Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 7 * FMDT 562B

Physiology of the Adrenal Glands

(Steriodogenesis Pathways)
(Blood Chemistry Analysis of Adrenal Dysfunction)

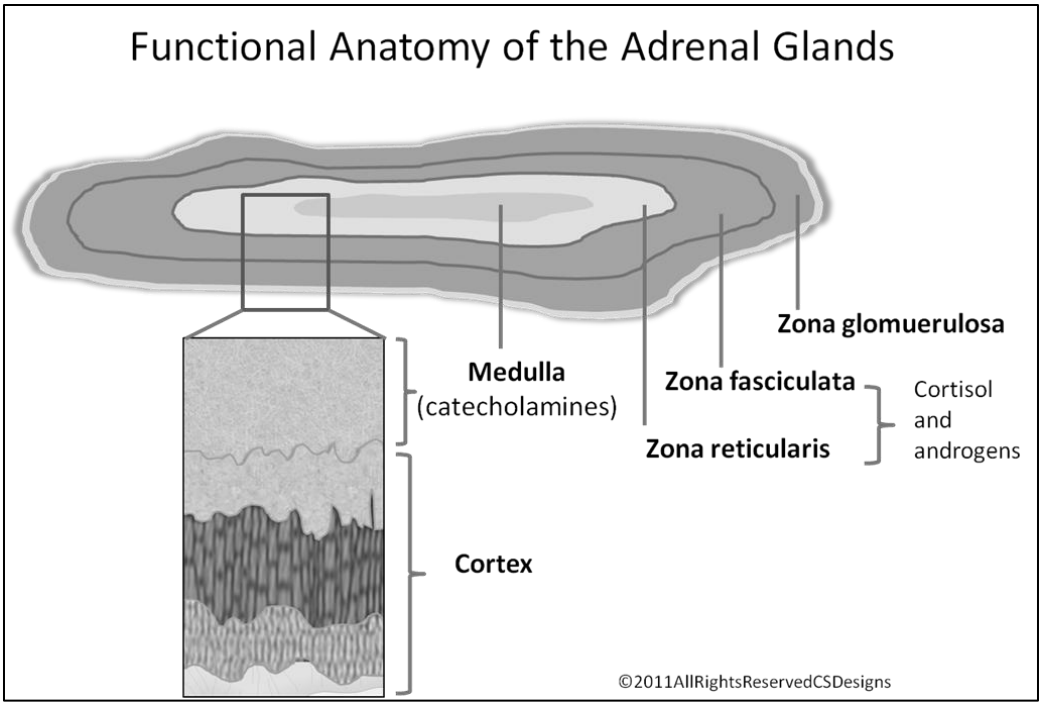
By Wayne L. Sodano, D.C., D.A.B.C.I. & Ron Grisanti, D.C., D.A.B.C.O., M.S.
http://www.FunctionalMedicineUniversity.com

Functional Medicine University's
Functional Diagnostic Medicine Training Program
Module 7 FDMT 562B Physiology of the Adrenal Glands
By Wayne L. Sodano, D.C., D.A.B.C.I. & Ron Grisanti, D.C., D.A.B.C.O., M.S.
http://www.FunctionalMedicineUniversity.com

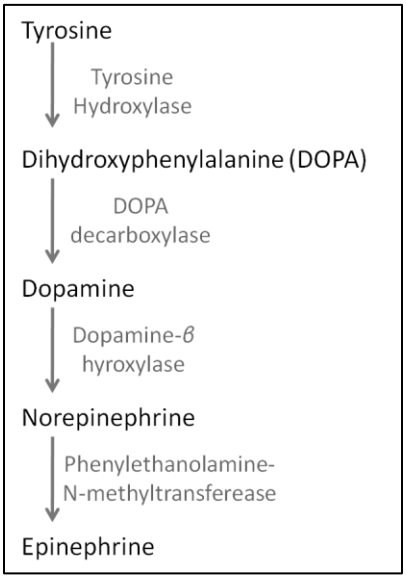
Contents

Functional Anatomy of the Adrenal Gland

The adrenal glands are located on the upper pole of each kidney. Each gland weighs about four grams.



There are two distinct parts to the adrenal glands; the inner part is called the medulla and the outer part is called the cortex. The medulla is innervated by preganglionic sympathetic fibers and secretes the hormones, epinephrine and norepinephrine (also known as catacholamines) in response to sympathetic stimulation.

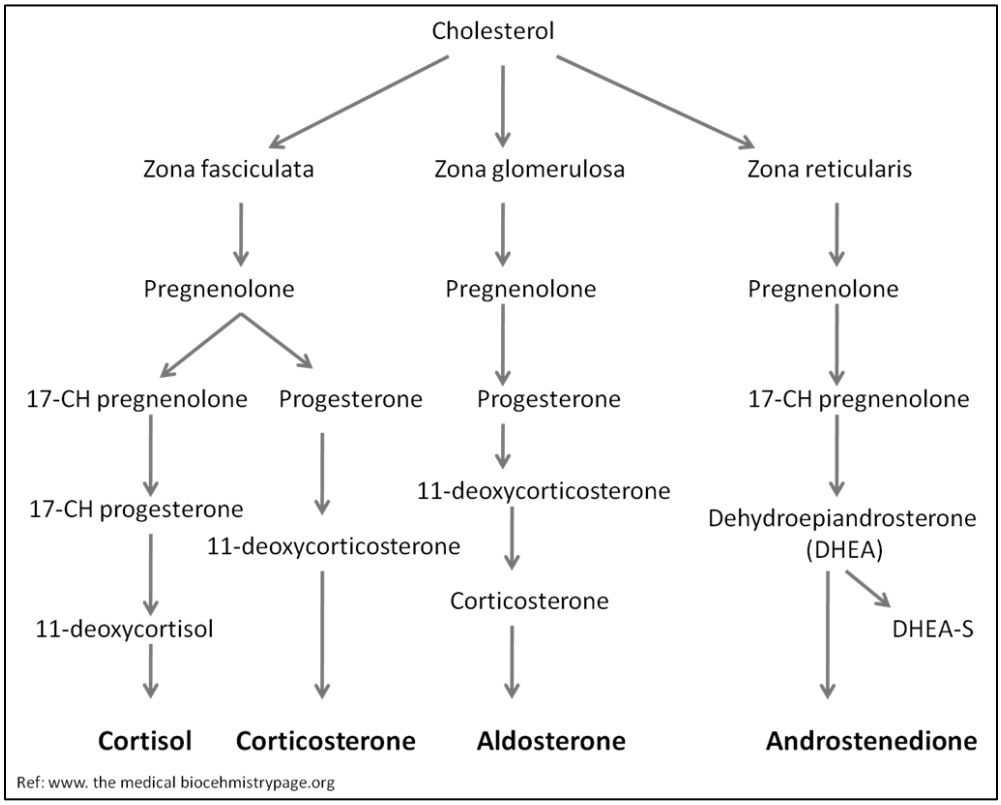


(You should recall that tyrosine is the amino acid used for the production of thyroid hormone, norepinephrine, epinephrine and dopamine. The synthesis of dopamine and the catecholamines requires methylfolate for the enzyme tyrosine hydoxylase to function properly.)

