

# **Functional Medicine University's Functional Diagnostic Medicine Training Program**

## **INSIDER'S GUIDE #11 THE ENDOCRINE SYSTEM: ADRENALS, THYROID, PARATHYROID & SEX HORMONES**

**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**

<b>The Focus of this Insider's Guide.....</b>	<b>13</b>
Upon completing this module you will have: .....	13
<b>The Components of the Endocrine System .....</b>	<b>13</b>
<b>The Endocrine System.....</b>	<b>14</b>
What is a hormone?.....	14
What types of hormones are there?.....	14
What are the functions of the different types of hormone? .....	17
How do hormones exert their effect? .....	19
What are cell surface receptors and second messenger systems? .....	20
Cell surface receptors .....	20
G Protein Linked Receptors .....	20
Non-G protein coupled receptors .....	21
cAMP .....	22
IP3 and DAG .....	23
Calcium .....	23
What are intracellular receptors? .....	23
<b>The Journey of the Endocrine System .....</b>	<b>25</b>
Hypothalamus-Pituitary-Adrenal (HPA) axis .....	25
The Pituitary Gland .....	25
The Hypothalamo-adenohypophysial System .....	26
Adrenocorticotrophic Hormone (ACTH).....	27
Thyroid Stimulating Hormone (TSH)/Thyrotrophin.....	27
Growth Hormone(GH)/Somatotrophin .....	27
Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).....	28
Prolactin (PRL) .....	28
What does the Neurohypophysis do? .....	29
Vasopressin .....	29
Oxytocin .....	30
<b>The Parathyroids .....</b>	<b>31</b>
Anatomy and Physiology of the Parathyroid Glands.....	31
Nerve supply .....	31
What do the Parathyroids do? .....	31
What does parathyroid hormone do? .....	31

Calcitonin .....	32
Why is calcium regulation important? .....	33
<b>Assessing Parathyroid Dysfunction .....</b>	<b>33</b>
Signs and Symptoms of Parathyroid Dysfunction .....	33
High Blood Calcium Levels (Hypercalcaemia)? .....	33
Low blood calcium (hypocalcaemia)? .....	34
Assessing the Parathyroids: Blood Testing .....	34
Alarm Range .....	34
Calcium .....	34
PTH .....	34
The Calcium - PTH Relationship .....	35
Clinical Implications .....	35
Parathyroid Hyperfunction .....	35
Pattern .....	35
Parathyroid Hypofunction .....	36
Pattern .....	36
<b>The Thyroid .....</b>	<b>37</b>
Physiology and Biochemistry of the Thyroid .....	37
Review of thyroid hormones .....	37
A summary of TSH Function .....	39
A summary of the regulation of thyroid hormone .....	39
A brief look at the physiology of each of the different hormones .....	40
T4 .....	40
T3 .....	41
Reverse T3 .....	42
Summary of Thyroid Hormone Physiology .....	42
Thyroid Binding Proteins .....	44
Factors affecting peripheral metabolism of thyroid hormone .....	44
Factors associated with an increased reverse T3 level .....	46
Is it necessary to measure reverse T3? .....	46
rT3 and Basal Body Temperature Testing .....	46
Factors that increase the conversion of T4 into T3 .....	46
Summary .....	47
<b>Assessing For Thyroid Dysfunction .....</b>	<b>48</b>
Signs and Symptoms of Thyroid Dysfunction .....	48

Signs and Symptoms of Low Thyroid Hormone Production .....	48
Signs and Symptoms of High Thyroid Hormone Production .....	49
Assessing the Thyroid: Physical Examination Techniques .....	49
Palpating the thyroid gland.....	49
The Achilles Return Reflex.....	50
Directions .....	50
Results .....	50
Interfering factors.....	50
Assessing the Thyroid: In-Office Testing .....	50
The Iodine Patch Test .....	50
Functions of Iodine .....	51
Results .....	51
When would you run this test?.....	51
Clinical implications .....	51
Assessing the Thyroid: A Take Home Test.....	51
Body Temperature Test .....	51
When would you run this test?.....	52
Taking and Plotting Temperatures.....	52
What kind of thermometer do you recommend?.....	52
Directions of how best to take temperatures: .....	52
Recording Temperatures on a Graph .....	53
Interpreting the Temperature Graph .....	53
Stable but low temperatures on graph .....	53
Considerable variability and instability on graph- Sharp and Spiky.....	53
Rising in average temperatures on graph- stable or unstable.....	53
Increase in variability- an expansion pattern .....	53
A contracting/Rising pattern – a sign of improvement .....	54
Using the Graph to Monitor Thyroid Therapy.....	54
Using the Graph to Monitor Adrenal Therapy .....	54
A Question of Timing .....	55
Form Download .....	55
Assessing the Thyroid: Blood Testing.....	57
Functional Analysis of Thyroid Dysfunction.....	57
Primary Hypothyroidism .....	57
Pattern .....	58

Secondary Hypothyroidism.....	58
Pattern .....	58
Tertiary Hypothyroidism.....	58
Problems using TSH alone as a marker for Hypothyroidism .....	58
Euthyroid Sick Syndrome .....	59
Low T3 Syndrome .....	59
Euthyroid Sick Syndrome and T3 Syndrome Pattern- Pattern .....	59
Low Body temperature- Wilson's Thyroid Syndrome.....	59
Hyperthyroidism- Pattern.....	60
Iodine Insufficiency .....	60
Selenium Deficiency .....	60
The Functional Thyroid Scale .....	60
Normal versus Optimal in terms of the thyroid lab values.....	61
The Functional Thyroid Scale .....	61
What lab tests do you need to use the Functional Thyroid Scale?.....	61
This is what the Functional Thyroid Scale looks like:.....	62
How to use the scale .....	62
Hyperthyroidism .....	63
Adrenal Fatigue.....	63
Thyroid Hormone Interpretation.....	64
Adrenal Fatigue.....	64
Primary Hypothyroidism .....	64
Hypothyroid due to Pituitary dysfunction .....	65
Hypothyroid and Adrenal Fatigue.....	65
Poor ATP Production .....	65
Iodine Insufficiency .....	65
Selenium Deficiency .....	65
Auto-Immune Thyroiditis.....	66
Hashimoto's Disease .....	66
Late stage Hashimoto's Disease .....	67
Grave's Disease.....	67
Different Types of Grave's Disease .....	67
A diagnosis of Graves: .....	68
How do we know if a patient has Hashimoto's or Graves? .....	68
<b>Treating the Thyroid.....</b>	<b>70</b>

Thyroid Repair – The Basics .....	70
Foods to Support Thyroid Function .....	70
Foods to Lower Thyroid Function .....	70
Other Therapies .....	70
Some Nutrients/Supplements to Consider .....	71
Thyroid Repair and Medication .....	71
T4 Medications .....	72
T3 Medications .....	72
Desiccated Thyroid Hormone Medications .....	72
Thyroid Medication and Thyroid Tests .....	73
Compounded Thyroid Medication .....	73
What to do if the reverse T3 is elevated? .....	73
Some of the common causes of an increased reverse T3 include: .....	73
Consider the following if you see a high reverse T3 and thyroid symptoms exist: ..	74
Positive Thyroid Antibodies .....	74
<b>The Adrenals .....</b>	<b>75</b>
Physiology and Biochemistry of the Adrenals .....	75
The cortex consists of three distinct zones. ....	75
Nerve supply .....	76
What do the adrenal glands do? .....	76
Adrenals - The Cortex .....	76
Cortisol: Zona fasciculata .....	77
Summary of the Functions of Cortisol Include: .....	77
Aldosterone: Zona glomerulosa .....	79
Functions of aldosterone include: .....	79
Summary of the Functions of Aldosterone .....	79
Regulation of Blood Pressure .....	80
Sex steroids: Zona reticularis .....	80
DHEA .....	81
Functions of DHEA include: .....	81
The Adrenal Glands and Stress – An Epidemic of Giant Proportions .....	81
Stress comes in many forms: .....	82
Clinical and Sub-Clinical Stressors .....	82
Sources of Chronic Stress .....	83
Environmental Toxins .....	83

Heavy Metals .....	84
Viruses .....	85
Infections of the GI Tract.....	86
The Challenge of Parasitic Pathogens .....	86
Oral Infections.....	86
Mold and Mycotoxins .....	87
The Stress Response: The Real Story .....	87
Catecholamines.....	87
Physiologic Effects of Catecholamines .....	88
Summary of Catecholamine Activity in the Body.....	89
Cortisol .....	89
Physiologic Effects of Cortisol.....	89
Summary of Cortisol Activity in Body .....	91
The Stress Response Gone too Far! .....	91
Stress-Related Diseases and Conditions .....	92
The Hypothalamic-Pituitary-Adrenal Axis: The Conductor of Homeostasis.....	93
The Disharmony of Cortisol and DHEA.....	94
Ratio of Cortisol to DHEA.....	96
Pregnenolone Steal or Cortisol Escape .....	97
The Steroid Hormone Pathways.....	97
Beyond Cortisol.....	98
The Stages of the Stress Response.....	98
The Alarm Reaction.....	98
The Compensation Stage Moving Towards Decompensation (Adrenal Hyperfunction) .....	99
The Fatigue Stage (adrenal hypofunction) .....	99
Summary of the Stages of Adrenal Exhaustion.....	100
Stage I .....	100
Stage II .....	100
Stage III .....	101
<b>Assessing Adrenal Function.....</b>	<b>102</b>
Signs and Symptoms of Adrenal Dysfunction.....	102
Signs and symptoms of Adrenal Hyperfunction.....	102
Signs and Symptoms Adrenal Hypofunction/Insufficiency and of a decreased Cortisol/DHEA ratio .....	103
Assessing the Adrenals: Physical Examination Techniques.....	104

Ragland's Postural Hypotension Test .....	104
Discussion .....	104
Directions .....	104
Results .....	105
Clinical implications .....	105
Interfering Factors .....	105
Paradoxical Pupillary Response Test.....	106
Discussion .....	106
Directions .....	106
Results .....	106
Clinical implications .....	106
Interfering Factors .....	106
Reflex Testing .....	107
Sargent's White Line .....	107
Assessing the Adrenals: In-Office Testing .....	107
Urinary Adrenal Stress Test (Koenisburg Test, Urinary Chloride Test) .....	107
Discussion .....	107
Directions .....	108
Description of the test.....	108
Results .....	108
Clinical implications .....	109
High Urine Chloride.....	109
Low Urine Chloride .....	109
Assessing the Adrenals: Blood Testing .....	109
Serum Potassium and Sodium.....	109
Adrenal Hypofunction/Insufficiency.....	109
Adrenal Hypofunction- Pattern .....	109
Adrenal Stress .....	110
Adrenal Stress Pattern .....	110
Advanced FDM Testing and Treatments .....	110
<b>SPECIAL TOPIC: Assessing Metabolic Energy Problems.....</b>	<b>111</b>
Using the Metabolic Symptom Survey .....	111
Signs and Symptoms of Thyroid and Adrenals .....	112
Weight Gain.....	112
Poor connective tissue .....	112



Digestion - Thyroid .....	112
Bowel Function .....	112
Digestion – Adrenals .....	112
Bowel Function .....	112
Blood Sugar Control- Adrenals .....	113
<b>The Female Endocrine System .....</b>	<b>114</b>
Physiology and Biochemistry of the Female Endocrine System and Female Hormone Metabolism .....	114
Steroidal Hormone Pathways.....	115
Estrogen Synthesis .....	116
Effects of estrogens on female physiology .....	117
Role of Estrogen.....	117
Role of Progesterone.....	117
Effects of progesterone on female physiology .....	118
The Metabolism of Estrogen .....	118
<b>Assessing the Female Hormonal System .....</b>	<b>120</b>
Signs and Symptoms of Female Endocrine Dysfunction .....	120
Assessing the Female Endocrine System: Physical Examination Techniques .....	121
Assessing the Female Endocrine System: Blood Testing.....	122
Estradiol Reference ranges.....	122
Normal reference range.....	122
Optimal reference range .....	122
Clinical Implications.....	122
Low levels of Estradiol .....	122
Osteoporosis and Bone Fractures .....	122
Migraine Headaches .....	122
Increased Levels of Estradiol.....	123
The Asian Advantage .....	123
Free Testosterone reference ranges.....	124
Effects of testosterone on female physiology .....	124
Normal reference range.....	124
Optimal reference range .....	124
FSH and LH Testing.....	124
Advanced FDM Testing .....	125
Estrogen Metabolism Testing.....	125

Background .....	125
Who should have this test? .....	125
Metabolites Tested .....	125
Treatment Options.....	125
Who does this test? .....	125
<b>The Male Endocrine System.....</b>	<b>127</b>
Physiology and Biochemistry of the Male Hormonal System.....	127
What is testosterone? .....	127
What happens to testosterone levels over the course of a man's lifetime? .....	127
Male Hormone Imbalance .....	127
Testosterone and Male Hormone Physiology .....	128
Testosterone .....	128
Dihydrotestosterone .....	128
Androstenedione .....	128
Estrone .....	129
Effects of testosterone on female physiology .....	129
Andropause: Male Menopause .....	130
<b>Assessing the Male Hormonal System.....</b>	<b>133</b>
Signs and Symptoms of Male Hormonal Dysfunction .....	133
Key symptoms of testosterone deficiency include:.....	133
Assessing the Male Endocrine System: Physical Examination Techniques .....	134
Assessing the Male Endocrine System: Blood Testing.....	134
Free Testosterone.....	134
Reference Ranges.....	134
Normal reference range .....	134
Optimal reference range .....	134
Clinical Implications .....	134
Low testosterone levels are associated with the following: .....	134
Physical symptoms associated with low testosterone function include: .....	135
High testosterone levels.....	135
Estradiol Reference ranges.....	136
Normal reference range.....	136
Optimal reference range .....	136
Importance of Estradiol in Men.....	136
Coronary artery disease .....	136

Prostate Specific Antigen .....	136
PSA: Background .....	137
Prostate Cancer and risk factors .....	137
PSA Ranges .....	137
Expanding PSA Readings .....	138
PSA Velocity (PSAV) .....	138
PSA Doubling Time (PSADT) .....	138
PSA Density (PSAD).....	138
Other Primary Bio-Markers For Prostate Cancer to Consider: .....	138
Prostatic Acid Phosphatase (PAP).....	138
Prolactin .....	139
Other tests to consider .....	139
D-Dimer.....	139
Fibrinogen.....	139
Interleukin-6 (IL-6) and C-Reactive Protein (CRP).....	139
Insulin and Metabolic Syndrome .....	139
References .....	140
Treating Prostate Problems .....	140
Drugs .....	140
Natural Methods.....	141
Green Tea .....	141
Soy .....	141
Curcumin .....	141
Boron.....	141
Lycopene.....	141
Other treatment options .....	141
<b>Resources.....</b>	<b>142</b>
Reference Manuals.....	142
In-Office Lab Testing Book.....	142
In-Office Testing Resources .....	142
Oxidata Test Supplier.....	142
Functional Urinalysis Supplies .....	142
Rocky Mountain Reagents Inc.....	142
Blood Testing Resource .....	142
Doctor's Choice .....	142

Advanced FDM Companies .....	143
Genova Diagnostics .....	143
Diagnos-Techs .....	143
BioHealth Diagnostics .....	143
Metamatrix Clinical Laboratory.....	143
Doctor's Data, Inc.....	143
Supplement Companies .....	144

## **The Focus of this Insider's Guide**

This module is focused on the endocrine system. In this Insider's Guide we will explore the various facets of the endocrine system (the adrenal hormones, the thyroid hormones and the sex hormones) and how they interconnect with one another. We will look at the ways the endocrine system manifests its dysfunction and the best ways to assess and effectively treat our patient's endocrine system.

### ***Upon completing this module you will have:***

1. An understanding of the various components of the endocrine system (the hypothalamus, the pituitary, the thyroid, the parathyroid glands, the adrenals, and the sex hormones.)
2. The ability to assess each area of the endocrine system using Primary and Advanced Functional Diagnostic Medicine (FDM) techniques.
3. **Treatment techniques** to bring about harmony and balance in the endocrine system and resolve dysfunctions that have a primary endocrine location.

## **The Components of the Endocrine System**

This Insider's Guide will be split up into the various sections of the endocrine. The information is presented this way to make it easier to understand the complex nature of this system. As you can imagine all of these "parts" of the endocrine system are interconnected and it is rare for someone to suffer a dysfunction in one area of the endocrine system that is independent from the others.

### **We will look at the following areas of the endocrine system:**

1. A general look at the endocrine system
2. The parathyroid glands
3. The Thyroid gland and thyroid hormone metabolism
4. The adrenal glands and the impact of stress
5. The male and female sex hormones

### **Within each of these systems we will explore the following areas:**

1. The primary physiology and biochemistry
2. Primary and Advanced F.D.M. Testing and Assessment Techniques
  - a. The signs and symptoms
  - b. Physical examination techniques
  - c. In-office labs
  - d. Blood testing
  - e. Advanced FDM tests.

### 3. Treatment Protocols and Techniques

## **The Endocrine System**

The endocrine system is one of the control systems of the body. Endocrine glands release chemicals called **hormones** into the bloodstream. These hormones travel to their target organs and cells. They then bind to receptors either on cell surfaces or inside the cell. This results in a change in the activity of those cells.

These responses are relatively slow, taking from seconds to days to occur. In comparison, the nervous system, which uses electrical signalling directly to muscles and other tissues produces responses within milliseconds. However, once initiated, endocrine effects tend to be more prolonged.

### ***What is a hormone?***

A hormone is a chemical messenger released by an endocrine gland into the bloodstream where it is carried to a distant site to exert its effect. There are a wide variety of hormones; they are different in their chemical nature, their site of production and release, and the effects they induce.

### ***What types of hormones are there?***

**Hormones can be divided up on the basis of their chemical structure into 5 groups:**

Those derived directly from the **amino acid tyrosine**, including:

- thyroxine
- triiodothyronine
- adrenaline
- noradrenaline

Those made up of **short chains of amino acids**, including:

- adrenocorticotrophic hormone (ACTH)
- corticotrophin releasing hormone (CRH)
- thyrotrophin-releasing hormone (TRH)
- gonadotrophin-releasing hormone (GnRH)
- growth hormone releasing hormone (GHRH)
- vasopressin
- oxytocin
- somatostatin
- gastrin

- glucagon
- calcitonin

Those made up of **long chains of amino acids**, including:

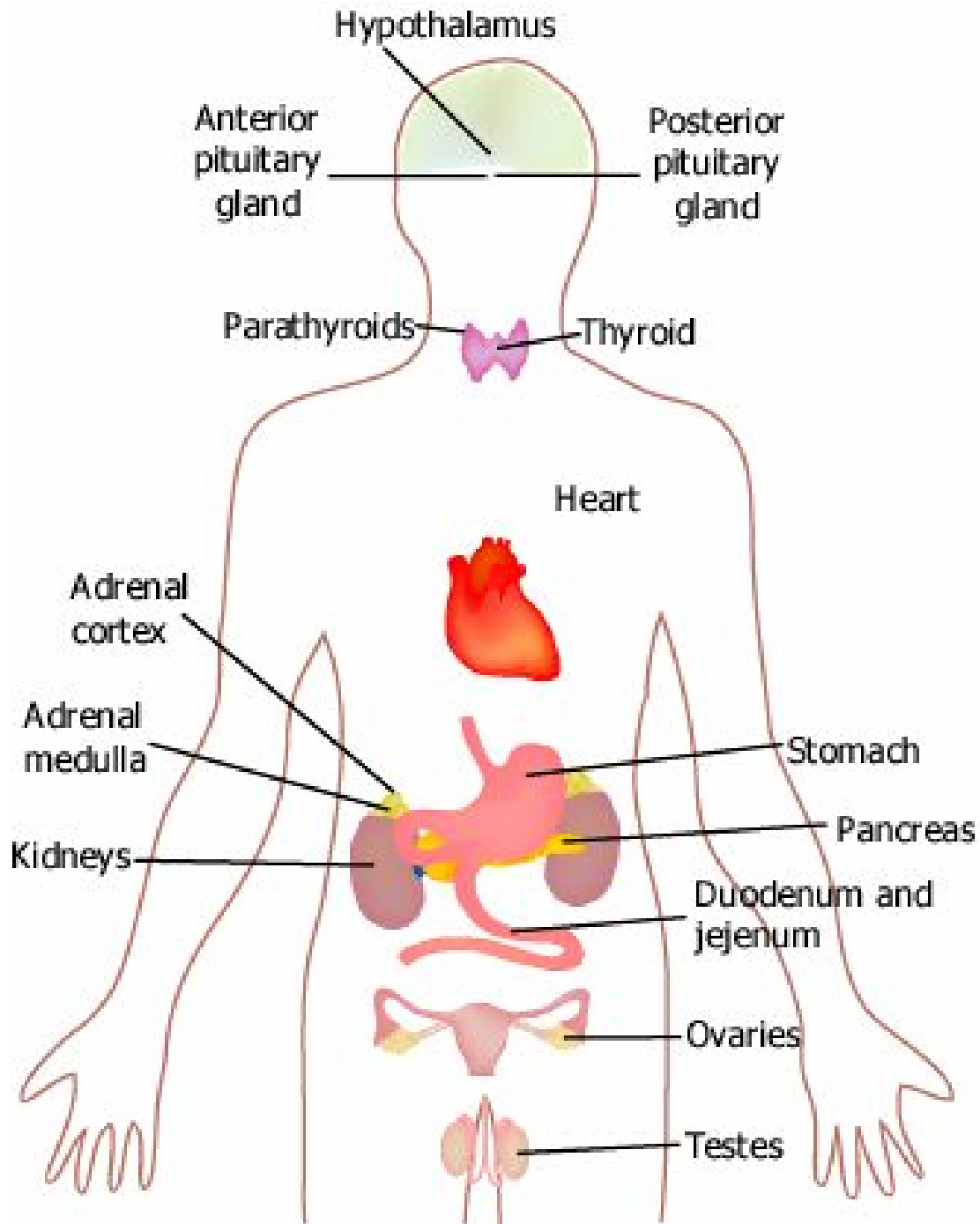
- insulin
- growth hormone (GH)
- prolactin
- parathyroid hormone (PTH)
- cholecystokinin (CCK)
- secretin

Those made up of proteins linked with glucose molecules forming glycoproteins, including:

- thyroid stimulating hormone (TSH)
- follicle stimulating hormone (FSH)
- luteinising hormone (LH)

Those derived from cholesterol thus forming lipid soluble steroid hormones, including:

- estrogens
- progesterones
- testosterone
- androstenedione
- aldosterone
- cortisol





## ***What are the functions of the different types of hormone?***

<b>Endocrine gland</b>	<b>Hormone</b>	<b>Main tissues acted on by hormone</b>	<b>Main function of hormones</b>
<b>Hypothalamus</b>	Thyrotrophin releasing hormone (TRH)	Anterior pituitary	Stimulates release of thyroid stimulating hormone (TSH) from the anterior pituitary
	Somatostatin	Anterior pituitary	Inhibitory hormone that prevents release of hormones such as growth hormone from the anterior pituitary
	Gonadotrophin releasing hormone (GnRH)	Anterior pituitary	Stimulates release of follicle stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary
	Corticotrophin releasing hormone (CRH)	Anterior pituitary	Stimulates adrenocorticotrophic hormone (ACTH) release from the anterior pituitary.
	Growth Hormone Releasing Hormone (GHRH)	Anterior pituitary	Stimulates release of growth hormone (GH) from the anterior pituitary
<b>Anterior pituitary</b>	Thyroid stimulating hormone (TSH)	Thyroid gland	Stimulates release of thyroxine and tri-iodothyronine from the thyroid gland
	Luteinising hormone (LH)	Ovary/Testis	Females: promotes ovulation of the egg and stimulates oestrogen and progesterone production. Males: promotes testosterone release from the testis
	Follicle stimulating hormone (FSH)	Ovary/Testis	Females: promotes development of eggs and follicles in the ovary prior to ovulation Males: promotes production of testosterone from testis
	Growth Hormone (GH)	Bones, cartilage, muscle, fat,	Acts to promote growth of bones and organs

		liver, heart	
	Prolactin (PRL)	Breasts, brain	Stimulates milk production in the breasts and plays a role in sexual behaviour
	Adrenocortico-trophic hormone (ACTH)	Adrenal glands	Stimulates the adrenal glands to produce mainly cortisol
<b>Posterior pituitary</b>	Vasopressin (anti-diuretic hormone, ADH)	Kidney, blood vessels, blood components	Acts to maintain blood pressure by causing the kidney to retain fluid and by constricting blood vessels
	Oxytocin	Uterus, milk ducts of breasts	Causes ejection of milk from the milk ducts and causes constriction of the uterus during labour
<b>Thyroid gland</b>	Thyroxine (T4)	Most tissues	Acts to regulate the body's metabolic rate
	Tri-iodothyronine (T3)	Most tissues	Acts to regulate the body's metabolic rate
<b>Parathyroid glands</b>	Parathyroid hormone (PTH)	Kidney, Bone cells	Increases blood calcium levels in the blood when they are low
	Calcitonin	Kidney, Bone cells	Decreases blood calcium levels when they are high
<b>Adrenal cortex</b>	Cortisol	Most tissues	Involved in a huge array of physiological functions including blood pressure regulation, immune system functioning and blood glucose regulation.
	Aldosterone	Kidney	Acts to maintain blood pressure by causing salt and water retention.
	Androgens	Most tissues	Steroid hormones that promote development of male characteristics. Physiological function unclear.
<b>Adrenal medulla</b>	Adrenaline and noradrenaline (the catecholamines)	Most tissues	Involved in many physiological systems including blood pressure regulation, gastrointestinal movement and patency of the airways.
<b>Pancreas</b>	Insulin	Muscle, fat tissue	Acts to lower blood glucose levels
	Glucagon	Liver	Acts to raise blood glucose levels

	Somatostatin	Pancreas	Acts to inhibit glucagon and insulin release
<b>Ovary</b>	Estrogens	Breast, Uterus, Internal and external genitalia	Acts to promote development of female primary and secondary sexual characteristics. Important role in preparing the uterus for implantation of embryo.
	Progesterone	Breast Uterus	Affects female sexual characteristics and important in the maintenance of pregnancy.
<b>Testis</b>	Testosterone	Sexual organs	Promotes the development of male sexual characteristics including sperm development
<b>Stomach</b>	Gastrin	Stomach	Promotes acid secretion in the stomach
	Serotonin (5-HT)	Stomach	Causes constriction of the stomach muscles
<b>Duodenum and jejunum</b>	Secretin	Stomach, Liver	Inhibits secretions from the stomach and increases bile production
	Cholecystokinin (CCK)	Liver, Pancreas	Stimulates release of bile from the gall bladder and causes the pancreas to release digestive enzymes
<b>Kidney</b>	Erythropoietin	Bone marrow	Stimulates red blood cell development in the bone marrow
<b>Heart</b>	Atrial natriuretic factor (ANF)	Kidney	Lowers blood pressure by promoting salt and water loss
<b>Skin</b>	Vitamin D	Small intestine, Kidney, Bone cells	Stimulates the uptake of calcium in the small intestine, retention of calcium and release of calcium from bone stores

## ***How do hormones exert their effect?***

At the level of the cell hormones act by binding to receptors (molecules that recognise the hormone's shape). **Receptors** can be either on the cell surface or **intracellular**. Binding of hormones to cell surface receptors activates second messenger systems; intracellular processes normally involving the phosphorylation (addition of a phosphate group) or dephosphorylation (removal of a phosphate group) of proteins. Eventually this leads to changes such as altered enzyme activity, gene activation or membrane permeability changes that alter the activity of that cell. Binding of hormones to

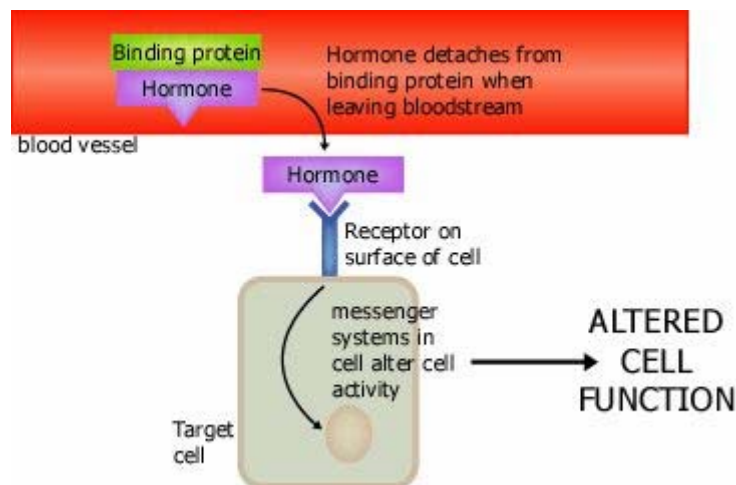
intracellular receptors forms a complex that directly interacts with DNA to alter cell function.

The process by which the chemical message is turned into altered cell activity is known as **signal transduction**.

## ***What are cell surface receptors and second messenger systems?***

### **Cell surface receptors**

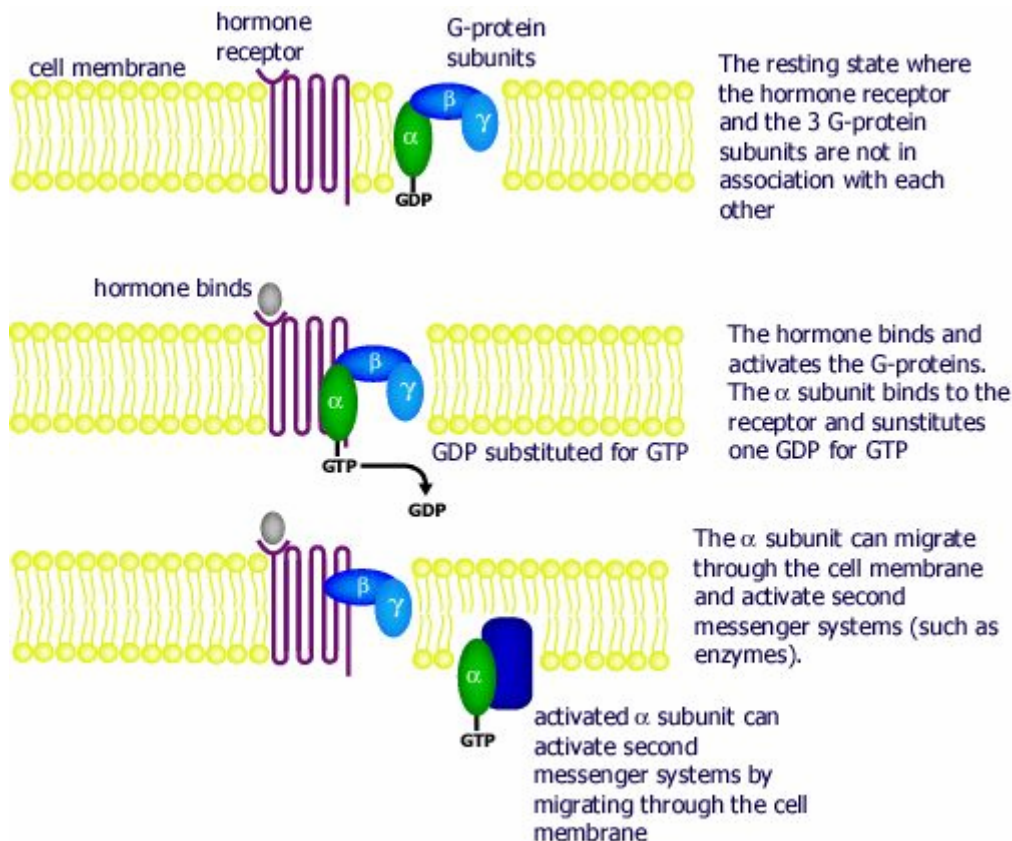
Most types of hormone are not fat-soluble. This means that they cannot dissolve in the cell membrane to gain entry into the cell. Instead they are transported around the blood, normally on transport proteins (such as albumin), to the target tissue where they bind to receptors on cell surfaces.



