Adrenal – Thyroid Diagnostics
Dr. Nigel Abraham
Scientific Director
08th – 10th September 2009

“The adrenal glands are the glands of stress but are the first glands to fail under stressful conditions.”
(Hans Selye)

“A large percentage of what we think of when we discuss stress related problems are problems of excessive stress responses”.
(Dr. Robert Sapolsky)

Adrenal Gland Control of Stress Response

SHORT-TERM STRESS RESPONSE
1. Glycogen broken down to glucose; increased blood glucose
2. Increased blood pressure
3. Increased breathing rate
4. Increased metabolic rate
5. Change in blood-flow patterns, leading to increased alertness and decreased digestive and kidney activity

LONG-TERM STRESS RESPONSE
1. Retention of sodium ions and water by kidneys
2. Increased blood volume and blood pressure
1. Proteins and fats broken down and converted to glucose, leading to increased blood glucose
2. Immune system may be suppressed

Adrenal Gland Control of Stress Response

Effects of Stress

• Life events such as divorce, job loss, relocation and death in the family are associated with an increased risk of breast cancer.
10,808 Finnish women assessed over 15 years.

• Immunologic function or hormone balance.

Why Physicians Do Not Recognise Adrenal Fatigue.

It is not looked for.
• Physicians have been taught that the only deficiency of the adrenal glands is Addison’s disease, near or total failure of the adrenal glands.
• So unless the adrenal glands are failing (Addison’s disease), they are not considered in the diagnosis

Why Physicians Do Not Recognise Adrenal Fatigue.

It is not properly diagnosed when the S&S are present.
• The common S&S of adrenal fatigue are not the classic S&S of adrenal failure (Addison’s) and so are not recognised by the doctor.
• Subtle endocrine disorders often do not progress to the more classic S&S but continue as vague and seemingly unrelated symptoms for years.
• Because of their close interrelationship, more than one endocrine gland is often involved.
• Furthermore, the same symptoms can result from disorders of different endocrine glands.
Why Physicians Do Not Recognise Adrenal Fatigue.

Laboratory tests are not properly used or understood.
- If doctors do suspect a problem with the adrenal glands, they usually order the wrong tests.
- The usual lab tests have excessively broad reference ranges, making accurate diagnosis difficult.
- Statistical norms are confused with physiological norms.
- There are no reference ranges for optimal functioning or allowance for biochemical individuality.
- Diurnal or cyclic hormonal variations may not be provided as part of standard reference ranges.

Salivary Diagnostics

- For many years saliva has been used as a biological fluid for the detection of different biomarkers such as electrolytes, hormones, drugs and antibodies.
- Sample collection is non invasive, painless and very convenient.
- Can be collected at any time, and where blood collection is difficult or inadvisable.
- Saliva is, in effect, the specimen of choice in a variety of health measurements.

Salivary Diagnostics

- Steroid hormone assessment from saliva allows specific determination of biologically active or ‘free’ fraction of target hormone.
- This fraction represents 1 – 5% of the steroid total concentration in serum.
- There is currently no reliable immunoassay for the measurement of such ‘free’ fractions in serum.
- Assays need to be extremely sensitive as the concentration of such fractions are significantly lower than the analyte in serum.

Mean Diurnal Cortisol in Saliva

Highest levels found 30 to 90 minutes after average wake up time.

Diurnal Rhythm of Salivary Cortisol, different wake-up times

- Normal Cortisol concentration in human saliva during the day is highly dynamic.
- Diurnal profiles of three individuals showing typical Cortisol peak in the morning.
- This is not dependent upon the absolute time and not influenced by daylight.
- It is dependent on wake-up timing of each individual.
• Found evidence of impaired function of the hypothalamic-pituitary-adrenal (HPA) axis in chronic fatigue syndrome (CFS) using a more naturalistic test undertaken in a home setting.
• The HPA axis responses were not affected by the presence or absence of comorbid depression.
• Changes to the HPA axis may represent one of the biological factors contributing to the maintenance of fatigue and other symptoms in CFS.

