate assessment of adrenal dysfunction for each patient.

Cortisol Rhythm (4 Timed Samples)

The salivary free fraction of the adrenal cortisol output is reported because of its high clinical correlation with both serum free fraction testing and with patient's symptoms. The sum of four individual cortisol levels is taken at specified intervals throughout the day: in the morning between 6-8 am, near noon between 12-1 pm, in the late afternoon between 4-5 pm, and at nighttime between 10 pm-12 am. The normal reference range used for the ARK 201/205 assessment includes a sum of these four cortisol readings between 23-42 nM, with the ideal being 34-36 nM. (Note: reference ranges used by other labs may be slightly different or utilize different units of measurement).

DHEA-S Average (Value of 2 samples)

DHEA is the major precursor of testosterone and the estrogens. The more active, sulfate form of DHEA is DHEA-S, which provides a more reliable measure of DHEA levels. We report the average of two DHEA-S values, taken between 12-1 pm and between 4-5 pm. The normal DHEA-S level is 2.0-10.0 ng/ml and the ideal is 7.0-8.0 ng/ml. DHEA is an important modulator of many physiological processes. It promotes the growth and repair of protein tissue, especially muscle, and acts as a counter-regulatory agent to cortisol, negating many of the harmful effects of excess cortisol. Over extended periods of an increased demand for cortisol, DHEA levels decline, and DHEA is then no longer able to counter-regulate the negative effects of excess cortisol. Depressed DHEA levels serve as an early warning of potential adrenal exhaustion.

"Stage 1" Acute Adrenal Dysfunction: Mechanism of Action

An Initial Increase in Cortisol Output

Stage 1

At least One Cortisol is High

Total Cortisol Sum is High

DHEA is Borderline Low, Low, or Normal

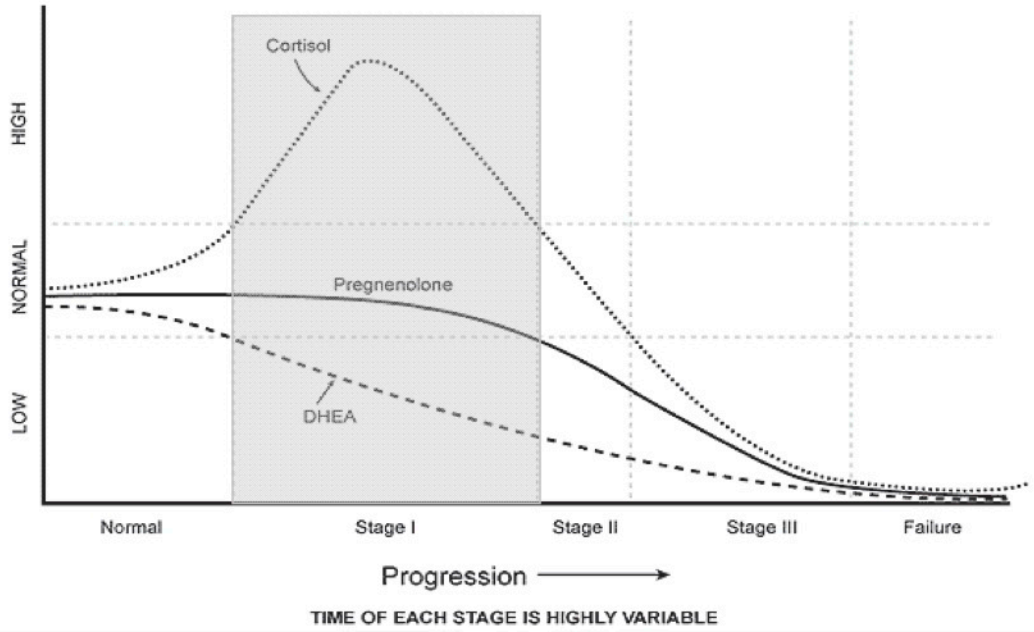
Distinguishing features:

- (↑) anterior pituitary output of ACTH
- (↑) adrenocortical stimulation
- (↑) cortisol output
- (↑) probability of pregnenolone steal
- (↑) probability of (↓) DHEA

Acute Adrenal dysfunction is defined as a prolonged, increased excitatory stimulus to the adrenals having resulted in a prolonged, increased cortisol output, usually with a corresponding prolonged decrease in DHEA. In the hypothalamic-pituitary-adrenal control loop (HPA axis), an increase in ACTH output from the pituitary gland stimulates the adrenal glands. The level of cortisol is regulated through the HPA negative feedback. Continued demand for increased cortisol production necessitates ongoing ACTH release by the pituitary, but the adrenals can eventually experience difficulty in meeting the demand. This difficulty begins during the first stage of adrenal exhaustion.