The catecholamines are released from the adrenal medulla in response to stress such as; emotional, hypotension, hypoxia, muscle exertion, exposure to cold, etc. The physiological effects of the adrenal medullary hormones include the following:

- Dilation of the pupils
- Dilation of the bronchioles
- Increased metabolic rate
- Constriction of blood vessels
- Stimulation of lipolysis in fat cells
- Inhibition of gastric secretions and motor activity
- Increased heart rate
- Increase rate of conversion of glycogen to glucose (glycogenolysis) in the liver

The adrenal cortex has three distinct layers which secretes hormones of steroid origin. The adrenal cortex is responsible for the production of three major classes of steroid hormones: glucocorticoids, which regulate carbohydrate metabolism; mineralocorticoids, which regulate the body levels of sodium and potassium; and androgenic hormones, which are similar to that of steroids produced by the male gonads.[1] More than 30 steroids have been isolated from the adrenal cortex.[2]



As previously stated, the adrenal cortex is composed of three main tissue regions: zona glomerulosa, zona fasciculata, and zona reticularis. Although the pathway to pregnenolone synthesis is the same in all zones of the cortex, the zones are histologically and enzymatically distinct, with the exact steroid hormone product dependent on the cytochrome P450 enzymes.[1]

Zona Glomerulosa - The cells of the zona glomerulosa secrete the hormone, aldosterone, mainly in response to extracellular fluid concentrations of potassium and angiotensin II.

Zona fasciculata - The cells of the zona fasciculata secrete the glucocorticoids, cortisol and corticosterone, as well as small amounts of androgens and estrogens. The secretion of this zone is under the control of the adrenocorticotropic hormone (ACTH).

Zona reticularis – The cells of the zona reticularis secrete the androgen hormones, dehydroepiandrosterone (DHEA) and androstenedione, as well as small amounts of estrogens and some glucocorticoids.

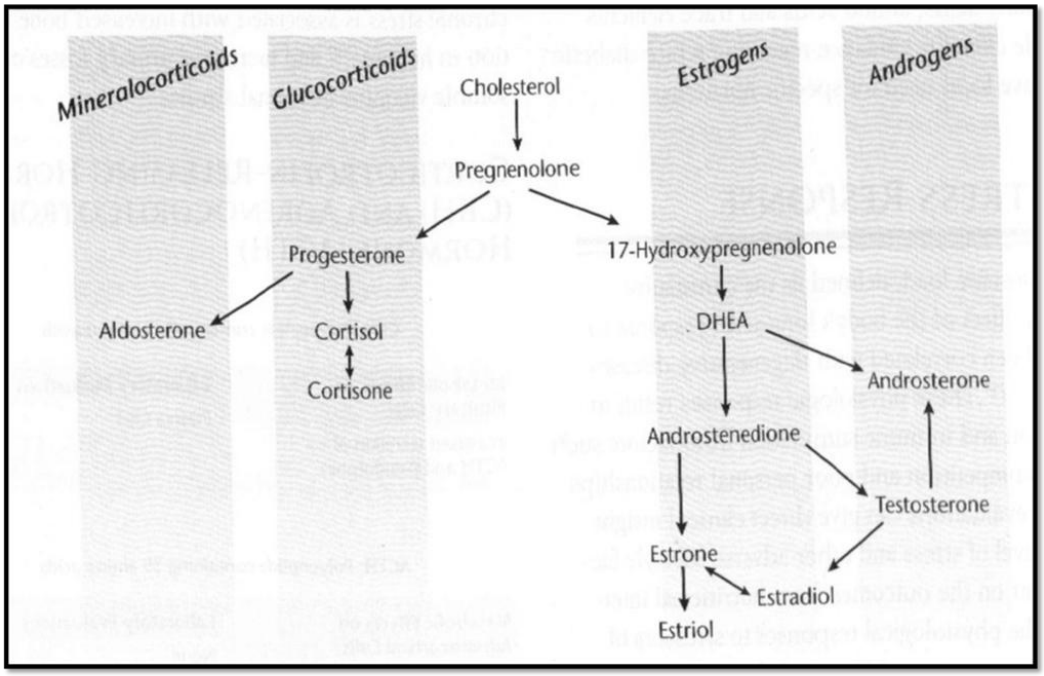
Steroid Hormone Biosynthesis Reactions

From a functional medicine perspective, you must always keep in mind that steroid hormone production is initiated by certain peptide hormones. For example, luteinizing hormone stimulates the production and secretion of progesterone and testosterone, and ACTH stimulates the production and secretion of cortisol. All human steroid hormones are synthesized from cholesterol. Although most cells can manufacture cholesterol, a significant percentage of cholesterol for the production of steroid hormones comes from the low-density lipoproteins in the circulation plasma. Once cholesterol has entered the cell (or is produced *de novo* from acetyl coenzyme A), two main organelles are responsible for steroid hormone synthesis; the mitochondria and the endoplasmic reticulum.

The first reaction in converting cholesterol to steroids involves the cleavage of a 6-carbon group from the cholesterol and is the principle committing, regulated and rate-limiting step in steroid hormone synthesis. The enzyme system that catalyses the cleavage reaction is known as P450-linked side chain cleaving enzyme (P450ssc) or cholesterol desmolase, and is found in the mitochondria of steroid producing cells.[1] Once the cholesterol molecule is cleaved, it is transformed to the molecule pregnenolone. (Note: This is the rate limiting step in the formation of other hormones. Since this reaction takes place in the mitochondria, the effect of oxidative stress on hormone production becomes quite clear.)

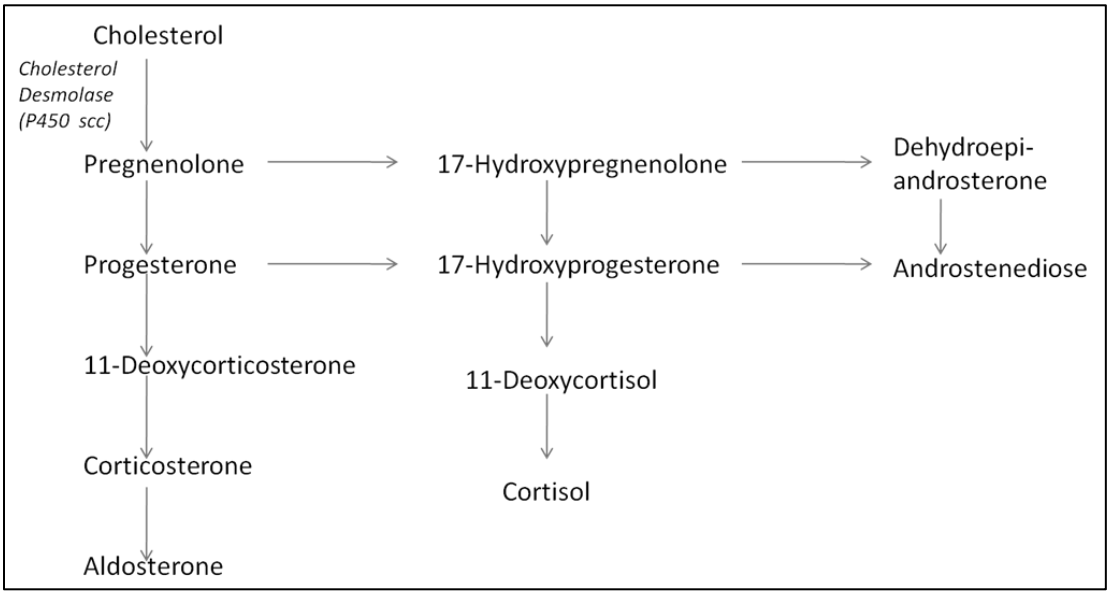
Biosynthesis of Steroid Hormones[3]

Four classes of steroid hormones are produced from cholesterol. The key intermediates are: pregnenolone, progesterone, and DHEA.



Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine; 2nd ed., Richard Lord, J. Alexander Bralley

The Pathway of Synthesis of Steroid Hormones by the Adrenal Glands



Functions of the Adrenal Steroid Hormones

Glucocorticoids – Without glucocorticoids, the body cannot survive even minor illnesses or physical or mental stress. This is due to the fact that the glucocorticoids, mainly cortisol, are involved in metabolism and utilization of proteins, fats and carbohydrates.

- Effect on Carbohydrate metabolism
  - Stimulation of gluconeogenesis (amino acids to glucose)
  - Decreased glucose utilization by the cells
  - Elevated blood glucose concentration ("adrenal diabetes") – caused by gluconeogenesis and reduced glucose utilization. The effect causes an increase in plasma insulin.
- Effect on Protein Metabolism
  - Reduction in cellular protein – caused by decreased protein synthesis and increased protein catabolism. Cortisol excess causes muscle atrophy.
  - Increased liver and plasma proteins
- Effect on Fat Metabolism
  - Mobilization of fatty acids – from adipose tissue
  - Enhanced oxidation of fatty acids (excess cortisol will cause increased oxidative stress through this mechanism)
  - Obesity caused by excess cortisol

Cortisol, Stress and the Immune System – Physical and psychological stress cause the release of ACTH which in turn causes the release of cortisol. The increased cortisol makes amino acids and fats available for the synthesis of other substances needed by the body under stress. Cortisol also has anti-inflammatory effects. The anti-inflammatory effects are as follows:

- Cortisol stabilizes the lysosomal membrane which causes a decrease in the release of proteolytic enzymes.
- Decease in capillary permeability
- Decrease in white blood cell migration to the affected area
- Suppresses the immune system – decreased lymphocyte production, especially T-lymphocytes
- Reduces fever by attenuating interleukin -1

Adrenal Androgens – The main adrenal androgen is dehydroepiandrosterone (DHEA). DHEA is the precursor to testosterone and the estrogens, therefore DHEA affects other hormone concentrations. DHEA is involved with development, growth, immune response (immune-modulating) and cardiovascular function.[3] DHEA is the most abundant steroid hormone in the body. DHEA has been shown to exert many of its effects via the androgen receptor and/or estrogen receptor after its enzymatic conversion to androgen or estrogen, although direct effects of DHEA on androgen and estrogen receptors have also be demonstrated.[4] DHEA receptors have been found on human muscle cells.[5]

Assessing DHEA status can be performed by evaluating blood, urine or saliva. Since the concentration of DHEA-sulfate in serum is about 1000 times the concentration of DHEA, DHEA-S has been used as the main serum analyte. Salivary DHEA concentrations have been shown to correlate with plasma levels; however these levels might be influenced by the level of hydration and saliva production.[5] Keep in mind that there is little research whether the concentrations of DHEA or DHEA-S reflect tissue concentrations of DHEA.[5]

Mineralocorticoids – Mineralcorticoids play a critical role in regulating the concentration of minerals, in particular sodium and potassium, in extracellular fluids. Aldosterone accounts for about 90 percent of all mineralocorticoid activity and its main target is the kidney. Other mineralocorticoids include desoxycorticosterone and corticosterone. The main regulators of aldosterone secretion are angiotensin II and the concentration of potassium ions in the extracellular fluid. (Increased potassium in the serum can stimulate aldosterone secretion.) Aldosterone increases renal tubular reabsorption of sodium and secretion of potassium. Excess aldosterone causes low serum potassium and therefore muscle weakness; low aldosterone causes an increase in serum potassium which is toxic to the heart.

Physiological Aspects of Cortisol and DHEA

The adrenal hormones cortisol and DHEA have genetic influence on the body, they penetrate cells and enter the nucleus, where DNA is unlocked and transcribed. Cortisol is the main hormone that directs immune function and its levels are tremendously valuable in assessing overall health. Cortisol and DHEA are also involved in carbohydrate, protein and fat metabolism; eicosanoid modulation; detoxification capacity; endocrine function; and the health of muscle, bone and neural tissues.

Maintaining physiological balance is an important aspect of vibrant health, and nowhere is this more evident when it comes to cortisol. 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.

The adrenal glands produce both cortisol and DHEA in the adrenal cortex under the stimulation of adrenocorticotropic hormone (ACTH), which is released by the pituitary gland. 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.

Optimal adrenal function exists when the ratio of cortisol to DHEA is in proper balance. When cortisol levels are elevated and DHEA is low we are considered to be in a Chronic Stress Response. 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.

