



G^{DX} Genova Diagnostics
Innovative Testing for Optimal Health

Adrenal – Thyroid Diagnostics

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 08th – 10th September 2009



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



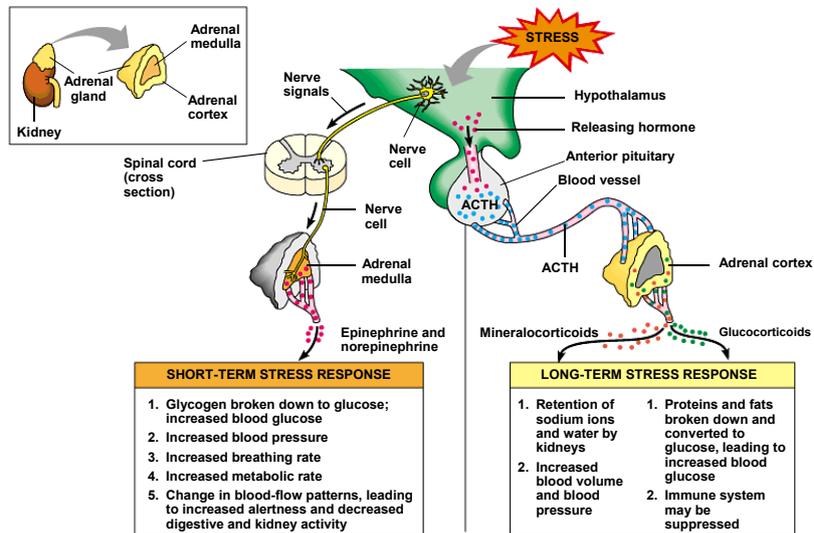
I'M REALLY CONCERNED ABOUT YOUR STRESS LEVEL, JACKSON!

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



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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.
March 1st 2003 *Am J Epidemiol* 2003;157:414-423.



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.



Hormones in Saliva: Mode of Entry and Consequent Implications for Clinical Interpretation

Ross F. Vining, Robynne A. McGinley, and Richard G. Symons

Assay of hormones in saliva would be more convenient than assay in blood, but there is no information on the route by which hormones enter saliva, information that would provide insight into the clinical value of such assays. We have examined the mode of entry of various hormones into saliva. The results suggest that unconjugated steroids enter saliva by diffusing through the cells of the salivary glands and that

gonadotropin were from healthy pregnant women, all of whom subsequently delivered normal infants. Gingival fluid was collected from subjects with mild gingivitis by drying the gums with a tissue and applying a disposable micropipette directly to the junction between tooth and gum. Gingival fluid was drawn into the micropipette by capillary action. Parotid saliva was obtained by placing a modified

- Unconjugated steroids enter saliva by diffusing through the cells of the salivary glands and that their concentration in saliva does not depend on the rate of saliva production.
- We conclude that the salivary concentration of unconjugated steroids reflect the concentration of free (nonprotein-bound) steroids in plasma

may also be clinically useful. Many recent studies have been concerned with the relationship between concentrations of various steroid hormones in saliva and plasma (1), but there has been little discussion of the route by which steroids (or other hormones) enter saliva. We have examined the relation between saliva flow rate and salivary steroid concentration and between concentrations in serum and saliva of steroid hormones, thyroid hormones, and chorionic gonadotropin. We believe the resulting insight into the mode of entry of steroids and other hormones into saliva has important implications for the clinical usefulness of measuring these compounds in saliva.

Materials and Methods

Collection of Samples

While chewing unsweetened chewing gum, subjects collected whole saliva directly into a small plastic vial (3). Such specimens were obtained from normal men and women except that those used for the studies of estradiol and chorio-

Unconjugated estradiol in serum and saliva was determined by RIA as previously described (3).

The nonprotein-bound fraction of both cortisol and unconjugated estradiol was determined by centrifugal ultrafiltration (3, 5-7) and the absolute concentration of free hormone in serum was then obtained by inference from the total serum concentration.