The two main types of cell surface receptor are:

### **G Protein Linked Receptors**

These are protein receptors that sit in the cell membrane, with an extracellular domain and an intracellular domain. The peptide chain that forms the protein always spans the membrane. When the hormone binds to the extracellular domain, this causes a change in shape of the receptor (a conformational change). This causes the intracellular domain to activate G proteins. G proteins have 3 main parts: an  $\alpha$  subunit, a  $\beta$  subunit and a  $\gamma$  subunit. When activated, firstly the  $\alpha$  subunit substitutes a GDP molecule for a GTP molecule. This results in the activation of the G proteins. They can be either stimulatory or inhibitory i.e. they can cause an increased level of enzyme activity or a decreased level of activity in the second messenger systems.



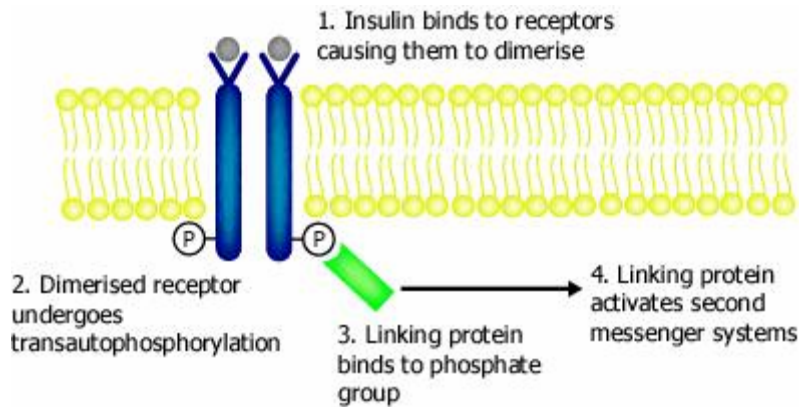
## Non-G protein coupled receptors

These are receptors with an intracellular domain that is activated when the hormone binds to the extracellular domain. The intracellular portion either

- has intrinsic enzyme activity itself
- or
- activates other enzymes inside the cell

These enzymes are generally involved in the phosphorylation of proteins (so-called kinase activity).

An example of one type of these is the tyrosine-kinase receptor for insulin. Here, once insulin binds, the intracellular domain is activated resulting in the dimerisation of (the fusion together of) two receptors. A kinase enzyme on one of the two receptors phosphorylates the tyrosine amino acids of the other receptor, a process called transautophosphorylation. Other intracellular proteins that recognise the phosphorylated dimerised receptors bind to them. These proteins activate second messenger systems.



## Second Messenger Systems

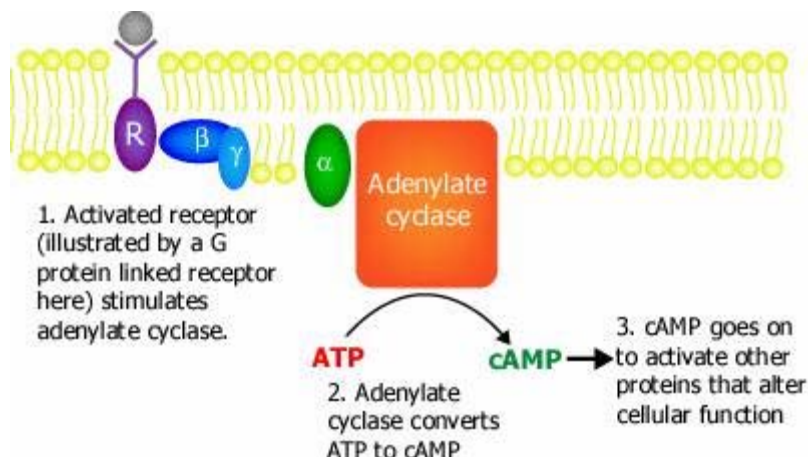
These are systems within the cell that are activated upon stimulation of the receptor. They act to amplify the signal. Although only one hormone molecule can stimulate one receptor (at any one time), the stimulated receptor can produce multiple second messengers, each of which can stimulate other molecules within the cell. One hormone molecule can therefore cause a large effect. This accounts for the fact that concentrations of hormone in the blood are so low.

The main types of second messengers are:

- cAMP (cyclic adenosine monophosphate)
- IP<sub>3</sub> (inositol 1,4,5-triphosphate) and DAG (diacylglycerol)
- Calcium

### cAMP

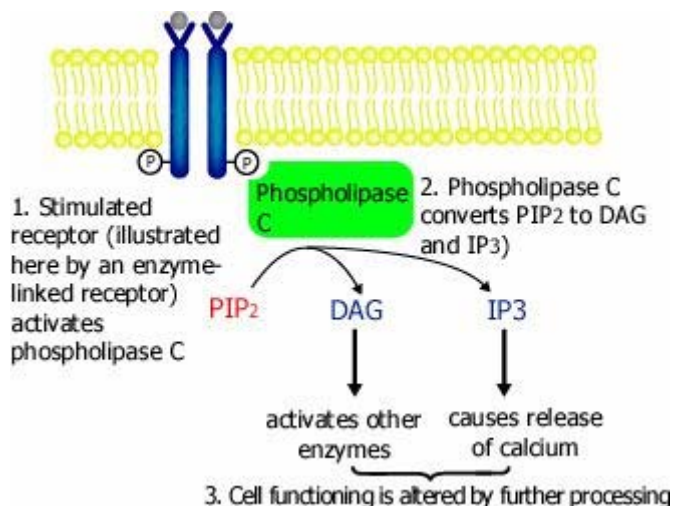
cAMP is produced from ATP (adenosine triphosphate) by the enzyme adenylate cyclase. Adenylate cyclase can be stimulated by several mechanisms. The enzyme is activated by stimulatory subunits of G proteins and other proteins activated by phosphorylated enzyme-linked receptors. It is inhibited by other inhibitory G proteins. cAMP goes on to activate other enzymes which affect the expression of certain genes in the cell.





## IP3 and DAG

IP3 and DAG are produced from another molecule PIP2 (phosphatidylinositol 4,5 - bisphosphate) by the enzyme phospholipase C. Phospholipase C is activated again by stimulatory G proteins and other proteins activated by phosphorylated enzyme-linked receptors. IP3 goes on to release calcium from intracellular stores. Calcium together with DAG can then go on to activate other enzymes (such as protein kinase C, PKC) which in turn activate proteins that alter cell activity.

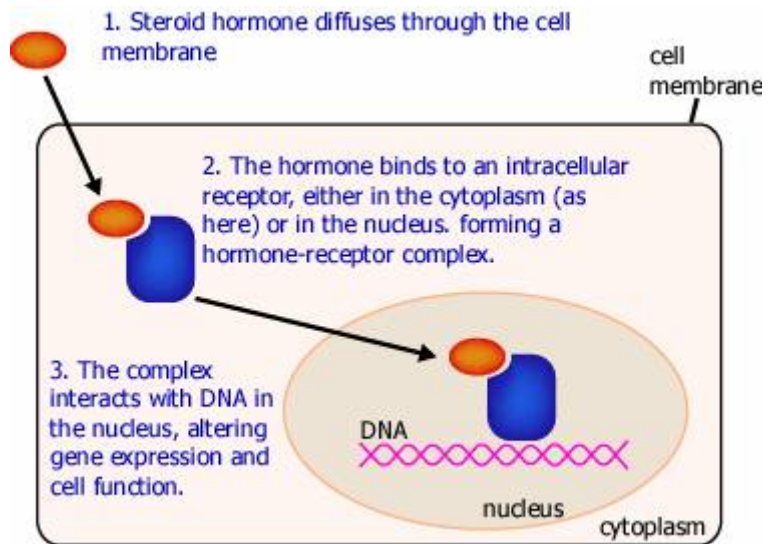


## Calcium

Calcium is released from intracellular stores by **IP3**. It can then go on to activate enzymes such as protein kinase C with DAG. It can also bind to a molecule called **calmodulin**. This molecule can activate many other proteins producing a wide range of effects that ultimately alter cell activity and function

## What are intracellular receptors?

These are used specifically by the steroid hormones such as **cortisol, aldosterone, testosterone, estrogens and progestogens**. Steroid hormones are **lipid soluble**, therefore they diffuse through the cell membrane and gain direct access to the cell. Inside, they bind to steroid receptors. This forms a hormone-receptor complex. This complex then binds to parts of DNA in the nucleus of the cell called hormone responsive elements. The binding process changes the physical shape of the DNA in the nucleus and means that the pattern of gene expression is altered in that cell.





# The Journey of the Endocrine System

## *Hypothalamus-Pituitary-Adrenal (HPA) axis*

The **Hypothalamus-Pituitary-Adrenal (HPA)** axis is one of the key part of the human endocrine system. As its name suggests, it comprises three endocrine glands:

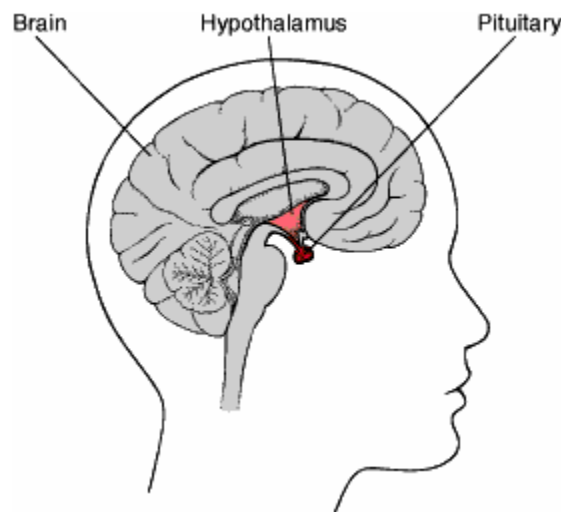
**Hypothalamus**

**Anterior pituitary**

**Adrenal gland cortex**

These glands work together by sending chemical signals, the hormones. Of them, the major role in the HPA axis are playing the **corticotropin-releasing hormone (CRH)**, **corticotropin itself (ACTH)**, and **cortisol**. While CRH and ACTH are just intermediate messengers in the HPA axis affecting the pituitary and adrenal glands only, **cortisol** is playing the vital role for the whole organism.

## *The Pituitary Gland*



The pituitary gland (hypophysis) is an endocrine gland that lies in a bony cavity in the skull. This cavity lies in the sphenoid bone and is called the sella turcica. The gland is attached to the base of the brain by a stalk (infundibular stalk) and is contained in a capsule that is continuous with the dura mater (a tough membrane surrounding the brain).

The gland is composed of two main lobes: **an anterior lobe (the adenohypophysis)** and **a posterior lobe (the neurohypophysis)**.

An important anatomical relation to the pituitary gland is the optic chiasm, which lies just above the pituitary fossa. Therefore, any expanding lesion of the pituitary or hypothalamus can present with **visual field defects**.

## ***The Hypothalamo-adenohypophysial System***

The hypothalamus produces many neurosecretions that can either stimulate or inhibit the release of other hormones from the pituitary gland. The names and actions of the principal hypothalamic releasing and inhibiting hormones are listed below.

<b>Hypothalamic Hormone</b>	<b>Action</b>
<b>Thyrotrophin-releasing Hormone (TRH)</b>	This hormone stimulates the release of Thyrotrophin and Prolactin from the Adenohypophysis.
<b>Gonadotrophin-releasing Hormone (GnRH)</b>	This hormone stimulates the release of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) from the Adenohypophysis.
<b>Corticotrophin-releasing Hormone (CRH)</b>	This hormone stimulates the release of Corticotrophin from the Adenohypophysis.
<b>Somatotrophin-releasing Hormone(SRH) or Growth Hormone-releasing Hormone (GHRH)</b>	This hormone stimulates the release of Somatotrophin (Growth Hormone) from the Adenohypophysis.
<b>Somatostatin (SS)</b>	This hormone inhibits the release of Thyrotrophin and Somatotrophin from the Adenohypophysis.
<b>Antidiuretic Hormone (ADH)/Vasopressin</b>	This hormone stimulates the release of Corticotrophin from the Adenohypophysis.
<b>Dopamine</b>	This hormone inhibits the release of Prolactin from the Adenohypophysis.

## ***Adrenocorticotrophic Hormone (ACTH)***

The main function of this hormone is to **stimulate the adrenal glands to release cortisol in response to stress**. Cortisol is released in response to stress, which can be emotional (e.g. anxiety) or physiological (e.g. fluid deprivation or injury).

Stressors cause a release of **Corticotrophin Releasing Hormone (CRH)**. This travels in the portal system of the hypothalamus to the anterior pituitary (the adenohypophysis). There, it stimulates the cleavage of Pro-opiomelanocortin (POMC) into several molecules including melanocyte stimulating hormone (MSH) and Adrenocorticotrophic Hormone (ACTH). ACTH travels in the bloodstream to the adrenal cortex stimulating the production and release of cortisol. Cortisol then travels to the tissues where it exerts its effects. Cortisol inhibits the release of CRH and ACTH from the hypothalamus and pituitary gland respectively, preventing further cortisol release. Cortisol is inactivated in the liver to inactive cortisone.

A daily pattern (circadian rhythm) is also seen, with cortisol being at its lowest concentration at midnight, rising to a peak between 6am and 8am, falling throughout the rest of the day.

## ***Thyroid Stimulating Hormone (TSH)/Thyrotrophin***

Thyroid stimulating hormone is released in low-amplitude pulses following a diurnal rhythm (the highest levels reached during the night). The **main role of TSH is to stimulate the thyroid gland to release two of its own hormones into the bloodstream**. The actions of the two thyroid hormones released (T3 (triiodothyronine) and T4 (thyroxine)) are discussed in the Thyroid section. The control of TSH release is by the hypothalamic hormone Thyrotrophin releasing hormone (TRH). The other major control factor is the negative feedback mechanism exerted by the thyroid hormones themselves at the level of the pituitary and the hypothalamus.

## ***Growth Hormone(GH)/Somatotrophin***

Growth hormone exerts its actions on many tissues. The main role of this hormone, as its name would suggest, is the promotion of linear growth in a variety of tissues. The hormone promotes growth in two major ways:

The stimulation of protein synthesis

Increasing amino acid transport through cells

Growth hormone stimulates many tissues, mainly the liver, to produce substances known as somatomedins. These substances are capable of stimulating cell division and cell proliferation. The liver produces two main somatomedins which both have great homology to **insulin**. The two somatomedins are therefore known as insulin-like growth factors I and II (IGF-I and IGF-II). The main actions of the somatotrophin and somatomedins are listed below.

Increase in growth of soft and skeletal tissues

Somatotrophin stimulates the uptake of non-esterified fatty acids (NEFA) by muscle

Somatotrophin stimulates hepatic glycogenolysis to raise blood glucose levels

Intestinal absorption of calcium is increased and the urinary excretions fall

Somatotrophin seems to enhance T-cell proliferation.

The roles of somatotrophin and insulin seem to complement each other in regard to cell division and growth. Their roles, however, seem to oppose each other in respect to blood glucose levels. Insulin will reduce blood sugar levels whereas somatotrophin will act to increase blood sugar levels. The picture is even more complicated as the somatomedins will tend to reduce glucose levels due to their insulin-like actions.

The release of somatotrophin follows a diurnal variation with the greatest impulses occurring during deep sleep.

## ***Follicle stimulating hormone (FSH) and Luteinizing hormone (LH)***

The two gonadotrophins produced by the gonadotrophe cells in the adenohypophysis are follicle stimulating hormone (FSH) and luteinizing hormone (LH). The actions of these hormones vary in both men and women.

In women, LH acts on the ovaries to stimulate steroid hormone production. In males, LH acts by stimulating Leydig cells in the testes to secrete testosterone. The control of LH release is primarily by the gonadotrophin-releasing hormone (GnRH) produced by the hypothalamus. The pulsatile release of LH is dependent on the pulsatile release of GnRH. LH is also regulated by a number of other hormones such as dopamine, prolactin and most importantly by negative feedback from the sex steroids.

FSH stimulates the follicular development in the ovary in women, whereas in males it stimulates the sertoli cells to initiate spermatogenesis. FSH is regulated in similar way to LH except from the production of a specific inhibitory protein, produced by the FSH target cells, called inhibin. Inhibin allows for the specific inhibition of FSH release and plays an important role in the menstrual cycle.

## ***Prolactin (PRL)***

Prolactin is synthesised and released from lactotrophe cells in the adenohypophysis. Prolactin has two main roles:

The growth and development of the breasts

The maintenance of lactation in women.

Prolactin requires other hormones to complete these actions. Prolactin also has an important role in the male in the regulation of gonadal function by stimulating LH receptor synthesis in the Leydig cells.

Prolactin release is primarily under the control of the hypothalamus. The two hypothalamic hormones involved in prolactin regulation are thyrotrophin releasing hormone (TRH) and dopamine. The predominant hormone in the regulation is the

inhibitory dopamine. The hypothalamus receives afferent sensory nerve cell input primarily from the nipples of lactating women. This feedback loop increases lactation during suckling by inhibiting dopamine release and stimulating TRH release.

Prolactin is released in a diurnal rhythm with the highest levels occurring at night.

## ***What does the Neurohypophysis do?***

The two most important products of the neurohypophysis are the hormones **vasopressin and oxytocin**.

### **Vasopressin**

There are two different types of vasopressin produced by animals. The vasopressin that is found in humans contains the **amino-acid arginine and is referred to as arginine vasopressin**. The other type of vasopressin contains **lysine and is found in pigs and is referred to as lysine vasopressin**. Some of the paraventricular vasopressinergic neurones project to various parts of the brain where it acts as a neurotransmitter. Vasopressin has been identified in many parts of the body including the adrenals, the gonads, the pancreas and the sympathetic ganglia.

In order to fully understand the different actions of vasopressin, it is important to realise that there are two very distinctive types of vasopressin receptors. The most important of these receptors is the v2 receptor. The v2 receptor is found in the collecting ducts of the kidney where it plays a vital role in the reabsorption of water in the kidney. The vasopressin acts on the v2 receptors in the collecting ducts and stimulates the up-regulation of water channels (aquaporins) in the membrane. When there are high levels of vasopressin in the blood the volume of urine produced will be small and highly concentrated. It is for this reason that vasopressin is often referred to as '**anti-diuretic hormone**'.

The v1 receptors are found in many other tissues and have a variety of different functions. These other effects are listed below:

- Vasoconstriction (especially in the skin and splanchnic bed) mediated via the v1 receptors
- Increases sodium reabsorption in the kidney
- Stimulates corticotrophin release from the adenohypophysis
- Involved in behaviour and memory
- Stimulation of hepatic glycogenolysis
- Stimulation of the synthesis of factor VIII in the liver.

The most important control mechanism for vasopressin synthesis and release is the **plasma osmolality**. An increase in osmolality will result in an increase in vasopressin release which acts to decrease osmolality. The increase in osmolality is detected by specialised cells known as osmoreceptors, which in turn stimulate the vasopressinergic neurones. Another important mechanism involved in the control of vasopressin release are volume receptors.

### **There are two main types of volume receptors:**

1. Low pressure receptors - these are found mainly in the left atrium of the heart and the walls of the main veins.
2. High pressure receptors (baroreceptors) - these are found in the carotid sinus and the aortic arch.

A fall in blood volume will result in the activation of these receptors. These receptors usually tonically inhibit the vasopressinergic neurones and so a fall in blood volume will result in a decrease of the usual inhibition of vasopressin release.

Higher centers of the brain can also exert an effect on vasopressin release so that massive release of vasopressin can occur in times of emotion and physical stress to the body.

## **Oxytocin**

This is the other important hormone produced by the **posterior pituitary**. Oxytocin is produced in both males and females, but its main physiological roles seem to take place in the female. In the female, oxytocin is involved in a number of important physiological actions:

**Stimulates the contraction of the uterus (myometrium)**

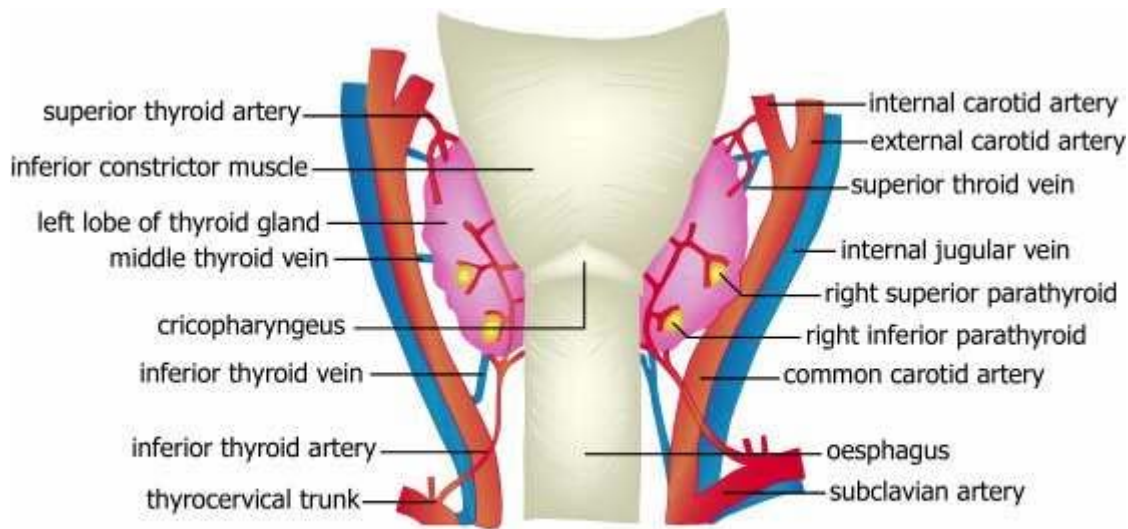
**Stimulates the contraction of the myoepithelial cells that eject milk from the breast.**

The most important control mechanism for the release of oxytocin is the suckling of the nipple in the newborn. This stimulation results in the activation of afferent nerves that stimulate the oxytocinergic neurones in the hypothalamus.

# The Parathyroids

## *Anatomy and Physiology of the Parathyroid Glands*

The parathyroid glands are oval structures the size of millet seeds, weighing around 30 mgs each. There are usually four of them and they lie on the posterior surface (the back) of the thyroid gland. Normally they are symmetrically arranged with the two superior (higher) parathyroids lying about 1cm above the point where the inferior thyroid artery enters the thyroid. The two inferior (lower) parathyroids lie 1cm below this point.



**Schematic diagram of the posterior view of the thyroid showing the parathyroid glands and their blood supply**

## **Nerve supply**

The parathyroids are supplied by thyroid branches of the cervical sympathetic ganglia with a mainly sensory function, detecting stretch within the glands that gives rise to the sensation of pain in some disorders.

## ***What do the Parathyroids do?***

The parathyroid glands are involved in the **control of blood calcium levels in the body**. They secrete one principal hormone, **parathyroid hormone (PTH)**.

## **What does parathyroid hormone do?**

PTH is a peptide hormone that acts to **raise blood calcium levels**. It is released when calcium sensors (specialised receptor molecules) on the surface of the parathyroid glands detect low blood calcium levels in the circulation. The release of PTH is therefore



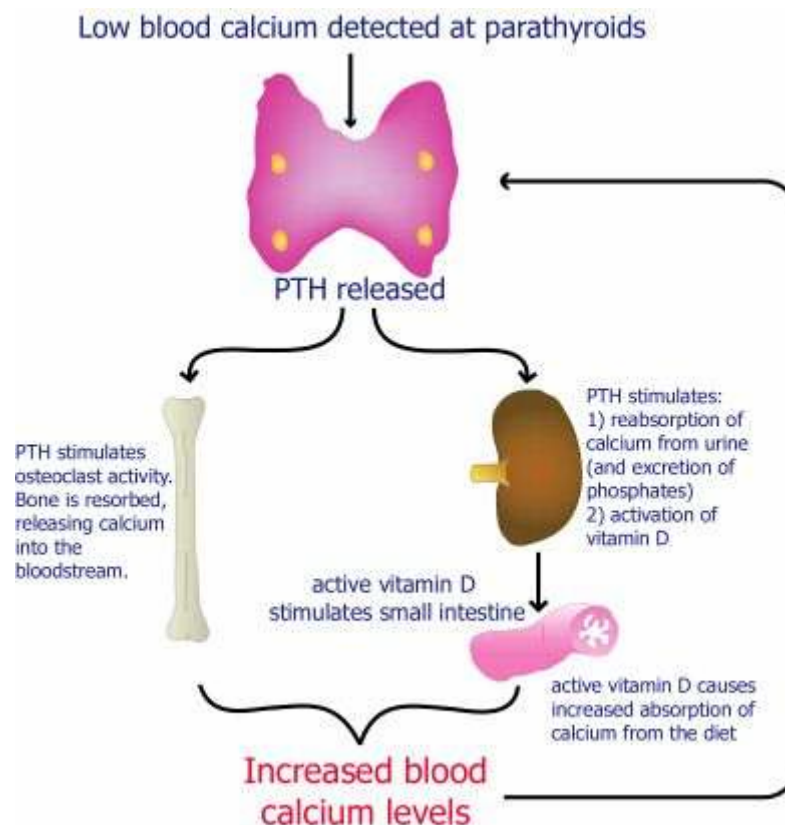
inversely proportional to the calcium levels in the blood. In addition high blood magnesium levels promote the release of PTH.

**PTH acts to raise blood calcium in three main ways:**

1. It activates osteoclasts - these are bone cells that resorb (degrade) bone, thus releasing some of the calcium stored in bone in times of hypocalcaemia (low blood calcium) for other functions.
2. It promotes the reabsorption of calcium from the urine - PTH stimulates cells of the kidney to reabsorb calcium (and excrete phosphate) from the urine, reducing the loss of calcium in hypocalcaemia.
3. It promotes the activation of vitamin D precursors in the kidney - active vitamin D (1.25-cholecalciferol) promotes the uptake of calcium from digested food in the small intestine. This raises calcium levels when they are low.

As the calcium levels become normal, the rising calcium acts to inhibit further PTH release.

**The diagram below illustrates this system.**



## Calcitonin

The other main hormone involved in calcium regulation is calcitonin produced by the C cells of the thyroid (parafollicular cell). This is released in response to a rise in blood



calcium and acts to reduce it. It does this by inhibiting the osteoclasts' resorption of bone and decreasing calcium reabsorption by the kidney. The role of calcitonin in calcium control is still not fully understood.

## **Why is calcium regulation important?**

99% of the body's calcium is contained within the skeleton as calcium salts making up the inorganic parts of the bone. The remaining 1% is found in several forms in the blood. The blood calcium levels are tightly controlled within a very narrow range of 2.1-2.6 millimoles per litre. The reason for this is that the movement of calcium ions across cell membranes affects many fundamental processes such as:

- intracellular cell signalling (as described in the Introduction to Endocrinology)
- muscle cell contraction
- nerve cell activity

## **Assessing Parathyroid Dysfunction**

As mentioned above the parathyroid glands help to regulate calcium levels in the body so parathyroid dysfunction is very closely associated with signs and symptoms of calcium excess or calcium deficiency

Tiny alterations of blood calcium levels upset this delicate balance of calcium movement and can lead to a wide range of problems.

## ***Signs and Symptoms of Parathyroid Dysfunction***

### **High Blood Calcium Levels (Hypercalcaemia)?**

**When excess blood calcium accumulates the following can occur:**

- The formation of stones - the excess calcium can form stones (calculi) in organs such as the kidneys.
- Fractures - hypercalcaemia often indicates excessive resorption (degradation) of bones making them prone to break after only minor trauma (pathological fractures).
- Proximal myopathy - weakness in the proximal muscles (the muscles of the upper limbs) due to insufficient calcium for efficient muscle contraction.
- Pancreatitis - calcium deposits in the pancreas can result in inflammation of the pancreas causing pain, nausea and vomiting.
- Mental changes - alterations in brain activity due to abnormal nerve function can lead to depression, confusion, memory loss and parkinsonism-type symptoms..

## Low blood calcium (hypocalcaemia)?

When blood calcium becomes too low the following can occur:

- Paraesthesia - this is a sensation of numbness in areas of the body and is due to impaired activity of sensory nerves.
- Cramps - altered calcium levels cause abnormalities of muscle contraction resulting in cramps around the body. In particular it can cause laryngospasm, (spasm of the muscles of the larynx).
- Tetany - this is prolonged sustained involuntary contraction of muscles due to muscle nerve conduction problems.
- Agitation and seizures - abnormal levels of brain activity can cause seizures and agitation.

## Assessing the Parathyroids: Blood Testing

The 2 main diseases associated with the parathyroids are **hypoparathyroidism** and **hyperparathyroidism**. These are not functional disorders but overt pathological conditions concerned with the excess or deficient output of parathyroid hormone.

PTH is measured in several different manners such as N-terminal, intact, and C-terminal. Reference ranges will differ depending upon the type of test used and a standard reference range cannot be given.

	Normal Range	Optimal Range
Calcium	8.5 – 10.8	9.2 – 10.00 mg/dl
	2.13 – 2.70	2.30 – 2.50 mmol/L

## Alarm Range

### Calcium

< 7.0 or > 12.0 mg/dL

< 1.75 or > 3.00 mmol/L

You should evaluate serum PTH if you have calcium levels in these ranges.

### PTH

Values < 9.0 pg/mL generally indicate parathyroid hypo-function and values > 47.0 pg/mL generally indicate parathyroid hyper-function.

If both PTH and calcium levels are normal you can be pretty sure that the body is regulating calcium well.

## The Calcium - PTH Relationship

- If calcium levels are low and PTH levels high, then the parathyroid glands are responding as they should and producing appropriate amounts of PTH. You should investigate other reasons for a low calcium level. Check vitamin D, phosphorous, and magnesium levels (intracellular levels are best).
- If your patient's calcium levels are low and you check PTH and the levels are normal or low, then the parathyroid is not responding to the low calcium levels and your patient probably has hypoparathyroidism.
- If calcium levels are high and PTH levels are high, then your patient's parathyroid glands are producing inappropriate amounts of PTH. In this case you may want to refer out for x-rays or other imaging studies to check for the cause and severity of hyperparathyroidism.
- If calcium levels are high and you check the PTH levels and they are low, then the parathyroid glands are responding normally. You will want to check for other causes of high calcium levels (impaired cell membrane health, ovarian hypofunction, Vitamin D (excess ingestion), adrenal hypofunction, hypothalamic-pituitary axis dysfunction, neoplasm, epilepsy, osteoporosis)

Calcium	PTH	Interpretation
Normal	Normal	Calcium regulation by parathyroid functioning optimally
Low	High	Parathyroid responding properly. Investigate other causes of hypocalcemia
Low	Normal/Low	Parathyroid not responding correctly. Probably hypoparathyroidism
High	High	Parathyroid gland is producing too much PTH. Do imaging to check for hyperparathyroidism
High	Low	Parathyroid responding correctly. Check other causes of hypercalcemia.

## Clinical Implications

### Parathyroid Hyperfunction

Parathyroid hyperfunction will cause an increase in PTH levels, which can lead to significantly increased serum calcium.

#### **Pattern**

If the serum calcium is significantly increased ( $>10.5$  or  $2.5$  mmol/L) with a decreased phosphorous ( $<3.0$  or  $<0.97$  mmol/L) parathyroid hyperfunction is **possible**. Alkaline phosphatase levels may also be increased ( $>100$ ), along with a normal or decreased serum or RBC magnesium.

Follow-up with a serum parathyroid hormone test. If parathyroid hormone levels are also increased, presume clinical hyperparathyroidism exists.