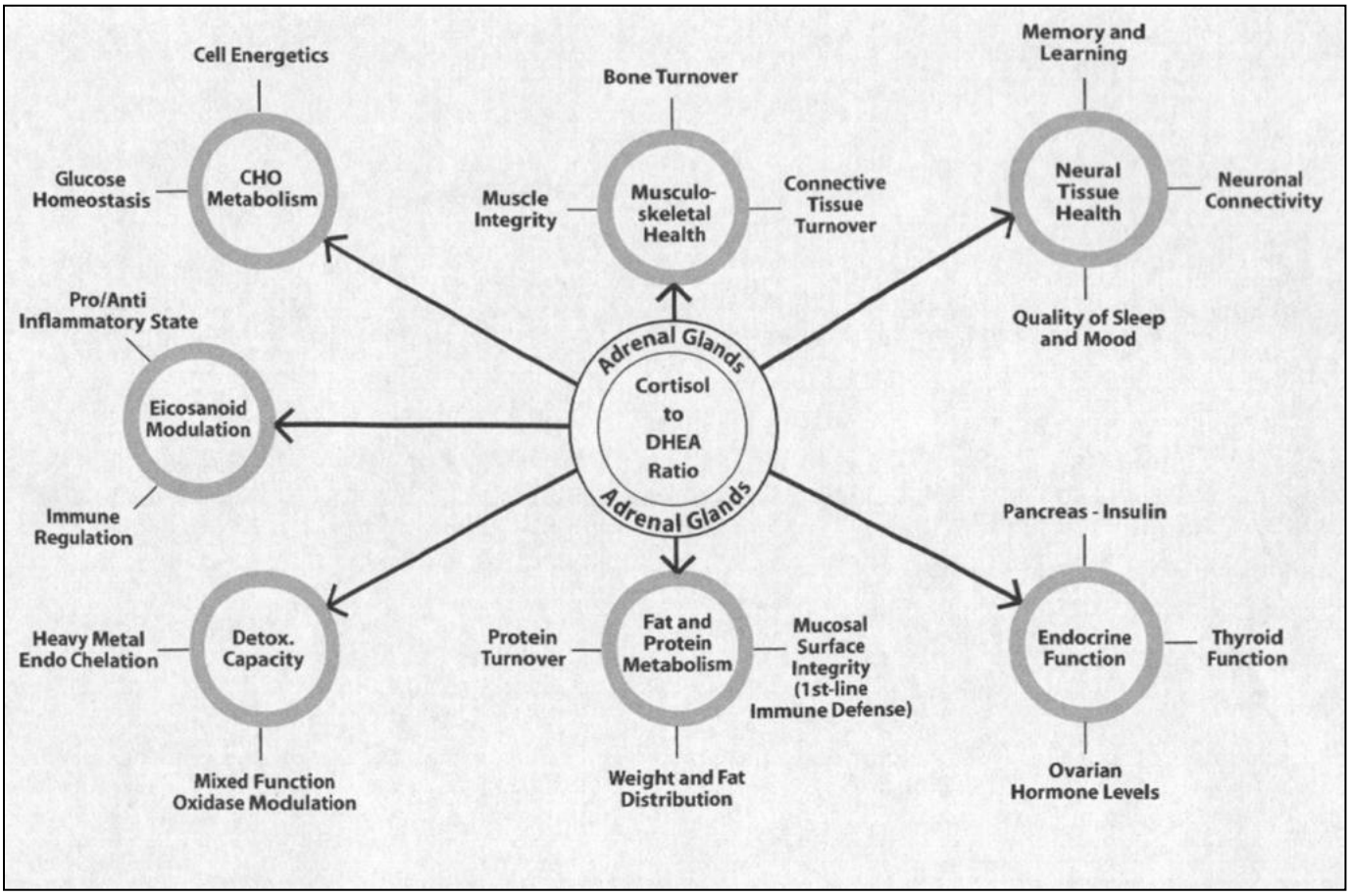
For example, if cortisol levels are too high at night, rather than getting the rest and recovery necessary to maintain optimal physical repair and psychic regeneration, the body will be in a catabolic state (high nighttime cortisol levels inhibit the release of growth hormone necessary to repair and rebuild body tissues). This high cortisol will also have a negative effect on brain function, memory, learning and mood. This is especially true if this condition is ongoing.

We all have noticed individuals who have excess fat around their hips, thighs or waist and yet they do not seem to be particularly overweight. In fact, these people may be slender except for those "problem" areas. More than making them uncomfortable wearing a bathing suit in public, this unsightly accumulation of fat is a telltale sign of adrenal dysfunction and hormone imbalance, specifically an elevated ratio of cortisol to DHEA.

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.

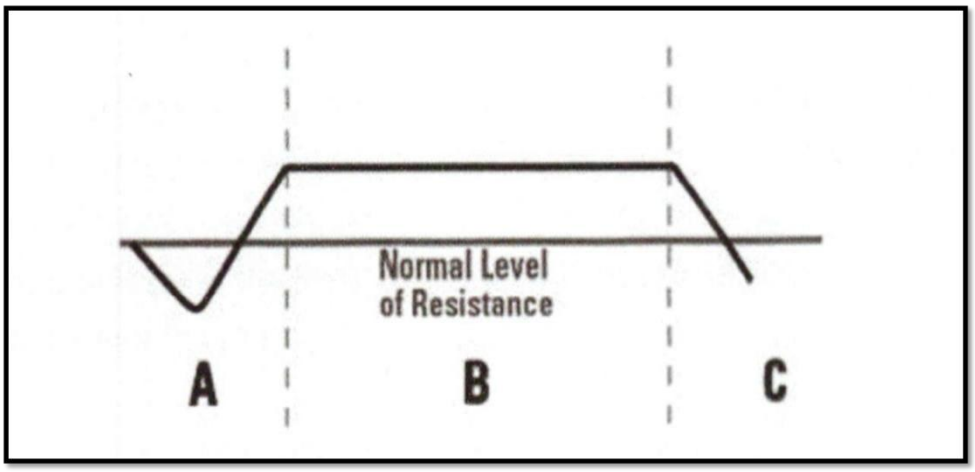


Ref: printed with permission: http://www.biodia.com/

The General Adaptation Syndrome

The scientist Hans Selye introduced the General Adaptation Syndrome model in the 1930's showing the three phases of the stress response. These phases include the [A] alarm phase (acute stress); the [B] resistance phase (chronic stress); and the [C] exhaustion phase (burnout). His theory suggested that stress is a major cause of disease because chronic stress causes long term chemical changes in the body.

[Keep in mind that stress is not limited to psychological factors. Stress includes any insult on the body such as chronic infections, environmental toxin exposure, malnutrition, pharmaceuticals and non-pharmaceutical agents, and trauma.]



The three phases of the general adaption syndrome (GAS)

A. *The Alarm Phase (Acute Stress)* – This phase is the body's first response to stress. The body recognizes a threat and prepares to deal with it. This is the flight or fight response. The limbic system is activated which in turn activates the HPA axis and the sympathetic nervous system. This stimulation the release of the main stress hormones (epinephrine, norepinephrine and cortisol) to provide instant energy for the body. Once the stress has been eliminated, the body needs to rest in order to maintain a normal level of response, in other words, to recharge itself. The typical recovery phase can last for 24 to 48 hours. The alarm phase is considered dysfunctional if there is not appropriate hormonal release during this phase. Prolonged alarm phase may be associated with weight loss, gastric ulcer or immunosuppression to name a few.

