INSIDER’S GUIDE

Stress

By Ron Grisanti, D.C. & Dicken Weatherby, N.D.

http://www.FunctionalMedicineUniversity.com

Limits of Liability & Disclaimer of Warranty

We have designed this book to provide information in regard to the subject matter covered. It is made available with the understanding that the authors are not liable for the misconception or misuse of information provided. The purpose of this book is to educate. It is not meant to be a comprehensive source for the topic covered, and is not intended as a substitute for medical diagnosis or treatment, or intended as a substitute for medical counseling. Information contained in this book should not be construed as a claim or representation that any treatment, process or interpretation mentioned constitutes a cure, palliative, or ameliorative. The information covered is intended to supplement the practitioner's knowledge of their patient. It should be considered as adjunctive support to other diagnostic medical procedures.

This material contains elements protected under International and Federal Copyright laws and treaties. Any unauthorized reprint or use of this material is prohibited.
Contents

CONTENTS .............................................................................................................................................................. 2
The Stress Response: The Real Story ............................................................................................................. 3
Catecholamines ............................................................................................................................................................. 3
  Physiologic Effects of Catecholamines................................................................................................................. 3
  Summary of Catecholamine Activity in the Body .............................................................................................. 4
Cortisol........................................................................................................................................................................... 5
  Physiologic Effects of Cortisol............................................................................................................................ 5
  Summary of Cortisol Activity in Body ................................................................................................................... 6
The Stress Response Gone too Far! .............................................................................................................. 6
Stress-Related Diseases and Conditions ............................................................................................................ 7
The Hypothalamic-Pituitary-Adrenal Axis: The Conductor of Homeostasis ..................................................... 8
The Disharmony of Cortisol and DHEA .............................................................................................................. 10
Ratio of Cortisol to DHEA ................................................................................................................................. 12
Pregnenolone Steal or Cortisol Escape ............................................................................................................... 13
  The Steroid Hormone Pathways ......................................................................................................................... 13
Beyond Cortisol.................................................................................................................................................. 14
The Stages of the Stress Response ................................................................................................................. 14
  The Alarm Reaction ......................................................................................................................................... 14
  The Compensation Stage Moving Towards Decompensation (Adrenal Hyperfunction)............................. 15
  The Fatigue Stage (adrenal hypofunction) ........................................................................................................ 15
Summary of the Stages of Adrenal Exhaustion ............................................................................................... 16
  Stage I ................................................................................................................................................................. 16
  Stage II ............................................................................................................................................................... 16
  Stage III ............................................................................................................................................................. 17
THE THINKING PROCESS............................................................................................................................ ERROR! BOOKMARK NOT DEFINED.
The Functions of Progesterone ......................................................................................................................... ERROR! BOOKMARK NOT DEFINED.
  Underlying Cause .............................................................................................................................................. ERROR! Bookmark not defined.
  Hormones Therapy ............................................................................................................................................ ERROR! Bookmark not defined.
  Progesterone .................................................................................................................................................... ERROR! Bookmark not defined.
The Stress Response: The Real Story

The stress response involves 2 Major Systems: Catecholamines (Epinephrine/NorEpinephrine) and Cortisol

- **Catecholamines** — Prepare the body to act
- **Cortisol** — Mobilizes energy (glucose) and other substances to fuel the action.

### Catecholamines

Stress loads will cause the release of *epinephrine and norepinephrine*. **Epinephrine** goes to the liver and skeletal muscle but is then rapidly metabolized. Epinephrine has its influence on cardiac action specifically:

- Myocardial contractility increasing heart rate and increasing venous return to the heart, all of which increases cardiac output and blood pressure
- Epinephrine dilates blood vessels of skeletal muscles.