Hyperparathyroidism may be due to space-occupying lesions on one or more of the glands. Surgical removal may be necessary to determine if there is a neoplasm.

A patient with increased serum calcium and an increased PTH should be checked by an endocrinologist, as hyperparathyroidism is a serious condition.

## **Parathyroid Hypofunction**

Parathyroid hypofunction will lead to decreased PTH levels that can cause decreased serum calcium.

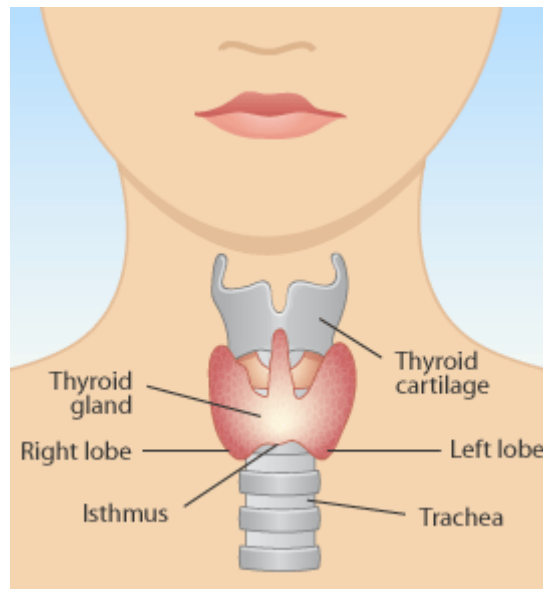
### ***Pattern***

If calcium is decreased ( $<9.2$  or  $2.3$  mmol/L) along with a high phosphorous level ( $>4.0$  or  $1.29$  mmol/L), parathyroid hypofunction is **possible**. Alkaline phosphatase levels may also be normal or decreased ( $<70$ ).

Follow up with a serum parathyroid hormone test. If parathyroid hormone levels are also decreased presume clinical hypoparathyroidism exists.

# The Thyroid

## ***Physiology and Biochemistry of the Thyroid Gland and Thyroid Hormone Metabolism***

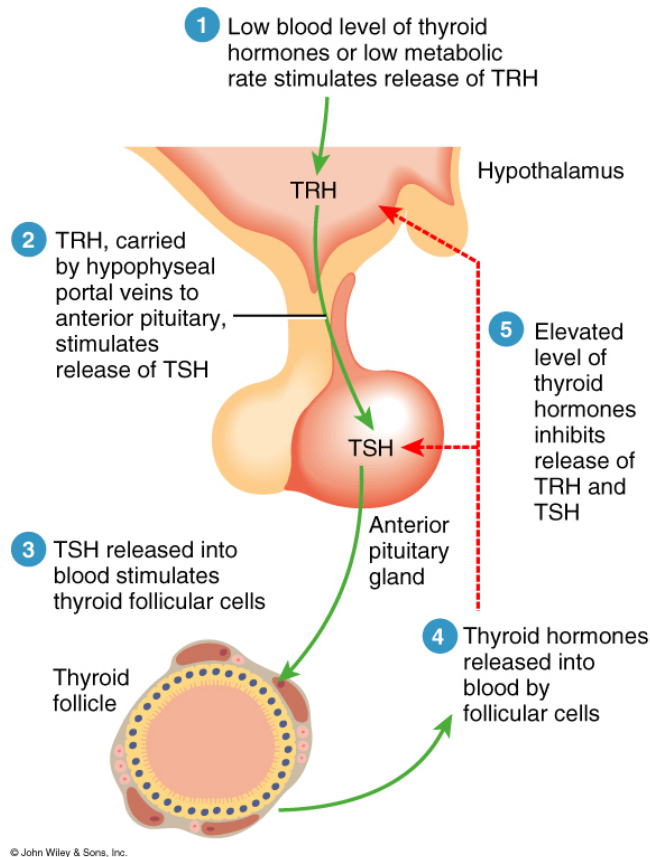


The thyroid gland is a butterfly shaped structure that lies on the windpipe below the Adam's Apple. The thyroid can be likened to a butterfly. The thyroid lobes can be imagined as wings that wrap themselves around the windpipe while the body lies in front of the windpipe and is called the thyroid isthmus. The isthmus usually lies over the second and third tracheal rings opposite the fifth, sixth and seventh cervical vertebrae. The lobes of the thyroid are almost always asymmetrical with the right lobe larger than the left. The thyroid is usually larger in women than men. The total weight of the thyroid is approximately 20-25 grams but is smaller in parts of the world where supplies of iodine are abundant.

The thyroid is a very vascular organ and is surrounded by a sheath. This sheath attaches the thyroid to the larynx and the trachea. Anteriorly, the sternohyoid and sternothyroid muscles overlie each of the lobes. A pyramidal lobe is also often present and it projects upwards *from the isthmus as seen in the diagram*. A fibrous or muscular band frequently connects the pyramidal lobe to the hyoid bone.

### **Review of thyroid hormones**

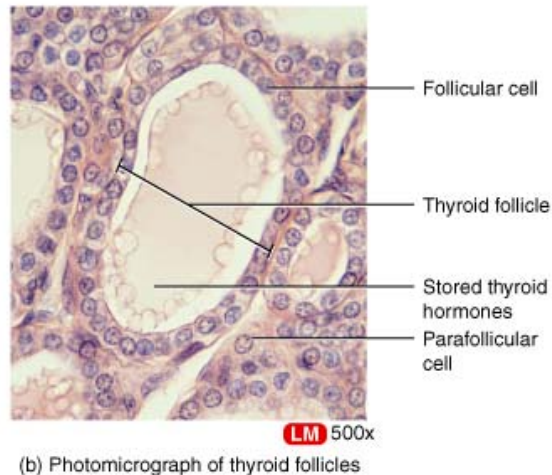
The thyroid gland influences the rate of metabolism in the body through the production of a hormone called T4 from the thyroid and the peripheral conversion of T4 into the more metabolically active T3 (triiodothyronine) or reverse T3.



The hypothalamus constantly assesses the need for more metabolic energy in the body and in response to a falling level of T4 and T3 it releases a hormone called Thyroid Releasing Hormone (TRH), which stimulates the pituitary to produce a hormone called Thyroid Stimulating Hormone (TSH). This is the first step in thyroid regulation. When metabolic energy reaches a normal state a negative feedback occurs and the hypothalamus stops producing TRH. Basically high hormone levels suppress TRH (High T3 is the strongest inhibitor of TRH). Low hormone levels increase production of TRH (Low T4 levels are the biggest stimulant of TRH).

Hypothalamic Releasing Hormones (such as TRH for the thyroid) travels from the hypothalamus to the pituitary and stimulates the pituitary to produce its regulatory hormones. TSH is made by the pituitary to control thyroid function.

The pituitary gland responds to not only TRH but also the cells of the pituitary are responsive to feedback from T4 and T3, which decrease TSH release. There is also evidence that the pituitary is sensitive to TSH itself; a decrease in TSH feedback to the pituitary causes TSH release.



The only significant role of TSH is that it stimulates the thyroid gland. TSH travels in the blood stream to the thyroid gland. TSH receptors on the cell membrane interface with TSH to cause the following:

- Increased production of thyroid hormone in the thyroid follicles
- Storage of thyroid hormone in the thyroid follicle
- Release of thyroid hormone into the bloodstream

Without TSH stimulation the thyroid gland atrophies, produces no hormone and shrinks.

### A summary of TSH Function

- TSH describes the pituitary's desire for more thyroid hormone (T4 or T3), which is done in relation to the body's ability to use energy.
- A high TSH is the pituitary or body's way of saying "we need more thyroid hormone".
- A low TSH is a reflection of pituitary or body's low need for thyroid hormone.
- Optimal TSH levels tell us that the thyroid hormone levels match the body's current need and/or ability to utilize the energy.
- Levels of TSH are fairly stable and show little diurnal variation though there is some evidence that levels are at their highest at noon so either consider testing at Noon or make sure you test TSH levels at roughly the same time.

### A summary of the regulation of thyroid hormone

Thyroid hormone regulation follows a simple feedback mechanism. When the brain tissue is exposed to more thyroid hormone the hypothalamus produces less TRH. The pituitary subsequently produces less TSH and the thyroid makes less thyroid hormone.

## A brief look at the physiology of each of the different hormones

There are 4 hormone variants of the thyroid hormone. They are named based on the number of iodine atoms each molecule contains: T4, T3, rT3 and T2

Hormones are released in the following proportions:

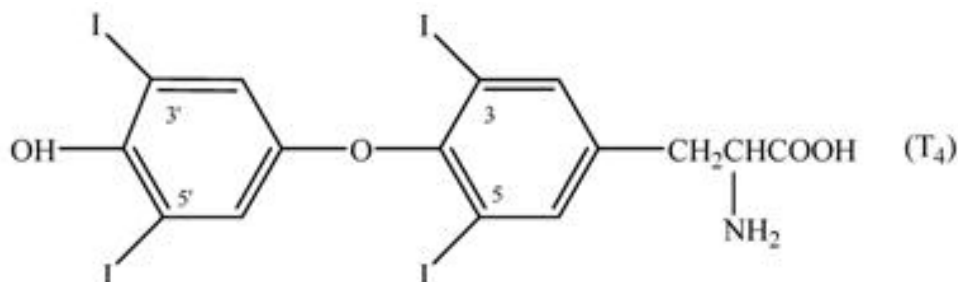
T4 90%

T3 10%

rT3 1%

Very small amounts of T2

### T4



The above is an illustration of the chemical structure of T4. T4 is synthesized from the amino acid tyrosine and iodine, is produced in the thyroid in response to TSH, and is converted into either **T3 (triiodothyronine)** or **Reverse T3 (rT3) in the peripheral tissue**.

An enzyme called Thyroid peroxidase (TPO) attaches iodine molecules to the tyrosyl residues forming T4. The first tyrosine ring is considered the prime ring and the locations of iodine are at the 3' and 5' position (see illustration above). T4 is really a pre-hormone because it does little until it is activated within our cells.

T-4 is either stored in the follicle of gland (see the illustration on the previous page) or released from thyroid into the blood stream primarily bound to thyroid binding globulin (TBG).

Deficiencies of zinc, copper, and vitamins A, B2, B3, B6 and C will cause a decrease in production of T4 by the follicles of the thyroid gland.

#### INTERESTING FACT

**The thyroid gland is the only gland to store its own hormone. It stores approximately a 100 day supply.**

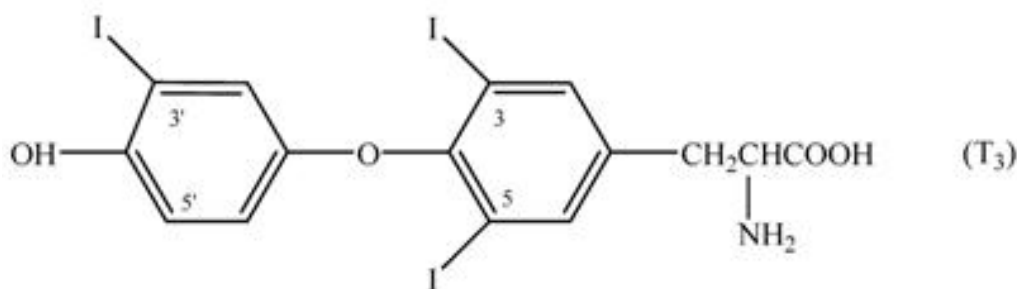
Only about 0.03 – 0.05% of circulating T4 is in a free form. The rest is bound to thyroid binding globulin, albumin, thyroid-binding prealbumin and a few other minor proteins (see the section below for a further discussion of the binding of thyroid hormone).



T4 is either converted to T3 or rT3, or eliminated via conjugation, deamination or decarboxylation in the liver. It is estimated that about 70% of T4 produced in the thyroid is eventually deiodinated in peripheral tissues into either T3 or rT3 via the **deiodinase enzyme** that cleaves an iodine molecule from the quaternary form.

Total T4 reflects the total amount of T4 present in the blood i.e. amount bound to thyroid binding globulin and free levels. High levels of estrogen (BCPs or pregnancy) will increase the amount of thyroid binding globulin that binds to T4. This can give misleading elevated T4 levels, which looks like hyperthyroidism when it's not. We recommend that you check Free T4 in the presence of conditions that affect binding protein levels. This will give you a more accurate assessment of thyroid function.

### T3

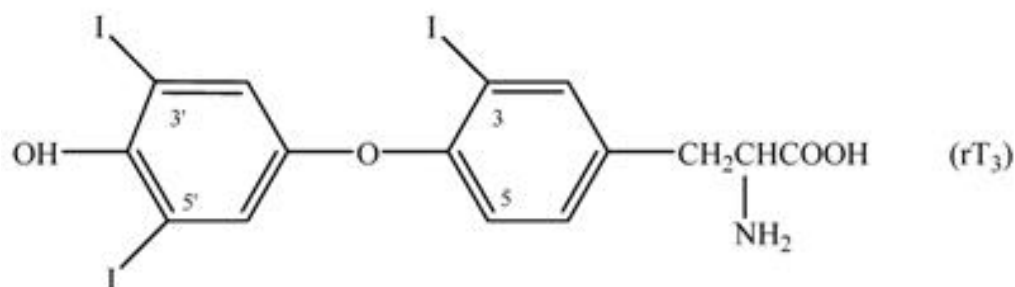


T-3 is considered the most metabolically active thyroid hormone. T-3 is 4 -5 times more metabolically active than T-4 and its systemic effects and half-life are shorter. Although some is produced in thyroid, **approximately 80 – 85% is produced outside the thyroid**, primarily by conversion of T4 in the liver and kidneys. Within the liver and kidney, the enzyme responsible for the peripheral conversion of T3 is **a selenium dependent enzyme called 5'-deiodinase**. Iodine is removed from the 5' site on the first tyrosyl residue.

T3 has a direct on the mitochondria to increase the output of ATP through oxidative phosphorylation. It also has a direct effect on the heart probably through the same action on the mitochondria.

Similar to T4, the majority of T3 is in a protein bound form. Total T3 reflects the total amount of T3 present in the blood i.e. amount bound to protein and free levels. Free T3 represents approximately 8 – 10% of circulating T3. Free T-3 is more available for tissue receptors and provides a more accurate measurement for thyroid assessment in the presence of factors that affects binding proteins (next slide)

## Reverse T3



T4 can also be converted into a molecule of reverse T3 (rT3) in the peripheral tissues. Small amounts of rT3 are made within the thyroid; however, 95% of rT3 is produced from peripheral conversion of T4. The enzyme responsible for this conversion is 5-deiodinase and is not believed to be dependent on selenium. Iodine is removed by this enzyme from the 5 location on the second tyrosyl residue.

Under normal conditions, 45 – 50% of the daily production of T4 is transformed into rT3. Reverse T3 can be seen as a sort of "blocker molecule" that fits in and occupies the T3 receptors on the cell membrane. It does not permit T3 to enter and increase energy production. It acts as a metabolic break to slow down ATP synthesis within the cell. Current research also suggests that rT3 inhibits 5'-deiodinase, suggesting it might interfere with peripheral conversion of T4 into T3. The production of rT3 is also subject to a range of environmental, lifestyle and physiological influences.

## Summary of Thyroid Hormone Physiology

- Our body needs to not only turn energy production on but also switch it off.
- Throughout the day there are times when our system requires either more or less energy, depending on the level of activity.
- Short term control is governed by the conversion of T4 into active T3 for stimulating ATP production or into reverse T3 or rT3, which acts as a metabolic brake.

**T3 and T4 are associated with the same physiological action:**

Function	Detail
Basal Metabolic Rate	T3 and T4 increase the basal metabolic rate of almost all the cells in the body. In the presence of high levels of iodothyronines, there is a slight increase in body temperature and a decrease in heat tolerance. In the presence of low levels of iodothyronines there is a decrease in basal metabolic rate and a decreased tolerance to the cold.

**Fat Metabolism**

T3 and T4 increase the breakdown of fat (lipolysis), and high levels will result in a depletion of stores of body fat and a fall in body weight. Low levels of T3 and T4 will result in the opposite.

**Carbohydrate Metabolism**

T3 and T4 increase all aspects of carbohydrate metabolism.

**Protein Metabolism**

Iodothyronines stimulate both protein synthesis and degradation. High levels of T3 and T4 will result in more protein degradation compared to protein synthesis. This will result in a fall in muscle mass and body weight. Iodothyronines play an important role in normal growth and development.

**Cardiovascular System**

The iodothyronines have a direct effect on the heart by potentiating the catecholamines. This explains the tachycardia associated with high levels of T3 and T4. When the levels of T3 and T4 are high, the increase in BMR will result in an increase in temperature. There is a physiological increase in blood flow to the skin to try and reduce the body temperature.

**Bone**

High levels of T3 and T4 are associated with increased bone turnover. Bone cells are stimulated to both increase bone resorption and bone synthesis. The more profound effect of resorption results in demineralisation of bone and therefore increases the risk of fractures and mineral abnormalities i.e hypercalcaemia.

**Central Nervous System**

The effects of the iodothyronines on the central nervous system are thought to be due to the potentiation of their catecholamine activity. The iodothyronines are also essential for mental development.

## Thyroid Binding Proteins

As we discussed above, total T4 and total T3 measure the free hormone level **plus** hormone bound to binding proteins. When evaluating thyroid hormone levels we need to keep in the back of our minds the various factors that affect binding protein.

The main binding protein is called Thyroid Binding Globulin (TBG). It is primarily produced in the liver and is affected by liver dysfunction or liver disease, prolonged illness, and certain medications especially estrogens from HRT or Birth Control Pills (BCPs).

A progesterone-estrogen imbalance can interfere with thyroid function. It can also be caused by diminished thyroid function. High levels of estrogen (BCPs or pregnancy or HRT) will increase the amount of thyroid binding globulin that binds to T4. This can give misleading elevated T4 levels, which looks like hyperthyroidism when it's not.

Estrogen and thyroid hormone have opposite effects on the body: estrogen causes calories to be turned into fat, and thyroid hormone causes fat calories to be turned into energy. So, when progesterone is low and estrogen is dominant (even when TSH blood levels are normal), and symptoms of hypothyroidism are present, high estrogen levels could be the cause. Weight gain can also upset the progesterone-estrogen balance causing an increased estrogen level and a decreased progesterone level. After testing to verify that this is happening you may want to consider supplementing with progesterone creams. Higher levels of progesterone activate estrogen receptor sites in the body and cause the estrogen to be used before it can do harm. The progesterone-estrogen balance can be determined by a monthly saliva test or by progesterone and estrogen blood tests.

We recommend that you check Free T4 in the presence of elevated estrogen levels. This will give you a more accurate assessment of thyroid function.

Other factors that affect binding globulin include:

- Insulin resistance
- Severe acute illness
- Chronic illness
- Malnutrition

## Factors affecting peripheral metabolism of thyroid hormone

As mentioned above the liver and kidney have a primary influence on circulating levels of thyroid hormones. So, the health and function of the liver plays a critical role in thyroid hormone function.

The following have been shown to influence deiodination leading to decreased circulating T3 levels and increased circulation of rT3:

- Liver dysfunction
- Liver disease
- Oxidative stress, antioxidant insufficiency and lipid peroxidation within the liver

- Heavy metals (cadmium, mercury and lead)
- Toxicity: Fluoride, pesticides, radiation, PCBs, Dioxins, Phthalates
- Medications:
  1. Beta blockers
  2. Birth control pills
  3. Estrogen
  4. Lithium
  5. Phenytoin
  6. Theophylline
  7. Chemotherapy
  8. Glucocorticoids
  9. Interleukin 6
  10. Clomipramine

The health of the kidney will have an influence on circulating levels of thyroid hormone.

#### **Factors that Affect 5'-deiodinase Production**

Selenium deficiencies, stress, heavy metal toxicity: cadmium, mercury, or lead, inadequate protein intake, high-carb diet, increased cortisol, decreased kidney or liver function.

Inflammation and the production of inflammatory cytokines inhibit the function of the 5'-deiodinase enzyme.

**Lifestyle factors** will have a significant impact on peripheral metabolism of thyroid hormones. The following have been shown to influence deiodination leading to decreased circulating T3 levels and increased circulation of rT3:

- High stress and elevated cortisol levels
- Selenium deficiency
- Diet:
  - High in cruciferous vegetables (goitrogen containing foods)
  - Low protein
  - Low fat
  - Low carb
  - Increased alcohol use
  - Soy
  - Walnuts
- Poor nutrition and nutrient deficiencies: Iodine, iron, selenium, zinc, vitamins A, B2, B6, B12
- Fasting
- Calorie restriction

- Lack of exercise
- Alcohol intake

There will be a point at which enough of these factors will lead to significant thyroid dysfunction. We recommend that you always keep these factors in the back of your mind when assessing whether or not a patient needs thyroid hormone. It may not actually be the lack of thyroid hormone that is the problem but dysfunction in the liver and/or kidney and associated lifestyle factors that cause the presentation of hypothyroidism.

## **Factors associated with an increased reverse T3 level**

- Diabetes
- Elevated cytokine levels: IL06, TNF-alpha, IFN-2
- Fasting
- Free radicals
- Heavy metals: Cadmium, Mercury, or Lead
- Increased epinephrine or norepinephrine
- Prolonged illness
- Stress

## **Is it necessary to measure reverseT3?**

The availability of “cheap” reverse T3 measurement in the serum has made this an important test to add to your advanced thyroid panel (see below for more details). However, one can make a good estimation of reverse T3 levels from knowing T3 and T4 levels. T4 will become either T3 or rT3. If T4 is elevated and T3 is low, we know that the body is producing more rT3 and this will be elevated. We can also determine reverse T3 from basal metabolic temperature assessments (see below).

### ***rT3 and Basal Body Temperature Testing***

Reverse T3 levels tend to increase overnight, which causes a slowing down of the metabolism. The body enters a hibernation state: decreased cortisol, increased melatonin and HGH. To determine ability of the body to produce T3 as opposed to rT3 and increase metabolism you want to look at the difference between early AM temperatures and mean daytime temperatures. If the temperatures are similar there is a likelihood that the body is producing higher than optimal levels of rT3. You want to be able to stimulate metabolism and tell body to get out of hibernation state. Eat a good breakfast to give the body the message that it needs to increase T3 and decrease rT3. Skipping breakfast will cause a decrease in t3 and maintain the hibernation state.

## **Factors that increase the conversion of T4 into T3**

1. High protein diet
2. Estrogen

3. Glucagon
4. Insulin
5. Melatonin
6. Nutrients: Selenium, potassium, iodine, iron, zinc, vitamins A, B2, E
7. Testosterone
8. Tyrosine

## Summary

Just like a car needs an accelerator and brakes for proper function, the same is true of the body. T3 is the accelerator and reverse T3 is more like the break. If there is a sudden need for less energy production, we make more rT3 from T4. If this reduced need for energy persists over months, we make less T4 by reducing the output of TSH from the pituitary. This leads to a situation of low normal TSH, which in turn reduces T4 production and produces a low normal level of T3. The body, in its infinite wisdom, wastes less effort in manufacturing thyroid hormone that will not be used. Ultimately T3 and rT3 help the body manage its energy needs.

In this next section we will discuss how to use Primary and Advanced FDM Testing to help assess the thyroid.

# **Assessing For Thyroid Dysfunction**

## ***Signs and Symptoms of Thyroid Dysfunction***

### **Signs and Symptoms of Low Thyroid Hormone Production**

1. Anxiety/panic attacks
2. Brittle, striated, thickened nails
3. Constipation
4. Decreased memory
5. Depression
6. Fluid retention (this may be seen as pre-tibial edema)
7. Headaches/migraine headaches
8. Inability to concentrate
9. Menstrual irregularities
10. Nails easily broken
11. Poor circulation
12. Rough dry skin
13. Slow reflexes
14. Slow speech
15. Weight gain
16. Poor concentration
17. Muscle and joint pain
18. Bradycardia
19. Slow movements
20. Morning stiffness
21. Loss of hair from legs, axilla, and arms
22. Loss of eye lashes or lashes that are thinning
23. Itchy, dry, scaly ear canal
24. Excess ear wax (cerumen)
25. Loss of one-third of the eyebrows
26. Hair loss in front or back of head
27. Myxedema



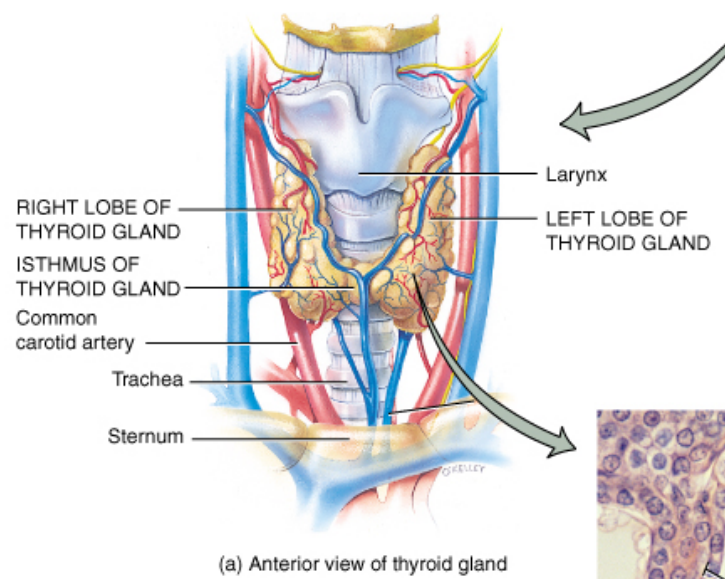
## Signs and Symptoms of High Thyroid Hormone Production

1. Goiter
2. Tachycardia
3. Warm, fine, moist skin
4. Tremor
5. Atrial fibrillation; widened pulse pressure
6. Nervousness and hyperactivity
7. Increased perspiration; < heat
8. Palpitations: tachycardia
9. Weight loss; increased appetite
10. Insomnia; fatigue; weakness
11. Increased bowel movements
12. Exophthalmos; blurred and double vision
13. Myopathy: often involving the shoulder
14. Infiltrative dermopathy (aka. Pretibial myxedema): red and very itchy lesion

## Assessing the Thyroid: Physical Examination Techniques

### Palpating the thyroid gland

This is a test that is often omitted and not done. You have to examine the gland itself. If the gland is palpable it is to some extent abnormal.



The above illustration shows you exactly where the thyroid gland is located. A normal gland can be palpated but it is in no ways hard or enlarged. It feels very velvety not unlike palpating a lipoma. A basic rule of thumb when palpating the thyroid you should say to yourself “There it was, I think!”

If you can say “Here’s the thyroid” it’s probably abnormal. Another thing is to look for flushing of the skin overlying the gland after palpation. Don’t palpate too hard as this can cause an increase in hormone.

## The Achilles Return Reflex

In the absence of spinal lesions a bilateral delay in the achilles return reflex is a strong indication for low thyroid activity. If the patient has brisk Achilles return reflexes and they have symptoms of low thyroid function, consider looking for other causes for their symptoms before treating the thyroid.

### Directions

1. Have patient kneel or lie with the foot dangling over the edge of the table or chair
2. Tap the tendon directly, with your left hand dorsiflexing the foot for optimal stretching of the tendon
3. As you tap the tendon, the foot should plantar flex briskly, without any delay

### Results

**Normal:** Brisk return of the Achilles reflex bilaterally

**Delayed reflex bilaterally:** Suspect hypothyroidism

### Interfering factors

Neurological deficits e.g. spinal lesions

## Assessing the Thyroid: In-Office Testing

### The Iodine Patch Test

The iodine patch test is a functional assessment for iodine status in the body. By painting the skin with a 2% solution of iodine we can see how quickly the body absorbs the available iodine. If there is a deficiency or need for iodine the slightly brownish yellow stain will fade in less than 24 hours. This indicates that there is not sufficient enough iodine to normalize thyroid secretions. The quicker the iodine fades, the greater the deficiency can be assumed to be.

## Functions of Iodine

Principal role in the manufacture of thyroid hormone

Modulation of the effect of estrogen on breast tissue

The conversion of estrone and estradiol into estriol

## Results

**Color lasts for > 24 hours**

Sufficient iodine

**Color fades in < 24 hours**

Deficient iodine

## When would you run this test?

1. When iodine deficiency is suspected
2. Patients present with signs of hypothyroidism
3. Patients with low basal body temperatures

## Clinical implications

As was mentioned above, the quicker the iodine fades, the greater the deficiency can be assumed to be. The following protocol should be implemented until sufficiency is obtained i.e. the stain remains for a minimum of 24 hours:

**20-30 drops of liquid iodine as potassium iodide (Biotics Research) per day**

## *Assessing the Thyroid: A Take Home Test*

### Body Temperature Test

It is well known that body temperature closely reflects an individual's metabolic energy state. The optimal average day time temperature is 98.6°F. A temperature below that reflects a less than optimal metabolic state. From our previous discussions we know that a lower than optimal metabolic state is most often controlled at the level of the thyroid, but the adrenals have a hand in it too. Body temperature can be used diagnostically to check the level of metabolic activity and can be used to monitor treatment.

This is a great tool since it doesn't cost anything and gives patients instant feedback.

If you put a patient on a protocol to correct imbalances seen in the metabolic energy states you can quickly see if the protocol is working. Ideally you should see a stable and gradual rise from low and /or unstable temperatures to an optimal 98.6°F.

As you will see below, unstable temperatures i.e. a wide variability in body temperature from day to day is a reflection of a weak or fatigued adrenal system.

## When would you run this test?

1. To assess the hormonal influences on metabolism
2. To help identify sub clinical hypothyroidism
3. To identify adrenal and blood sugar influences on basal metabolism

## Taking and Plotting Temperatures

The best tool to monitor metabolic changes is a simple thermometer and a temperature graph. Temperatures are measured orally because underarm or axillary temperatures are cooler than oral temperatures and tend to be variable in adrenal stress. Taking temperatures by ear is the least reliable. We recommend good old fashioned oral temps. In order for the temperature to be accurate you must explain to your patients that they need to place the thermometer deep under the tongue. They should avoid taking temperatures after activity (even climbing up stairs can alter the temperature), eating, or drinking for at least 20 minutes.

We recommend that they take 3 temperatures across the day approximately 3 hours apart. They should take their first morning temperature approximately 3 hours after waking up.

If your patient rises at 7:30 AM, their temperatures should be taken at 10:30 AM, 1:30 PM, and 5:30 PM. It is best to ask them not to take a number of temperatures in a row because experience shows that the temperature will rise with each subsequent reading.

Something as simple as the movement of muscles in the mouth can raise the temperature! So it is recommended that your patients take one temperature reading 3 times/day.

## What kind of thermometer do you recommend?

There are a number of excellent models available at your local drug store. You can either purchase a number of them and rent or lend them to your patients, or just make a recommendation of a brand you have tried, is accurate, and gives a quick reading.

You may want to look at the Lumiscope Digital thermometer. Sadly mercury thermometers are not the most ideal. I say sadly because they are extremely accurate but they contain mercury, can break, are too slow, and if you want to get reproducible temperatures a mercury thermometer must be left in the mouth for the same length of time each time you take a temperature.

## Directions of how best to take temperatures:

1. Take 3 temperatures a day 3 hours apart from one another.
2. Take the first temperature approximately 3 hours after getting up
3. Avoid activity, eating, and drinking 20 minutes prior to testing
4. Use a digital thermometer, not a mercury or an ear thermometer
5. Take only one reading each time

6. Fill out the temperature chart and bring it back to the clinic at the next appointment

## Recording Temperatures on a Graph

Have your patients calculate the average of the 3 daily temperatures taken. The daily average is then plotted on the graph. They can use an X but I recommend that they use a number that represents the number of temperatures taken that day. Thus if they only took 2 temperatures on one day they put a number 2 in the cell that corresponds to the average daily temperature and the day of the week the temperature was taken.