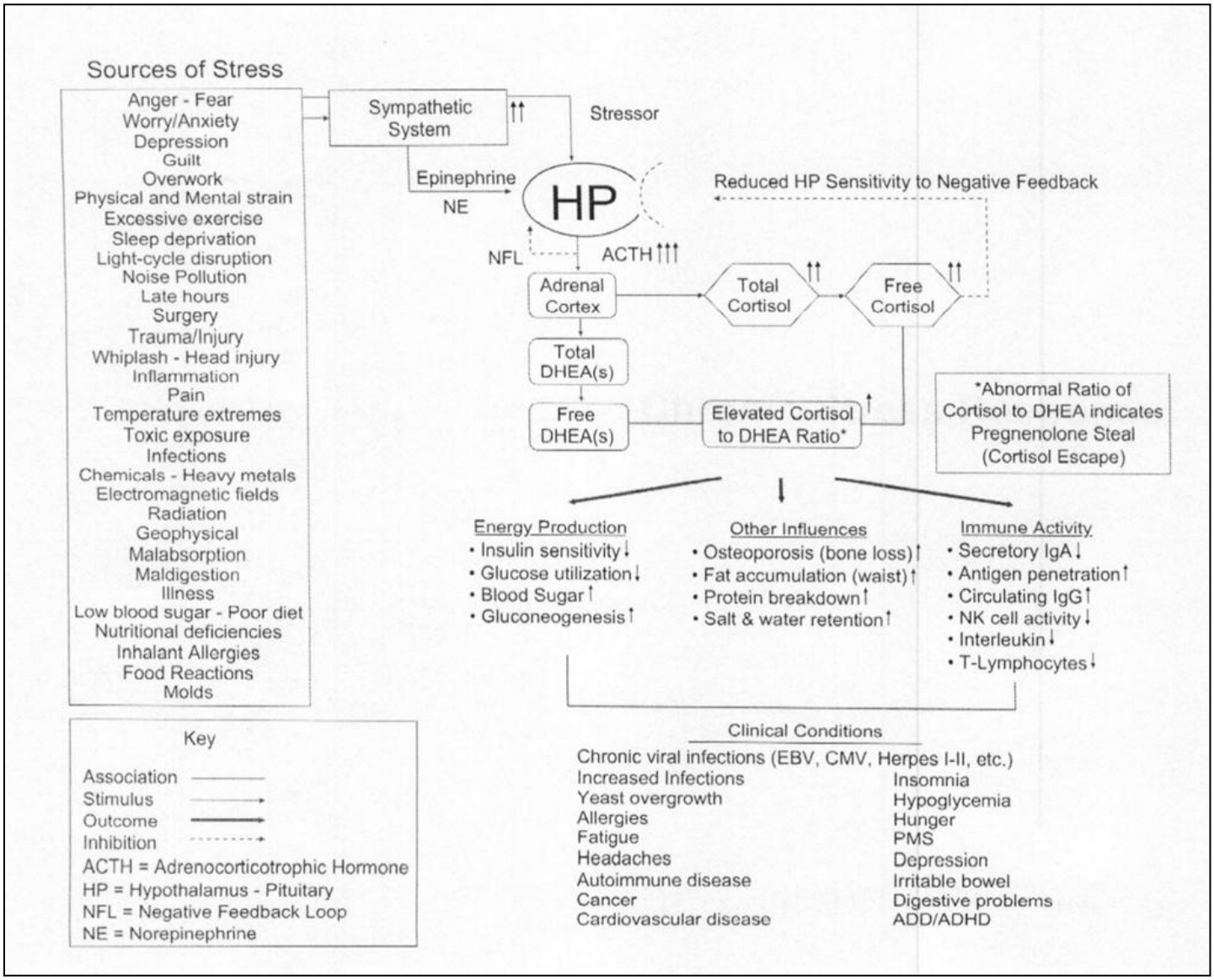
B. *The Resistance Phase (Chronic Stress)*- During this phase the perceived stressors remain. The person is still reacting to the stresses, however the physical signs and symptoms usually differ from the alarm phase. Chronic stress may lead to weight gain, opportunistic infections allergies, arthritis, autoimmune disease, insulin resistance, hypertension and cardiovascular disease.

C. *The Exhaustion Phase (Burnout)* – Chronic stress will eventually lead to adrenal exhaustion, which will result in a deficiency of the adrenal hormone production. Keep in mind that once cortisol production and secretion is low, all other hormones become imbalanced. Also keep in mind that adrenal glands also produce DHEA from pregnenolone, which is the precursor to progesterone and cortisol. Increased demand for cortisol will result in a shift of hormone production away from DHEA. DHEA is the precursor to testosterone and the estrogens. DHEA is involved with development, growth, immune response and cardiovascular function. Insufficient DHEA contributes to fatigue, loss of muscle mass and therefore loss of strength, depression, impaired immune function and decreased libido**.**

The symptoms of adrenal exhaustion include:

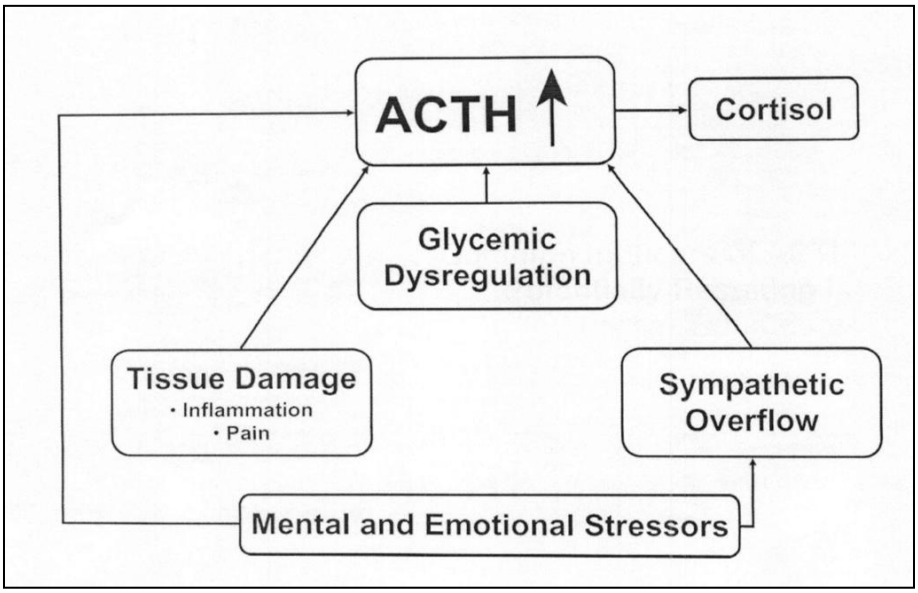
- Anxiety
- Fatigue (extreme)
- Depression (due to hormonal imbalance)
- Insomnia (the body may produce adrenaline in adrenal exhaustion in an attempt to compensate for low cortisol, which leads to insomnia)
- Body aches
- Increased chemical sensitivity
- "New" allergies
- Increased susceptibility to infections
- GI dysfunction
- Increase in VAT (visceral adipose fat tissue)
- Craving for salty foods and sweets
- Reproductive hormone imbalance symptoms
- Thyroid dysfunction (increased levels of cortisol block the peripheral conversion of T4 to T3

Overview of the Chronic Stress Response



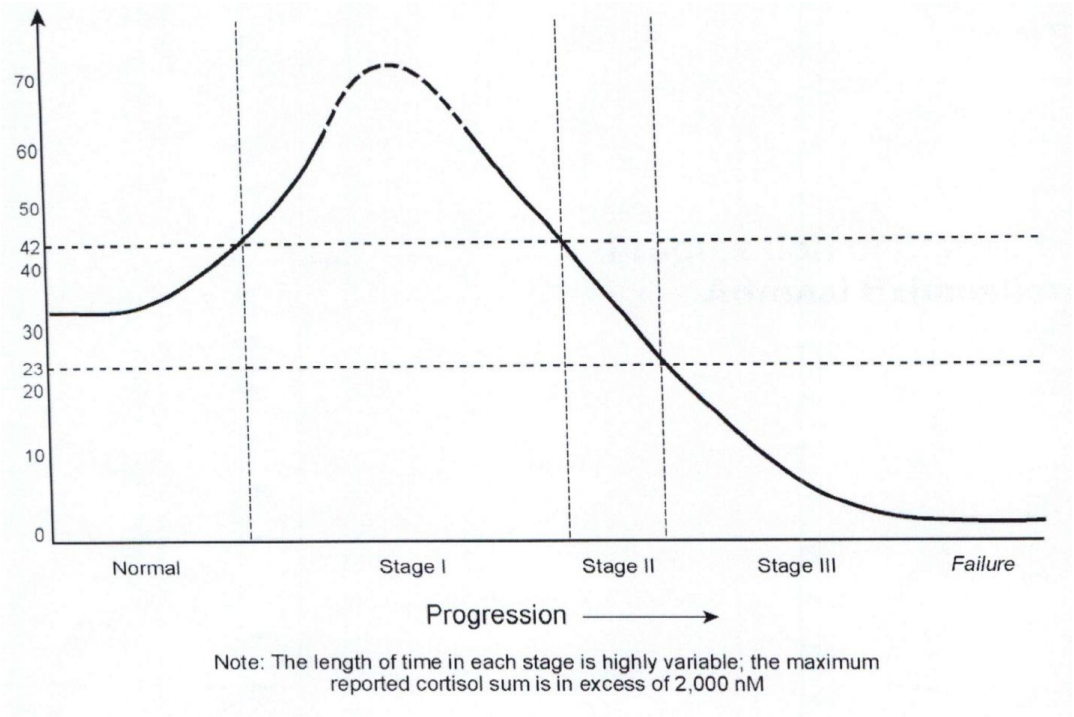
Ref: printed with permission: http://www.biodia.com/