Epinephrine also has the unique function of **metabolic regulation**:

- Epinephrine causes transient hyperglycemia by activating enzymes whose actions promote gluconeogenesis and glycogenolysis in the liver while inhibiting glucose breakdown.
- Epinephrine decreases glucose uptake in the muscle and other organs and decreases insulin release from the pancreas.
- The decrease in insulin release prevents glucose from being taken up by the peripheral tissue and thus preserves it for the CNS.
- Epinephrine mobilizes free fatty acids and cholesterol by stimulating lipolysis, freeing triglycerides and fatty acids from fat stores, and inhibiting the degradation of circulating cholesterol to bile acids.
- Epinephrine increases oxygen supply, bronchodilation and increased ventilation.
- Epinephrine decreases protein synthesis

The **catecholamine norepinephrine** rarely if any reaches distal tissue and principally is involved in the regulation of blood pressure. It is the primary constrictor of smooth muscle in all blood vessels. During stress, norepinephrine raises blood pressure by constricting peripheral vessel, inhibits gastrointestinal activity and dilates the pupils of the eyes.

### Physiologic Effects of Catecholamines

<table>
<thead>
<tr>
<th>Organ</th>
<th>Process or Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Increased blood flow</td>
</tr>
<tr>
<td></td>
<td>Increased glucose metabolism</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased rate and force of contraction</td>
</tr>
</tbody>
</table>
Peripheral vasoconstriction

Pulmonary system
Increased oxygen supply
Bronchodilation
Increased ventilation

Muscle
Increased glycogenolysis
Increased contraction
Increased dilation of skeletal muscle vasculature

Liver
Increased glucose production
Increased gluconeogenesis
Increased glycogenolysis
Decreased glycogen synthesis

Adipose tissue
Increased lipolysis
Increased fatty acids and glycerol

Skin
Decreased blood flow

Skeleton
Decreased glucose uptake and utilization (decreases insulin release)

Gastrointestinal and genitourinary tracts
Decreased protein synthesis

Lymphoid tissue
Increased protein breakdown (lymphoid tissue shrinks)

**Summary of Catecholamine Activity in the Body**

- Increases HR, return of blood to heart, cardiac output, and blood pressure
- Dilates blood vessels of skeletal muscle
- Increases blood sugar — promotes glucose formation
- Decreases Insulin release from the pancreas
- Prevents glucose uptake from peripheral tissues
- Increases FFA’s and cholesterol in bloodstream
- Overall effect is to conserve energy for the Central Nervous System, and skeletal system for proper body function in relation to a stressful situation.
**Cortisol**

The adrenal cortex is activated during stress by adrenocorticotropic hormone, increasing adrenocortical secretion of glucocorticoid (steroid) hormones, primarily cortisol. Cortisol is also known as hydrocortisone.

Cortisol circulates in the plasma, both protein bound and free. The main plasma-binding protein is called corticosteroid-binding globulin. The unbounded, or free, fraction is approximately 8% of the total plasma cortisol and is the most biological active fraction of cortisol.

**Physiologic Effects of Cortisol**

<table>
<thead>
<tr>
<th>Functions Affected</th>
<th>Physiologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate and lipid metabolism</td>
<td>Diminishes peripheral uptake and utilization of glucose; promotes gluconeogenesis in liver cells; enhances gluconeogenic response to other hormones; promotes lipolysis in adipose tissue</td>
</tr>
<tr>
<td>Protein metabolism</td>
<td>Increases protein synthesis in liver and depletes protein synthesis (including immunoglobulin synthesis) in muscle, lymphoid tissue, adipose tissue, skin, and bone; increases plasma level of amino acids; stimulates deamination in liver</td>
</tr>
<tr>
<td>Inflammatory effects</td>
<td>Decreases circulating eosinophils, lymphocytes, and monocytes; increases release of polymorphonuclear leukocytes from bone marrow; decreases accumulation of leukocytes at site of inflammation; delays healing; permissive for vasoconstrictive action of norepinephrine</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Lipolysis in extremities and lipogenesis in face and trunk</td>
</tr>
<tr>
<td>Immune reserve</td>
<td>Decreases tissue mass of all lymphoid tissues (e.g., decreases protein synthesis); promotes rapid decrease in circulating lymphocytes, eosinophils, basophils, and macrophages; inhibits production of interleukin-1 and interleukin-2; consequently, also blocks cell-mediated immunity and generation of</td>
</tr>
<tr>
<td>Function</td>
<td>Effect</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Digestive function</td>
<td>Promotes gastric secretion</td>
</tr>
<tr>
<td>Urinary function</td>
<td>Enhances urinary excretion</td>
</tr>
<tr>
<td>Connective tissue function</td>
<td>Decreases proliferation of fibroblasts in connective tissue (thus delaying healing)</td>
</tr>
<tr>
<td>Muscle function</td>
<td>Maintains normal contractility and maximal work output for skeletal and cardiac muscle</td>
</tr>
<tr>
<td>Bone function</td>
<td>Decreases bone formation</td>
</tr>
<tr>
<td>Vascular system and myocardial function</td>
<td>Maintains normal blood pressure; permits increased responsiveness of arterioles to constrictive action of adrenergic stimulation; optimizes myocardial performance</td>
</tr>
<tr>
<td>Central nervous system function</td>
<td>Somehow modulates perceptual and emotional functioning, essential for normal arousal and initiation of daytime activity</td>
</tr>
</tbody>
</table>