Eventually, other pathways must compensate to facilitate the production of sufficient cortisol. One such compensation is shunting or "stealing" of pregnenolone from the DHEA/sex hormone pathway to the progesterone/cortisol pathway. In this steal, the pathway from progesterone to cortisol becomes preferential over the pathway from DHEA to the sex hormones. There is consequently a decrease in DHEA and its metabolites, which include testosterone and the estrogens. Progesterone either remains normal or decreases, and cortisol increases. Despite elevated cortisol, pregnenolone steal reliably indicates that chronic stress has begun to exceed the body's ability to respond.

Fig. 7 **Progression of Stages of Adrenal Exhaustion**



Stage 2- Adrenal Fatigue: Mechanism of Action

The Transition from Increased to Decreased Cortisol Output

Distinguishing features:

- (↑) anterior pituitary output of ACTH
- (↑) adrenocortical stimulation
- normal total cortisol output
- low or borderline-low morning, noon, or afternoon cortisol level
- normal nighttime cortisol level
- (↑) probability of pregnenolone steal
- (↑) probability of (↓) DHEA

Stage 2

AM, Noon or Afternoon Cortisols are Low or Borderline Low

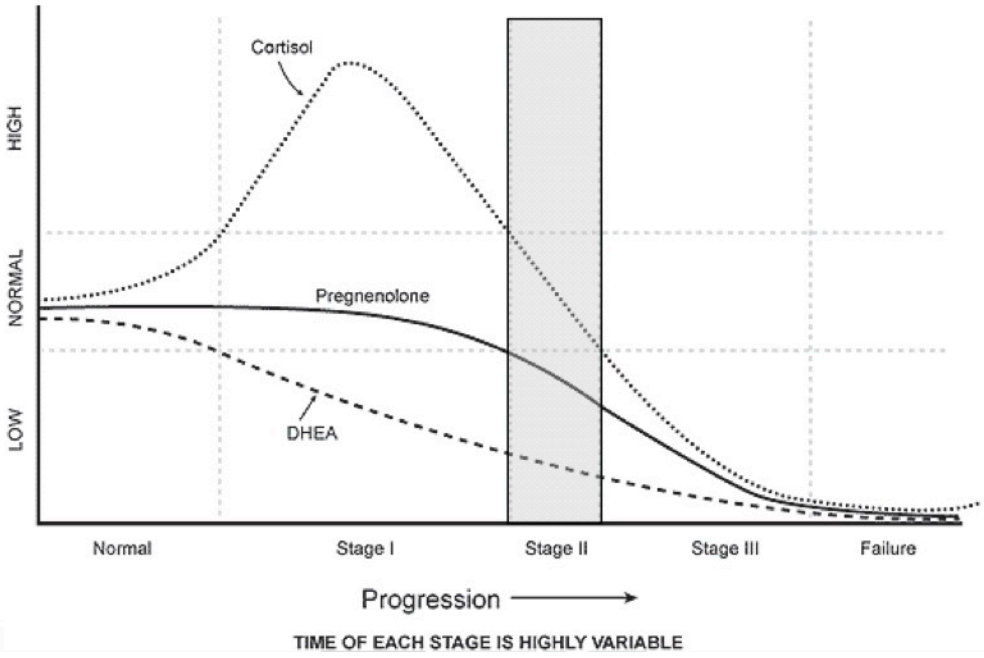
Total Cortisol Sum is Normal

DHEA Borderline Low or Low

Adrenal Fatigue is a transitional phase. It signifies a continuing decline in cortisol output from levels above normal to those below normal, although ACTH stimulation remains high or even increases. There is a gradual change from increased to decreased cortisol output due to a decreasing response of the adrenal glands to protracted ACTH stimulation. Any one or more of the morning, noon or afternoon cortisol values is low or borderline-low, but the nighttime cortisol level is usually normal. The decreasing cortisol output is a marker of mid-stage adrenal exhaustion. In this stage, the sum of the four cortisol levels is normal. Pregnenolone steal from the DHEA/sex hormone pathway to the progesterone/cortisol pathway can assist in maintaining normal overall cortisol levels at the continued expense of DHEA. DHEA usually remains low or borderline-low a reliable indicator of pregnenolone steal and that demands from stress are greater than the body's ability to respond.