Cortisol Response in CFS

Fig 1. Response to awakening in patients with chronic fatigue syndrome (CFS), n = 56, and controls, n = 30. The graph shows the increase over time; the bar chart shows the mean area under the curve (AUC), with error bars representing the standard error of the mean. The HPA axis significantly reduced in patients, and individual values at 45 and 60 min were significantly lower in patients (p < 0.05). Roberts et al. British Journal of Psychiatry 2004

Their mothers also showed low cortisol levels, a sign someone is affected by PTSD the researchers say. (Journal of Clinical Endocrinology and Metabolism.)
• The researchers will follow the babies as they grow up to see if those with lower cortisol levels go on to develop psychological disorders.
• Previous research, which had largely focused on children of Holocaust survivors, also found low cortisol levels in the offspring.
• However, scientists then concluded the finding was due to the stress of hearing their parent describe their experiences, or living with a parent who was distressed or anxious.

• In addition to abnormalities in social and communication development, a ‘need for sameness’ and ‘resistance to change’ are features of autistic spectrum disorders.
• Our ability to react to change is modulated by the hypothalamic-pituitary-adrenal (HPA) axis, a feature of which is a dramatic increase in cortisol upon waking, the Cortisol Awakening Response (CAR).
• Whilst a significant CAR was evidenced in the control group, this was not the case for those with AS.
• The implication is that individuals with AS may have an impaired response to change in their environment due to a refractory HPA axis.

Absence of a normal Cortisol Awakening Response (CAR) in adolescent males with Asperger

The Stress of Life

Hans Selye, 1956
• General adaptation syndrome (stress response):
  - The body’s non specific response to generic unpleasantness.
  - The impact of the “usual and customary” stresses of everyday life, as well as the cumulative impact, over time, of unusual and extreme stress.
  - The body’s ongoing efforts to restore its balance in the face of both acute and chronic stress.

Babies inherit 9/11 mums’ stress

Pregnant women who witnessed the World Trade Center attack on 9/11 passed on biological signs of stress to their babies, researchers suggest.

- Their mothers also showed low cortisol levels, a sign someone is affected by PTSD the researchers say. (Journal of Clinical Endocrinology and Metabolism.)
- The researchers will follow the babies as they grow up to see if those with lower cortisol levels go on to develop psychological disorders.
- Previous research, which had largely focused on children of Holocaust survivors, also found low cortisol levels in the offspring.
- However, scientists then concluded the finding was due to the stress of hearing their parent describe their experiences, or living with a parent who was distressed or anxious.
Three Stages of Selye's Stress Response. The General Adaptation Syndrome

- First stage: Alarm stage – Heightened arousal and mobilisation of the body’s defences in the interest of self-protection.
- Arousal: rapid increases in catecholamines and slower increases in corticosteroids

Adrenal Stress Profile (Saliva)

- Anabolic / Catabolic Balance
  - “Wear and Tear” vs “Rest and Recovery”

The Steroidogenic Pathways

- Catabolic
- Anabolic
Three Stages of Selye’s Stress Response. The General Adaptation Syndrome

- Second stage: Resistance and adaptation: Intensification of the body’s defensive efforts to fend off (resist) the stressor or to make whatever internal adjustments are necessary to live with (adapt to) the stressor.
- Adaptation: sustained increases of corticosteroids and alarm molecules, with alterations in glucose tolerance, blood pressure, thyroid hormone, and sex hormone metabolism

If you can’t beat (resist) it, then join (adapt to) it!

Stress Responses of Cortisol & DHEA

- When forced to respond to continued, chronic stress the adrenal glands enter a compensated phase in which production of hormones is divergent.
- Because of the difference in response to ACTH, the production of DHEA falls as Cortisol remains elevated.
- Later phases of compensated response result in a continued fall in DHEA production, followed by a fall in Cortisol, leading to a state of adrenal exhaustion.

Three Stages of Selye’s Stress Response. The General Adaptation Syndrome

- Third Stage: Exhaustion, breakdown, and collapse. No longer able to adapt, the body will collapse, accompanied by progressive deterioration in structure and function. Final stage of dyshomeostasis, and chronic illness.
- Exhaustion: degenerative diseases as a result of the adverse influence of sustained high levels of corticosteroids and alarm molecules
Thyroid Hormone Affects Many Organs and General Health

- Brain
- Uterus
- Kidney
- Liver
- Heart
- Skin
- GI Tract
- Lungs
- Eyes

Who Has Thyroid Disease?

- 27 million Americans have overactive or under-active thyroid glands, but more than half remain undiagnosed.
- More than 8 out of 10 patients with thyroid disease are women.
- Women are 5 to 8 times more likely than men to suffer from hypothyroidism.
- 15 to 20% of people with diabetes and their siblings or parents are likely to develop thyroid disease. (compared to 4.5% of the general population).