They can also put in additional data such as mood, energy level, changes in supplement protocols or medication etc. This can be helpful when a temperature is out of the usual pattern. Finally have them connect the numbers in a line so you get a graphical representation of the temperatures. If they miss a day have them stop and restart the line. Do not have them connect the days either side of the missing day.

## Interpreting the Temperature Graph

There are some very distinct patterns you can see on a temperature graph:

### ***Stable but low temperatures on graph***

Patients with a **low functioning thyroid or hypothyroidism** typically have very stable, but low temperatures. The graph in this situation will be low but the actual temperature will not vary from day to day. A stable pattern is also seen in healthy individuals. In these cases the temperatures will be at 98.6

### ***Considerable variability and instability on graph- Sharp and Spiky***

Adrenal types i.e. people with **low adrenal function or adrenal fatigue** show considerable variability and instability in their temperatures. Adrenal types are hot in the heat and cold in the cold. This can produce a very unstable pattern. Values may fluctuate from low 98s to low 96s from day to day. The pattern looks very sharp and spiky.

As your adrenal patients begin to heal you may notice a pattern of contraction in their highs and lows i.e. the differences between their highs and lows are not as extreme.

**This is a sign that healing is taking place** and shows stabilization in the pattern. This may be due to either a reduction in stress i.e. a stressful burden has been lifted or there is less thyroid stimulation, or they are getting stronger because of a protocol they are on.

### ***Rising in average temperatures on graph- stable or unstable***

**As the metabolic energy increases** in your patients you may notice a rising in the average temperatures on the graph. The pattern may be stable or unstable.

### ***Increase in variability- an expansion pattern***

You may also note an increase in variability that can be described as an expansion pattern. **Greater stress on the adrenals** or an **increase in thyroid stimulation** causes

the temperatures to be less stable. This pattern shows that the patient is unable to handle the increasing stress on the body. The pattern may be transient i.e. a one off stressful event (a short term increase in workload) or prolonged showing a movement towards maladaptation and worsening adrenal fatigue. The thyroid can contribute to this and you will often see this when patients are on T3 therapy and are on a dose that they cannot handle.

## **A contracting/Rising pattern – a sign of improvement**

A sign that a patient is improving is a contracting/rising pattern. The highs and lows are getting closer together and there is a general rise in body temperature.

**NOTE:** A sudden rise in temperature lasting one or more days is a sign of an infection producing a fever in the body.

## **Using the Graph to Monitor Thyroid Therapy**

In a thyroid case the baseline temperatures are going to be low. This may be as low as 96.5°F. The low temperature is typically stable. When thyroid therapy (either supplements or armor thyroid) is started you will see a rising pattern in the graph. This is often seen after starting or increasing therapy. A pattern that has plateaued and is stable is a sign that the current dose of therapy has taken the body to a particular level of metabolic activity. If the plateau is below 98.6°F you may want to increase the dosage of medication. When the therapy has brought the temperature up to 98.6°F and the pattern is stable you know that the correct level of medication has been reached. However, you may have reached a level of thyroid support that has taken the body to a level of metabolic energy that is too much for the adrenals to handle. In this situation don't be surprised to see an expansion pattern with a concomitant drop in temperatures. This is a good time to look at adrenal support to allow the body to better handle an increase in metabolic activity.

## **Using the Graph to Monitor Adrenal Therapy**

A baseline pattern of a patient in adrenal fatigue will be the unstable pattern as mentioned above. The temperatures are typically below 98.6°F but can fluctuate from day to day, with highs in the low 98s and lows in the 96°F range. The temperatures will rise in warm or hot weather and drop in cold or cool weather. When adrenal support is started you will notice a decrease in variability and a contraction in the pattern. The highs are not as high and the lows are not as low. As adrenal function improves we actually see a stabilization of the pattern but temperatures remain low. This is a good sign. The first sign that your adrenal support is working will be the reduction in variability in the temperatures. Continued adrenal support will cause a stabilization in the pattern followed by a gradual rise towards an optimal temperature of 98.6°F, which is a hallmark of a healthy metabolic state.

## A Question of Timing

If the adrenal support is working well you should expect to get to the rising stable pattern after a few months. This is of course entirely dependent on how long the adrenal fatigue has been a problem. If the fatigue is severe and chronic each of the above phases may last longer, so you might see it take a month for the variability to reduce, a month for the temperatures to stabilize and start to rise, and another month for the optimal temperature to be achieved.

If you see no response or change in the pattern after a couple of months you may need to change the protocol or consider some other cause, i.e. the patient may be suffering from toxicity.

## Form Download

Please download a master copy of the Body Temperature Testing chart at this link:

<http://www.functionalmedicineuniversity.com/members/163.cfm>

The form below is the handout to give your patients.

---

---

## Body Temperature Test Instructions

---

---

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Your body temperature reflects your metabolism, which is largely determined by the hormones secreted by the thyroid and to a lesser degree, the adrenal glands. Although blood hormone testing is common, there is considerable evidence that the current tests for the diagnosis of hypothyroidism (low thyroid function) are insensitive and somewhat lacking in accuracy. With adrenal function taken into consideration, the function of the thyroid gland can be observed by simply measuring your body temperature. All that is needed is a thermometer.

### Instructions:

1. Please measure your temperature orally and place the thermometer deep under your tongue. Do not take your temperature underarm or use an ear thermometer.
2. Avoid taking temperatures after activity (even climbing up stairs can alter the temperature), eating, or drinking for at least 20 minutes.
3. Take 3 temperatures across the day approximately 3 hours apart.
4. Take your first morning temperature approximately 3 hours after waking up i.e. if you rise at 7:30 AM, your temperatures should be taken at 10:30 AM, 1:30 PM, and 5:30 PM. Please do not take a number of temperatures in a row because experience shows that the temperature will rise with each subsequent reading.

### What kind of thermometer do you recommend?

There are a number of excellent models available at your local drug store. We recommend the Lumiscope Digital thermometer.

### Summary

- Take 3 temperatures a day 3 hours apart from one another.
- Take the first temperature approximately 3 hours after getting up
- Avoid activity, eating, and drinking 20 minutes prior to testing
- Use a digital thermometer, not a mercury or an ear thermometer
- Take only one reading each time
- Fill out the temperature chart and bring it back to the clinic at the next appointment

### Recording Temperatures on a Graph

- Please calculate the average of the 3 daily temperatures taken and plot that average on the graph.
- We recommend that you use a number that represents the number of temperatures taken that day when writing on the graph.
- Thus if you only took 2 temperatures on one day you put a number 2 in the cell that corresponds to the average daily temperature and the day of the week the temperature was taken.
- You can also put in additional data such as mood, energy level, changes in supplement protocols or medication etc. This can be helpful for us to work out the pattern of the temperature changes.
- Finally please connect the numbers in a line so we get a graphical representation of the temperatures. If you miss a day please stop and restart the line i.e. do not connect the days either side of the missing day.
- Please plot your averages on the graph on the next page.



## Assessing the Thyroid: Blood Testing

	Normal Range	Optimal Range
<b>TSH</b>	0.4 -5.5	1.3 – 2.0
<b>Total T3</b>	1.23 – 3.53 nmol/L 60 – 80 (US)	1.84 – 1.91 (SI) 120 – 125 (US)
<b>Total T4</b>	61.8 – 169.9 nmol/L 4.5 – 12.5 (US)	96.53 – 104.25 (SI) 7.5 – 8.1 (US)
<b>Free T3</b>	2.3 – 4.2 pmol/L	3.0 – 3.25 pmol/l
<b>Free T4</b>	9.1 – 31.0 nmol/L 0.7 – 2.4 (US)	12.9. – 19.31 pmol/L (SI) 1.0 – 1.5 (US)
<b>Reverse T3</b>	90 – 350 pg/ml	50 – 150 pg/ml

These are the reference ranges for the tests on a thyroid panel. Please note that some of the older tests T7, FTI or T3 uptake are not necessary to run if you run these tests. The one we want to mention is T3 uptake. T3 uptake is **NOT** a measure of T3. It measures the open T3 binding sites on carrier proteins. T3 uptake is to free t3 as TIBC is to free serum iron. It's not actually that good because T3 shares some of its binding sites with T4. The lab uses T3 uptake with total T4 to calculate the T4 index which is a calculated estimate of free T4. Don't ask for these and just order free T4!

This section will focus on the patterns you can find using this type of analysis. In a later section we will introduce a different way of looking at the thyroid panel and present a concept called the Functional Thyroid Scale.

## Functional Analysis of Thyroid Dysfunction

Here are some functional thyroid problems that can be assessed using Blood chemistry analysis

- **Hypothyroidism**
- **Hyperthyroidism**
- **Iodine insufficiency**
- **Selenium insufficiency**

### Primary Hypothyroidism

There are a number of different classifications of clinical hypothyroidism, depending on the endocrine gland that is dysfunctional.

In primary hypothyroidism the problem is located in the thyroid gland itself, which fails to produce thyroid hormone. Primary hypothyroidism is often preceded by autoimmune thyroid disease. If you have a patient with suspected thyroid disease you should screen for thyroid antibodies (see below).

### **Pattern**

- TSH levels increased above 2.0
- Normal or decreased total T4 level ( $<77.2$ ) and/or T-3 ( $<1.54$ ), free T4  $<9.1$ , free T3  $<3.59$
- Increased cholesterol ( $>5.69$ ) and triglyceride level ( $>1.24$ )

## **Secondary Hypothyroidism**

In secondary hypothyroidism the problem is due to an anterior pituitary hypofunction, which fails to produce optimum levels of TSH to stimulate the thyroid. Thyroid hypofunction secondary to an anterior pituitary hypofunction (*Secondary Hypothyroidism*) is getting more common. Anterior pituitary hypofunction is a common problem and one that is frequently mistaken for thyroid hypofunction (the subjective indications are usually identical and the patient's axillary temperature will frequently be below normal).

### **Pattern**

Suspect anterior pituitary dysfunction if the subjective indications of thyroid hypofunction are present and the following pattern is seen :

- A decreased TSH ( $<1.30$ )
- A decreased T-3 uptake ( $<0.27$ )
- A normal T-4, T-3 and FTI

The likelihood increases if serum triglycerides are elevated ( $>1.24$ ) and the total cholesterol levels are increased ( $>5.69$ ).

## **Tertiary Hypothyroidism**

A third form of Hypothyroidism called tertiary hypothyroidism exists. In tertiary hypothyroidism, the hypothalamus shuts down protectively in response to stress, producing low levels of TSH, T4, and T3. This is often linked to chronic fatigue syndrome and fibromyalgia, this condition can cause low body temperatures, a tendency toward infections, and the other metabolic consequences of low thyroid.

It has been suggested that problems with the mitochondria, the cellular structures that furnish us with energy, may cause this suppression of the hypothalamus.

## **Problems using TSH alone as a marker for Hypothyroidism**

TSH is often insensitive to mild or borderline cases of hypothyroidism. In many cases TSH levels may be within normal limits yet the patient is suffering from all the classic signs and symptoms of low thyroid.

Look at the following to help diagnose what is often called sub-clinical hypothyroidism

- Basal body temperature
- Achilles return reflex
- Iodine status
- Free T3 and Free T4 levels
- History, and clinical signs and symptoms.

## **Euthyroid Sick Syndrome**

Euthyroid sick syndrome is used to describe non-thyroidal illness. It is a condition of normal thyroid gland activity with a reduced peripheral 5'-deiodination conversion of T4 into T3 due to liver or renal dysfunction or disease.

## **Low T3 Syndrome**

Low T3 syndrome is similar to Euthyroid sick syndrome except that there's no underlying liver or renal dysfunction or disease. Low T3 syndrome is likely to be due to many of the conditions that affect the peripheral conversion of T4 into T3 with a rise in reverse T3 levels (stress, malnutrition, low calorie diets, lack of exercise etc.)

In both cases there will be an increase in rT3

### ***Euthyroid Sick Syndrome and T3 Syndrome Pattern- Pattern***

- Low total (<1.54) and Free T3 levels (<3.59)
- Total T4 levels are usually normal
- Free T4 levels are normal
- TSH is either normal or decreased (<1.3)

For Euthyroid Sick Syndrome we see other findings on blood chem screen with evidence of liver or renal dysfunction:

- Decreased albumin (<40), increased BUN (>5.71), Increased creatinine (>97.2), decreased potassium (<4.0) and increased sodium (142) (high cortisol), increased SGPT/ALT (>30)

With Low T3 Syndrome we don't see any liver or kidney dysfunction

## **Low Body temperature- Wilson's Thyroid Syndrome**

In this condition patients have all of the symptoms of thyroid disease but their thyroid labs are normal. The thyroid gland in Wilson's Thyroid syndrome is usually functioning normally. In most cases the thyroid hormone tests, such as TSH and T4 are normal.

There may be an associated low normal or decreased total T-3 (<1.54), free T3 (<3.59) and T-4 level (<77.2) and an increased reverse T3 level. There is a frequent history of high stress, fasting, dieting which causes impaired conversion of T4 into T3. This leads to a low T3:rT3 ratio. There is often a low average daytime oral temperature (<97.8). In

Wilson's thyroid syndrome there is often a low average daytime oral temperature (<97.8). Low daytime oral temperatures are associated with increased reverse T3 levels

## **Hyperthyroidism- Pattern**

Although less common than hypothyroidism, the following pattern may help elucidate a developing or existent hyperthyroid state.

### **Hyperthyroidism is possible if:**

- TSH is low (<1.3)
- The likelihood increases when there is also an increased T3 (>3.53), Free T3 (>6.56), T3 uptake (>0.37), FTI (>11.0) and/or T4 (>154.4) .
- Consider running thyroid antibody studies to rule out Hashimoto's thyroiditis and Grave's disease.

## **Iodine Insufficiency**

Iodine is an essential nutrient for the production of thyroid hormone. Although thought of as rare, iodine deficiency is actually quite common as there are many reasons for its deficiency:

- A poor diet
- Exposure to many halogen compounds can interfere with iodine metabolism (i.e. chlorine, bromine, fluoride).

These common compounds render normal iodine uptake extremely difficult and may displace normal stores.

In iodine insufficiency the total T4 will often be decreased (<7.5), the total T3 is often increased (> 125) and there is usually a normal or mildly elevated TSH (>2.0)

Suspected iodine deficiency can be followed by using the Iodine Patch Test

## **Selenium Deficiency**

Selenium is an essential nutrient for 5'-deiodinase activity, the enzyme involved in the peripheral conversion of T4 into T3. Low selenium levels are associated with a diminished deiodination of T4 into T3. Selenium is also necessary to degrade rT3

Consider selenium deficiency If the total T3 is reduced (<120) and/or freeT-3 is reduced (<3.0) or T-3 uptake is reduced along with a normal TSH and T-4 level

## **The Functional Thyroid Scale**

As you can tell from the section above blood levels of thyroid hormones are very important when trying to determine the cause of your patients thyroid dysfunction. Unlike other values on a chemistry screen, the tests on a thyroid panel are very closely inter-related. Sometimes it's hard to appreciate this interconnectedness when looking at the individual values on the chemistry screen which is why we recommend you use something we call the Functional Thyroid Scale.

The Functional Thyroid Scale is a method of looking at the inter-relationships between blood hormone levels. Looking at thyroid values in term of high, optimal, and low doesn't really help when trying to understand this close inter-relationship.

The following analogy may help us to see why.

## Normal versus Optimal in terms of the thyroid lab values

Let's say the normal height for a man is 5 foot 3 inches to six foot and normal weight is 130 to 200 pounds. The results column of a lab report would declare that a 5 foot 3 inch man weighing 200 pounds to be just as normal as a six foot man weighing 130 pounds! Both would be considered normal and we can presume that they are both in the same state of health! In the real world we know that the first man is obese and the second is severely undernourished. The two are unlikely to be in the same state of health. Looking at the thyroid values this way may not be the best way to get interpretive information.

## The Functional Thyroid Scale

The Functional Thyroid Scale is an optimal scale that converts different thyroid hormone values to a common unit of measurement. By looking at values relative to an optimal scale we get to see and describe the complex relationship that exists between these hormones.

-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
LOW	<----- Optimal -----> i.e. still within the "normal" range										HIGH		

**On the above scale zero reflects the absolute optimal range.**

- 1 = Possibly high/low
- 2 = Mildly high/low
- 3 = Moderately high low
- 4 = high/low
- 5 = Very high/low
- +5 = Extremely high/low

## ***What lab tests do you need to use the Functional Thyroid Scale?***

We recommend the following tests be on your general metabolic panel to maximize your use of Functional Thyroid Scale

- TSH
- Total T3

- Total T4

We also recommend that you add free T4 and Free T3 with those patients that have conditions that can shift binding proteins: patients with high levels of estrogen (BCPS, HRT, pregnancy), insulin resistance, acute illness, chronic illness, malnutrition

Do not order FTI, T3 Uptake etc. as they are antiquated ways to approximate T4 and T3 levels. Analyze your results using the Functional Thyroid Scale

## This is what the Functional Thyroid Scale looks like:

Functional Thyroid Assessment Scale														
Functional Thyroid Assessment Scale Standard US Reference Ranges														
Labs	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
TSH	0-0.5	0.6	0.7-0.8	0.9-1.0	1.1-1.2	1.3-2.0	2.1-2.5	2.6-3.5	3.6-4.5	4.6-5.4	5.5-6.4	6.5-7.6	7.7-8.4	8.5-99
TT4	0-4.5	4.6-5.2	5.3-6.1	6.2-6.9	7.0-7.4	7.5-8.1	8.2-9.0	9.1-10.2	10.3-11.3	11.4-12.4	12.5-13.6	13.7-14.8	14.9-16.0	16.1-99
TT3	0-60	61-75	76-90	91-106	107-119	120-125	126-137	138-152	153-166	167-180	181-195	196-210	211-225	226-999

Functional Thyroid Assessment Scale Standard International Reference Ranges														
Labs	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
TSH	0-0.5	0.6	0.7-0.8	0.9-1.0	1.1-1.2	1.3-2.0	2.1-2.5	2.6-3.5	3.6-4.5	4.6-5.4	5.5-6.4	6.5-7.6	7.7-8.4	8.5-99
TT4	0-57.9	57.8-66.9	67.0-78.5	78.6-88.8	88.9-96.4	96.5-104.3	104.4-115.8	115.9-131.3	131.4-145.4	145.5-159.6	159.7-175.0	175.1-190.5	190.6-205.9	206.0-1000
TT3	0-0.93	0.94-1.16	1.17-1.39	1.40-1.63	1.64-1.83	1.84-1.92	1.93-2.11	2.12-2.35	2.35-2.55	2.56-2.76	2.77-3.00	3.01-3.23	3.24-3.46	3.47-16.0

A working copy is included in the handouts section of the FMU library.

<http://www.functionalmedicineuniversity.com/members/163.cfm>

## How to use the scale

Plot the thyroid values on the scale using the provided lab ranges. Remember, this is not an absolute but a way to understand what is going on. The next section will present some common patterns on the scale and look at the clinical implications.

### Healthy

	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
TSH						1.3								
TT4						7.6 (97.8)								

TT3						125 (1.9)									
-----	--	--	--	--	--	--------------	--	--	--	--	--	--	--	--	--

The above example indicates a person who might be called metabolically healthy.

### ***Hypothyroid***

	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
TSH											5.5			
TT4		(4.7) 58.0												
TT3				98 (1.5)										

In a hypothyroid situation the TSH is high telling us that the pituitary and body desire/need thyroid hormone. TT4 is low but in the “normal” range and T3 is to the right of it in low but “normal” range. This is a typical pattern of a thyroid gland that is unable to keep up T4 production to meet body’s needs. The body compensates by converting as much T4 in T3 as it can. This is a classic case of hypothyroidism.

### ***Hyperthyroidism***

	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
TSH			0.8											
TT4											13.9 (177)			
TT3						122 (1.85)								

In a hyperthyroid situation e.g. Hashimoto’s thyroiditis, the TSH is low. The TT4 is high because of damage to the cells of the thyroid, which release T4 into the blood stream.

The TT3 will be relatively lower than TT4 because the body is jamming on metabolic breaks to protect itself from excessive stimulation. More TT4 is converted into reverse T3. Both hormones may be high but TT3 is to left of TT4. In this pattern it is important to measure thyroid auto-antibodies and to get a reverse T3 reading.

### ***Adrenal Fatigue***

	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
--	----	----	----	----	----	---	----	----	----	----	----	----	----	----

TSH					1.1									
TT4				7.1										
				(89.0)										
TT3				98										
				(1.5)										

In cases of adrenal fatigue the body can only handle a low amount of metabolic energy so TSH is usually below optimal. This low level of stimulation causes T4 and T3 to be below optimal at roughly the same place.

## Thyroid Hormone Interpretation

State of Health	TSH	T4	T3
Healthy	Optimal	Optimal	Optimal
Adrenal Fatigue	Low	Low	Low
Primary Hypothyroidism (problem with gland itself)	High	Low	Low to right of TT4

### **Adrenal Fatigue**

Symptoms predominate in the adrenal column of the Metabolic Symptom Survey (See the section on Metabolic Energy below). This may be mistaken for hypothyroidism but TSH will be lower in adrenal problems. Also, this should not be confused with pituitary trouble. Body temperatures will be very unstable and low- a classic sign of adrenal weakness.

### **Primary Hypothyroidism**

In this case there's a high conversion of T4 to T3 because there is a high demand for T4/T3 (note high TSH). Body is getting as much T3 out as possible. The body temperatures will be low and very stable- a classic thyroid sign.

State of Health	TSH	T4	T3
Hypothyroidism due to low pituitary function	Low	Low	Low to right of TT4



Hypothyroid and Adrenal Fatigue	Optimal to High	Low	Low to right of TT4
---------------------------------	-----------------	-----	---------------------

### ***Hypothyroid due to Pituitary dysfunction***

This pattern looks just like primary hypothyroidism but the TSH is low. There's a high demand for T4/T3 because of the high conversion of T4 to T3 but the TSH doesn't rise to help T4 production because the pituitary gland is under producing TSH. The temperatures are low and very stable, which is a classic thyroid sign.

### ***Hypothyroid and Adrenal Fatigue***

In this case we have a mix of adrenal fatigue with thyroid hypofunction. The T3 is only mildly to right of T4. This is similar to the adrenal fatigue pattern but symptoms are mixed on the metabolic Symptom Survey (see below). This may also be a late stage Hashimoto's thyroiditis. There's a high demand for T4/T3 because of high conversion of T4 into to T3 and the TSH doesn't rise to help T4 production. Temperatures are low and unstable.

### ***Poor ATP Production***

State of Health	TSH	T4	T3
Poor ATP production from mitochondria	Mildly high	High	High to the right of T4

This may be due to nutrient deficiency esp. EFAs, viral damage, or toxic burden. Temperature will be low and moderately stable.

### ***Iodine Insufficiency***

State of Health	TSH	T4	T3
Iodine insufficiency	Mildly high	Low	High

### ***Selenium Deficiency***

State of Health	TSH	T4	T3
Selenium insufficiency	Optimal	Optimal	Low

Selenium is an essential nutrient for 5'-deiodinase activity, the enzyme involved in the peripheral conversion of T4 into T3. Low selenium levels are associated with a diminished deiodination of T4 into T3. Selenium is also necessary to degrade rT3.

## Auto-Immune Thyroiditis

Auto-immune thyroiditis (AIT) is the most common auto-immune disease in the U.S. and is the most common cause of hypothyroidism in the U.S. It affects women 4X more than men:

- Up to 20% of menopausal women
- Up to 24% of allergic women
- 5 to 10% of postpartum women

Women may be at a greater risk because of a key autoimmunity related locus on the X chromosome. Most AIT cases occur because T cell reactivity initiates the production of autoantibodies directed against thyroid-related antigens. The autoantibodies are specific to particular thyroid tissue. Understanding this will make your understanding of the various auto-antobody tests a lot clearer:

**Extracellular – thyroglobulin (TG)**

**Cell surface – Thyroid Receptor (TR)**

**Intracellular – TPO (TPO is the enzyme that puts iodine molecules on the tyrosyl residue to form T4) or “microsomal” enzymes**

**When immunoglobulins attach to their target tissue 3 things happen:**

1. They may cause **Hypo**thyroidism
2. They may cause **Hyper**thyroidism
3. May have no effect

Whether the patient becomes hypo or hyper thyroid also depends on a number of things:

- **Anti-TPO and anti-Tg antibodies** destroy the thyroid gland itself. They attack the enzyme TPO that creates T4 and they attack the protein (thyroglobulin Tg) made by the thyroid cells in which thyroid hormone is stored.
- **Anti-TR antibodies** usually speed up the gland by attaching to the Thyroid Receptors (TR) on the thyroid cells and either stimulate or block function depending on which type of receptor they grab. There's no feedback control on this type of activity.
- Large amounts of **stimulating** TR-ab causes Grave's disease.
- High amounts of **blocking** TR-ab causes hypothyroidism or atrophic Hashimoto's

## Hashimoto's Disease

State of Health	TSH	T4	T3
-----------------	-----	----	----

<b>Early Hashimoto's (Hypothyroid)</b>	Very low	High	High to the left of T4
--	----------	------	------------------------

Classic Hashimoto's disease presents with a moderate amounts of destructive autoantibodies. In the early stage there is gland destruction causing spillage of T4 into blood stream leading to **hyperthyroid** effect. The body reacts to this by trying to lower T4. It does this by lowering the output of TSH from pituitary. This hypermetabolic effect stresses adrenals and causes adrenal fatigue. The body deals with the hypermetabolic state by reducing conversion of T4 to T3 and increasing T4 to rT3. Hence you will see the T3 to left of T4. This is like jamming on the brakes in a car that is going too fast

## Late stage Hashimoto's Disease

Late stage Hashimotos is marked by decreased T4 and gradual hypothyroidism. Now there is adrenal fatigue and hypothyroidism.

On palpation, the gland can be abnormally firm but not usually enlarged

## Grave's Disease

Grave's disease is marked by high levels of stimulatory TR-Ab which over-stimulates the gland and T4 and T3 become very high. Because of this the TSH is very low. This is classic Grave's disease.

State of Health	TSH	T4	T3
<b>Classic Grave's Disease</b>	Very low	Very High	Very High to the right of T4
<b>Euthyroid Graves</b>	N	N or slightly high	N or slightly high
<b>Subclinical Graves</b>	Low	N	N

**Antibodies:** TR-Ab positive in 90% of cases, TSI positive in 80%

The classic pattern for Grave's disease is like a car that is speeding out of control (i.e. high T3 to the right of T4) and the driver continues to step on the accelerator.

Typically temperatures are above 98.6F or 37.1C and stable in early phase. These drop and become unstable in the later phase, which is usually due to the adrenal fatigue from prolonged T4 elevation.

## Different Types of Grave's Disease

When a patient makes a little TR-Ab they may never become hyperthyroid because the pituitary makes less TSH so a small amount of TR-Ab makes no difference.

A little TR-Ab causes "**Euthyroid Grave's disease** (TSH is normal)

A little more TR-Ab causes "**Subclinical Graves**" (Low TSH, Normal T4 and T3)

It's important to note that many people present with a mix of destructive (anti-TPO or anti-TG) and TR-Abs (which may be inhibitory or excitatory) especially people presenting with Graves.

### **A diagnosis of Graves:**

- **High levels of thyroid hormones**
- **High thyroid gland function**
- **Low TSH**
- Antibodies: TR-Ab positive in 90% of cases, TSI positive in 80% (I'll cover these in a minute)

### **How do we know if a patient has Hashimoto's or Graves?**

A gland under attack by the immune system may run too fast (Graves) at normal speed (Euthyroid graves) or Too slowly (Classic Hashimotos) depending on the types and amounts of autoantibodies attacking it. Use the following to find out:

#### **Take a careful history**

- Symptoms?
- Treatments taken?
- How did tx affect them?

#### **Perform a physical exam**

#### **Get records from current and past treating physicians**

#### **Order lab tests and imaging**

- Full thyroid panel – TSH, Total T4 and Total T3 (all 3 can be used with the thyroid scale and should be on your basic metabolic panel) add Free T3 and Free T4 and reverse T3 if you think it's necessary. Add those to your advanced thyroid panel.
- You may wish to run anti-thyroid antibody studies (i.e. anti-thyroglobulin antibody, thyroid anti-microsomal, TR-Ab and thyroid peroxidase antibody) with known or suspected thyroid abnormality.
- These tests help differentiate between multiple auto-immune conditions (i.e. Hashimoto's, Grave's disease and sub-acute thyroiditis) and is based upon these antibody titers.
- With Hashimoto's and Grave's disease the titers will be significantly elevated.
- With sub-acute thyroiditis, the levels are usually slightly increased
- TPO-Ab is the most commohnly positive auto-antibody
- TR-Ab tests both stimulating and blocking antibodies.
- A newer test called the TSI is a bio-assay in which a patient's serum is placed over a rat thryodi cell culture. Hormone output is compared to normal control.

The TSI reports effect on cell activity as a %. It is used only for stimulating antibodies normal is <130%)

# Treating the Thyroid

The following section may contain products from various products and supplements available to practitioners. Please feel free to substitute sources of supplements from other companies that you may know better. Please note neither Dr. Grisanti nor Dr. Weatherby have any fiduciary relationships with any supplement company. These protocols and product recommendations are provided for your information only.

## ***Thyroid Repair – The Basics***

A supplemental and dietary approach for mildly poor thyroid function is needed. Use foods and supplements specific for restoring thyroid function.

## **Foods to Support Thyroid Function**

1. **Iodine:** from fish, sea vegetables like kelp, dulse, arame, hijiki, nori, wakame, kombu, and sea salt. Iodised salt is a source, but not the best, as it usually contains aluminium. Cod liver oil also contains traces of iodine.
2. **Zinc:** from beef, oatmeal, chicken, seafood (especially oysters), liver, dried beans, tuna, spinach, seeds & nuts.
3. **Copper:** from liver and other organ meats, eggs, yeast, legumes, nuts, raisins.
4. **Tyrosine:** beef, chicken, fish

## **Foods to Lower Thyroid Function**

Millet is a grain that has potent anti-thyroid properties. People with hyperthyroidism may want to add millet into the diet. People with thyroid hypofunction should obviously avoid millet.

The brassica family of vegetables (Cabbage, broccoli etc.) contain molecules that act as goitrogens in the body. Goitrogens prevent iodine from being available to the thyroid and should be avoided by people with hypofunction and consumed with people who have hyperthyroidism.

## **Other Therapies**

Consider constitutional homeopathy and acupuncture to reverse imbalances and correct some of the underlying factors that contribute to thyroid problems.

Exercise, especially aerobic exercise, may actually be supportive of the thyroid. The actual mechanism is unclear but may involve an upregulation of cellular receptor activity or an increase in peripheral conversion of T4 into T3. Consider having patients with thyroid dysfunction (not hyper) to do aerobic exercise at least three or four times a week for up to 30 minutes. This in conjunction with a supplement program may be helpful to restore thyroid function.

## Some Nutrients/Supplements to Consider

**L-Tyrosine** 500 – 100 mg/day

**Iodine** – 1 mg/day

**Selenium** – 200 – 600 mcg/day

**CoQ10** – 100 – 200 mg/day

The following supplements are some of the thyroid support supplements from Biotics Research and Allergy Research. Please refer to these companies for indications of when each supplement is indicated.

### **GTA or GTA Forte II**

A Thyroid glandular designed to support both the thyroid and the pituitary so it is good for primary and secondary hypothyroidism. It contains no active thyroid hormone.