Fig. 8

Progression of Stages of Adrenal Exhaustion



Stage 3 Adrenal Exhaustion: Mechanism of Action

The Advanced Stage with Decreased Cortisol Output

Stage 3

Most Cortisols are Low or Borderline Low

Total Cortisol Low

DHEA Borderline Low or Low

Distinguishing features:

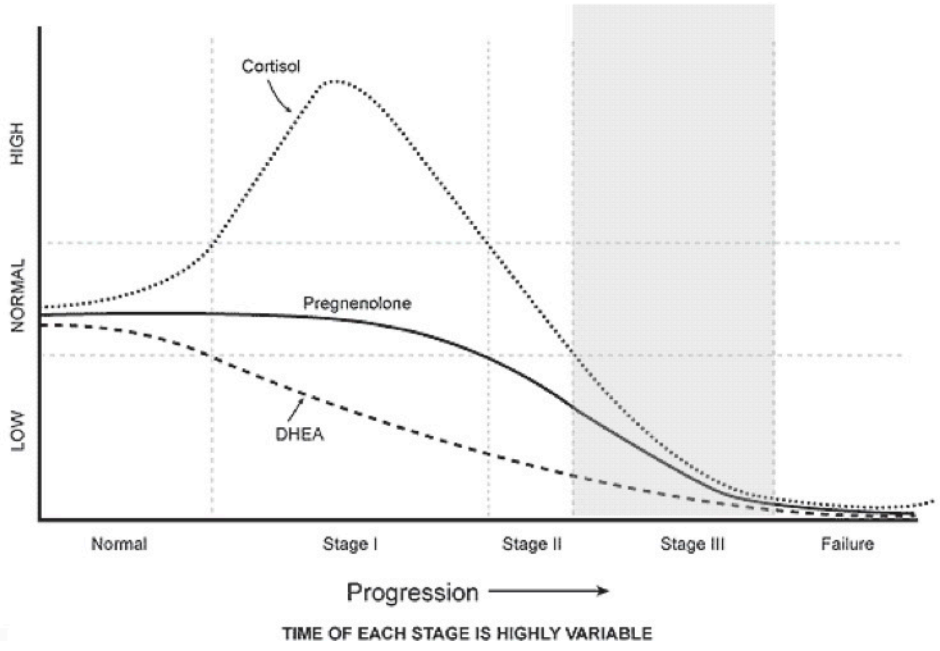
- (↑) anterior pituitary output of ACTH
- (↑) adrenocortical stimulation
- (↓) total cortisol output
- (↑) probability of (↓) nighttime cortisol level
- (↑) probability of pregnenolone steal
- (↑) probability of (↓) DHEA

Stage 3 is a severe and late stage of adrenal exhaustion. It is marked by the failure of the adrenals to produce enough cortisol to reach even normal levels in response to continued, increased ACTH stimulation. The sum of the four cortisol levels is below normal and DHEA is usually low or borderline-low. Endocrine and autonomic pathways, through endogenous and/or exogenous stress, have been conditioned by a complex of stimuli to respond beyond normal physiological ranges. This conditioning ultimately results in adrenal gland inability to produce the amount of cortisol demanded by the degree of stimulation. The result is a hypothalamic-pituitary-adrenal axis "crash," in which essential neuroendocrine feedback loops are endogenously unable to return the system to homeostasis. In such a case there is often a decreased nighttime cortisol, which is a marker of high adrenal exhaustion.

A wide variety of seemingly unrelated symptoms usually appears; a situation which reflects the global nature of the dysfunction. Severe imbalances in other hormone systems are to be expected. Subclinical disorders are common, indicating the insidiousness of advanced adrenal exhaustion. Without intervention adrenal failure is a possibility, as are cardiovascular, thyroid, and GI complications.

Fig. 9

Progression of Stages of Adrenal Exhaustion



The 205 Test

The 205 test is instrumental for women, both pre-menopausal and post-menopausal, as well as men of all ages. In pre-menopausal women it is necessary to know when during the cycle the patient collected her sample for best interpretation of E2, E3 and Progesterone. Reference ranges vary depending on collection days, i.e. follicular phase, mid-cycle and luteal phase.