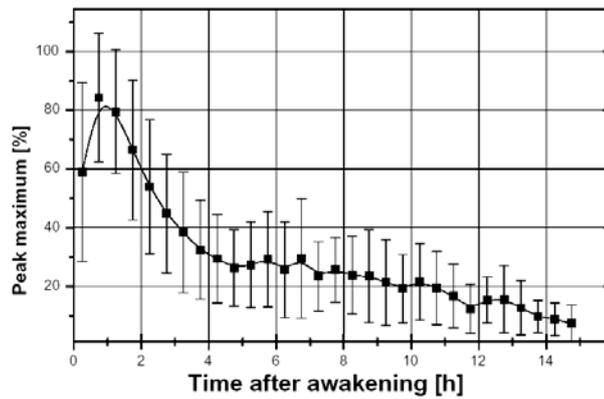
Conjugated estradiol in serum and saliva was measured by first hydrolyzing the conjugates enzymically and then measuring the unconjugated estradiol by RIA as previously described (3).

Human chorionic gonadotropin was measured by RIA with the use of an antiserum that bound equally the whole molecule of chorionic gonadotropin and its beta subunit, but showed only a 10% cross reaction with human lutropin (lutetizing hormone). The assay included a second-antibody precipitation step to separate free and bound hormone, and the standard used was the International Reference Preparation 75/537.

Thyroxin (T4) in serum was measured by RIA with use of an antibody raised in sheep against a T4-bovine serum albumin conjugate. 8-Anilino-1-naphthalene sulfonic acid was added to block binding of T4 to endogenous proteins, and dextran-coated charcoal was used to separate bound and



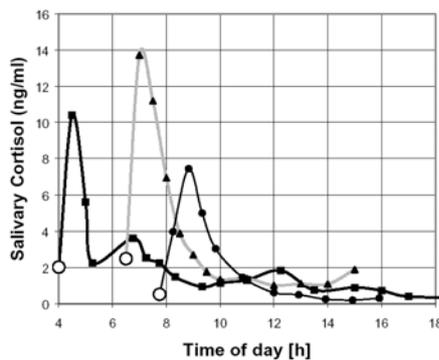
Mean Diurnal Cortisol in Saliva



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.



Salivary cortisol response to awakening in chronic fatigue syndrome

AMANDA D. L. ROBERTS, SIMON WESSELY, TRUDIE CHALDER, ANDREW PAPADOPOULOS and ANTHONY J. CLEARE

for CFS by a psychiatrist; included subjects had to fulfil both of the major international consensus criteria for CFS (Sharpe *et al.*, 1991; Fukuda *et al.*, 1994). Subjects then were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; World Health Organization, 1994) adapted for DSM-IV (American Psychiatric Association, 1994) – subjects who had an established psychiatric diagnosis

- 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.

response to awakening, measured by the area under the curve.

Conclusions This naturalistic test of the HPA axis response to stress showed impaired HPA axis function in CFS.

Declaration of interest None. Funding detailed in Acknowledgements.

awakening – to ‘awaken’ an indication of the status of the HPA axis in CFS.

METHOD

Subjects Patients aged 18–65 years with CFS were recruited into the study from consecutive referrals to the CFS clinic at King's College Hospital, London. A total of 56 patients agreed to participate. Patients had undergone thorough medical screening to exclude a detectable organic cause for their fatigue, including physical examination and relevant investigation, with a minimum of urinalysis, full blood count, urea and electrolytes, thyroid function tests, liver function tests, 9 a.m. cortisol and erythrocyte sedimentation rate. All patients initially were interviewed using a semi-structured interview (Sharpe *et al.*, 1997)

men were taking antidepressants (or women were taking additional hypnotics and one was taking sodium valproate) and one was taking pirofen for migraine. All female subjects were tested during days 1–7 of their menstrual cycle.

The institutional ethics committee approved all procedures. All patients and controls gave written informed consent.

Questionnaires

Subjects filled out the following questionnaires to assess illness characteristics: the Chalder Fatigue Scale (Chalder *et al.*, 1993) and a global fatigue rating scale (Vermeulen *et al.*, 1997) for fatigue severity; the Beck Depression Inventory (Beck *et al.*, 1961) and General Health Questionnaire-12 (Goldberg, 1972) for symptoms of depression and anxiety; the Symptom Checklist (Wittensborn & Buhler, 1979)