**Summary of Cortisol Activity in Body**

- Increases glucose formation, and protein breakdown
- Increases glucose utilization by the CNS
- Increases "insulin resistance" in peripheral system
- Suppresses gastric emptying, slows digestion
- Inhibits sex hormone effects and production, alters reproduction
- Increases sodium retention — high blood pressure
- Suppresses immune function
- Alters thyroid function, production, and effectiveness
- Depletes the body of Magnesium, Zinc, Glutamine, Carnitine, etc

**The Stress Response Gone too Far!**

**Chronic Illness/Conditions Influenced by the Stress Response:**

- Diabetes Mellitus
- Cardiovascular disease, high blood pressure, elevated blood fats
- Infectious diseases
- Gastrointestinal illness
- Autoimmune/Inflammatory illnesses
- Increased drug sensitivity — Both can magnify each other
- Infertility, menstrual irregularities
- Decreased growth in children
- Osteoporosis -
- Detoxification problems, e.g. Multiple Chemical Sensitivities
- Brain damage & psychiatric illnesses, e.g. Alzheimer's, Depression
- Chronic Fatigue Syndrome
- Cancer

Glucocorticoid (cortisol) receptors are found in almost every cell in the body.

The stress response is initiated by the nervous and endocrine systems, specifically corticotrophin-releasing factor (CRF) from the hypothalamus, the pituitary gland and the adrenal gland.

The SNS is stimulated during the stress response causing the medulla of the adrenal gland to release catecholamines (epinephrine, norepinephrine, and dopamine).

Simultaneously, the hypothalamic CRF stimulates the pituitary gland to release antidiurectic hormones from the posterior pituitary, prolactin, growth hormone and adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH in turn stimulates the cortex of the adrenal gland to release cortisol.

### Stress-Related Diseases and Conditions

<table>
<thead>
<tr>
<th>Target Organ or System</th>
<th>Diseases and Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Coronary artery disease Hypertension</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Disturbances of heart rhythm</td>
</tr>
<tr>
<td>Muscles</td>
<td>Tension headaches</td>
</tr>
<tr>
<td></td>
<td>Muscle contraction backache</td>
</tr>
<tr>
<td>Connective tissues</td>
<td>Rheumatoid arthritis (autoimmune disease)</td>
</tr>
<tr>
<td></td>
<td>Related inflammatory diseases of connective tissue</td>
</tr>
</tbody>
</table>
Pulmonary system
Asthma (hypersensitivity reaction)
Hay fever (hypersensitivity re-action)

Immune system
Immunosuppression or immune deficiency
Autoimmune diseases

Gastrointestinal system
Ulcer
Irritable bowel syndrome Diarrhea
Nausea and vomiting Ulcerative colitis

Genitourinary system
Diuresis Impotence Frigidity

Skin
Eczema Neurodermatitis Acne

Endocrine system
Diabetes mellitus Amenorrhea

Central nervous system
Fatigue and lethargy Type A behavior
Overeating Depression Insomnia

The Hypothalamic-Pituitary-Adrenal Axis: The Conductor of Homeostasis

When an individual is exposed to stressful stimuli, the release of hypothalamic CRH is stimulated. CRH then stimulates production and release of adrenocorticotropic hormone (ACTH).
The ACTH enters the systemic circulation and reaches the adrenal cortex of the adrenal gland, where its stimulates the synthesis of the glucocorticoid hormone CORTISOL and also androgenic hormones such as androstenedione and dehydroepiandrosterone (DHEA), both of which may ultimately be converted into the more potent testosterone or dihydrotestosterone (DHT) in peripheral tissues.