To determine endogenous production of hormones it is necessary to discontinue any hormone therapy prior to test collection. The length of time the patient should be off therapy prior to testing will depend on the delivery system of the hormone therapy. For sublingual therapies discontinue for 3-5 days. For oral/swallowed doses wait 7-10 days before testing and for patches and creams it is suggested to wait 21-28 days. Patients taking creams for prolonged therapy may want to consider initial testing as soon as therapy is discontinued to assess accumulated buildup of hormone followed by periodical retesting to monitor the "wash out" of hormone over the next several months. It can take a full year of more for heavy buildup of some hormones to wash out.

If the goal of testing is to monitor the effects of hormone therapy, collect the test samples concurrent with therapy administration. Consider temporary conversion of sublingual delivery to oral delivery in anticipation of salivary collections.

When deciding when to collect samples, consider that luteal phase deficits in progesterone are most easily seen during the midpoint of the luteal phase. For women with 26-30 day cycles the optimal time to test is day 18-21. If the last menstrual period is not known, consider a pregnancy test and collect basal body temps for one month. This should reveal a temperature spike of .5-1.0 degree on the day of ovulation. Once the day of ovulation is identified the test collection should follow 5-7 days after. If testing to discern hormonal contribution of other periodic symptoms such as migraines or cramping it is best to test during days of symptom occurrence.

In post menopausal women, including cases of hysterectomy induced menopause, initial testing can be collected any time. Subsequent testing should be collected near the same time each month.

Estradiol (E2) is the most potent of the three estrogens yielding the strongest trophic effects on tissue receptors. Prolonged and excessive stimulation of estrogen receptors can lead to unwanted proliferation of breast and uterine tissue. This proliferation can contribute to lesions such as: breast cysts, endometrial hyperplasia and neoplastic changes. Elevated levels of E2 can also be associated with migraine headaches. Low estrogen levels can be correlated with symptoms such as low energy, infertility, vaginal dryness, low libido.

Estriol (E3) is considered the most abundant of the three estrogens but exerts lesser effects on tissue receptors than does E2.

Progesterone is a key intermediate between the conversion of Pregnenolone to Cortisol/Cortisone and the adrenal cortex can supply up to 30% of a cycling woman's total Progesterone needs. But this is not the case when a woman is in pregnenolone steal and Progesterone is being pulled to Cortisol/Cortisone in an attempt to respond to chronic adrenal stress. Low progesterone is a common finding and correlates with PMS symptoms, infertility,

anxiety, insomnia, fibrocystic breast disease, uterine fibroids and uterine bleeding. In men the primary symptoms associated with low progesterone is insomnia and anxiety.

Progesterone is facilitative of the GABA/chloride channel in neurologic tissues and deficiencies can contribute to symptoms of GABA deficiency such as anxiety, insomnia, and excessive rumination.

In postmenopausal states a ratio of Progesterone to E2 ratio in excess of 30:1 has been reported to be protective against excessive estrogen stimulation leading to estrogen related cancers of the breast.

Excess progesterone levels, often seen with users of progesterone creams, can lead to weight gain, lethargy and depression. As toxic levels of hormone cream build in the adipose tissues the body will retain fat to buffer itself from the "toxins" and the excessive release of Progesterone from the depot will chronically stimulate GABA release in the brain contributing to abnormal and continuous inhibition of neurologic tissues causing depressed mood and fatigue.

Testosterone is a key hormone both for men and women to support libido and a sense of vitality. Use of androgen creams, especially testosterone gels, are increasingly common therapies but can be problematic if not carefully monitored. For those undergoing testosterone therapy an aromatase inhibitor to prevent conversion to estrogen and to prevent increases in dihydrotestosterone (DHT) a type II 5-alpha-reductase inhibitor should be considered.

Melatonin is a beneficial hormone secreted from the pineal gland that helps to initiate and maintain sleep. Low levels can be related to poor sleep hygiene such as irregular sleep times, excessive light prior to or during sleep and frequent travel in different time zones. 5-hydroxy tryptophan is an immediate precursor to melatonin and vitamin B6 is a critical cofactor in the conversion from 5-HTP to melatonin. A deficiency of either can lead to low melatonin output. Excessive melatonin augmentation/supplementation can lead to daytime grogginess and lethargy. If the melatonin sampling on this test is abnormal it is advised to obtain a melatonin biorhythm looking at 4 samples through the night and into the morning to get a look at timing of melatonin release in addition to peak output. If the output is good but the timing is irregular light therapy may be required.