Common Inducers of ACTH Potentially Resulting in Adrenal Exhaustion



Ref: printed with permission: http://www.biodia.com/

The Physiological Stages of Adrenal Exhaustion



Ref: printed with permission: http://www.biodia.com/

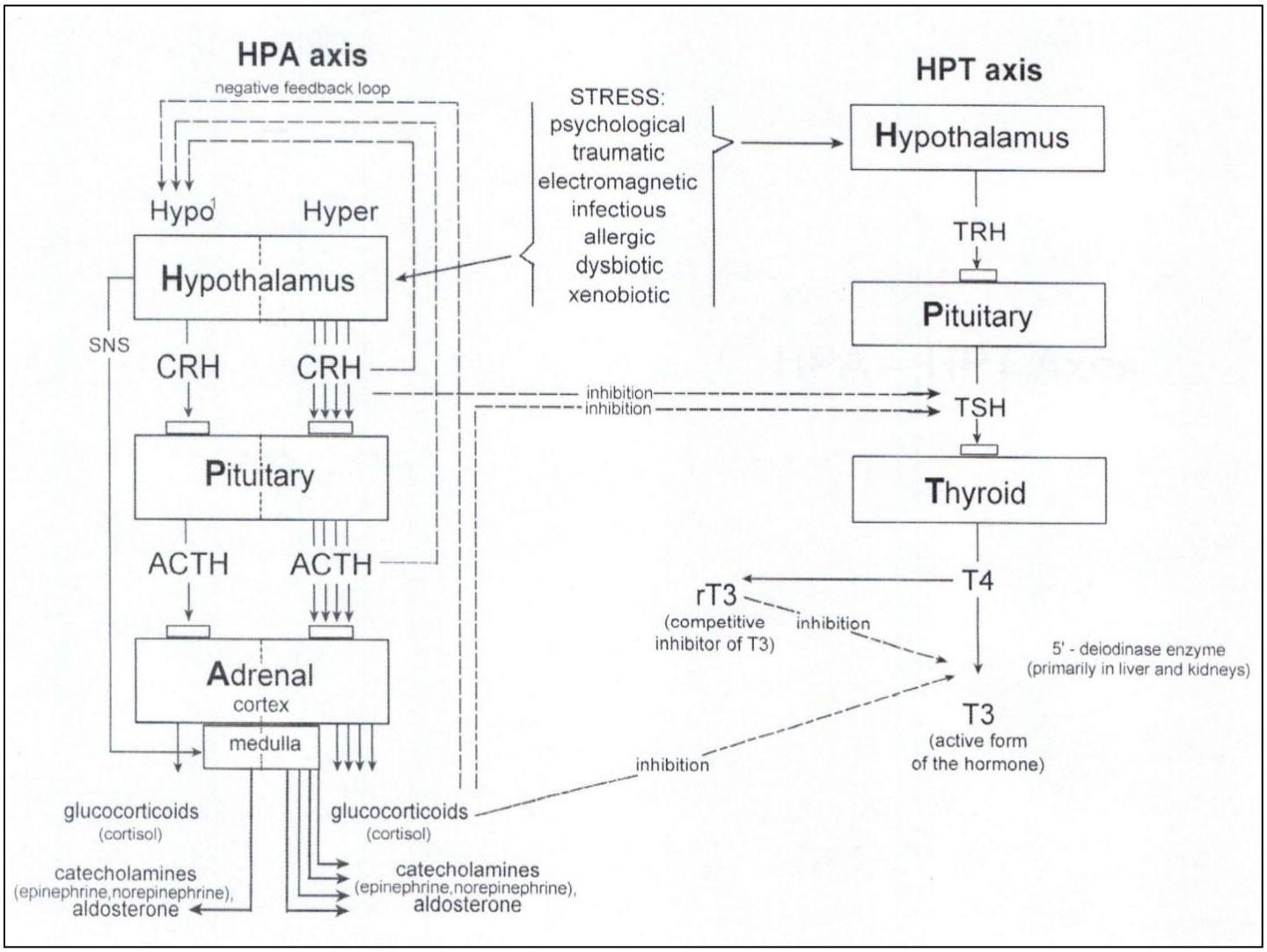
Adrenal exhaustion progresses in three stages.

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.. When in a Chronic Stress Response, pregnenolone, the common precursor to cortisol, DHEA and other hormones is preferentially diverted to cortisol production at the expense of the rest of the steroidal hormones . Generally in Stage I cortisol increases and DHEA and its metabolites decrease or an imbalance occurs especially between testosterone and estrogen.

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 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.