In addition, the cortisol also participates with aldosterone (the mineralocorticoid hormone) in driving sodium reabsorption by the kidney tubules. This serves the important function of conserving electrolytes and water within the vasculature to help maintain blood and perfusion pressures to critical organs and tissues that are participating in the fight or flight reactions.

During the stress response, the blood concentrations of cortisol will rise until the cortisol starts to exert its negative feedback effect upon both the CRH neurons and the pituitary corticotrophs that manufacture ACTH, in order to reduce their increased levels of secretion back to their normal baseline.
This homeostatic mechanism, when working correctly, prevents overproduction or prolonged elevations in CRH, ACTH, and cortisol.

When an individual experiences chronic stress along with maladaptive responses or a lack of coping, cortisol levels may remain inappropriately elevated due to persistent stimulation of the **CRH-ACTH-cortisol axis.**

**The Disharmony of Cortisol and DHEA**

When cortisol and DHEA work together in harmony (maintaining a normal ratio between cortisol and DHEA), the body is in a normal state of adaptation to stress. When unable to maintain this normal state of adaptation, the body can now enter into a prolonged state of maladaptation to stress.

Maintaining physiological balance between cortisol and DHEA is an important aspect of vibrant health. The production of too much cortisol can literally burn up the body, and insufficient
cortisol production causes the body's internal machinery to malfunction, especially at the cellular level.

As was mentioned, the adrenal glands produce both cortisol and DHEA in the adrenal cortex under the stimulation of adrenocorticotrophic hormone (ACTH).

ACTH acts like a whip on the adrenals. It is in many ways similar to a jockey whipping a horse to make it run faster. If the jockey ignores the clues that his horse is fatigued and keeps whipping it, the horse will keep running until it collapses in total exhaustion or death. In the case of the human body, if we allow stress levels to become chronic and out of control, we can sooner or later expect the same result.

Metabolically, this can take a toll on the organism.

The ongoing high concentrations of cortisol may keep blood glucose levels high for prolonged periods, cause redistribution of fat from the thighs and buttocks to the abdominal and cervical regions ("buffalo hump") due to mobilization of free fatty acids; cause insulin resistance to develop; cause fluid retention and hypertension; produce proteolysis in muscle, bone, and connective tissues; and inhibit peptide and protein hormone formation (especially by the pituitary gland).

Elevated cortisol concentrations can decrease the number and functions of blood lymphocytes, eosinophils, basophils, monocytes/macrophages, and neutrophils.

Further, cortisol can inhibit the production of immune cell-signaling molecules such as the proinflammatory cytokines interleukin (IL)-1, 1L-2, IL-2 receptor, 1L-6, tumor necrosis factor (TNF), and gamma interferon.

Chromically elevated glucocorticoids can also decrease antibody and immunoglobulin production.

Consequently, prolonged stress that activates CRH-driven sympathetic outflow would be expected to lead to greater **susceptibility to disease, infections, and cancer in human patients with a chronically suppressed immune system.**

In other words, with unregulated or untreated chronic stress, excessive exposure to cortisol may **disable the negative restraint on stimulated CRH secretion.**

The HPA axis is in many ways the **conductor of the homeostatic symphony.** It is probably apparent at this point that the CRH of the brain is intertwined in some way with virtually every physiological system of the body.
Ratio of Cortisol to DHEA

Optimal adrenal function exists when the **ratio of cortisol to DHEA is in proper balance.** This is why measuring this ratio is the best way to both evaluate adrenal function and determine the effects stress is having on overall health.

(Source: Diagnos-Techs, Inc.)

When cortisol levels are elevated and DHEA is low we are considered to be in a Chronic Stress Response.
This is now referred to as a chronic stress response (i.e. pregnenolone steal/cortisol escape/elevated cortisol to DHEA ratio). The longer one stays in a state of chronic stress the more compromised all aspects of body function become.