When the Thyroid Doesn’t Work

- Hyperthyroidism
  - Too Much Thyroid Hormone
  - Metabolism Speeds Up
- Hypothyroidism
  - Too Little Thyroid Hormone
  - Metabolism Slows Down

Thyroid Hormone

- T3
- T4

Iodide Transport – traps iodide, moving it into thyroid against a gradient and then oxidises it.

Organification – Iodine combines with tyrosine to form monoiodotyrosine (T1) and/or diiodotyrosine (T2)

Coupling – two T2 form thyroxine (T4) or one T1 and one T2 forms triiodothyronine (T3)

Storage – Hormones migrate to colloid space in the centre of the thyroid follicle. 100 days supply.

Secretion – Release of hormones by reversing process of storage and reversal of migration through cell membrane.
Thyroid Regulation

Central regulation
- Of the HPT axis is well understood and characterised as primary or secondary hypothyroidism based on:
  - TSH levels from pituitary
  - T4 levels from the thyroid gland

Peripheral action
- Yet thyroxine is a peripherally acting hormone
  - T4 is converted to T3 in the liver or kidney.
  - T3 binds to nuclear receptors, up-regulating metabolic rate.
  - 95% of all circulating T3 is of peripheral origin (liver or kidney).

Causes of Hypothyroidism
- Failure of Control (secondary or tertiary)
- Primary Failure
- Failure of Conversion of T4 $\rightarrow$ T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency

Anti –TG & Anti – TPO Antibodies
- Most sensitive measure to diagnose chronic thyroiditis
- Elevated in 85-90% of chronic thyroiditis patients
- Elevated in 97% of patients with Graves Disease or Hashimoto’s thyroiditis
- Titres fall with successful treatment of either Graves or Hashimoto’s

Stimulating Auto-antibodies (Graves’ disease)
- Auto-antibody to receptor

Blocking Auto-antibodies (Hashimoto’s disease)
- Auto-antibody to receptor

Hashimoto’s Thyroiditis
- Autoimmune disease predominates in 30-50 year old women HLA-DR5 positive.
- Development of antibodies against peroxidase – antimicrosomal antibodies and anti-thyroglobulin antibodies.
- Also antibodies against TSH receptor (mostly blocking antibodies).
- Increased incidence of other autoimmune diseases (SLE, Sjögren’s).
Hashimoto’s Thyroiditis

- Antibodies latch onto receptors within the thyroid, and may switch them on to promote over-activity, for a period of months or years.
- But sooner or later, this goes into reverse.
- The initial over-active phase may not occur, or is not noticed. Antibodies should always be looked for.
- Picture of progressive deterioration. Gland may enlarge or shrink.

Hashimoto’s Thyroiditis - Cortisol

- The primary source of antigenic stimuli for the production of these autoantibodies is likely to be gut-derived antigens.
- Cortisol suppresses secretory immunoglobulin (sIgA) in the gastrointestinal tract, which leads to impaired gut antigen sampling.

Hashimoto’s Thyroiditis - Cortisol

- Cortisol alters the consistency of the gastrointestinal mucosal barrier. The combined result of these effects is an enhanced immune response to gut-derived antigens and increased translocation of antigenic material to systemic circulation.
- Both of these processes could directly lead to the production of antibodies that would cross react to TSH receptors, leading to the development of Hashimoto’s thyroiditis.

Therapeutic Strategies for Auto-Immune Diseases

- Reduce the total antigenic load:
  - Dysbiosis, Mycology, Parasitology
  - Food Intolerance assessment
  - Intestinal Permeability
- Calm Immune Responses:
  - Cod Liver Oil, Vitamin C, Quercetin
  - Vitamin E, DHEA (10-25 mg/d)

Case # 2 Mary
46 Y/O Female

- 2002 total hysterectomy
- Followed by excessive weight gain >45lbs.
- Pallor & dark shadows.
- Severe fatigue. Neck, shoulders and lower back stiff and painful.
- Hands and feet always cold.
- Frontal headaches daily.
- Depression, poor concentration & memory.