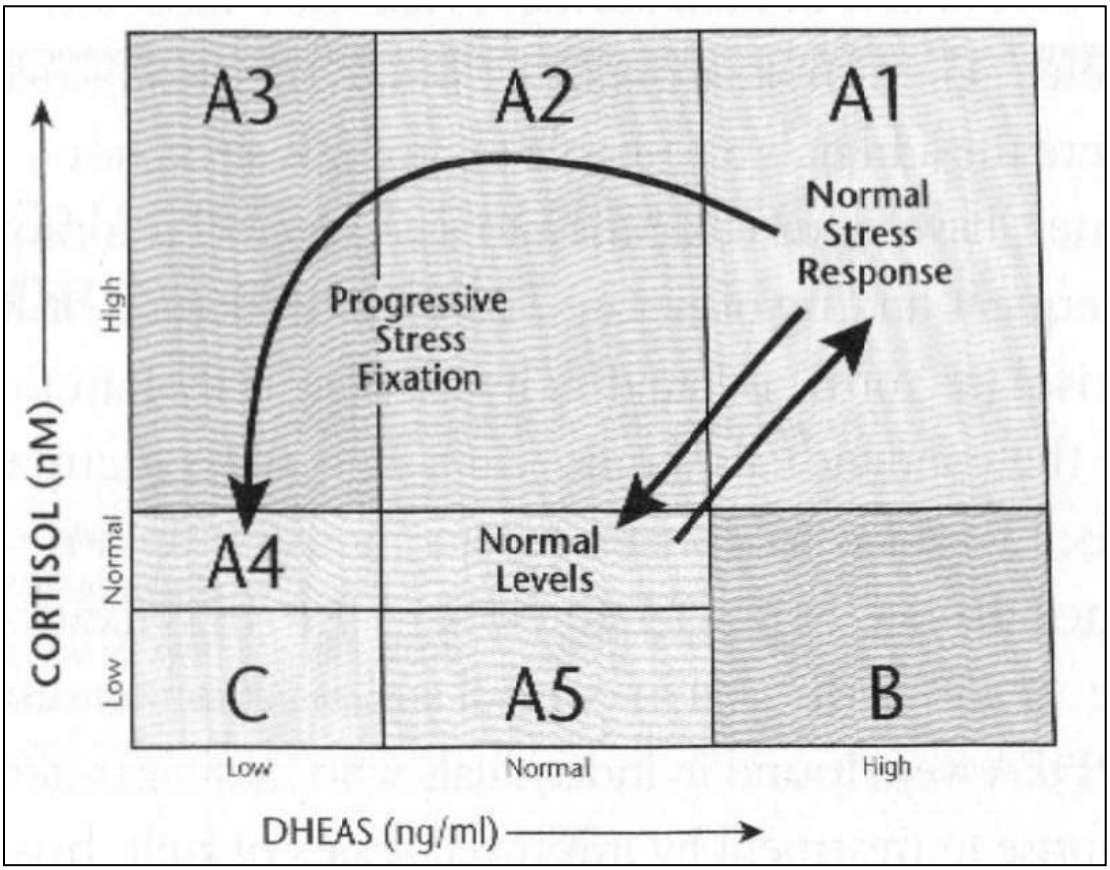
HPA-HPT Axes



Ref: printed with permission: http://www.biodia.com/

Patterns of Adaptive Responses

The adrenal glands normally produce more DHEA than cortisol. Cortisol and DHEA affect carbohydrate metabolism, protein metabolism and lipid metabolism. They also serve as anti-inflammatory agents, modulate thyroid function, and increase resistance to stress. Therefore, fluctuating amounts of DHEA and cortisol may signal important alterations in adrenal function that can profoundly affect individual's energy levels, emotional state , disease resistance and sense of well being.[3] The entire process is illustrated graphically below.



Reprinted with permission: Laboratory Evaluations for Integrative and Functional Medicine; 2nd ed., Richard Lord, J. Alexander Bralley

[The values that are plotted are the average of noon and 5 pm levels for salivary cortisol and DHEA. The quadrants represent normal and abnormal patterns, with A1 to A4 representing progressive failure of the normal ACTH response.]

- **A1** – A1 represents the normal initial stress response pattern. With a normal functioning of the HPA axis and low physiological or psychological stress, the cortisol and DHEA levels should return to normal with proper rest and nutrition. As higher cortisol is required to shut down the adrenal responses and bring ACTH into a normal range, the negative feedback of cortisol on the hypothalamus is lost.[3] The resulting condition, known as "physiological hypercortisolemia", affects enzymatic activities and leads to central adiposity.[3]

- **A2 – A5 (Progressive Stress Fixation) –** These phases represent a compensation response to continued stress. As the cortisol remains high the DHEA output falls from high to normal to low. (Note that a normal DHEA salivary test result does not mean the adrenal glands are not under stress) The low levels of DHEA contribute to such conditions as osteopenia, loss of lean muscle mass, and increased body fat. Sector A5 indicates a low reserve of both hormones and a non-adaptive state to stress. With continued stress the person falls into sector C.

- **Sector C (Adrenal Fatigue) –** Prolonged stress will cause the production of both hormones to decrease. Persons with Addison's disease fall into this sector.

- **Sector B -** Sector B is marked by an elevation in DHEA and a low to normal cortisol. This test result is uncommon and indicates a hypothalamic dysfunction. (Note a low stress occupation is recommended)

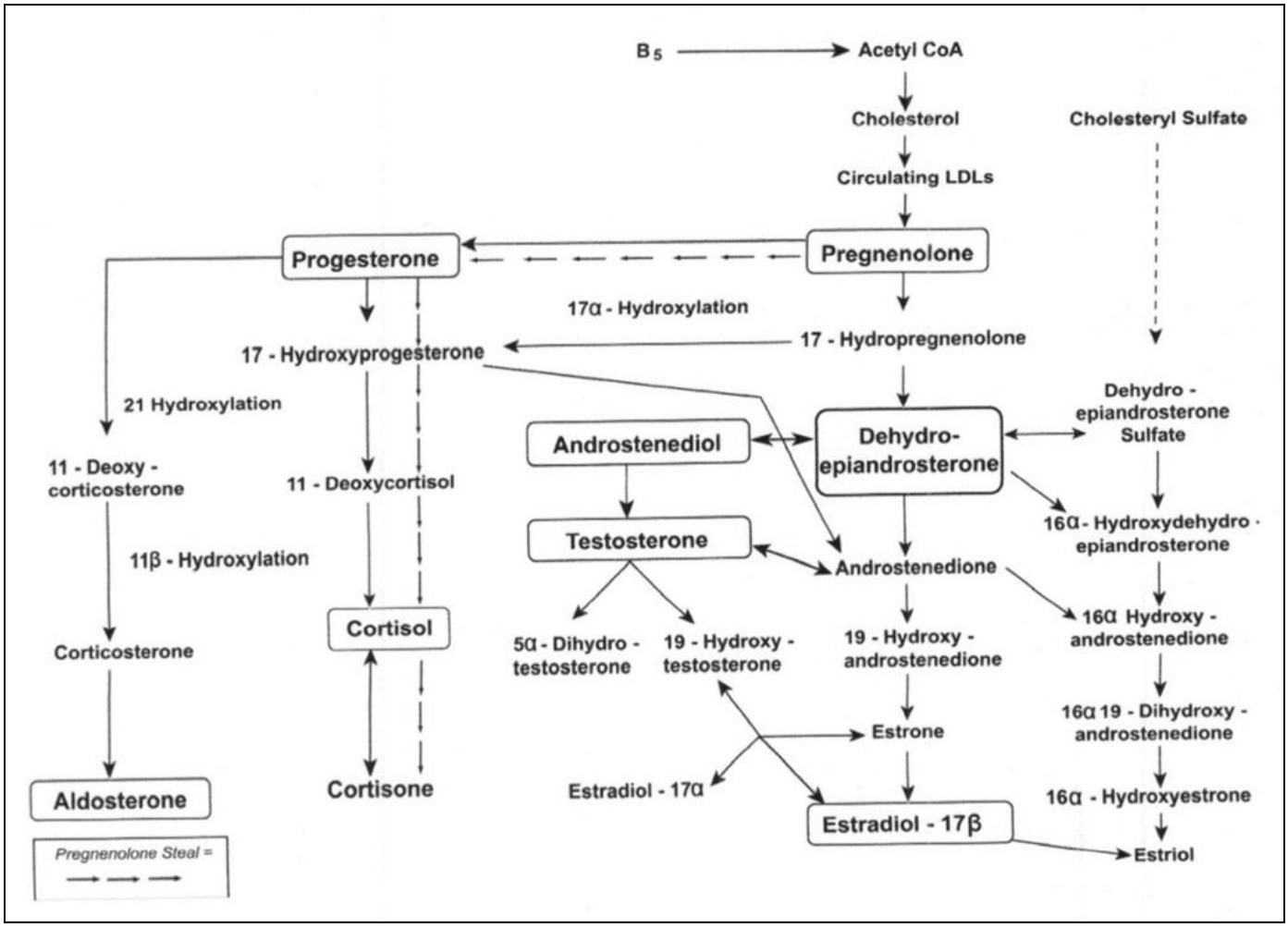
[Clinical Pearl: DHEA increases 10% after exercising]

Markers of Stress

- *Secretory IgA* – sIgA forms the immune barrier of the gastrointestinal system. Chronic stress decreases the production of this immunoglobulin and therefore, can be used as a biomarker of stress. The measurement of sIgA as a biomarker for the functional impact of chronic stress greatly enhances the interpretation of stress hormones because single-point elevation of cortisol may only be a normal temporary stress response.