**Pregnenolone Steal or Cortisol Escape**

The body's preferential pathway under chronic stress is called Pregnenolone Steal or Cortisol Escape. When the body is in a "chronic stress response", pregnenolone, the precursor to all the rest of the steroidal hormones, is diverted to cortisol – cortisone. This is at the detriment of all the other steroidal hormones; i.e. progesterone, aldosterone (mineral/cortical pathway/sodium-potassium pump), DHEA and its metabolites: the sex hormones, estrogens and testosterone.

As pregnenolone is diverted to cortisol-cortisone, DHEA becomes depleted. The result is an elevated cortisol to DHEA ratio. This is measurable with the Functional Adrenal Stress Profile. Simply divide the cortisol sum by the DHEA(s) average to get the ratio. A normal ratio is approximately 5:1 to 6:1.

**The Steroid Hormone Pathways**

This can ultimately result in hormone, immune and metabolic systems breakdown. When this happens we are losing (or have already lost) our ability to modulate bodily functions and are on the road to further hormone, immune, and metabolic breakdown.

For example, if cortisol levels are too high at night, rather than getting the rest and recovery necessary to maintain optimal physical repair and psychic regeneration, the body will be in a catabolic state (high nighttime cortisol).
levels inhibit the release of growth hormone necessary to repair and rebuild body tissues).

Beyond Cortisol

An elevated cortisol to DHEA ratio will also interfere with the surface integrity of the body's mucosal linings that act as its first-line immune defense. This mucosal barrier is primarily under the direction of the adrenal glands, specifically cortisol and DHEA. Cortisol and DHEA systemically modulate the production and turnover of specialized immune cells called immunocytes (also known as plasmacytes) that produce the secretory antibodies that protect us.

The primary antibody of defense is secretory IgA (sIgA). When cortisol is elevated and DHEA is low, suppression of these mucosal immune cells occurs, compromising our first-line immune defense, resulting in low sIgA output.

The longer a person is in a state of chronic stress (high ratio of cortisol to DHEA), the more compromised his or her first line of immune defense will be and the greater the risk for opportunistic infections and allergic reactions to foods. This could ultimately lead to cancer, cardiovascular disease as well as autoimmune disease, a variety of degenerative diseases and accelerated aging.

In a Chronic Stress Response all body functions have become compromised due to prolonged hormone, immune and metabolic breakdown that can lead like falling dominoes to a cascade of chronic degenerative diseases from which the weakened body has a reduced chance to recover.

The Stages of the Stress Response

The adrenals have a hard time interpreting "bad" stress as described above, or good stress such as the adrenaline rush of skiing down a big mountain. The adrenals deal with stress through the production of the hormones cortisol and DHEA. We evolved to be able to use our adrenal glands to help us deal with short term stress. If we live in stress for long periods of time, we begin to lose the ability to keep up with the stress and begin to function as if the adrenals are fatigued.

As the adrenals fatigue they go through a number of phases of fatigue, described below:

The stress response progresses through a number of different adaptive stages before fatigue sets in. The stress response can be divided into three stages:

1. The alarm reaction
2. The Compensation/decompensation stage (Adrenal hyperfunction)
3. The Fatigue Stage (adrenal hypofunction)

The Alarm Reaction

The alarm reaction is the normal stress response and has the following characteristics:
The sympathetic nervous system responds to stressors within seconds, causing the release of catecholamines (Epinephrine and Norepinephrine) from the adrenal medulla, which get the body into a “fight or flight” mode.

The catecholamines stimulate the hypothalamic-pituitary system causing the release of ACTH. ACTH stimulates the adrenal cortex causing the release of cortisol and increases the levels of free cortisol in the body.

ACTH also causes an increase in DHEA from the adrenal cortex.

Increased cortisol acts on the pituitary to stop the further release of ACTH and thereby quietening the stress response.

The cortisol and the catecholamines cause short-term high blood sugar via the action on the liver to breakdown glycogen increase gluconeogenesis and breakdown fat.

The increased steroid hormones return to normal after the stressor is removed.