### **Cytozyme PT/HPT**

#### **Medastim**

This was developed to normalize the thyroid without using glandulars. It helps the body to adjust to thyroid fluctuations. Persons needing Meda-Stim may have subjective indications for thyroid, which cannot be verified by blood tests. Meda-Stim helps support the conversion of T4 to T3. They will be making enough T4 but not converting it to T3, so blood tests show normal. Meda-Stim acts at the cellular level. Persons in adrenal alarm use the nutrients and enzymes necessary to make this conversion for adrenal support and at the expense of the thyroid. Check adrenals. Consider L-Tyrosine. Meda-Stim will not over-stimulate thyroid.

#### **Thyrostim**

#### **Liquid Iodine**

## ***Thyroid Repair and Medication***

If the thyroid condition is very severe patients may require a prescription medication.

Giving T4 (Levothyroxine, Synthroid, Unithroid, Levoxyl etc.) is a good choice if T4 is the missing component.

With poor conversion from T4 to t3, a desiccated thyroid preparation works best (e.g. Armor Thyroid). This will provide the needed T3. Armor thyroid is best taken in 3 divided doses across the day. This provides for more stable T3 levels. Taking the dose all at once in the AM tends to be stressful for the adrenals. This may leave those with weak adrenals feeling very tired in the afternoon.

For some individuals the adrenals may be too weak to handle desiccated thyroid. In these cases the patient responds initially with better energy and fewer symptoms. This is followed soon by a crash in which the energy drops to lower levels than prior to desiccated thyroid. We may start to see adrenal symptoms emerge (anxiety, insomnia, and palpitations). This is also seen with T3 preparations (cytomel).

## T4 Medications

The following are straight T4 preparations. They may contain lactose, which in certain individuals may interfere with absorption. The absorption of these drugs may vary from person to person. All are prepared for immediate release.

1. Synthroid
2. Levothyroid
3. Levoxyl
4. Eltroxin

## T3 Medications

All of the following preparations of T3 are for immediate release into the body.

1. Cytomel
9. Triostat (injectible T3)
10. Liothyronine sodium (generic)

There may also be slow release T3 preparations available that we are unaware of.

## Desiccated Thyroid Hormone Medications

The following are some of the desiccated thyroid hormone medications available. We have put the ratios of T4 to T3 in these medications.

Medication	Ratio of T4:T3
Armor	4:1
Thyroid USP (may contain lactose, sucrose, dextrose, and/or starch. Approx. 99% of this medication is <b>not</b> thyroid.)	4.2:1
Thyroid Strong	3.1:1
Thyrar (bovine)	Unknown
S-P-T (Porcine thyroid in soybean oil)	Unknown
Liotrix	4:1
Thyrolar	4:1



Euthroid	4:1
----------	-----

## Thyroid Medication and Thyroid Tests

TSH	T4	T3
<ul style="list-style-type: none"><li>▪ Optimal if dose is proper</li><li>▪ High if dose too low</li><li>▪ Low if dose too high</li></ul>	If TSH is optimal, T4 will be low	If TSH is optimal, T4 will be high

If you are using the temperature testing to follow your thyroid and adrenal patients you may notice that temperatures are unstable especially with cytomel but not so with desiccated preparations such as Armor.

## Compounded Thyroid Medication

Using a compounding pharmacist may be the best option for prescribing thyroid medication for your patients if you have a license to prescribe drugs. You can have a preparation prepared in any ratio of T4:T3 and have important nutrients added to the preparation such as selenium, zinc, or iodine.

## What to do if the reverse T3 is elevated?

Excess reverse T3 will inhibit the conversion of T4 into T3 and occupy the same receptor sites as free T3. While free T3 activates the receptor reverse t3 will not. High levels of reverse T3 may cause hypothyroidism while the labs are normal.

If the patient is on T4 you may want to lower the dose of thyroid medication because the T4 in the medication is being converted into reverse T3. An option may be to give the patient T3 (see above for recommendations), which will cause the TSH to come back into balance.

When you see an elevated reverse T3, make sure to test cortisol and DHEA levels with the Adrenal Stress Index.

## Some of the common causes of an increased reverse T3 include:

- Yo-yo dieting
- Physical and mental stress
- Infections

- Heavy metal toxicity
- It's common in Chronic Fatigue Syndrome and Fibromyalgia

### **Consider the following if you see a high reverse T3 and thyroid symptoms exist:**

- Eliminate stress
- Treat selenium and/or iodine deficiency
- Meda Stim (Biotics Research) – 1-3 per day
- Se-Zyme (Biotics Research) – 1-3 per day
- Phos Serine Complex (Allergy Research) 1 at breakfast & dinner
- Cytozyme PT / HPT (Biotics Research) - 1 at breakfast & dinner
- Super EPA (Allergy Research) - 3 p.d.
- GlucoBalance (Biotics Research) - 1-2 at each meal
- ADHS (Biotics Research) if the cortisol is elevated on the Adrenal Stress Index

### ***Positive Thyroid Antibodies***

Elevated antibodies indicate an auto-immune condition of thyroid (Hashimoto's Thyroiditis or Grave's Disease). Also consider whether or not the patient has food tolerances especially wheat. Hashimoto's disease is correlated with gluten intolerance.

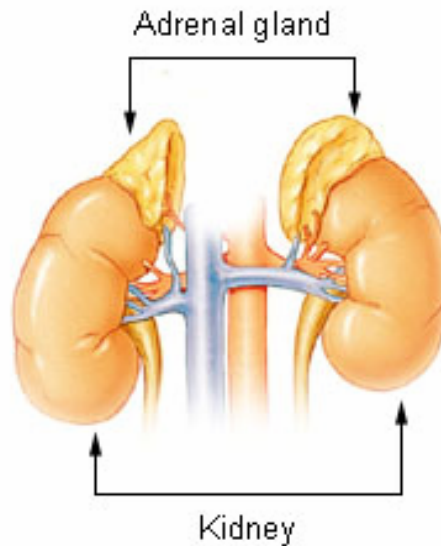
#### **Consider the following:**

- GTA (Biotics Research) - 1 at each meal
- Or consider GTA Forte II (Biotics Research) at 1 -2 per day
- Meda Stim (Biotics Research) - 1 at breakfast & dinner

# The Adrenals

## *Physiology and Biochemistry of the Adrenals Glands and Adrenal Hormone Metabolism*

The two adrenal glands (also called the suprarenal glands) are situated in the abdomen, above the kidneys and below the diaphragm.



They have a high cholesterol content giving them a yellowish color. They are contained within the same membrane as the kidney but separated from them by a fibrous layer of tissue. The right gland is tetrahedral in shape and lies lower than the left, which is semilunar in shape and usually the larger of the two. Each gland weighs approximately 5 grams and measures approximately 50mm vertically, 30mm across and 10mm thick.

When cut in half each gland consists of an **outer cortex**, yellow in color and an **inner medulla**, which is dark red, or grey.

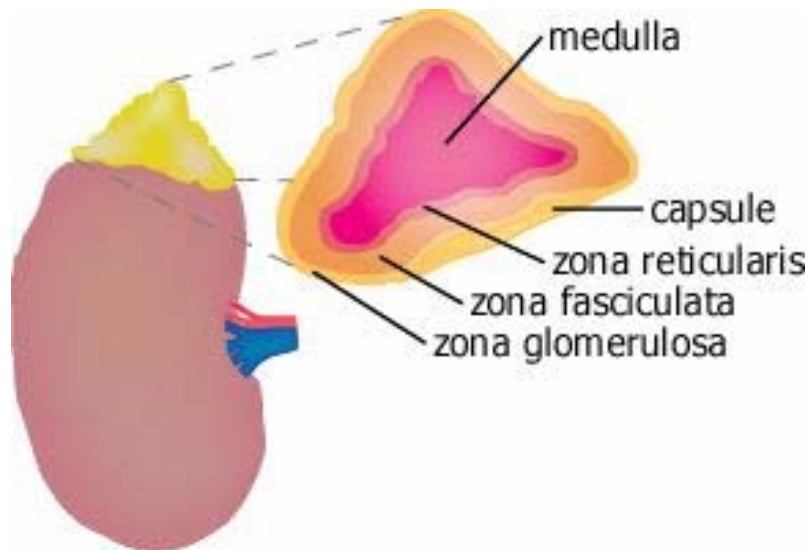
### **The cortex consists of three distinct zones.**

They are:

**Zona glomerulosa**

**Zona fasciculata**

**Zona reticularis**



Each zone has a characteristic histology and secretes different types of hormones. **The zona glomerulosa secretes a mineralocorticoid (aldosterone) which is responsible for the regulation of salt and water balance in the body.**

The **zona fasciculata** secretes a **glucocorticoid (cortisol)** which regulates the level of carbohydrate in the body.

The **zona reticularis** secretes **sex hormones (progesterone, oestrogen precursors and androgens)** which have a role in the development of sexual characteristics.

The adrenal medulla has a simple make up. It contains **chromaffin cells** (also called phaeochromocytes) which are surrounded by a meshwork of blood vessels called venous sinusoids. The chromaffin cells, when stimulated by the sympathetic nervous system **secrete noradrenaline and adrenaline into the sinusoids**, which are delivered by the bloodstream to the rest of the body.

## Nerve supply

The adrenal glands have a rich nerve supply. These nerves are derived from the coeliac plexus and the thoracic splanchnic nerves. The nerves supply the chromaffin cells of the medulla, but careful microscopy has shown that nerve trunks and plexuses may also appear in the cortical layers.

## What do the adrenal glands do?

The adrenal glands produce different hormones with a variety of functions. They are involved in the co-ordination of many physiological activities. The cortex and medulla are quite separate in their functions and are discussed in their own sections.

## Adrenals - The Cortex

The cortex is a region rich in enzymatic activity, where cholesterol is converted into the main steroid hormones. These are cortisol, aldosterone and the sex steroids (principally

the androgens androstenedione and dehydroepiandrosterone sulphate, DHEAS). Each layer produces one of these, although all the layers produce small amounts of the remaining hormones. The principal sites of production of each hormone are:

The hormones are produced these distinct histological areas:

### **Cortisol: Zona fasciculata**

Cortisol activity is regulated by the hypothalamic-pituitary-adrenal axis. Secretion of cortisol is stimulated by the release of Adrenocorticotrophic hormone (ACTH) from the pituitary. ACTH is regulated by Corticotropin releasing factor (CRF) released by the hypothalamus. A feedback inhibition loop exists between CRF and ACTH. Cortisol levels fluctuate over the day and night according to the circadian rhythms, which are regulated by the sleep-wake cycle. A steep increase in cortisol output occurs in the morning, peaking at approximately 8 a.m. This is followed by a tapering off until midnight, when cortisol levels are at their lowest.

Cortisol is a 'glucocorticoid' (a cortical hormone that increases blood glucose levels). It acts on a wide range of tissues and organs eliciting a wide range of effects. The main ones are:

#### **Increasing glucose levels in the blood in times of fasting by**

- Increasing production of glucose in the liver (gluconeogenesis)
- Decreasing utilisation of glucose by the tissues

#### **Break down of tissues such as muscle, skin and bone**

- To release amino acids, some of which can also be used to produce more glucose.

#### **Break down of fat into fatty acids and glycerol**

#### **Modulation of the immune system**

- Cortisol is released in response to infection or injury.
- Excess cortisol causes decreased white blood cell production and activity resulting in an impaired ability to fight infection and heal wounds.

#### **It acts like aldosterone**

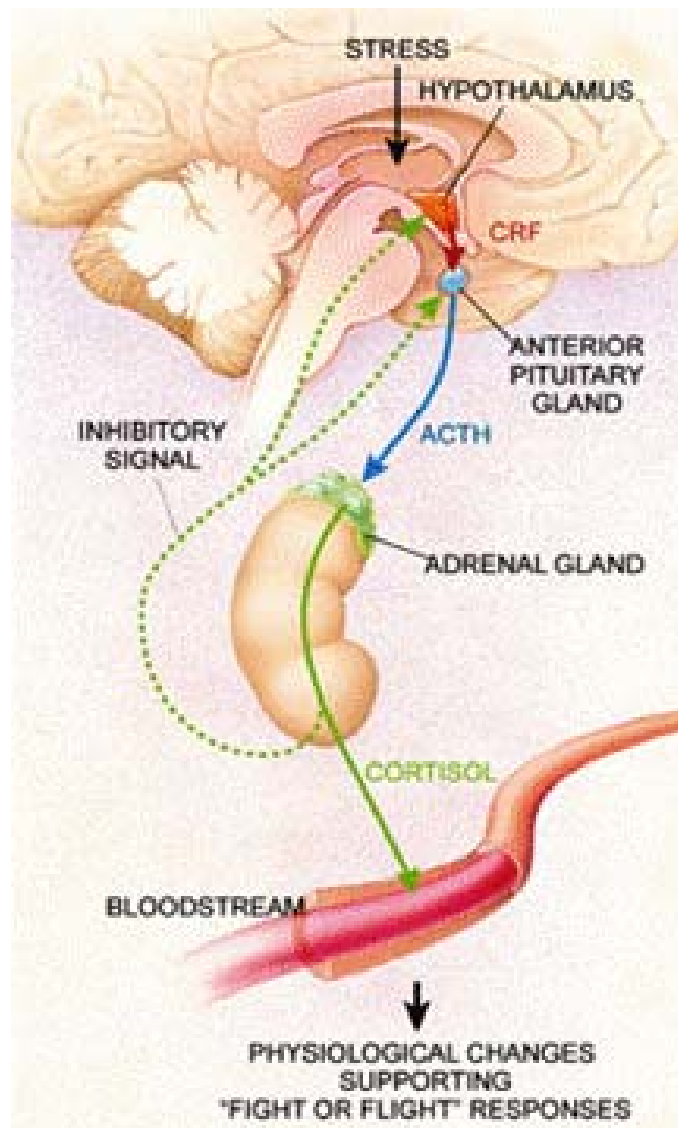
- This is a mineralocorticoid, which has the effect of raising blood pressure by the constriction of small arteries and the retention of fluid by the kidney. This effect is limited however by the inactivation of cortisol to inactive cortisone by a specific enzyme.

Cortisol is released in response to stress, which can be emotional (e.g. anxiety) or physiological (e.g. fluid deprivation or injury).

#### ***Summary of the Functions of Cortisol Include:***

1. Mobilizes and increases amino acids in blood and liver by promoting protein catabolism
2. Stimulates liver to convert amino acids to glucose

3. Stimulates increased glycogen in the liver
4. Inhibits glucose utilization in the peripheral tissue
5. Mobilizes and increases fatty acids in the blood by supporting synthesis of hormone sensitive lipase
6. Counters inflammation and allergies
7. Prevents loss of sodium in urine and helps maintain blood volume and blood pressure
8. Sustains tissue responsiveness to catecholamines
9. Maintains resistance to stress
10. Maintains personality and emotional stability
11. Modulates thyroid function



Stressors cause a release of **Corticotrophin Releasing Hormone (CRH)**. This travels in the portal system of the hypothalamus to the anterior pituitary (the adenohypophysis).

There, it stimulates the cleavage of Pro-opiomelanocortin (POMC) into several molecules including melanocyte stimulating hormone (MSH) and **Adrenocorticotrophic Hormone (ACTH)**. ACTH travels in the bloodstream to the adrenal cortex stimulating the production and release of cortisol.

Cortisol then travels to the tissues where it exerts its effects. Cortisol **inhibits** the release of CRH and ACTH from the hypothalamus and pituitary gland respectively, preventing further cortisol release. **Cortisol is inactivated in the liver to inactive cortisone.**

A daily pattern (circadian rhythm) is also seen, with cortisol being at its lowest concentration at midnight, rising to a peak between 6am and 8am, falling throughout the rest of the day.

### **Aldosterone: Zona glomerulosa**

Aldosterone is a '**mineralocorticoid**' (a cortical hormone that regulates salt balance) and has a narrower range of action than cortisol. It acts **principally to maintain blood pressure**. It is produced in the Zona glomerulosa in the adrenal cortex and is the most important mineralocorticoid hormone. Mineralocorticoids regulate the transport of sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ) in the kidney and other organs (gall bladder, intestines, sweat glands, salivary glands etc.). The levels of aldosterone in the body fluctuate according to Sodium chloride ( $\text{NaCl}$ ) intake and the time of the day. The rate of its secretion is at its highest in the early morning and is lowest in the late evening, a pattern that is not dissimilar to cortisol. The release of aldosterone is stimulated by a reduction in blood volume, hyponatremia (low sodium in the blood), hyperkalemia (high potassium in the blood) and the action of Angiotensin II. ACTH also stimulates the formation of aldosterone.

#### ***Functions of aldosterone include:***

1. Increases sodium retention throughout the body
2. Increases potassium excretion
3. Increases water retention
4. Increases extracellular volume
5. Enhances the activity of the sodium/potassium pump
6. Helps “bring on line” the sodium and potassium channels in the luminal membrane in the kidneys

#### ***Summary of the Functions of Aldosterone***

- Retention of sodium and water by the kidney, resulting in a rise in blood pressure.
- Excretion of potassium and hydrogen ions by the kidney.

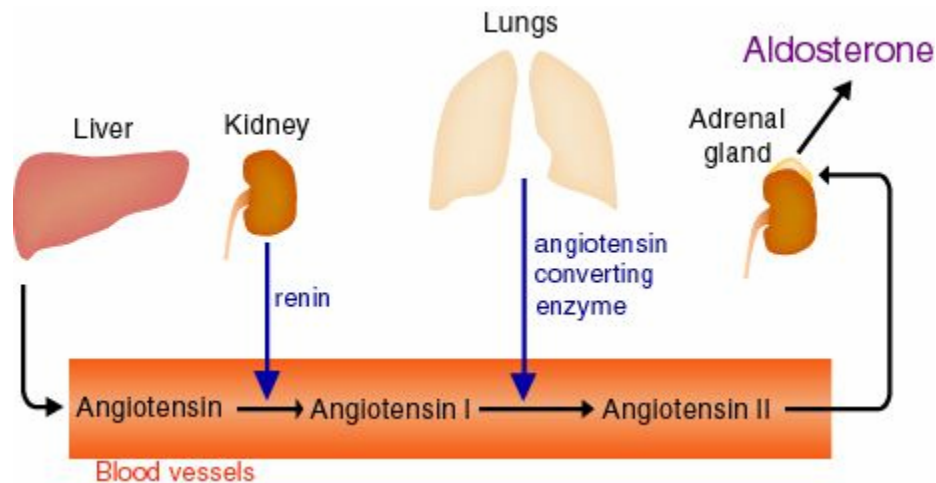
- Aldosterone is produced in the last step of a pathway initiated by a fall in blood pressure.

### **Regulation of Blood Pressure**

Blood pressure is regulated via a system known as the **renin-angiotensin system**.

**Low blood pressure causes a release of the enzyme renin from the kidney.**

Renin converts angiotensinogen to angiotensin I. Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II in the lung. Angiotensin II travels in the bloodstream to the adrenal cortex causing aldosterone release from the zona glomerulosa. The release of aldosterone then increases blood pressure.



Aldosterone release is also stimulated by **high potassium levels** and to a more limited extent, by ACTH from the pituitary.

### **Sex steroids: Zona reticularis**

Sex steroids are hormones produced mainly by the testes in men and the ovaries in women. They are responsible for producing the male and female primary sexual characteristics (the genitalia) and secondary sexual characteristics (body hair distribution, voice pitch, breast development etc.).

The adrenals also play a small role in producing mainly virilising hormones (hormones which induce male developmental characteristics) such as Dehydroepiandrosterone Sulphate (DHEAS) and androstenedione.

The adrenal glands are two small endocrine organs that lie on top of the kidneys.

The gland is composed of two distinct areas, the cortex in the outer layer and the medulla in the inner layer. Each layer is responsible for producing various types of hormones.:

The **cortex** produces corticosteroid hormones, which include the mineralcorticoids (aldosterone), Glucocorticoids (cortisol), and anabolic and sex hormones (DHEA).

The **medulla** produces catecholamines (Epinephrine and Norepinephrine).

The three main hormones we will be talking about are Cortisol, DHEA and Aldosterone.



## DHEA

Dehydroepiandrosterone (DHEA) is primarily produced from the adrenal cortex. It is produced from the steroid precursor pregnenolone, which is synthesized from cholesterol. DHEA has a very short half life (about 30 minutes) and subsequently about 95% of circulating DHEA is in the more stable sulfate form DHEA-S. DHEA-S follows a similar daily circadian rhythm to cortisol, but it shows a less well defined pattern over the course of the month. DHEA-S levels may respond to seasonal changes. Higher levels of DHEA-S have been recorded from autumn to spring.

### ***Functions of DHEA include:***

1. Acting as an androgen with anabolic activity
2. Precursor to testosterone
3. Precursor to estrogen and progesterone
4. Reverses immune suppression caused by excessive cortisol level and therefore improves resistance to viruses, bacteria, candida albicans, parasites, allergies and cancer
5. Stimulates bone deposition and remodeling, which can help prevent osteoporosis
6. Improves cardiovascular status by lowering total and LDL cholesterol levels, lessens incidence of heart attack
7. Increases muscle mass
8. Decreases percentage body fat
9. Reverses many of the unfavorable effects of excess cortisol
10. Can help create an improvement in: energy, vitality, sleep, PMS, and mental clarity
11. Can help with quicker recovery from any kind of acute stress: insufficient sleep, excessive exercise, mental strain etc.

## **The Adrenal Glands and Stress – An Epidemic of Giant Proportions**

Stress refers to anything that disturbs an individual's physical, mental, or emotional equilibrium. The body has numerous stress response mechanisms and stress can affect the body in many different ways.

In fact the same form of stress might cause one individual to get a migraine, a second person to have an ulcer attack, and a third to have elevated blood pressure. It is important to realize that stress is not all bad. Stress is a normal part of life. What really matters is how much stress, what kind of stress, and ultimately, how each individual handles his or her stresses.

The adrenal glands have many metabolic functions in the body. One of the most important of which is to help the body maintain stability and equilibrium in the face of both exogenous and endogenous stress.

### **Stress comes in many forms:**

<b>External Stressors</b>	<b>Internal or Physiological</b>	<b>Mental</b>
Toxic exposure Light cycle disruptions Allergies Temperature extremes Trauma Overwork (physical and/or mental)	Dietary imbalances: increased refined carbohydrates Nutrient deficiencies Lack of sleep Blood sugar dysregulation Chronic infections Pain Excessive exercise Chronic inflammation	Emotional strain: anger, fear, worry, guilt Anxiety Depression

### **The Neglected Adrenals**

Persistent and unrelentless stress places constant hyperstimulation of the adrenal glands resulting in adrenal exhaustion.

Many chronic illnesses can be traced back adrenal gland malfunction, yet mainstream medicine does not even consider this part of the human anatomy when prescribing treatments.

The chronic fatigue, immune dysfunction, and stress that so many people are stricken with often emanates from the adrenals.

The key to reversing adrenal exhaustion is to identify the **sources of stress** that have become chronic in nature.

Evaluating both clinical and subclinical sources of chronic stress is paramount to clinical success.

However, failure to properly diagnose and treat the cause (source) of chronic stress will result in further adrenal exhaustion, and over time, hormone, immune, and metabolic systems breakdown.

### **Clinical and Sub-Clinical Stressors**

There are two general categories of stressors, **seen or clinical stressors and unseen or sub-clinical stressors**.

Seen stressors are typically associated with lifestyle factors and have to do with internalization of mental/emotional stress, blood sugar control, exercise, rest and recovery. These lifestyle factors can become sources of chronic stress. Usually they are easily identifiable by observing a person's habits.

Unseen or sub-clinical physiological stressors represent the rest of the sources for chronic stress.

The following list of potential sources of chronic stress will give you a good overview of the areas to consider relative to diagnosing the underlying cause or causes of health problems including chronic degenerative diseases such as autoimmune, cancer and cardiovascular disease, as well as depression, insomnia, allergies, fatigue, etc.

Regardless of the clinical conditions and/or symptoms, this list will help you to understand where to look to investigate the stress or stressor that could be chronic in nature thus resulting in an ongoing chronic stress response that ultimately results in hormone, immune and metabolic breakdown.

As you can see, many potential chronic stressors can occur sub-clinically (without noticeable symptoms). If the source(s) of chronic stress are not diagnosed and treated, optimal health cannot be restored.

Anger	Overwork	Inflammation
Anxiety	Lifecycle Disruption	Toxic Exposures
Noise Pollution	Gluten Intolerance	Heavy Metals
Geo-Physical Stressors	Food Allergies	Poor Diet
Mal-digestion	Fear	<b>Low Blood Sugar</b>
<b>Excessive Exercise</b>	Pain/ Injury	Infections
<b>Nutritional Deficiencies</b>	Mal-absorption	Electromagnetic Fields
<b>Worry</b>	<b>Late hours</b>	<b>Depression</b>
<b>Guilt</b>	<b>Inhalant Allergies</b>	<b>Traumas</b>
<b>Sleep Deprivation</b>	<b>Surgery</b>	<b>mental/emotional/physical)</b>
<b>Lactose Intolerance</b>	<b>Whiplash</b>	<b>Temperature Extremes</b>
<b>Molds</b>	<b>Sucrose</b>	<b>Chemicals</b>
		<b>Radiation</b>

## Sources of Chronic Stress

### *Environmental Toxins*

Chemicals are a common source of chronic stress. What makes them so insidious is that many of the sources of exposure cannot be seen. Examples in the air we breathe include **auto exhaust, smog, smoke stacks, and out-gassing from mattresses, carpets, drapes, upholstery, plastics and man-made building materials.** Examples

in the foods we eat include hormones and antibiotics used in raising animals whose meat we eat, pesticides and herbicides used on fruits and vegetables (that are also concentrated in the bodies of animals that we eat) and **plasticizers from plastic containers** that we buy and heat our food in. Examples in things that touch our skin are pesticides and herbicides that our sprayed with reckless abandon on the lawns and gardens that our children and pets play on. In fact scores of volatile organic chemicals can be measured in each exhalation of every person living in the industrialized world.

Free radicals, which are potentially destructive by-products of oxidative stress in the body, can be produced by chemicals, by-products of chemicals or infectious agents, as well as by our own normal metabolic processes. Our first line of defense against free radical damage is a very complex group of chemical reactions involving the body's sulfhydryl line of defense. A free radical is a chemical compound containing a highly reactive unpaired electron; the sulfhydryl group neutralizes the free radical by binding with the unpaired electron, rendering the chemical compound non-reactive.

In the event any free radicals elude the sulfhydryl line of defense, they are entrapped and scavenged by antioxidants like Vitamin C, Vitamin E, Vitamin A, Selenium, Glutathione and others. If you have good antioxidant function, and good levels and reserves of the nutrients needed to mobilize the entrapping and scavenging systems of your body, you can successfully neutralize your free radical load. The consequence of free radical production in excess of antioxidant capacity is oxidative stress which manifests as damage to cell membrane lipids, an increase in DNA Adducts and damage to cellular proteins that can cause increased risk for all degenerative diseases, especially cancer.

Toxic Chemicals can be extremely damaging to health and a significant source of chronic stress. They can create significant oxidative stress and free radical damage in the body. They can also disrupt DNA replication, leading to the growth of aberrant cells and ultimately cancer. Identifying elevated antibodies to a particular chemical qualifies that chemical as a source of chronic stress.

### ***Heavy Metals***

Heavy metals, especially **lead, mercury, nickel, cadmium and arsenic** have been implicated in a variety of disturbances of essential physiological pathways. They can bind sites normally occupied by essential minerals disrupting metabolic activity. They can also destroy the body's free radical defense systems, leaving the body more susceptible to free radical damage from chemicals. Vague and puzzling symptoms are sometimes related to abnormally high levels of heavy metals.

When heavy metals evoke an immune (antibody) response, it means that the body has attached specific liver enzymes to the metal forming an antigen-antibody complex of the metal. Antibody to a metal clearly indicates the body's inability to clear the metal and is therefore the best method of differentiating a potentially serious heavy metal problem.

The antibodies that form in response to the metal/enzyme complex are evidence of risk for autoimmune and potentially significant physiological pathway alteration and possible metabolic toxicity. The result can be an increased likelihood of a variety of illnesses including chronic degenerative disorders, including autoimmune conditions as well as cancer.

**Lead exposures** are most damaging in children. Lead damages cells, especially those of the nervous system. It can become incorporated in bone in place of calcium, weakening bone structure. Everyday lead exposures can come from solder in homes with copper pipes, pesticides on foods, paint chips and dust from older homes and inner city playgrounds (lead contamination still exists on city streets and playgrounds from the exhaust from leaded gasoline which was used until the 1970s).

**Mercury** is one of the most poisonous substances known to man. It is particularly dangerous because it is so easily absorbed through the skin, lungs and intestines. Although a metal, it is a liquid at room temperature and readily vaporizes and can be inhaled. Mercury is found in: **silver amalgam dental fillings; fish; some plastics, inks, water based paints, pesticides and fungicides; chlorine bleaches and even some vaccines.** Mercury is also found in some over the counter health care products like Preparation H and Iodine products.

Nickel depletes the **body's zinc stores** and compromises immune function. It is also used to create cancerous tumors in lab rats. It is a component of stainless steel cookware and it is also used in dental braces, bridges and posts. **Kelp, herring, oysters, legumes, cabbage and hydrogenated fats and oils may contain nickel.**

## **Viruses**

Viruses are infectious particles that are much smaller than bacteria and depend on the host cells that they infect to reproduce. **Viruses** can be extremely damaging to health and a significant source of chronic stress. When they come into contact with a host cell, the virus can insert its genetic material into the host and **literally take over the host's functions.** Infected cells produce viral protein and genetic material instead of its usual products.

Some viruses can remain dormant inside host cells for a long time. When a dormant virus is stimulated it can replicate and burst out of the host cell killing the host cell and then goes on to infect other cells. Viruses tend to be opportunistic.

**Often they are held in check by the immune system, until the host is weakened, possibly by an infection, a toxic exposure, a drug or cancer, then they begin to replicate causing secondary pathology.** opportunistic viruses can become a significant source of chronic stress as a secondary pathology.

**Common viruses to rule out include:**

- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Herpes-1 Virus
- Herpes-2 Virus
- Herpes Type 6 Virus
- Varicella Zoster Virus

## ***Infections of the GI Tract***

Gastrointestinal (GI) tract infections are common and can be either clinical (symptomatic) or sub-clinical (without symptoms). Some have active GI symptoms, others present with general complaints: fatigue, body pain, headaches, cognitive problems, light headedness, brain fog and/or general malaise.

### **The most prevalent infections are:**

- *Helicobacter pylori*, a bacterium that primarily inhabits the stomach, esophagus and upper duodenum
- *Cryptosporidium parvum*, an aggressive parasite that primarily inhabits the small intestine. It is known to damages the topography of the small intestine by invading the intestinal epithelial cells. In turn, absorption and assimilation of nutrients are impaired further weakening the body's defense against other opportunistic infectious agents.

### **Other commonly encountered parasite infections include:**

- *Entamoeba histolytica*
- *Giardia lamblia*
- *Blastocystis hominis*
- *Ascaris* (round worm).

## ***The Challenge of Parasitic Pathogens***

Even more ominous than having a primary GI infection is the tendency of invading microorganisms to metamorphosize into various stages of their life cycle, and to migrate to tissues and organs sometimes distant from the GI tract. For example *Cryptosporidium parvum* can sometimes be found in the lungs and conjunctiva of the eyes and *Helicobacter pylori* has been located in the oral cavity and even the prostate gland.

Gluten Intolerance whether clinical (manifesting as celiac sprue disease) or sub-clinical is a significant source of chronic stress for many people. Sub-clinical gluten intolerance is of particular concern because of the destruction done to the topography of the small intestine and resultant maldigestion and malabsorption, with no overt GI symptoms.

## ***Oral Infections***

Oral Infections can be extremely damaging to health and a significant source of chronic stress. The tooth is the only structure in the body that passes directly from the external environment to the internal environment of the body. As such, the tooth is a susceptible area for the invasion of pathogens into the body.