- *Antigliadin Antibodies* – Chronic stress can lead to gluten sensitivity and gluten sensitivity can lead to adrenal stress. Detection of IgA-class antigliadin antibody provides an immunohistochemical marker of celiac disease latency and gluten sensitivity.

Steroidal Hormonal Principle Pathways



Ref: printed with permission: http://www.biodia.com/

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 steroid hormones is diverted to cortisol and cortisone. This is at the detriment of all the other steroid hormones as you can see by the above illustration. As pregnenolone is diverted to cortisol-cortisone, DHEA depletion begins.

Some labs test the hormone 17-Hydroxyprogesterone along with cortisol, DHEA and other stress biomarkers. 17-hydroxyprogesterone evaluates the efficiency of the conversion of the adrenal precursors to cortisol. Certain adrenal fatigue patients who are genetically predisposed to low production of cortisol will not benefit from exogenous supplementation of pregnenolone or progesterone. Evaluating the level of 17-Hydroxyprogesterone allows for the identification of the subpopulation of maladapted and adrenal fatigue individuals who show impaired conversion to cortisol.

The normal cortisol to DHEA ratio is 5:1 to 6:1

This ratio is obtain by dividing the total salivary cortisol (the four reading) by the total DHEA

Signs and Symptoms of High Cortisol

- Difficulty losing weight
- Frequent colds
- Frequent infections

Signs and Symptoms of inability to secrete adequate cortisol

- Inflammatory disease
- Autoimmune disease
- Allergies

Signs and Symptoms of Adrenal Resistance Phase and Adrenal Exhaustion Phase

Sign/Symptom	Adrenal Resistance Phase (high cortisol)	Adrenal Exhaustion Phase (low cortisol)
Blood Pressure	Tends to be high	Low
Skin	Acne (increased sweat/oil)	Dry (low sweat even with increased ambient temperatures)
Blood glucose	High (insulin resistance)	Low (hypoglycemic)
Body weight	Truncal obesity	Sarcopenic obesity (low muscle mass)
Cholesterol/triglycerides	Increased triglycerides	Low cholesterol

Signs and Symptoms of Adrenal Dysfunction Compared to Thyroid Dysfunction

The reduction of metabolic energy is associated with both thyroid and adrenal hypofunction. There is often a mix of signs and symptoms of both adrenal and thyroid dysfunction. It is important to recognize and treat adrenal dysfunction if is exist first. Excess cortisol inhibits the peripheral conversion of T4 to T3 and increases corticotrophin releasing hormone, which inhibits TSH. Without evaluating for adrenal dysfunction, thyroid dysfunction will be difficult to manage due to the hormone interplay.

Sign/Symptom	Thyroid Dysfunction (Low)	Adrenal Dysfunction (Low)
Cholesterol	High	Low
Energy level	Low	Wired/tired
Body type	Difficulty losing weight	Difficulty gaining weight
Body temperature	Low and stable	Low and unstable

Patterns of Primary Blood Testing Associated with Adrenal Dysfunction

- Adrenal Hypofunction
  - Potassium: increased
  - Sodium: normal to decreased
  - Chloride: normal to decreased
  - Glucose: decreased
  - Renin: increased (plasma renin) (Persons with Addison's disease are hyponatremic, which is a strong stimulant to renin production.
  - Aldosterone: decreased

- Adrenal Hyperfunction
  - Potassium: decreased
  - Sodium: normal to increased
  - Chloride: normal to increased
  - Renin: decreased(plasma renin)
  - Aldosterone: increased

Ref: Balancing Blood Chemistry with Nutrition, 2007, Dr. Harry Eidenier

Hormonal/Nutritional/Herbal Considerations

- Adrenal Glandular Extracts – provides nutrient and small amounts of adrenal hormone
- Melatonin –may help with insomnia
- DHEA – used to support hormonal precursors and act as a cortisol antagonist
- Pregnenolone – precursor to DHEA
- Cortisol – important to consider for extremely low cortisol and/or low 17-Hydroxyprogesterone
- Vitamin C – needed for hormonal production and as an antioxidant
- Vitamin E – antioxidant
- Pantothenic Acid – need for the production of Acetyl CoA, which is used for energy production, as well as the production of cholesterol.
- Pyrioxal-5-Phosphate – B6 is a cofactor in many enzymatic reaction, as well as participating in metabolism of poly unsaturated fatty acids and homocysteine metabolism
- Magnesium – need for cellular energy production
- Calcium
- Essential fatty acids
- Phosphatidyl Serine – appears to lower excessive cortisol
- Ashwagandha – supports HPA axis
- Licorice root – increases cortisol/ mineralocorticoids-like activity (use caution in patients with hypertension)
- Korean ginseng – used to balance HPA axis
- Panex ginseng

Summary

Diseases of the adrenal cortex fall into two main categories: Hypofunction and Hyperfunction. Common causes of adrenal hypofunction include: autoimmune disease, as in Addison's disease; tumors; infection (TB); abrupt withdrawal of long-term steroids; surgery; and chronic or extreme acute stress. The etiology of adrenal hyperfunction is generally attributed to long term steroid use, stress and tumors. Primary aldosteronism , also known as Conn's disease, is an adrenal disorder that causes excessive aldosterone to be produced and secreted by the adrenal glands. Secondary aldosteronism is caused by excess renin production by the kidneys. Cushing's syndrome (hypercortisolemia) results from excess production of cortisol. Cushing's syndrome can develop from taking high dosages of corticosteroid, pituitary tumor, ectopic ACTH-secreting tumor, primary disease of the adrenal glands and rarely, a genetic predisposition.

From a functional medicine perspective, it's paramount to remember the steroidal hormonal pathways when assessing adrenal hormone dysfunction. Adrenal dysfunction can affect thyroid hormone and reproduction hormone balance. Adrenal gland health must be optimal to achieve an optimal result when addressing other hormonal imbalances.

References

1. http://themedicalbiochemistrypage.org/
2. Textbook of Medical Physiology, 11th ed., Guyton and Hall
3. Laboratory Evaluations for Integrative and Functional Medicine; 2nd ed., Richard Lord, J. Alexander Bralley
4. *Does DHEA Exert Direct Effects on Androgen and Estrogen Receptors, and Does it Promote or Prevent Prostate Cancer?*, Julia T. Arnold, Marc R. Blackman, Endocrinology 2005 146:4565-4567, doe: 10/121-/en.2005-0901
5. Nutritional Medicine, 2011, Alan R. Gaby, MD
6. Balancing Body Chemistry with Nutrition, 2007, Dr. Harry Eidenier