**The Compensation Stage Moving Towards Decompensation (Adrenal Hyperfunction)**

The compensation phase sets in when the above stressors are not removed and the cortisol levels remain high in relation to the DHEA levels. This stage has the following characteristics:

- The sympathetic nervous system still responds to the stressors and continues to cause the release of catecholamines (Epinephrine and Norepinephrine) from the adrenal medulla.
- The catecholamines stimulate the hypothalamic-pituitary system causing the continued release of ACTH.
- ACTH stimulates the adrenal cortex causing the release of cortisol and increases the levels of free cortisol in the body.
- The hypothalamic-pituitary system normally responds to increased cortisol levels by decreasing ACTH output. In the compensation stage hypothalamus-pituitary system begins to get insensitive to the presence of cortisol and cortisol levels continue to stay high.
- DHEA levels, instead of rising like the cortisol, remain normal or show no signs of increase leading to an increased cortisol/DHEA ratio that is out of balance.

Cortisol leads to adrenal hyperfunctioning

Decompensation begins to occur as the levels of DHEA begin to decrease due the failure of the adrenal cortex to produce DHEA upon ACTH stimulation.

**The Fatigue Stage (adrenal hypofunction)**

The fatigue stage sets in when the stressors continue to act on the body, which can no longer react, causing decreased cortisol and DHEA output. This stage has the following characteristics:

- The sympathetic nervous system continues to respond to the stressors and continues to cause the release of catecholamines (Epinephrine and Norepinephrine) from the adrenal medulla.
- The catecholamines continue to stimulate the hypothalamic-pituitary system causing the continued release of ACTH.
In the fatigue stage the hypothalamus-pituitary system is barely sensitive to the presence of cortisol.

ACTH levels continue to stay high and continue to stimulate the adrenal glands. The adrenal cortex, at this stage, is so fatigued that it can no longer respond to ACTH stimulation, causing a dramatic decrease in the secretion of hormones.

Free cortisol is decreased and DHEA is normal or decreased, which leads to a decreased cortisol/DHEA ratio.

**Summary of the Stages of Adrenal Exhaustion**

Adrenal exhaustion progresses in **three stages**.

**Stage I**

**Stage I** is distinguished by an increase in output of **ACTH by the anterior pituitary gland**, increased adrenocortical stimulation, increased cortisol output and an increased probability of pregnenolone steal and decreased DHEA. Generally in Stage I cortisol increases and DHEA and its metabolites decrease or an imbalance occurs especially between testosterone and estrogen.

**Stage II**

**Stage II Adrenal Exhaustion** is marked by the transition from increased to decreased cortisol output. This stage is characterized by continuing **high levels of ACTH** and thus: adrenocortical stimulation, normal total cortisol output, low or borderline low morning, noon or afternoon cortisol levels, normal nighttime cortisol level, and an increased probability of pregnenolone steal and a further decrease in DHEA. This is a transitional phase in which although ACTH stimulation remains high or even increases, the adrenal output of cortisol declines due to the adrenal fatigue associated with continued hyper stimulation.
Stage III Adrenal Exhaustion is an advanced stage of adrenal exhaustion characterized by decreased total cortisol output. This stage is characterized by continuing high levels of ACTH and thus adrenocortical stimulation, low total cortisol output, and increased probability of a low nighttime cortisol level and pregnenolone steal and even further decrease in DHEA. The adrenal glands are now exhausted to the point that even though there is ongoing hyperstimulation (high ACTH); they continue to lose their capacity and reserve to produce enough cortisol. The eventual result is a crash of the hypothalamic-pituitary-adrenal axis (HPAA) in which essential neuroendocrine feedback loops are unable to return the system to homeostasis.

During a high stress situation, levels of sIgA decrease. Secretory IgA protects the gut from pathogenic material. Chronic cortisol elevation may be associated with high antigliadin antibodies (gliadin is a protein component found in wheat) due to intestinal hyperpermeability.

Credit is contributed to the following labs for their advancement in the field of functional medicine:

**Diagnos-Techs, Inc.**
Clinical and Research Laboratory
6620 S. 192nd Place, Bldg. J.
Kent, WA 98032
1-800-878-3787