Mucous membranes line the entire mouth and the salivary glands produce massive amounts of immunoglobulins.

Healthy mucosal barriers in the mouth are of paramount importance. Patients should work with a skilled biological dentist, familiar with dental procedures that support patient health, especially those that do not compromise the mucosal barriers of the mouth.

Oral infections are often a "hidden" cause of chronic stress and can occur for a variety of reasons including:

- Root canals
- Improper dental work
- Improper dental materials
- Poor care of the gums
- Mechanical stresses due to teeth clenching and tmj
- Elevated antibody levels to any or all oral bacteria warrant further investigation by a biological dentist as active oral infections have been correlated with cardiovascular disease, autoimmune conditions, gum disease both clinical and sub-clinical, mucosal barrier breakdown and excessive dental plaque

### ***Mold and Mycotoxins***

Molds are one of the two largest groupings of fungi (the other is yeasts). Molds are parasitic and saprobic (they obtain food directly from decaying organic material) and most exist as multicellular filamentous colonies. The cell walls of all fungi contain substances that can be immunosuppressive, mitogenic and pro-inflammatory in humans.

Mold cell wall components can act synergistically with bacterial endotoxins to produce airway inflammation following inhalation exposure. Under certain metabolic conditions, many fungi produce particular mycotoxins, natural organic compounds that initiate a toxic response in humans. The primary modes of human exposure to mycotoxins **are inhalation of spores from mold contaminated materials.**

## **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 increasening venous return to the heart, all 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***

Organ	Process or Result
Brain	Increased blood flow Increased glucose metabolism
Cardiovascular	Increased rate and force of contraction 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 re-lease)
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 **adrenocorticotrophic 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***

<b>Functions Affected</b>	<b>Physiologic Effects</b>
Carbohydrate and lipid metabolism	Diminishes peripheral uptake and utilization of glucose  promotes gluconeogenesis in liver cells; enhances gluconeogenic response to

	other hormones
	promotes lipolysis in adipose tissue
Protein metabolism	Increases protein synthesis in liver and depresses protein synthesis (including immunoglobulin synthesis) in muscle, lymphoid tissue, adipose tissue, skin, and bone; increases plasma level of amino acids; stimulates deamination in liver
Inflammatory effects	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
Lipid metabolism	Lipolysis in extremities and lipogenesis in face and trunk
Immune reserve	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 fever
Digestive function	Promotes gastric secretion
Urinary function	Enhances urinary excretion
Connective tissue function	Decreases proliferation of fibroblasts in connective tissue (thus delaying healing)
Muscle function	Maintains normal contractility and maximal work output for skeletal and cardiac muscle
Bone function	Decreases bone formation
Vascular system and myocardial function	Maintains normal blood pressure; permits increased responsiveness of arterioles to constrictive action of adrenergic

Central nervous system function

stimulation; optimizes myocardial performance

Somehow modulates perceptual and emotional functioning, essential for normal arousal and initiation of daytime activity

### ***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 antidiuretic hormones from the posterior pituitary, prolactin, growth hormone and **adrenocorticotrophic 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

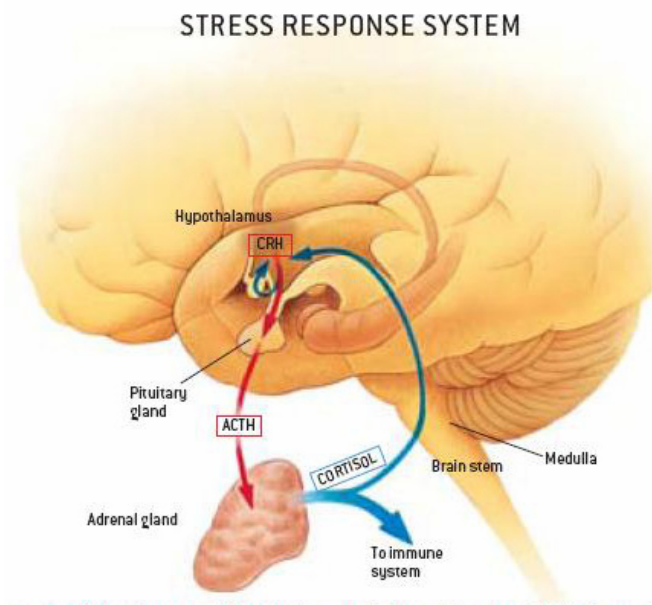
Target Organ or System	Diseases and Conditions
Cardiovascular system	Coronary artery disease Hypertension Stroke Disturbances of heart rhythm
Muscles	Tension headaches Muscle contraction backache
Connective tissues	Rheumatoid arthritis (autoimmune disease) Related inflammatory diseases of connective tissue
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 **adrenocorticotrophic hormone (ACTH)**.

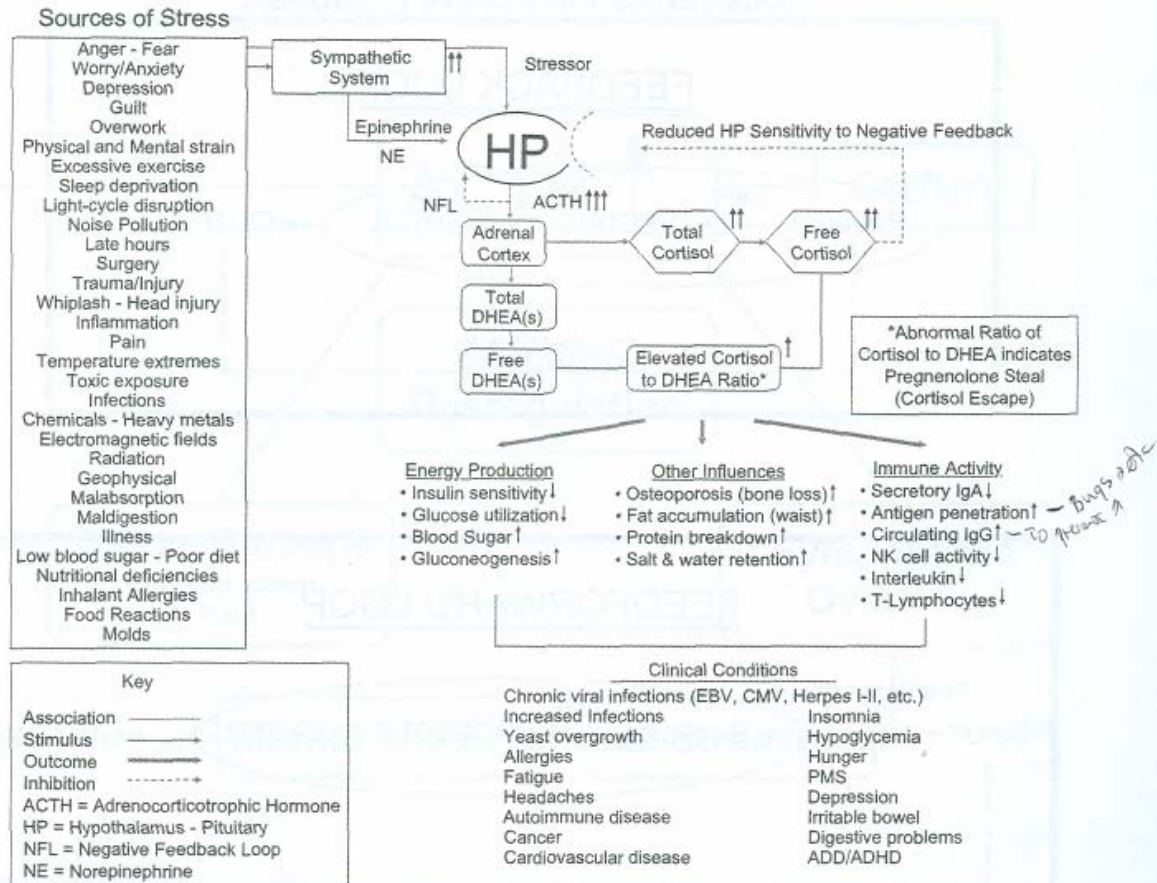


The ACTH enters the systemic circulation and reaches the adrenal cortex of the adrenal gland, where it stimulates the synthesis of the **glucocorticoid hormone CORTISOL** and also androgenic hormones such as **androstenedione** and **dehydroepiandrosterone (DHEA)**, both of which may ultimately be converted 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.

## Chronic Stress Response



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, IL-2, IL-2 receptor, IL-6, tumor necrosis factor (TNF), and gamma interferon.

Chronically 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.**

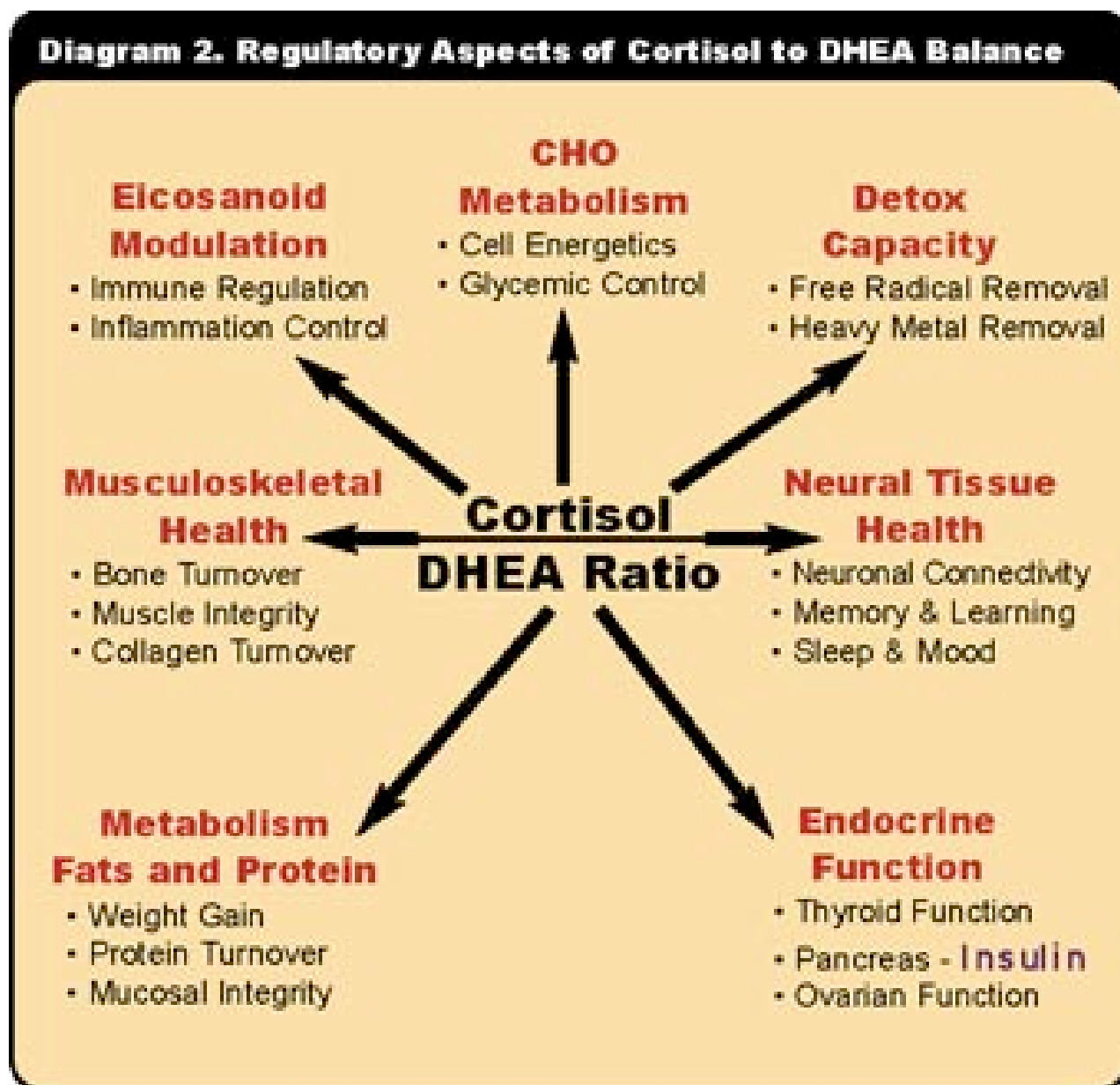
In other words, with unregulated or untreated chronic stress, excessive exposure to cortisol may **disable the negative restraint on stimulated CRH secretion.**

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.



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.

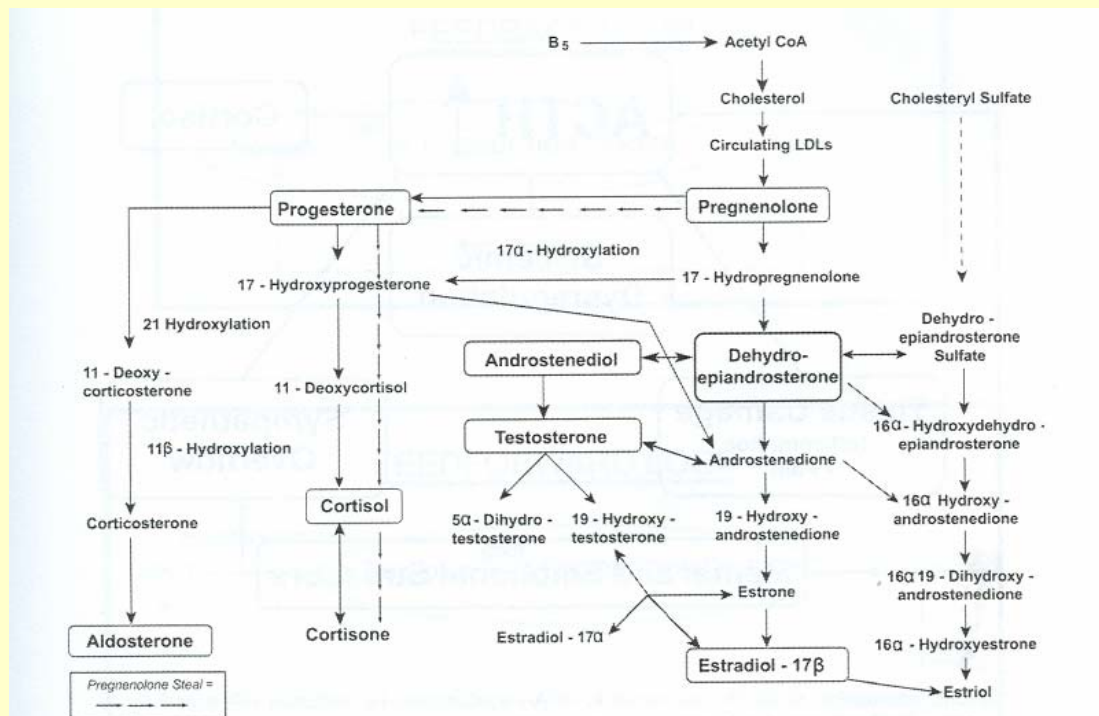


## Pregnenolone Steal or Cortisol Escape

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

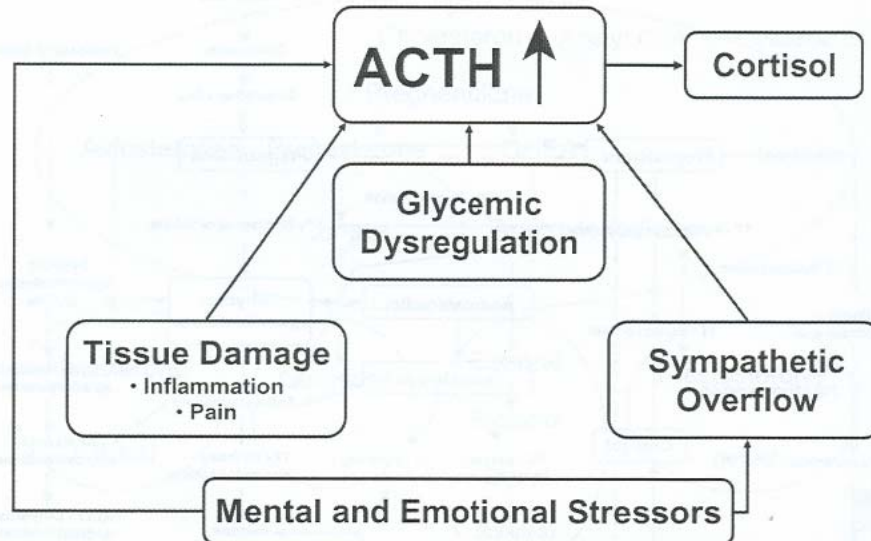
**Stage I** is distinguished by an increase in output of **ACTH by the anterior pituitary gland**, increased adrenocortical stimulation, increased cortisol output and an increased probability of pregnenolone steal and decreased DHEA.

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.

### Common Inducers of ACTH Potentially Resulting in Adrenal Exhaustion



## Stage III

**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.

# **Assessing Adrenal Function**

Adrenal function can be assessed using Primary and Advanced FDM Testing. The Primary FDM Testing includes signs and symptoms analysis, physical exam techniques such as the Ragland's test for postural hypotension and the Paradoxical Pupillary Reflex, and in-office testing, including using the Urine Adrenal Stress Test or Koenisburg test for urinary chloride. Although these tests will not give specific information on cortisol and DHEA levels, they are useful “gateway” tests for assessing the adrenal system. They are valuable screening tests prior to embarking on Advanced FDM Testing, which would include the salivary adrenal stress profiles offered by many of the alternative diagnostic laboratories.

## ***Signs and Symptoms of Adrenal Dysfunction***

The signs and symptoms of adrenal dysfunction fall into a number of different patterns depending on which level of decompensation the patient is in. The first stage of dysfunction is described as “The Compensation Stage Moving Towards Decompensation” or “Adrenal Hyperfunction”. This stage has unique signs and symptoms:

### **Signs and symptoms of Adrenal Hyperfunction**

1. Decreased insulin sensitivity leading to increased insulin resistance
2. Diminished glucose utilization by cell
3. Increased blood sugar levels
4. Salt and water retention due to excess aldosterone activity
5. Decreased protein synthesis
6. Increased gluconeogenesis: increased protein and fat breakdown leading to muscle wasting
7. Increased bone loss (osteoporosis)
8. Increased infections: chronic EBV, CMV
9. Shrinking of lymphatic tissue
10. Diminished lymphocyte numbers and functions
11. Decreased secretory antibody production (Secretory IgA)
12. Decreased immune function, which can lead to allergies, infections and cancer
13. Weight gain around the abdomen due to fat and water retention
14. Increased LDL cholesterol levels
15. Muscle wasting

16. Allergies
17. Insomnia
18. Reduced vitality
19. Hunger
20. PMS and other hormonal problems

The third stage of decompensation is called “The Fatigue Stage” or “adrenal hypofunction/fatigue”. This stage has its own set of signs and symptoms:

## **Signs and Symptoms Adrenal Hypofunction/Insufficiency and of a decreased Cortisol/DHEA ratio**

A decreased cortisol/DHEA ratio and adrenal hypofunctioning/Insufficiency causes a decrease in gluconeogenesis, leading to hypoglycemia, hunger, depression, low energy and the following signs and symptoms:

1. Irritability
2. Allergies
3. Inflammation
4. Reactive hypoglycemia
5. Increased carbohydrate sensitivity
6. Low blood pressure
7. Chronic inflammation due to up regulation of pro-inflammatory mediators
8. Fatigue
9. Excessive anxiety and apprehension
10. Reduced ability to concentrate
11. Poor memory
12. PMS and menstrual irregularities
13. Alcohol intolerance
14. Heart palpitations
15. Digestive complaints e.g. dyspepsia
16. Increased oxidative stress and increased tissue damage
17. Degenerative diseases



## ***Assessing the Adrenals: Physical Examination Techniques***

It is possible to assess for the state of the adrenal glands using a number of Physical Examination techniques. These would include the following:

1. Ragland's Test for Postural Hypotension
2. Paradoxical Pupillary Reflex Test
3. Medial knee tenderness
4. Inguinal ligament tenderness

### **Ragland's Postural Hypotension Test**

#### **Discussion**

Ragland's test for postural hypotension is used to determine the presence and severity of adrenal exhaustion or hypoadrenia. It assesses the body's ability to compensate for the hydrostatic effects of gravity by measuring a drop in systolic blood pressure from a recumbent to a standing position. Standing from a recumbent position causes pressure changes in the vascular system, which are controlled by the splanchnic veins. The splanchnic veins, being devoid of valves, are dependent upon nerve function, for their tone. The tone of the splanchnic nerves is under the direct control of the adrenal system.

#### **Directions**

1. Instruct the patient to lay supine on the treatment table
2. Place the blood pressure cuff on the arm of choice, determine the systolic pressure and release the pressure
3. Pump up the cuff again 15 mmHg higher than the supine systolic pressure and while supporting their arm, instruct the patient to stand up quickly
4. Immediately release the valve so that you can determine the standing systolic pressure within 5 seconds of the patient arising.
5. The test may be conducted sitting to standing but the BP may not drop as dramatically. Results may be halved.
6. You may want to repeat the standing BP after one minute to see how they are compensating.



## Results

Result	Clinical Implication
<b>Excellent</b>	<b>Result:</b> 6-10 point increase in systolic blood pressure upon standing <b>Implication:</b> An optimal response- good adrenal health. Consider that this may actually be the beginning of the alarm stage of adrenal exhaustion. The patient is compensating ok but in early stages of decompensation. If this continues you may see a BP drop.
<b>Fair</b>	<b>Result:</b> Systolic pressure remains the same <b>Implication:</b> Fair adrenal compensation
<b>Poor</b>	<b>Result:</b> Systolic pressure drops up to 10 points <b>Implication:</b> Beginning to see long term adrenal dysfunction
<b>Failure</b>	<b>Result:</b> Systolic pressure drops up to 20 points <b>Implication:</b> Adrenal fatigue
<b>Exhaustion</b>	<b>Result:</b> Systolic pressure drops over 20 points <b>Implication:</b> Adrenal fatigue probably very pronounced. <b>NOTE:</b> Repeat standing BP after one minute to see if there is additional compensation to bring BP under control. Some will decrease further, which is a problem

## Clinical implications

Clinical Implication	Additional information
<b>Adrenal hypofunction</b>	The autonomic nervous system control of pressure changes in the vascular system becomes compromised as adrenal output is diminished in adrenal hypofunction and exhaustion

## Interfering Factors

1. Neuropathic hypotension from neurological and other diseases (e.g. DM) can cause orthostatic hypotension
2. Decreased blood volume and anemia
3. Drugs and diseases that interfere with the autonomic regulation of vascular pressure changes

# Paradoxical Pupillary Response Test

## Discussion

The test is used to determine the presence and severity of adrenal exhaustion. It measures the ability of the pupil of the eye to respond to light. A reduced ability of the pupil to constrict with light stimulus is a reflection of the “tug of war” between the sympathetic and parasympathetic branches of the autonomic nervous system. Pupillary constriction is strongly influenced by the hormonal cascade from the adrenal system

## Directions

1. Darken the room and wait 15 seconds
2. Instruct the patient to look at a fixed point and not to blink
3. Come in from the side of the eye and direct the pen light at the pupil at approximately a 45° angle. Hold the light 6-12 inches from the patient's eye depending on the intensity of the light
4. Observe the reaction of the pupil for 20 seconds

## Results

Result	Description	Implication
Excellent	Pupil constricts and holds tight for 20 seconds without pulsing	An optimal response- good adrenal health
Fair	Pupil holds but pulses after 10 seconds	Fair adrenal compensation
Poor	Pupil pulses and becomes larger after 5-10 seconds	Beginning to see long term adrenal dysfunction
Failure	Pupil pulses and becomes gradually larger over the first 10 seconds	Adrenal fatigue
Exhaustion	Pupil immediately becomes larger or fails to constrict	Adrenal fatigue probably very pronounced

## Clinical implications

Clinical Implication	Additional information
Adrenal hypofunction and exhaustion	The autonomic nervous system control of the pupil's ability to react to light becomes compromised as adrenal output is diminished in adrenal hypofunction and exhaustion

## Interfering Factors

1. Drugs and neurological dysfunction can interfere with the autonomic regulation of pupillary constriction in response to light

## Reflex Testing

The medial or inner side of the knee is the insertion of the Sartorius muscle into the area known as the Pes Anserine. This area is one of the reflex areas for the adrenal glands. Tenderness in this area is an indication of adrenal insufficiency. Tenderness in the inguinal ligament is also another reflex area for the adrenals. It is obviously important to make sure that there are no structural problems in this area that may contribute to the musculoskeletal findings. These reflexes are not diagnostic but more prognostic of issues in the adrenal regulation system.

## Sargent's White Line

Use a blunt instrument to “draw” a line on the abdomen. A positive for this test will leave a white line for several minutes whereas a normal finding would be a red line.

Assessing for tenderness in the medial knee and the inguinal ligaments, the Ragland's test, and looking for an abnormal pupillary response to light will give you a larger view of the adrenal system, and whether or not it needs support.

## Assessing the Adrenals: In-Office Testing

### Urinary Adrenal Stress Test (Koenisburg Test, Urinary Chloride Test)

#### Discussion

The Urinary adrenal stress test measures the amount of chloride displaced into the urine. Increased or decreased levels of chloride in the urine are a useful way of assessing for adrenal stress or fatigue, kidney stress, mineral loss from the body and acid-alkaline imbalance. As outlined above adrenal stress is a major health problem. Adrenal hyperfunctioning or stress, as seen in the compensation stage of stress adaptation, leads to an increased output of adrenal hormones such as cortisol and aldosterone. High levels of aldosterone cause the resorption of sodium and chloride leading to low levels of sodium and chloride in the urine.

Adrenal hypofunctioning or insufficiency or fatigue, on the other hand, leads to a decreased output of cortisol and aldosterone. Low levels of aldosterone cause the increased loss of sodium and chloride into the urine. Exhausted adrenal glands can lead to chronic fatigue, chronic inflammations, a weakened immune system, problems with PMS, difficulties with blood pressure, be a contributing factor to insomnia and allergies as well as reducing the sex drive. The earlier the adrenal imbalances are cleared up, the more rapidly the patient's energy levels return to normal.

Poor sodium resorption causes an increased level of stress to the kidneys leading to possible kidney dysfunction. The loss of sodium and chloride from the body follows the loss of magnesium and potassium i.e. if we already have a decreased urinary chloride, then we can presume that we have a decreased level of magnesium and potassium in

the blood. The loss of these and other minerals leads to a loss of vital co-enzymes, essential for energy production in the cell.

## Directions

It is best to use the first morning urine. If patient is coming in later for an appointment, refrigerate in an airtight container. Patients should restrict salt intake for 2 days prior to testing.

1. Put 10 drops of urine into a small glass vial.
2. Add 1 drop of 20% Potassium Chromate—shake to mix.
3. Add 2.9% Silver Nitrate, one drop at a time—shake to mix.
4. Record the number of drops it takes to produce a deep brick red color i.e. no yellow color remaining.

## Description of the test

This test determines the chloride ion concentration of the urine using a simple titration with silver nitrate. 10 drops of urine are used with 1 drop of potassium chromate. As the silver nitrate solution is added to the urine/potassium chromate a precipitate of silver chloride forms. The test becomes significant when the end point of the titration has been reached and the solution turns brick-red in color. At this point all of the chloride ions are precipitated and any additional silver ions react with the chromate to form a red-brown precipitate of silver chromate.

**NOTE:** This test is most accurate with a urine sample pH 6.5 and higher. If the urine pH is lower than pH 6.5 the chromate ions may be removed by an acid-base reaction to form hydrogen chromate ions or dichromate ions, affecting the accuracy of the test.

**Please test the urine pH prior to doing this test and be aware that a low urine pH may make this test less accurate.**

## Results

# of drops to produce color change	Interpretation
1 – 6 drops	Low urinary chloride
7 – 8 drops	Normal
> 8 drops	High urinary chloride

**PLEASE NOTE:** The reagents used in this test are the ones obtained from Rocky Mountain Reagents. Other companies may provide reagents for the Urine Chloride test but they use a different concentration of potassium chromate and silver nitrate so the number of drops needed to get a change may be different. Please refer to their results chart and then use the clinical interpretations below.

## Clinical implications

### *High Urine Chloride*

Clinical Implication	Additional information
<b>Adrenal hypofunctioning</b>	Adrenal hypofunctioning causes a decrease in aldosterone secretion from the adrenal cortex, which leads to decreased sodium and chloride resorption, leading to an increased urine chloride.

### *Low Urine Chloride*

Clinical Implication	Additional information
<b>Adrenal hyperfunction</b>	Excess aldosterone is secreted from the adrenal cortex in adrenal hyperfunctioning, leading to increased resorption of sodium and chloride, causing a decrease in urine chloride.

## **Assessing the Adrenals: Blood Testing**

### **Serum Potassium and Sodium**

#### **Adrenal Hypofunction/Insufficiency**

As described above, adrenal hypofunction can cause a decrease in the secretions of both the glucocorticoid and mineralcorticoid hormones. A decrease in aldosterone, the major mineralcorticoid, from adrenal hypofunction will cause:

A decrease in the amount of renal potassium excretion, which will cause an increased serum potassium ( $>4.5$ ).

An increase in the amount of renal sodium excretion, which will lead to decreased serum sodium ( $<135$ )

#### **Adrenal Hypofunction- Pattern**

Adrenal hypofunction is possible if:

- Potassium levels are increased ( $>4.5$ )
- Sodium is normal or decreased ( $<135$ )
- Chloride values will often follow sodium

#### **Other values that may be out of balance include:**

- Increased triglyceride ( $>1.24$ ) and cholesterol levels ( $>5.69$ )
- Decreased aldosterone and Cortisol levels
- Urinary chloride will be increased.

Adrenal hypofunction can be confirmed with salivary cortisol studies.

## **Adrenal Stress**

Adrenal Stress can cause an increase in the secretions of both the glucocorticoid and mineralcorticoid hormones.

An increase in aldosterone from adrenal stress will cause:

- An increase in the amount of renal potassium excretion, which will cause a decrease in serum potassium (<4.0).
- A decrease in the amount of renal sodium excretion or increased sodium resorption, which will cause an increase in serum sodium (>142).

### ***Adrenal Stress Pattern***

Adrenal stress is possible if:

- Potassium levels are decreased (<4.0)
- Sodium is normal or increased (>142)
- Chloride values will often follow sodium

**Other values that may be out of balance include:**

- Decreased triglyceride (<0.79) and cholesterol levels (<3.9)
- Increased aldosterone and cortisol levels.
- Urinary chloride will be decreased.

Adrenal stress can be confirmed with salivary cortisol studies.

## ***Advanced FDM Testing and Treatments***

We are producing a stand alone assessment and treatment book for using the Adrenal Stress Index. We will have that available on our library.

# SPECIAL TOPIC:

## Assessing Metabolic Energy Problems

Sub-optimal thyroid and adrenal function are the most common causes of low metabolic energy. Both Low Metabolic Energy due to Thyroid and Adrenals have low metabolic states and low body temperature. Some of the signs and symptoms are shared by both. However many are not.

**The Metabolic Symptom Survey** is a questionnaire you can use with patients to help differentiate the commonalities and differences between the adrenals and the thyroid in terms of their influence on metabolic energy and the signs and symptoms you will see in your patients.