Primary Thyroid Failure - Surgery

- Similar to major trauma with lasting effects.
- Cholecystectomy (gall bladder removed)
- Hysterectomy: Followed by weight gain, exhaustion. Hormonal communication between uterus and thyroid.
- Even sterilisation, D&C or termination of pregnancy may have this effect.
- Tonsillectomy: Shared blood supply with thyroid. Often leads to damage. Compensated for a while then deterioration in function.
Hypothyroid and Cholesterol

<table>
<thead>
<tr>
<th>Lipid Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>6.78</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>0.96</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>5.77</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4.52</td>
</tr>
<tr>
<td>VLDL, mmol/L</td>
<td>0.62</td>
</tr>
<tr>
<td>Extended Values</td>
<td></td>
</tr>
<tr>
<td>Non-HDL Cholesterol</td>
<td>5.54</td>
</tr>
<tr>
<td>Total Cholesterol/HDL Ratio</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Hypothyroidism – Atherosclerosis

- A deposition of cholesterol within the arteries, leading to damage and narrowing.
- Low thyroid function is a bigger cause of cholesterol build up than diet!
- Cholesterol levels in low thyroid patients is almost always elevated.
- Triglycerides also elevated.
- These levels go down following treatment.

Hypothyroidism – Nervous Disorders

- Brain cells have more T3 receptors than any other tissue. Proper uptake is essential.
- Depression: 1/3 of depressed individuals may have unrecognised hypothyroidism.
- Loss of memory and thinking ability.

What Is a Normal TSH Level?

- Most laboratories, the official "normal" reference range for the Thyroid Stimulating Hormone (TSH) blood test runs from approximately 0.5 to 5.0.
- In January 2003, by the American Association of Clinical Endocrinologists, doctors "consider treatment for patients who test outside the boundaries of a narrower margin based on a target TSH level of 0.3 to 3.0."
- Late in 2002, National Academy of Clinical Biochemistry reported that: "In the future, it is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 mIU/L because more than 95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L."

Implications for Patients

- One study found that using a TSH upper normal range of 5.0, approximately 5% of the population is hypothyroid.
- However, if the upper portion of the normal range was lowered to 3.0, approximately 20% of the population would be hypothyroid.
Causes of Hypothyroidism

- Failure of Control (secondary or tertiary)
- Primary Failure
- Failure of Conversion of T4 → T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency

Causes of Hypothyroidism

Failure of Conversion

- Cortisol | DHEA | Failure T4 → T3
- Cortisol | C:D Ratio | Excess T4 → rT3
- Deiodinase Enzymes | Failure T4 → T3

Case # 3 Amy

41 Y/O Female

- Recent history of depression, suicidal anorexia, ? bulimia.
- Weight < 6 stone.
- Severe symptoms of IBS.
- Obsessed with Detox. Coffee enemas X8 daily for 3 years.
- Husband threatening? Divorce because of symptoms.

Case # 3 Amy

41 Y/O Female

- Long term severe stress.
- Elevated Cortisol inhibition of T4 to T3 conversion
- Production of rT3.

Structure of Thyroid Hormones

Take away one iodine atom and we have:

\[
\begin{align*}
\text{NH}_2 & \\
\text{HO} & - - O & - - \text{I} & - - \text{CH}_2 & - - \text{C} & - - \text{COOH} \\
\text{H} & \\
\end{align*}
\]

(T3) 3,5,3'-tri-iodothyronine

Take away a different iodine atom and we have:

\[
\begin{align*}
\text{NH}_2 & \\
\text{HO} & - - O & - - \text{I} & - - \text{CH}_2 & - - \text{C} & - - \text{COOH} \\
\text{H} & \\
\end{align*}
\]

(rT3) 3,3,5'-tri-iodothyronine
**Reverse T3**

rT3 is the inactive form of T3. Has about 5% the activity of T4.

Manufactured by the body for the recycling of Excess T3, T4 & Iodine.

Causes of raised levels of rT3:
- Stress
- Illness, Starvation
- Excess Adrenal Oestrogen

---

**5'- Deiodinase Inhibitors**

- Selenium deficiency
- Cd, Hg, Pb toxicity – Se antagonists
- Stress – elevated Cortisol
- Chronic illness
- Inadequate protein, excess carbohydrate
- Compromised liver or kidney
  - Impaired glucuronidation
  - Impaired sulphation?