Metabolic Symptom Survey				
Last Name	First Name	MI	Age	Date
Address		Phone number		
<ul style="list-style-type: none"><li>Please place a check mark to the left of each answer that BEST APPLIES to you</li><li>Choose only one answer per query</li><li>If no answer applies to you, leave that query unchecked/unanswered</li><li><b>IMPORTANT:</b> The choices as written may not describe you exactly. So it is VERY IMPORTANT that you choose the answer that <u>best describes</u> your TENDENCIES. The provided answer need not be a perfect description, just an indication of your <u>trend</u>. If you definitely fall somewhere in between, skip that query and go on to the next one.</li></ul>				
THYROID	SIGNS & SYMPTOM QUERY	ADRENAL		
I tend toward weight gain- global or localised Weight is extremely hard to lose	GENERAL BODY TYPE WEIGHT GAIN	I tend toward thin body type I cannot gain weight easily		
Tends towards coarseness. May be sparse.	HAIR	Tends towards thin and wispy. Dry and may fall out easily. May become straw-like. Sparse on forearms or lower legs.		
Tend towards oily. Poor healing. Normal thickness though may easily bruise.	SKIN	Dry and thin. May notice that the fingerprints are smoothed out. Can see longitudinal wrinkles over finger pads.		
Red and rosy complexion, including around the mouth.	FACIAL COLOR	Pale color especially around the mouth		
Tend to have puffy eyes with bags underneath the eyes.	TISSUE AROUND EYES	I often have dark circles under eyes. More sunken than puffy.		
Tend to lose outer 1/3 to 1/2 of the eyebrow	EYEBROWS	Tend towards fullness		
May be thick	NAILS	Tend towards thin and brittle		
I'm not that flexible	LIGAMENTS	I tend towards lax ligaments. I may be "double jointed". May complain of joint sprain or strains.		
My skin tends towards the oily. Fluid retention common, especially in lower legs.	GENERAL STATE OF FLUIDS AND SECRETIONS	I tend towards dryness and cannot hold onto water well.		
I'm not really that susceptible to night blindness or light sensitivity.	LIGHT SENSITIVITY	I often have light sensitivity and tend towards night blindness. I may see a strong after image when a strong light is shone in my face.		
I may complain occasionally of muscle and/or joint pain esp. in feet or lower legs	BODY PAINS	Tend towards headaches and/or migraines. I usually have pain in muscles rather than joints, though I can strain or sprain my joints easily.		
Tend towards a low body temperature usually below 97.6. The temperature is low, stable and does not fluctuate very much. Average can be low 90's to a little below 98.6	TEMPERATURE PATTERNS	I am a bit of a thermal chameleon because my temperature is never stable. I'm hot when it is warm and cold when it is cool. I can't regulate my temperature very well. My body temperature is low and usually below 97.6. I notice that my temperature is low and always changing.		
I'm cold anyway so I don't notice that I'm too intolerant to the cold.	COLD INTOLERANCE	I tend towards a strong intolerance to cold		
I tend towards a strong intolerance to heat	HEAT INTOLERANCE	I am occasionally intolerant of the heat		
I don't notice that my hands and feet are cold	COLD HANDS AND FEET	I notice I have very cold hands and feet		
I notice that I tend to be more oily than sweaty	PERSPIRATION	I used to sweat profusely but not any more OR I notice that I sweat profusely		

THYROID	SIGNS & SYMPTOM QUERY	ADRENAL
I tend not to over-react emotionally	EMOTIONS	I tend to over react emotionally
I have a tendency towards depression. I have little to no anxiety.	MOOD	I have a tendency towards anxiety, panic attacks, and insecurity. I have little to no depression.
I tend to be able to tolerate a marginal amount of stress.	STRESS	I cannot tolerate stress. It overwhelms me.
I notice I have poor focus, mental clarity, concentration, and short-term memory. I might describe it as "slow thinking".	MENTAL FUNCTION	I notice I have poor focus, mental clarity, concentration, and short-term memory. I might describe it as "brain fog".
I tend towards one or more of the following: sleepiness, narcolepsy, sleep apnea, and waking unrefreshed	SLEEP PATTERNS	I tend towards one or more of the following: sleeplessness, insomnia, waking up at night unable to go back to sleep, waking unrefreshed.
I complain mostly of being tired and feeling sluggish. I notice I have low motivation.	ENERGY PATTERN	My biggest complaint is fatigue or exhaustion. I might describe it as "wired and tired". I notice a lack of motivation and I can't persevere with things.
Exercise tires me out. I can't exercise much.	EXERCISE TOLERANCE	Exercise causes fatigue and I often finish my workout before it is finished because I am wiped out. I notice my body temperature drops after exercise.
I tend to eat everything	DIET HABITS	I find myself wanting to be a vegetarian or I notice I avoid certain foods.
I think it's great	DIGESTION	I can't digest meat or other proteins very well. I notice that certain foods are difficult to digest.
Sweets	FOOD CRAVINGS	Fats
I tend towards constipation	BOWEL MOVEMENTS	I tend towards a loose stool.
I tend towards normal blood sugar or my blood sugar is on the high side.	BLOOD SUGAR	I have a tendency towards hypoglycemia. I need small meals often or I will "crash"
My blood pressure runs normal to very high. It is poorly controlled by meds.	BLOOD PRESSURE	My blood pressure tends to run low. Ranges from 110/70 to 80/50.
I notice that my immune system tends to under-respond, which results in infections such as sinus, bladder, bowel, skin etc.	IMMUNE SYSTEM	I notice that my immune system tends to over-react, which results in allergies, and sensitivities.
SSX TOTALS		

This section to be filled in by your health care practitioner

THYROID	LAB & PE FINDINGS	ADRENALS
Usually high >220 or 5.7	TOTAL CHOLESTEROL	Usually low to low normal <160 or 4.14
Tends to be low <40 or 1.03	HDL CHOLESTEROL	Tends to be high >75 or 1.94
Usually 3.5 or more	HDL:CHOL. RATIO	Usually 3.0 or less
>4.5	SERUM POTASSIUM	<4.0
>135	SERUM SODIUM	<135
Mid normal range (around 7.0)	WHITE BLOOD CELLS	<5.0
Tends to normal or high normal >300	PLATELETS	Tends to low normal <200
Not elevated >90	MCV	>90
>13	RDW	>13
Type A	BLOOD TYPE	Type O
Negative	ORTHOSTATIC HTN	Positive
Negative	PUPILLARY REFLEX	Positive
Positive	ACHILLES REFLEX	Negative
SSX SECTION TOTALS		
LAB SECTION TOTALS		

Please download this form at this link:

<http://www.functionalmedicineuniversity.com/members/163.cfm>

## Using the Metabolic Symptom Survey

Have your patients fill out the survey. See how many symptoms are in each column. You can quickly see whether there is a predominance of thyroid, adrenal, or a mix of both. No one has all the symptoms. The more there are the more severe the dysfunction.



## Signs and Symptoms of Thyroid and Adrenals

Most patients with low body temperature have a mix of adrenal and thyroid symptoms (also called classic Wilson's Syndrome). This survey will help you sort out which system is most likely to be the cause of the low temperature.

### Weight Gain

Adrenal types, if they are on the heavy side, tend to be thin at top and heavier at the bottom.

### Poor connective tissue

Adrenal fatigue affects CT quality. You may see more mitral valve problems and an increased need for CT/Valve support.

### Digestion - Thyroid

The **thyroid** type will usually tell you that their digestion is good although if you probe further or look at their NAQ you will see that is not the case.

#### ***Bowel Function***

The thyroid type tends towards constipation because of poor peristalsis. Their bowel transit will be slow because food exits the stomach too slowly. This is caused by poor mechanical digestion and hypochlorhydria.

### Digestion – Adrenals

**Adrenal** types are pretty clear that their digestion is not good and will complain or report it. **Adrenal** types will often report that they have hyperacidity because of the heartburn they get and they will say that can't tolerate meat or protein.

They will also complain that the digestive enzymes you give them are causing them heartburn. It is important to investigate this because the real cause of this problem is not necessarily lack of stomach acidity or hypochlorhydria but a lack of gastric protection to the stomach mucosa.

You need to focus on healing and repairing the gastric lining so they are not irritated by normal gastric acidity. Gastrazyme from Biotics, DGL, Slippery elm, cabbage juice etc. can be very helpful.

**NOTE:** DGL must be sucked or chewed before swallowing. It gets activated by salivary enzymes. Take ½ hour before meals.

#### ***Bowel Function***

The **adrenal** type's bowel function has a tendency towards being irritable or hyper-reactive. They may have a fast bowel transit time because food exits the stomach too fast. This causes poor enzymatic digestion.



## Blood Sugar Control- Adrenals

The **adrenal** type has a tendency towards low blood sugar and hypoglycemia. The lack of cortisol output to raise blood sugar via gluconeogenesis causes hypoglycemic crashes and a need for small meals.

### Blood Sugar Control- Thyroid

The **thyroid** type tends towards higher blood sugar levels. May see it > 100 mg/dl or 5.55mmol/L.

# The Female Endocrine System

## ***Physiology and Biochemistry of the Female Endocrine System and Female Hormone Metabolism***

Hormones are powerful chemical messengers that circulate throughout the bloodstream to specific target cells, where they generate biological responses. Principal players in the body's process of homeostasis, hormones mediate such a prodigious array of physiological functions that they have become critical indicators for diagnosis and treatment of numerous health conditions.

Three steroid hormones-**estradiol, estrone, and estriol**-are known collectively by their function as estrogens. **In postmenopausal women, following the decline of ovarian function, these estrogens are produced primarily in the adrenal glands.**

Estradiol is synthesized from testosterone and androstenedione.

**Due to its potency, it plays a critical role in female sexual development, menstrual function, protein synthesis, cardiovascular function, bone formation and remodelling, cognitive function, emotional balance and other important health factors. It also may be the most stimulatory estrogen for promoting cell growth and proliferation.**

After menopause, estrone becomes the primary estrogen as the ovary loses its ability to manufacture estradiol. **Estrone is synthesized from androstenedione in the adrenal glands** and from peripheral tissues by aromatization. Fat cells are especially rich in the aromatase enzyme that converts androstenedione to estrone.

Estriol is considered to be the mildest and briefest-acting of the three estrogens. Estriol is formed in the liver by conversion of either estradiol or estrone. Although there is evidence that a certain amount of estriol can be recirculated into the body via the liver or gut hydroly-sis, its conversion is believed to be more fixed than the other two estrogens, with a reduced ability to reconvert into more potent forms of estrogen.<sup>20</sup>

Progestins are comprised of progesterone and 17-alpha hydroprogesterone, and they exhibit similar potency. Because 17-alpha hydroprogesterone is produced in minute quantities compared to progesterone, the latter is considered as the sole progestin. **In postmenopausal women, progesterone is produced mainly in the adrenal cortices.**

**Both progesterone and testosterone are formed from cholesterol.** Before menopause, in the follicular phase of the menstrual cycle, most of these steroids are converted to estrogens.

Conversion of estradiol to a less potent estrone or estriol lessens the potency of circulating estrogens, **and further functional degradation occurs as formation of**

**glucuronides and sulfates in the liver takes place.** Similarly, progesterone is functionally degraded to less potent steroids in the liver.

Progesterone also decreases at this point in the female life cycle. Lower levels of this hormone have been associated with dysfunctional uterine bleeding, and may play a role in osteoporosis and other age associated conditions.

For women as well as men, testosterone helps maintain libido. Imbalances of testosterone in postmenopausal women are associated with various forms of coronary heart disease and cardiovascular events, including myocardial infarction. In addition to influencing muscle mass and weight loss, testosterone also plays a role in the production of several other hormones.

There is growing awareness that hormone function plays a vital role in a man's health over the course of his lifetime. In particular, changes in the production of the sex hormone testosterone can exert a profound influence on sexual function, bone density, fat metabolism, mood states, energy levels, and even physical appearance (skin and muscle tone).

## **Steroidal Hormone Pathways**

Cholesterol forms pregnenolone in the adrenal glands. Pregnenolone then metabolizes into progesterone and DHEA. DHEA readily forms a sulfated metabolite, DHEA-S, which is the species usually measured because of its increased stability. Progesterone also forms cortisol, while DHEA forms testosterone and the three estrogens--estrone (E1), estradiol (E2), and estriol (E3).

Prior to menopause up to 30% of female hormones are produced in the adrenals, after menopause up to 50% are produced in the adrenals.



Estradiol (E2) is secreted into the blood stream where 98% of it circulates bound to sex hormone binding globulin (SHBG).

**Androstenedione**, produced in the adrenal gland and gonads, is the immediate precursor to both testosterone and estrone, both of which may be subsequently converted to estradiol.

## Effects of estrogens on female physiology

During puberty, estrogens play a significant role in the maturation of such female reproductive organs as the vagina, uterus, fallopian tubes, and ovaries. Estrogens also trigger secondary sexual characteristics, namely the development of breasts and increased osteoblastic activity resulting in characteristically feminine skeletal development.

Estrogens stimulate an increase in total body protein, promoting body development during puberty. These hormones also stimulate deposition of fat in subcutaneous tissues, particularly breasts, buttocks, and thighs. Estrogens influence development of vascular function and soft textured skin and have a minor effect on pubic and underarm hair growth. Furthermore, estrogens cause a slight retention of sodium and water by the kidneys and more pronounced retention during pregnancy.

## Role of Estrogen

Estrogens are hormones that prepare the endometrial cells of the uterus for pregnancy. Estrogens (estradiol and estrone) have many functions in the body, including:

- Cause ovulation, helping to rebuild the lining of the uterus following menstruation.
- Assist in the development of secondary sex characteristics, including breast development and distribution of body hair.
- Promote cholesterol balance and nourish the blood and circulatory system.
- Improve bone density and strength by increasing calcium and phosphate absorption.
- Increase the softness, smoothness, thickness, and elasticity of the skin.

When it's time to move beyond the child-bearing years, women's estrogen levels should gently fall, telling their bodies to cease preparing an environment for fertilized eggs. When menstruation stops abruptly, menopause brings with it some uncomfortable symptoms, such as **hot flashes and mood swings**.

On the other hand, if a woman takes too much estrogen to replace this loss, the estrogen overload can lead to other health problems, even cancer of the uterus or breasts.

## Role of Progesterone

Progesterone prepares the lining of the womb for pregnancy and implantation and decreases uterine contractions. Progesterone normally maintains fluid balance, acting

as a natural diuretic, by increasing sodium and water elimination from the body. Progesterone deficiency may cause various mild to severe symptoms.

The adrenal glands produce progesterone throughout the entire menstrual cycle, whereas the ovaries only produce it in significant amounts during the premenstrual phase of the cycle.

Progestins (progesterone and medroxyprogesterone) have a balancing effect on estrogen.

**When progesterone levels drop to near zero, estrogen dominance occurs with side effects including:**

- Water retention, swelling (edema)
- Fatigue, lack of energy
- Breast swelling
- Premenstrual mood swings
- Loss of sex drive
- Uterine fibroids
- Cravings for sweets
- Weight gain, fatty deposits in thighs and hips
- Cold hands, cold feet (low thyroid)

### ***Effects of progesterone on female physiology***

Like estrogen, progesterone plays a role in increasing the size of breasts by stimulating the development of lobules and alveoli. During the menstrual cycle, progesterone promotes secretory changes in the endometrium preparatory to the implantation of a fertilized ovum. Progesterone also has a minor effect on the retention of sodium, chloride, and water by the kidneys.

When a woman's adrenal function is compromised as a result of chronic stress, an outcome can be a reduction in sex hormones, with progesterone affected to a greater extent than the estrogens.

The potential impact of estrogen on a woman's health and wellbeing is enormous. Acting in a seeming paradoxical fashion, this powerful hormone can exert a strong influence in diverse conditions such as breast cancer, osteoporosis, heart disease, and autoimmune disorders.

## **The Metabolism of Estrogen**

Estrogen is metabolized in two ways. Along one pathway, it is converted into a powerful metabolite, **16alpha-hydroxyestrone (16alpha-OHE1)**, that acts to stimulate target tissues.

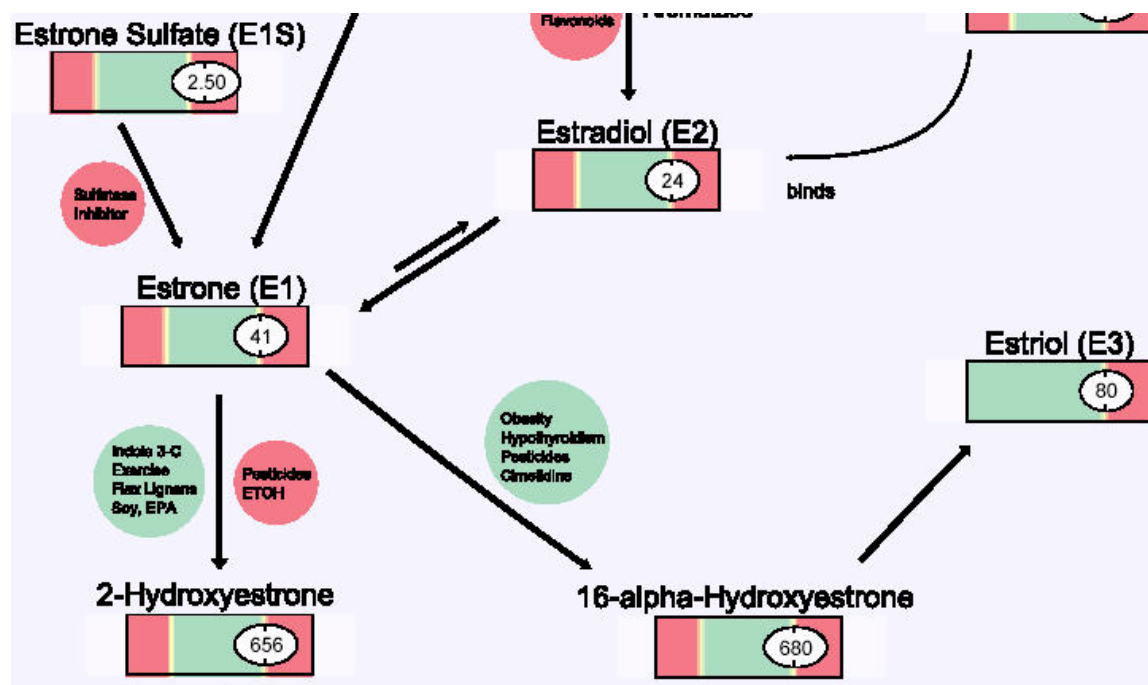
Levels of **16alpha-OHE1** can rise in response to obesity, alcohol consumption, and toxic exposure.

## Estrogen Metabolism

Hormone	Reference Range	Reference Range
2-Hydroxyestrone	656	112-656 pg/mL
16 $\alpha$ -Hydroxyestrone	680	213-680 pg/mL
2:16 $\alpha$ -Hydroxy-Estrone Ratio	0.96	0.40-1.40

High levels of this potent metabolite are linked with increased risk and poorer prognosis in conditions associated with estrogen excess, including breast cancer and lupus.

Alternately, the body can break down estrogen into a much weaker metabolite, called **2-hydroxyestrone (2-OHE1)**. This metabolite binds weakly to cell receptors and may slow cell proliferation. However, **excessive levels of 2-OHE1** may increase the risk of developing conditions associated with estrogen deficiency, such as heart disease, depression, and osteoporosis.



A proper balance between 2-OHE1 and 16 $\alpha$ -OHE1 is the key to optimal health.

Flaxseed (lignans), soy products (isoflavones), cruciferous vegetables (indole-3-carbinol), vigorous exercise, and omega-3 fatty acids are interventions that may reduce

the risk of estrogen-dependent disease by favorably modifying the 2:16alpha-OHE1 ratio.

## **Assessing the Female Hormonal System**

### ***Signs and Symptoms of Female Endocrine Dysfunction***

Many of the signs and symptoms associated with the female endocrine system involve issues of PMS, menopause, menstrual irregularity, and problems with fertility. All of these conditions have a variety of causes. You will find that in many cases simply addressing general health issues will make a huge difference for these dysfunctions. You can resolve a large number of the problems in the female endocrine system by resolving digestive dysfunction, mucosal barrier function, blood sugar dysregulation, thyroid hormone imbalance, nutritional deficiencies, and toxicity issues. For instance, mood swings during the menstrual cycle can be the result of poor thyroid function. Poor liver function or dysbiosis can cause imbalance between progesterone and estrogen. Menopausal hot flashes can be the result of poor adrenal function or EFA deficiency. It is best to treat root causes of health problems, but sometimes symptom management is necessary. You will need to decide on an effective and natural approach to this issue.

Helping your patients improve their diet is a good first step in improving health in relation to their menstrual cycle. The average American eats 150 pounds of sugar and ten pounds of chemical food additives every year. Most Americans get half of their calories from refined carbohydrates. People consume hydrogenated oils at an alarming rate. The resulting vitamin deficiencies and detrimental effects on all organs and systems of the body are the beginning of many health problems, including menstrual irregularities. Getting adequate exercise is also very important. Based on the results of the N.A.Q., and other findings, you will be able to find the best way to fix the root causes of problems with your clients' menstrual cycle and other women's health issues.

**Here are some of the signs and symptoms associated with female endocrine problems:**

- Depression during periods
- Mood swings associated with periods (PMS)
- Crave chocolate around periods
- Breast tenderness associated with cycle
- Excessive menstrual flow
- Scanty blood flow during periods
- Occasional skipped periods
- Variations in menstrual cycles
- Endometriosis



- Uterine fibroids
- Breast fibroids, benign masses
- Painful intercourse (dysparenia)
- Vaginal discharge
- Vaginal dryness
- Vaginal itchiness
- Gain weight around hips, thighs and buttocks
- Excess facial or body hair
- Hot flashes
- Night sweats (in menopausal females)
- Thinning skin

**When progesterone levels drop to near zero, estrogen dominance occurs with side effects including:**

- Water retention, swelling (edema)
- Fatigue, lack of energy
- Breast swelling
- Premenstrual mood swings
- Loss of sex drive
- Uterine fibroids
- Cravings for sweets
- Weight gain, fatty deposits in thighs and hips
- Cold hands, cold feet (low thyroid)

## ***Assessing the Female Endocrine System: Physical Examination Techniques***

There are few specific PE techniques associated with the female endocrine system. Dr. Frank Chapman used to check for tenderness in the area lateral to the pubic symphysis on the rami attachment of the Rectus abdominus muscle. This was a reflex to the ovaries and uterus.

You may also want to check for tenderness in the middle portions of the right and left ITBs on the lateral thigh. Tenderness in these areas may be due to dysfunction in the ovaries or the colon.

# **Assessing the Female Endocrine System: Blood Testing**

## **Estradiol Reference ranges**

### **Normal reference range**

- Women: 0 – 528 pg/ml

### **Optimal reference range**

- Women 352 – 528 pg/mL

The levels above are not specific to any particular phase of the menstrual cycle. They are a general assessment of estradiol.

## **Clinical Implications**

### **Low levels of Estradiol**

#### ***Osteoporosis and Bone Fractures***

Low levels of estradiol can be a risk factor for **osteoporosis** and **bone fracture**.

Researchers at the Creighton University School of Medicine in Omaha, NE, observed that in women aged 65-75, low levels of serum total and bioavailable estradiol correlated with low levels of bone mineral density in the femur, spine, and total body.

“Endogenous levels of serum estradiol and sex hormone binding globulin determine bone mineral density, bone remodeling, the rate of bone loss, and response to treatment with estrogen in elderly women”

Estradiol may improve quality of life in menopausal women. Italian scientists tested the effects of six months of transdermal estradiol therapy in women who were experiencing uncomfortable symptoms of early menopause. Eighty percent of the treated women reported improvement of hot flashes, insomnia, and irritability, and 61% reported an improved sense of well-being.

**Rigano A, Rigano M, Cancellieri F, Pulle C. Sexually and well-being in early menopause. Effect of transdermal estradiol therapy. Panminerva Med. 2001 Jun;43(2):115-8.**

#### ***Migraine Headaches***

Hormone imbalance may be a cause of migraine headaches in women. Declining estrogen levels during menstruation and meno-pause may trigger migraine head-aches. By contrast, sustained high levels of estrogen, as occur during pregnancy, frequently provide relief from headaches. Estrogen produces changes in body levels of prostaglandins and opioids, which may account for its effects in relieving headaches.

## Increased Levels of Estradiol

Increased levels of estradiol in woman suggest an increased risk of breast or endometrial cancer.

### One of the main reasons to check estradiol levels

Increased levels of estradiol in woman suggest an increased risk of breast or endometrial cancer so we think that it deserves to be on an annual female blood testing panel especially for patients with a family history of cancer.

## The Asian Advantage

Research has shown that Japanese women have higher levels of estradiol in their blood yet have a lower risk of breast cancer. How can that be?

This probably has more to do with environmental factors than genetics. When Japanese women adopt a Western diet their risk of breast cancer increases. The Asian diet likely has factors that help a woman regulate her own estrogen levels. It's worth remembering that how the body handles estrogens is far more important than the amount of estrogen

Researchers have extensively investigated three aspects of the Asian advantage: **soy, vegetables, and green tea**. Each is associated with a dramatically lower risk of breast cancer.

**Soy: Genistein (a soy isoflavone) has been called the “good estrogen” for its beneficial effects against estrogen-responsive breast cancer.** Soy isoflavones neutralize “strong” estrogens, converting them to estrogen metabolites that protect against breast cancer. It appears that the combination of soy and green tea is particularly effective.

**Vegetables:** Women who eat the most vegetables, beans such as lentils, and fiber reduce their risk of breast cancer risk by 50%.<sup>48</sup> Certain compounds found in vegetables favorably affect the way estrogen behaves in the body. These include **indole-3-carbinol**, which helps convert “strong” estrogens into benign or even helpful estrogens such as 2-hydroxyestrone, **Di-indole methane**, which is converted from ingested indole-3 carbinol. lowers harmful 4- and 6-hydroxylations.

**Melatonin:** Another nutrient to look at is **melatonin**. In estrogen-receptor-positive breast cancer cells, melatonin can bring cell growth to a halt. Research indicates that melatonin controls estrogen, and vice versa.

*(Girgert R, Bartsch C, Hill SM, Kreienberg R, Hanf V. Tracking the elusive antiestrogenic effect of melatonin: a new methodological approach. Neuro Endocrinol Lett. 2003*

## Free Testosterone reference ranges

### Effects of testosterone on female physiology

In the adult female, testosterone plays an important role in maintaining lean body mass, bone density, skin elasticity, and libido. In addition, testosterone is involved in blood cell production. Low testosterone levels have been linked to increased risk for osteoporosis, decreased lean body mass, and decreased libido, and may suggest ovarian insufficiency and/or adrenal insufficiency. Elevated testosterone levels have been linked to masculinization, hirsutism, and increased risk of insulin resistance. Elevated testosterone levels have been noted in polycystic ovary disease and adrenal hyperplasia and suggest the presence of ovarian dysfunction or adrenal dysfunction.

In women, high levels of free testosterone may indicate hirsutism, which causes excessive growth of hair on the face and chest, and is often indicative of polycystic ovaries. Increased testosterone in women also may indicate low estrogen levels due to the inverse relationship between testosterone and estrogen.

### Normal reference range

- Women: 0 – 2.2 pg/ml

### Optimal reference range

- Women: 1.4 – 2.2 pg/mL

Women only produce very small amounts of testosterone, yet there is evidence to suggest that testosterone plays a role in female endocrine physiology. It helps women maintain muscle strength, bone mass, and sexual function. Like many of the other female hormones, testosterone levels decrease with age and especially after menopause. Checking and restoring testosterone levels in your female patients may make a considerable difference in their health and wellness.

A study published in the *New England Journal of Medicine* examined the effects of transdermal testosterone patches on 75 women, aged 31-56. They all had decreased testosterone levels due to hysterectomy and removal of both ovaries. Women using a 300 mcg testosterone patch had significant improvements in sexual function, mood, and general well-being compared to the women using the 150-mcg patch or placebo.

*Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med. 2000 Sep 7;343(10):682-8.*

## FSH and LH Testing

You may want to assess pituitary hormonal influences by running serum FSH and LH levels.

## Advanced FDM Testing

We will be producing an interpretation and treatment guide for the female hormonal panel that is available from many of the advanced functional medicine testing labs.

## Estrogen Metabolism Testing

### Background

One of the main functions of the liver is the metabolism and detoxification of hormones. This test shows if the body is metabolizing estrogens properly. You can see if estrogens are being converted into the 16-a-hydroxyestrone metabolite, which has been shown to potentiate cancer.

**“The body metabolizes estrogens into several different metabolites that can impact cancer development. One metabolite, 2-hydroxyestrone (2-OHE1), tends to inhibit cancer growth. Another, 16-a-hydroxyestrone (16-a-OHE1), actually encourages tumor development. A woman’s “biochemical individuality” determines which of these metabolites predominates.”**

<http://www.metametrix.com/content/DirectoryOfServices/Estronex216OHRatio?cinfo>

### Who should have this test?

This test is essential for anyone on birth control pills or hormone replacement therapy.

### Metabolites Tested

- 2-Hydroxyestrogens (sum of 2-hydroxyestradiol and 2-hydroxyestrone)
- 16-alpha-Hydroxyestrone
- Creatinine

### Treatment Options

If the ratio between the **2-hydroxyestrone** and the **16-a-hydroxyestrone** ratio is too low, the use of foods or supplements containing **Indole -3-carbinol (I3C)** or **Diindolylmethane (DIM)** can stimulate the phase 1 conversion of estrogen to produce the cancer protective 2-hydroxy derivatives. Cruciferous vegetables are good food sources of DIM and I3C.

### Who does this test?

This is a short list of some of the well known labs who do this test.

**Metamatrix** – Estronex 2/16 OH Ratio

**Genova Diagnostics** – Essence (Women's Hormonal Health Assessment)

# **The Male Endocrine System**

## ***Physiology and Biochemistry of the Male Hormonal System***

The male hormonal system is really all about the hormone testosterone.

### **What is testosterone?**

Testosterone is a powerful anabolic hormone. That means it stimulates the body's development of muscle, bone, skin, and sex organs, along with masculine physical features, such as hair growth. Recently, scientists have discovered that testosterone also improves mental power, by enhancing visual and perceptual skills.

In men, testosterone is produced in the testes, by a group of cells known as Leydig cells. These cells begin secreting high doses of testosterone during puberty to trigger increased lean muscle mass, sex organ growth, bone formation, deeper voice, and higher energy levels. Peak testosterone levels are reached in a man's early to mid- 20s.

### **What happens to testosterone levels over the course of a man's lifetime?**

As a man ages, the Leydig cells that secrete testosterone begin to wear away. Because of this, between the ages of 40 and 70, the average man loses nearly 60% of the testosterone inside his body!

Eventually, imbalances of testosterone can set the stage for the development of even more serious diseases. Low levels can disrupt the body's blood sugar metabolism, leading to obesity and diabetes. Chronic deficiencies may also promote the early onset of osteoporosis and heart disease.

### **Male Hormone Imbalance**

The testes produce nearly 95% of all male testosterone. The balance is supplied by the adrenal glands. They also produce small amounts of estrogen. The brain produces the pituitary hormones follicle stimulating hormone (FSH) and luteinizing hormone (LH) which trigger hormone production from the testes. As a man gets older, testosterone levels fall and estrogen levels tend to rise. Lower testosterone levels may affect bone density, muscle strength, body composition and sex drive. The imbalance that occurs when testosterone is low in relation to estrogen may also contribute to prostate problems.

# Testosterone and Male Hormone Physiology

## ***Testosterone***

**Testosterone** plays many physiological roles in males. While it is important for primary and secondary male sexual characteristics, libido and sexual function, muscle and bone strength and growth of normal body hair, it also has favorable effects on mood, well being, energy and vitality. Most testosterone is produced in the testes with some produced in the adrenal glands. Excessive levels of testosterone have been correlated with high cholesterol, prostate problems, atherosclerosis and aggression. Testosterone is the direct precursor of dihydrotestosterone, an extremely potent androgen.

Testosterone is an anabolic steroid synthesized primarily by the Leydig cells in the testes in males, the ovaries in females, and adrenal glands in both sexes. It is synthesized from cholesterol, with androstenedione, androstenediol, dehydroepiandrosterone (DHEA), progesterone and pregnenolone acting as some of the intermediate substrates.

Testosterone production is regulated by hormonal secretions from the hypothalamus and the pituitary gland in the brain. The process begins as the hypothalamus secretes gonadotropin-releasing hormone (GnRH) in generative pulses. In response to these steady intermittent bursts of GnRH, the pituitary gland releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which act directly on the testes.

FSH activates the Sertoli cells which produce sperm (spermatogenesis). LH stimulates the Leydig cells to secrete testosterone in a daily rhythm characterized by peak levels in the morning and low levels in the evening. Once it reaches high levels, testosterone production generates negative loop feedback to the hypothalamus to downregulate LH release and diminish further testosterone production. In this way, testosterone inhibits its own secretion.

## ***Dihydrotestosterone***

**Dihydrotestosterone (DHT)** is made from testosterone by the enzyme 5-alpha reductase. Along with testosterone, it is responsible for the formation of primary sex characteristics of the male during embryonic life and secondary sex characteristics at puberty. **Increased production of DHT in adult males is thought to cause prostate growth (hyperplasia) and male pattern baldness.**

In males, progesterone acts to limit the conversion of testosterone to DHT. In cases of benign prostate hyperplasia (BPH), drugs like Propecia and Proscar are used to inhibit 5-alpha reductase, while not interfering with the beneficial effects of testosterone.

## ***Androstenedione***

**Androstenedione** is a weak androgen which is a metabolite of DHEA and a direct precursor of testosterone. Androstenedione can also be converted to estrone by the enzyme aromatase. In men, **excessive androstenedione results in excessive estrone production.**

**Progesterone** is largely made from pregnenolone in the adrenal glands of males. It is calming to the nervous system and activates the GABA chloride channel to help the



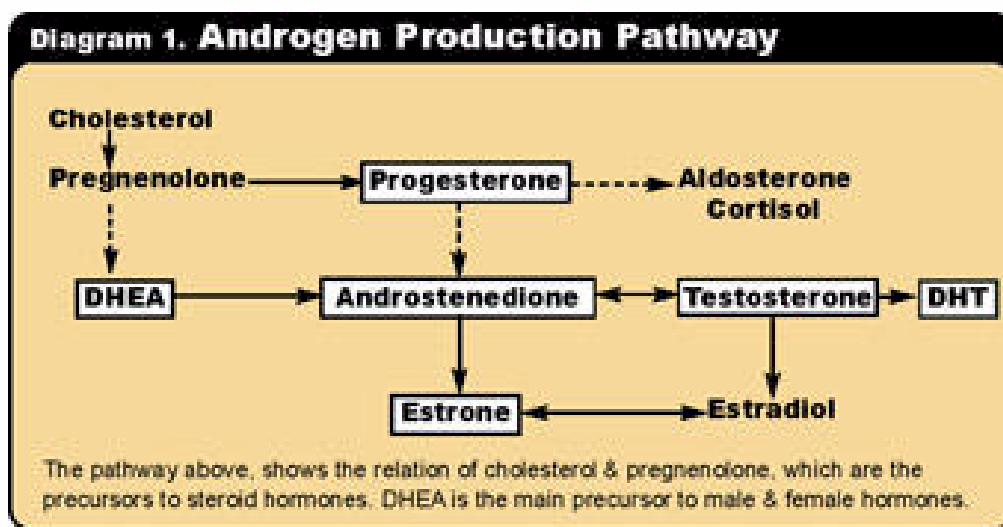
body shut down both physically and mentally for sleep, rest and recovery. As stated above, it acts to limit the conversion of testosterone to DHT and is an antagonist to the effects of estrogens in the bodies of males and females.

### **Estrone**

**Estrone** is an estrogen produced in the fat cells, muscle cells and skin of men and women. In men, almost all estrone is converted from androstenedione, which is produced in the testes and adrenal glands. Estrone is stored in adipose tissue: the more body fat the higher the level of estrone. This becomes a vicious circle as estrone promotes the storage of more fat. While a necessary antagonist to androgens in males, **excess estrone can lead to weight gain and prostate enlargement.**

After testosterone is secreted into the bloodstream via the Leydig cells, its fate can follow a few different pathways. Some testosterone attaches to sex hormone binding globulin, or SHBG. Testosterone not bound up with SHBG is known as free testosterone, and it is in this form that it can exert its powerful anabolic and androgenic effects on the human body.

Testosterone can also be converted via enzymatic pathways into different hormones. Through the actions of 5-alpha-reductase, an enzyme found in multiple tissues but especially high in the prostate gland, testosterone can be converted into **dihydrotestosterone (DHT).**



As if this news isn't bad enough, there are also steep declines (40% to 75%) in other steroid hormones, including dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) seen in men as they age from 20 to 80.

## **Effects of testosterone on female physiology**

In the adult female, testosterone plays an important role in maintaining lean body mass, bone density, skin elasticity, and libido. In addition, testosterone is involved in blood cell production. Low testosterone levels have been linked to increased risk for osteoporosis,

decreased lean body mass, and decreased libido, and may suggest ovarian insufficiency and/or adrenal insufficiency. Elevated testosterone levels have been linked to masculinization, hirsutism, and increased risk of insulin resistance. Elevated testosterone levels have been noted in polycystic ovary disease and adrenal hyperplasia and suggest the presence of ovarian dysfunction or adrenal dysfunction.

## Andropause: Male Menopause

Andropause is a condition that all men will experience to some degree as they age. Though similar to menopause in that both involve some drop of hormone levels, men do not have a specific event that tells them andropause is arriving.

While women have the cessation of menstrual cycles, hot flashes and other symptoms that occur quickly, men have vague signs and symptoms that slowly encroach on the quality of their lives and slowly that draw their attention to the changes taking place.

Between the ages of 40 and 55 men will start to experience a drop in the level of bioavailable testosterone. This is due in part to the drop of total testosterone levels, and in part due to the cells of the body no longer “listening” to the testosterone signal – due to decreased receptor function.

Andropause is therefore a condition of decreased testosterone levels and decreased testosterone function.

*Tang YJ, Lee WJ, Chen YT, Liu PH, Lee MC, Sheu WH. Serum testosterone level and related metabolic factors in men over 70 years old. J Endocrinol Invest. 2007 Jun;30(6):451-8.*

Sex hormone decline remarkably decreases metabolic function in elderly men. Many degenerative diseases may relate to testosterone deficiency.

**CONCLUSION:** Total testosterone level is significantly related to metabolic and inflammatory factors in elderly men. Low total testosterone may be a significant indicator for development of metabolic syndrome in elderly men.

*Rabijewski M, Kozakowski J, Zgliczynski W. The relationship between testosterone and dehydroepiandrosterone sulfate concentrations, insulin resistance and visceral obesity in elderly men] Endokrynol Pol. 2005 Nov-Dec;56(6):897-903*

Sex hormones deficiency--hypotestosteronemia (20-30% of men) and dehydroepiandrosterone sulfate deficiency (60-70% of men) are often observed in elderly men. In these men also changes of body composition (visceral obesity, increasing of fat mass), and metabolic disturbances (hypercholesterolemia, hyperinsulinism and insulin resistance) are common disorders. Probably also DHEA-S deficiency is the risk factor of visceral obesity and insulin resistance, but it is not clear, whether this possible influence is independent from testosterone deficiency.

**CONCLUSIONS:** DHEA-S and testosterone deficiency were independently associated with higher insulin resistance and obesity. WHR ratio seems to be more sensitive than BMI ratio to reflect the androgen deficiency on obesity and

body composition in elderly men.

Rabijewski M, Adamkiewicz M, Zgliczynski S. The influence of testosterone replacement therapy on well-being, bone mineral density and lipids in elderly men] Pol Arch Med Wewn. 1998 Sep;100(3):212-21

The aim of this study was to determine the influence of testosterone replacement therapy in elderly men on mood, bone mineral density, and lipids.

**CONCLUSIONS:** Patients with coronary heart disease demonstrated decreasing symptoms of angina pectoris and nitrate requirement. In summary, long-term testosterone replacement therapy in elderly men may have beneficial effects on well-being, libido, potency, dream, bone mineral density, lipids, blood cell count and body mass (BMI). This therapy appears to be safe and there is no adverse effect on prostate.

Rabijewski M, Zgliczyński W. Dehydroepiandrosterone therapy in men with angiographically verified coronary heart disease: the effects on plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) and fibrinogen plasma concentrations] Endokrynol Pol. 2007 May-Jun;58(3):213-9.

**INTRODUCTION:** The aim of this study was to analyze the influence of DHEA therapy on fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) plasma concentrations in men with decreased serum DHEA-S levels and angiographically verified coronary heart disease (CHD).

**CONCLUSIONS:** DHEA therapy in dose of 150 mg daily during 40 days in men with DHEAS levels < 2000 mg/l and angiographically verified coronary heart disease (CHD) was connected with significant decreasing of fibrinogen concentration and increasing of estradiol levels, and did not influence on plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) plasma concentrations.

Rabijewski M, Zgliczynski W. Positive effects of DHEA therapy on insulin resistance and lipids in men with angiographically verified coronary heart disease--preliminary study] Endokrynol Pol. 2005 Nov-Dec;56(6):904-10.

**OBJECTIVES:** The aim of this study was to analyze the influence of DHEA therapy on insulin resistance (FIRI, FG/FI) and serum lipids in men with angiographically verified coronary heart disease (CHD).

**CONCLUSIONS:** DHEA therapy in dose of 150 mg daily during 40 days in men with DHEA levels < 2000 microg/l decreased total cholesterol concentration, insulin and glucose levels and fasting insulin resistance index (FIRI). This therapy may be a beneficial against CHD risk factors.

Zietz B, Reber T, Oertel M, Gluck T, Scholmerich J, Straub RH. Altered function of the hypothalamic stress axes in patients with moderately active systemic lupus erythematosus. II. Dissociation between androstenedione, cortisol, or dehydroepiandrosterone and interleukin 6 or tumor necrosis factor. J Rheumatol. 2000 Apr;27(4):911-8.

**OBJECTIVE:** To investigate adrenocorticotropin, androstenedione (ASD), cortisol, or dehydroepiandrosterone sulfate (DHEAS) before and during a corticotropin releasing hormone (hCRH) test in patients with moderately active systemic lupus erythematosus (SLE) undergoing low dose longterm glucocorticoid therapy, and to examine these hormones in relation to interleukin 6 (IL-6) or tumor necrosis factor (TNF).

**CONCLUSION:** We found marked adrenal insufficiency and a shift in steroidogenesis to cortisol in patients with SLE, but a completely normal pituitary function (in absolute values and in relation to IL-6 or TNF). This may depend in part on prior longterm glucocorticoid therapy and changes of steroidogenesis due to cytokines. The situation in patients with SLE was not mimicked by high dose short term prednisolone in healthy subjects. Further longitudinal studies in untreated patients are needed to investigate the endocrine-immune interplay and its consequences during the course of SLE.

---

*Straub RH, Scholmerich J, Zietz B. Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases--substitutes of adrenal and sex hormones. Z Rheumatol. 2000;59 Suppl 2:II/108-18.*

A dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis was found in animal models of chronic inflammatory diseases, and the defect was located in more central portions of the HPA axis. This defect of neuroendocrine regulatory mechanisms contributes to the onset of the model disease. Since these first observations in animal models were made, evidence has accumulated that the possible defect in the HPA axis in humans is more distal to the hypothalamus or pituitary gland: In chronic inflammatory diseases, such as rheumatoid arthritis, an alteration of the HPA stress response results in inappropriately low cortisol secretion in relation to adrenocorticotrophic hormone (ACTH) secretion.

Furthermore, it has recently been shown that the serum levels of another adrenal hormone, dehydroepiandrosterone (DHEA), were significantly lower after ACTH stimulation in patients with rheumatoid arthritis without prior corticosteroids than in healthy controls. These studies clearly indicate that chronic inflammation alters, particularly, the adrenal response. However, at this point, the reason for the specific alteration of adrenal function in relation to pituitary function remains to be determined. Since one of the down-regulated adrenal hormones, DHEA, is an inhibitor of cytokines due to an inhibition of nuclear factor-kappa B (NF-kappa B) activation, low levels of this hormone may be deleterious in chronic inflammatory diseases. We have recently demonstrated that DHEA is a potent inhibitor of IL-6, which confirmed an earlier study in mice. Since IL-6 is an important factor for B lymphocyte differentiation, the missing down-regulation of this cytokine, and others such as TNF, may be a significant risk factor in rheumatic diseases. Since in these patients, administration of prednisolone or the chronic inflammatory process itself alters adrenal function, endogenous adrenal hormones in relation to proinflammatory cytokines change. Furthermore, these mechanisms may also lead to shifts in steroidogenesis which have been demonstrated in chronic inflammatory diseases. It was repeatedly demonstrated that the serum level of the sulphated form of DHEA (DHEAS) was significantly

lower in patients with chronic inflammatory diseases. Since DHEAS is the pool for peripheral sex steroids, such as testosterone and 17 beta-estradiol, lack of this hormone leads to a significant sex hormone deficiency in the periphery. This overview will demonstrate mechanisms why DHEAS is reduced in chronic inflammatory diseases. The importance of DHEAS deficiency will be demonstrated with respect to osteoporosis. As a consequence, we suggest a combined therapy with corticosteroids plus DHEA in chronic inflammatory diseases.

## **Assessing the Male Hormonal System**

### ***Signs and Symptoms of Male Hormonal Dysfunction***

The following are some of the symptoms associated with male hormonal issues:

- Prostate problems
- Difficulty with urination, dribbling
- Difficult to start and stop urine stream
- Pain or burning with urination Waking to urinate at night
- Interruption of stream during urination
- Pain on inside of legs or heels
- Feeling of incomplete bowel evacuation
- Decreased sexual function

### **Key symptoms of testosterone deficiency include:**

- Depression
- Fatigue
- Low sex drive
- Irritability
- Loss of facial/body hair
- Thinning and wrinkling of skin
- Weight gain
- Weakening of bone and muscle tissue
- Decrease in the size of the sex organ
- Bone loss
- Decreased mental clarity
- Decreased muscle strength

- Decreased stamina
- Decreased urine flow
- Increased abdominal fat
- Increased urge to urinate
- Irritability
- Mood swings
- Night sweats
- Poor concentration
- Sleep disturbances

## ***Assessing the Male Endocrine System: Physical Examination Techniques***

There are few specific PE techniques associated with the male endocrine system. Dr. Frank Chapman used to check for tenderness in the area lateral to the pubic symphysis on the rami attachment of the Rectus abdominus muscle. This is a reflex for the prostate.

You may also want to check for tenderness in the middle portions of the right and left ITBs on the lateral thigh. Tenderness in these areas may be due to dysfunction in the prostate.

## ***Assessing the Male Endocrine System: Blood Testing***

### **Free Testosterone**

Low testosterone levels in men are associated with many adverse health conditions, including diminished libido, erectile dysfunction, loss of muscle tone, increased abdominal fat, low bone density, depression, Alzheimer's disease, and heart disease.

### **Reference Ranges**

#### ***Normal reference range***

- Men: 6.6 – 26.5 pg/ml

#### ***Optimal reference range***

- Men: 15 – 26.5 pg/mL

### **Clinical Implications**

#### ***Low testosterone levels are associated with the following:***

- Metabolic Syndrome

- Diabetes
- Alzheimer's disease
- Increased risk of stroke
- Increased risk of heart failure

***Physical symptoms associated with low testosterone function include:***

- Decline in sexual activity
- Poor or no erections
- Loss of muscle mass and strength
- Increased risk of cardiovascular disease
- Chest pain
- Insulin resistance (with increased risk of diabetes)
- Loss of bone mass that can lead to osteoporosis
- Fatigue and loss of energy
- Reduction in body hair and skin thickness
- Development of hair in ears and nose
- Increase in upper and central body fat
- Increase in heart and artery disease
- Problems with circulation
- Sleep disturbances
- Decreased intellectual ability
- Trouble with memory
- Decreased interest in sex
- Difficulty focusing attention
- Depression
- Anxiety
- Agitation
- Irritability
- Decreased sense of well-being.

***High testosterone levels***

High testosterone levels are associated with the following:

- Increased risk for prostate cancer



## Estradiol Reference ranges

### Normal reference range

- Men: <54 pg/ml

### Optimal reference range

- Men: 10 – 30 pg/mL

## Importance of Estradiol in Men

Low levels of estradiol in men affect bone density and risk of fractures if too low.

At the University of California at San Diego, researchers showed that low levels of estradiol, but not of other hormones, increased the risk of vertebral fractures in older men.

Among 352 men with a median age of 66, “age-adjusted hormone levels differed by fracture status only for total and bioavailable estradiol.” The researchers concluded, “estrogen plays a critical role in the skeletal health of older men.”

Research from the now famous Framingham study found an association between suboptimal estradiol levels in men and osteoporosis risk. Researchers measured total testosterone, total estradiol, and luteinizing hormone in 405 men aged 68-96. The study results linked decreases in bone mineral density with declining levels of estradiol. The researchers noted, “The difference in mean mineral bone density between men in the lowest and highest estradiol quartile levels was similar to the effects of 10 years of aging on bone mineral density.” The authors concluded that in elderly men, low testosterone related to aging “has little influence on bone mineral density, but serum estradiol levels have a strong and positive association with bone mineral density.”

*(Amin S, Zhang Y, Sawin CT, et al. Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. Ann Intern Med. 2000 Dec 19;133(12):951-63.)*

### Coronary artery disease

There’s also a link with total cholesterol, estradiol levels and coronary artery disease. It seems that estradiol has a possible role in “promoting the development of atherogenic lipid milieu in men with coronary artery disease.” The research is not equivocal but it’s worth keeping an eye out for this.

## Prostate Specific Antigen

Prostate cancer is currently the second leading cause of cancer-related deaths in US men. Prostatic cells are more prone to mutation than other cells of the male reproductive system and evidence from autopsies showed that 34% of men aged 40 – 49 have histological evidence of prostate cancer. This rose to 70% in men aged 80 or



over<sup>i</sup>. With so many men experiencing health issues related to the prostate, it's essential for doctors to be screening for this. And as a functionally oriented physician, I appreciate the many tests available to us that help can steer a course to prevent, slow the progression of, and reverse prostate disease.

There is too much information to cover everything on blood testing for prostate cancer in this article, so I'll give a brief overview and mention several of the tests I like to run. PSA (Prostate Specific Antigen) is the one that comes to mind first, but many other tests complement the PSA result to create a more comprehensive diagnostic picture.

## **PSA: Background**

PSA, the most abundant protein synthesized in the prostate gland, is a serine protease enzyme that helps liquefy the male ejaculate to facilitate fertilization. The majority of the PSA stays within the prostatic ducts, which is why blood levels of PSA, in a healthy prostate, are typically less than 1.0 ng/ml. Unfortunately, the enzymatic activity of PSA can break up the extracellular matrix surrounding the cells and can actually hasten the spread of cancer as well as increase blood levels of PSA.

PSA is currently used as a biological marker or tumor marker that can be used to detect disease related to the prostate. Increased levels can indicate prostate cancer or less serious conditions such as benign prostate hyperplasia, and prostatitis.

## **Prostate Cancer and risk factors**

Age seems to be the most common risk factor, with a high percentage of prostate cancer cases occurring in men age 65 and older. As a preventative-oriented practitioner, I believe prostate issues begin long before most are detected, so I recommend that men over thirty-five begin testing for PSA levels annually, so you can establish PSA velocity and PSA doubling time (see below).

Other reported risk factors for prostate cancer are race, lifestyle/environmental factors, and family history. Men who have a father or brother with prostate cancer have a greater chance of developing prostate cancer. African American men have the highest rate of prostate cancer, while Asian and Native American men have the lowest rates.

There is new evidence that in obese men, PSA levels can be deceptively low in cases of prostate disease or cancer. So PSA alone should not be used to rule out cancer, especially in obese men.

## **PSA Ranges**

In the past, most doctors considered PSA values below 4.0 ng/ml as normal. However, most functionally oriented doctors have much tighter ranges. The *Journal of Urology* reported in 2004 that 22% of patients with PSA levels between 2.6 and 4.0 ng/ml had prostate cancer, and on biopsy the cancer was deemed "significant". The leading researchers concluded that "an important number of cancers could be detected in the PSA range of 2.6 to 4.0 ng/ml." <sup>ii</sup> Given this research I like to see PSA tests below 2.6 ng/ml.

## **Expanding PSA Readings**

It is unwise in medicine to rely on one method of evaluation and I recommend that you look at a number of other assessment modalities to increase your accuracy in the assessment of prostate health. PSA levels alone tell us something, but far more information is available if we look beyond the static measurement to the interrelationships between levels over time. I recommend that you use the following in a comprehensive risk assessment for your patients.

### ***PSA Velocity (PSAV)***

PSAV is based on changes in PSA over time. It seems that the rate of increase in PSA is actually more important as a predictor of mortality than the PSA reading itself. A sharp rise in the PSA level raises the suspicion of cancer. In a study published in the *New England Journal of Medicine* men who showed a 2.0 ng/ml or greater increase in PSA from the previous year's reading were 10 times more likely to die within seven years.<sup>iii</sup> In my opinion, men over thirty five should get a baseline PSA test, and then test annually to measure the level of increase (PSA velocity).

### ***PSA Doubling Time (PSADT)***

PSADT looks at the amount of time it takes for the PSA level to double and is a reflection of tumor growth. For instance, the average PSADT for prostate cancer is 48 months. Men with optimal prostate health have no appreciable rise in PSA. It is a cause for concern if the PSA level doubles in less than 12 years.

### ***PSA Density (PSAD)***

PSAD considers the relationship of the PSA level to the size of the prostate and is helpful in diagnosing prostate cancer. The size of the prostate can be determined by radiological or ultrasound evaluation. PSAD is calculated by dividing the PSA result (in nanograms/ml) by an accurate determination of prostate gland volume. PSAD results above 0.15 ng/cc are associated with a diagnosis of prostate cancer.

## **Other Primary Bio-Markers For Prostate Cancer to Consider:**

Tumor cells produce specific products that play a role in the growth, spread, and metastasis of the tumor. We can measure many of these products, which are known as biomarkers, in the blood. An increase in tumor activity and size is often accompanied by an increase in these biomarkers. The following are some of the biomarkers for prostate cancer that you should be aware of:

### ***Prostatic Acid Phosphatase (PAP)***

I firmly believe that you should be running baseline PSA tests and following the results over many years. I also think you should run a baseline PAP and regularly check this test as well. PAP levels will begin to rise when prostate cancer has begun to spread beyond the capsule to other parts of the body. Unlike PSA it is less likely to be elevated from other causes and is helpful for monitoring the effectiveness of treatment and as an

independent predictor of recurrence. Levels above 3.0 ng/mL are associated with a higher probability of disease outside the prostate.

### ***Prolactin***

Prolactin is a hormone produced in the pituitary glands of both men and women. Pioneering work by Dr. Nevalainen and colleagues at Georgetown University Medical Center showed that prolactin serves as a local growth factor for prostate cells.<sup>iv</sup> Normal levels of prolactin in men are 2.17 to 17.7 ng/ml.

## **Other tests to consider**

### ***D-Dimer***

Because prostate cancer can cause higher risk of thrombosis, it's a good idea to keep track of D-dimer levels, a sensitive marker of coagulation. D-dimer can indicate if the patient has an existing clot or a risk of a clot. Most doctors would read levels between 0-1 as acceptable, being fairly certain no clot is indicated. But as a functionally oriented physician, I like to see D-Dimer levels below .40, which to me is the optimal range.

### ***Fibrinogen***

This is a very important test in predicting cancer development or progression. Fibrinogen is the precursor of fibrin. Research suggests that cancer cells use fibrin to coat themselves in order to slow down their recognition by the immune system.

Like D-dimer, fibrinogen can also be a good predictor of blood clots. Patients with cancer often show a hyper-coagulation state with elevated fibrinogen playing a major role. Anti-coagulant drugs such as heparin, which break down fibrin in the body, have been shown to improve survival rates.

Levels are best kept below 350 mg/dl

### ***Interleukin-6 (IL-6) and C-Reactive Protein (CRP)***

It is known that inflammation is involved in prostate cancer development and progression. IL-6 and CRP are two of the inflammatory markers that have been most strongly connected with prostate cancer. High C-reactive protein levels in men are associated with a 40% higher risk of prostate cancer and a high pre-diagnostic IL-6 reading may lead to a less than optimal prostate cancer outcome.<sup>v</sup> High levels of IL-6 and CRP may be responsible, at least in some part, to creating an environment in which cancer is more likely to develop and progress.

I like to see numbers of CRP below 0.55 mg/L for men and 0.8 mg/L for women, and levels of IL-6 below 150 pg/mL

### ***Insulin and Metabolic Syndrome***

There seems to be a link between insulin resistance and prostate cancer. So it's a good idea to keep an eye on fasting insulin, glucose, hemoglobin A1C, IGF-1, C-peptide, lipid panels and leptin levels.

There is more and more research coming out on preventing, tracking, and treating prostate cancer. I have only introduced the topic of blood testing for prostate disease, with the aim of illustrating the possibilities that exist. I urge all of you alternative practitioners to use what's available to help your patients, and to keep up with the exciting advancements in this field.

## References

- <sup>1</sup> Holund B. Latent prostatic cancer in a consecutive autopsy series. Scand J Urol Nephrol. 1980;14(1):29-35.
- <sup>2</sup> Nadler RB, Loeb S, Roehl KA, et al. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. J Urol. 2005 Dec;174(6):2154-7.
- <sup>3</sup> D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004 Jul 8;351(2):125-35.
- <sup>4</sup> Nevalainen, M. Researchers Discover Effective Method For Killing Prostate Cancer Cells, AScribe News, Inc. May, 2003, Georgetown University Medical Center
- <sup>5</sup> Stark, JR., IL-6, CRP Levels Tied to Prostate Cancer Development, Lethality, American Association for Cancer Research's Frontiers in Cancer Prevention Research Meeting in Boston, Nov. 2006., Reuters Health Information 2006.

## Treating Prostate Problems

The easiest way to reduce PSA levels by half is to inhibit the enzyme 5-alpha reductase, which is the enzyme that transforms testosterone into dihydrotestosterone (DHT). As mentioned above, DHT has a growth-promoting effect on prostate cells that is significantly greater than that of testosterone. Therapy to reduce the risk of prostate cancer should focus on reducing DHT levels. This can be done with drugs or natural therapeutics.

## Drugs

There are two main types of 5-alpha reductase- type 1 and 2. Proscar, one of the most popular prostate drugs, blocks only type 2 5-alpha reductase. Avodart®, unlike the more popular Proscar®, blocks both type 1 and type 2 5-alpha reductase, thus reducing blood DHT levels by 93%.

Avodart® drug therapy appears to be safe and effective not only for improving urinary flow symptoms, but more importantly for potentially reducing prostate cancer risk. Avodart® appears to accomplish these effects by reducing the growth-promoting effects of DHT on prostatic tissue, while decreasing the cancer-inducing properties of PSA by reducing PSA synthesis in the prostate gland. However it's not without side-effects:

- Expensive \$3.00/capsule or £1.50
- Side-effects include: decreased libido (4%), impotence (7%)

## Natural Methods

The following therapeutic choices have been demonstrated to be an effective way to treat the prostate:

### Green Tea

- Green tea appears to lower the incidence of prostate cancer
- A potent flavanoid of green tea called EpiGalloCatechin Gallate (EGCG) appears to be very effective at reducing PSA expression and inhibiting cancer-promoting properties of PSA

### Soy

- Another potential way to lower PSA levels is to increase soy consumption. It has long been known that human populations that consume soy products have a lower risk of prostate cancer.

### Curcumin

- curcumin inhibits the growth of prostate cancer cells and then activates genes that tell cancer cells to self-destruct (also referred to as apoptosis).
- The research on curcumin is so promising that pharmaceutical companies are currently developing curcumin analogs that can be patented as anti-cancer therapies.

### Boron

- a report from UCLA showed that men with the highest dietary boron intake reduced their prostate cancer risk by 54% compared to men with the lowest boron intake. A dose ranging from 6 to 15 mg/day may be a cost effective adjuvant treatment.

### Lycopene

- Lycopene is a flavanoid found in tomatoes and research has shown that prostate cells readily take up lycopene.
- Lycopene exerts a number of influence on prostatic tissue including apoptosis of hyperplastic prostate cells.
- It also is a useful treatment in the most aggressive form of prostate cancer, which is the hormone-refractory prostate cancer, the type that is most likely to metastasize and spread

### Other treatment options

Vitamin D, Vitamin E, Gamma Tocopherol, fish oil, selenium, and indole 3 carbinol

# **Resources**

## ***Reference Manuals***

### **In-Office Lab Testing Book**

Please download from the training site:

<http://www.functionalmedicineuniversity.com/members/116.cfm>

## ***In-Office Testing Resources***

### **Oxidata Test Supplier**

To order this test please contact Apex Energetics

**Telephone:** (800) 736-4381

**To order fax:** (888)-286-1676

<http://www.oxidata.com>

<http://www.ApexEnergetics.com>

## **Functional Urinalysis Supplies**

Rocky Mountain Reagents is your source for all of the reagents and equipment needed to run the Functional Urinalysis tests mentioned in Dr. Weatherby's In-Office Lab Testing book.

### **Rocky Mountain Reagents Inc**

3207 West Hampden Avenue, Englewood, CO 80110

**Telephone:** (303) 762-0800

<http://www.rmreagents.com>

## ***Blood Testing Resource***

### **Doctor's Choice**

Professional Laboratory & Radiology Service  
1555 W. Mockingbird Lane,  
Suite 206  
Dallas, TX 75235

**Telephone:** (888) 8-LAB-RAD

<http://.net www.LabRad>

**e-mail:** [info@LabRad.net](mailto:info@LabRad.net)

## ***Advanced FDM Companies***

### **Genova Diagnostics**

63 Zillicoa Street  
Asheville, NC 28801  
<http://www.gdx.net>

**Telephone:** (800)522-4762  
**Fax:** (828)252-9303

### **Diagnos-Techs**

Clinical and Research Laboratory  
6620 S. 192nd Place, Bldg. J.  
Kent, WA 98032  
<http://www.Diagnostechs.com>

**Telephone:** (800)878-3787

### **BioHealth Diagnostics**

2929 Canon Street  
San Diego, CA 92106  
<http://www.biodia.com>

**Telephone:** (800)570-2000

### **Metamatrix Clinical Laboratory**

3425 Corporate Way  
Duluth, GA 30096  
<http://www.metamatrix.com>

**Telephone:** (770)446-5483

### **Doctor's Data, Inc**

3755 Illinois Avenue  
St. Charles, IL 60174-2420  
<http://www.doctorsdata.com>

**Telephone:** (800)323-2784

**In the UK:** 0871 218 0052

## Supplement Companies

Company	800 Number
Thorne Research	(208) 263-1337
Integrative Therapeutics	917-3690
Biotics Research	231-5777
Allergy Research	545-9960
Nutrasal.com	777-1886
Pure encapsulations	753-2277

---

<sup>i</sup> Holund B. Latent prostatic cancer in a consecutive autopsy series. Scand J Urol Nephrol. 1980;14(1):29-35.

<sup>ii</sup> Nadler RB, Loeb S, Roehl KA, et al. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. J Urol. 2005 Dec;174(6):2154-7.

<sup>iii</sup> D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004 Jul 8;351(2):125-35.

<sup>iv</sup> Nevalainen, M. Researchers Discover Effective Method For Killing Prostate Cancer Cells, AScribe News, Inc. May, 2003, Georgetown University Medical Center

<sup>v</sup> Stark, JR., IL-6, CRP Levels Tied to Prostate Cancer Development, Lethality, American Association for Cancer Research's Frontiers in Cancer Prevention Research Meeting in Boston, Nov. 2006., Reuters Health Information 2006.