---

**Causes of Hypothyroidism**

- Failure of Control (secondary or tertiary)
- Primary Failure
- Failure of Conversion of T4 → T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency
Causes of Hypothyroidism

Receptor Uptake Deficiency

- Resistance at Receptor Site
- Reduction of Receptors or Desensitisation
- Environmental Toxins e.g. fluoride, mercury
- Prolonged Illness
- Genetic Predisposition

Effects of thyroid hormones in individual tissues are determined by many factors beyond their serum levels, including local deiodination and expression and activity of thyroid hormone transporters. Intriguingly, most of these associations are independent of serum thyroid hormone levels, which highlights the importance of local regulation of thyroid hormones in tissues. Future research might reveal novel roles for thyroid hormones in obesity, cardiovascular disease, osteoporosis and depression and could have implications for interpretation of thyroid function tests and individualization of thyroid hormone replacement therapy.

Causes of Hypothyroidism

- Failure of Control (secondary or tertiary)
- Primary Failure
- Failure of Conversion of T4 → T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency

Adrenal Insufficiency

Weakened Adrenal Response damages:

- Thyroid Hormone Production
- T4 → T3 Conversion
- Receptor Uptake
- Tissue Response
- Adrenal Oestrogen Production Balance
Adrenal & Thyroid Connection

- If thyroid hormone is not being produced nothing works properly – including the adrenal glands.
- Compounded by the fact that low thyroid output is a stress inducing situation.
- To cope with low thyroid output, the adrenals increase the level of cortisol.
- In time the adrenals begin to fail leading to low adrenal reserve.

- General health, nutrition, lifestyle and other stresses all play a part.
- The length of time the thyroid problem has gone on for and how badly.
- The cause of the deficiency: Surgery & I131 a particular problem for adrenal glands.
- Supplementary thyroid hormone may itself cause stress if the system cannot cope, by using wrong dose or ignoring adrenal support.

- Throxine T4 has to be converted to active T3 by action of 5′-deiodinase enzymes.
- In low adrenal reserve this process fails leading to toxic build up of unused and unstable T4.
- T3 has to be taken up by receptors within the cell wall, this uptake is degraded in adrenal insufficiency.
- The receptors become dormant or may disappear or become resistant.
- Even if T3 is available, the system can become toxic.

- Optimal functioning of the adrenal glands is absolutely vital for correct Thyroid function.
- Equally as important is to provide adrenal support when low adrenal reserve is present.
- The failure of thyroid supplementation to restore normal health may well be due to a adrenal problem.

*Results:* A score of the 8 main symptoms of hypothyroidism, serum thyroxine radio-immunooassay (T4-RIA), serum T4-RIA/thyroid binding globulin (TBG), 24h urine free triiodothyronine(T3) were considered before and after treatment.

- The score of these 8 main symptoms is a reliable expression of their illness in 97% of hypothyroid patients.
- 24h urine freeT3 correlates better with the clinical status of hypothyroid patients than serum T4-RIA, and even better thanT4-RIA/TBG.
- Other investigators were unable to find any correlation between serum thyroid stimulating hormone (TSH) or serum freeT4 and thyroid symptoms. The dosage of natural desiccated thyroid (NDT) has a correlation with 24h urine T3.

*Conclusions:* In this study symptoms of hypothyroidism correlate best with 24h urine freeT3.
There is a large body of evidence to support the use of 24 hour urine testing for thyroid dysfunction. Excellent papers are available to point out their efficacy but have been ignored. Analytical and clinical validation has been shown to anyone who will read it, or listen. The 24 hour urine thyroid function test is generally to be preferred over standard serum TFT because it shows the amount of thyroid being used, not simply how much is there – and perhaps not being used.

An observational study yielded no noticeable changes of thyroid parameters in the serum of humans treated with Lycopus europaeus, whereas a reduction of tachycardic episodes and an improvement of vegetative and psychic complaints was observed. The T4 excretion in urine is significantly increased in the Lycopus europaeus group as compared to the control group. This study shows for the first time a measurable change of thyroid-related hormone parameters in human beings.

Check list

- Thyroid function
- Adrenal function
- Sex hormones
- Comprehensive Digestive Stool Analysis -'leaky gut' & dysbiosis, malabsorption
- Food allergies and intolerances
- Poor liver detoxification.
To quote just one patient:

“The ignorance, arrogance and incomprehension of the medical doctors I have been subjected to in my search for diagnosis and treatment leaves me incandescent with rage. Even as a qualified health professional working for a major DGH I remain powerless to prevent the cumulative long term health risks associated with lack of treatment; I am voiceless, neutered, patronised, and crawling day-to-day through what used to be my vital and colourful life. I would give everything I have for an open minded and creative diagnostician, and more for a little compassion, but this seems to be entirely beyond the capability of the modern medic. God help us all.”