Cortisol Response in CFS

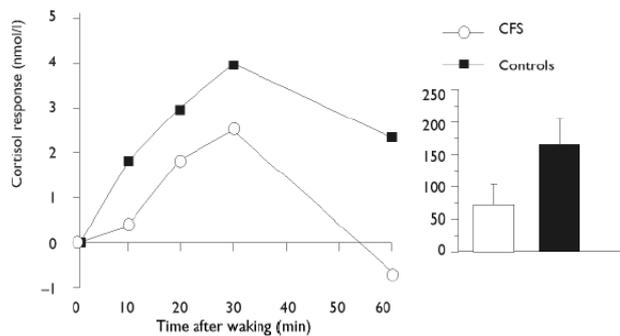
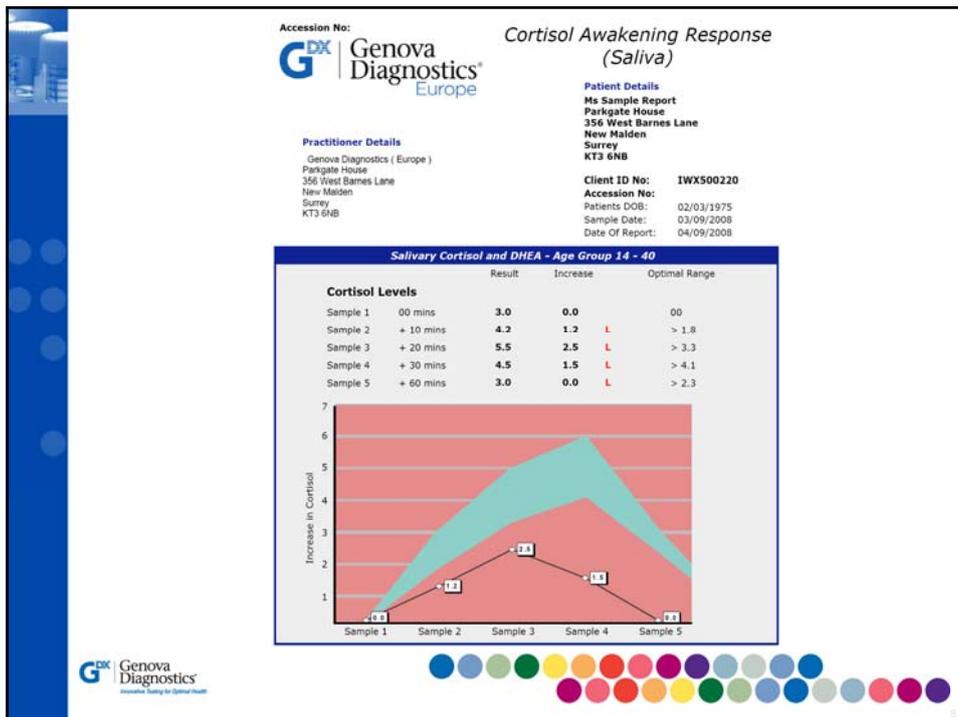


Fig. 1 Response to awakening in patients with chronic fatigue syndrome (CFS, $n=56$) and controls ($n=35$). The graph shows the mean value over time; the bar chart shows the mean area under the curve (AUC), with error bars representing the standard error of the mean. The AUC was significantly reduced in patients, and individual values at 10 min and 60 min were significantly lower in patients (all $P \leq 0.05$).

Roberts *et al.* British Journal of Psychiatry 2004





BBC NEWS

Babies inherit 9/11 mums' stress

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

“ It may be that stress has an effect on the developing brain of a foetus

” Scientists from Edinburgh and New York say tests on infants when they were a year old showed they had low levels of the stress hormone cortisol.

Professor Jonathan Seckl, University of Edinburgh

The women were either in or near the World Trade Center on 9/11

- 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.

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

- 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.



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.



Commentary

GENERAL INFORMATION FOR PATIENTS

General:
An important part of any abnormal stress response, should include identifying and reducing the cause(s) of stress. The body interprets physiological stressors, such as lack of sleep, imbalanced blood sugar levels or intensive athletic training, in the same way as psychological stress due to bereavement or divorce for example. Adrenal function is significantly influenced by blood sugar levels, therefore much of the dietary advice below aims to stabilise levels of sugar in the blood.

Dietary:

- Never skip meals! Ensure that you eat at least every 3 or 4 hours, taking healthy snacks as necessary. Small, regular meals help to maintain energy levels and mood, while decreasing tiredness, irritability and fat storage.
- Avoid highly refined foods such as white bread/ pasta/ rice, chocolate, biscuits, sweets or anything with added sugars. Hidden sugars are also included in many cereals, breads, tinned produce, and processed/ packaged foods. Replace processed foods with the unrefined foods, such as wholemeal bread, brown rice, oats and rye. Note that excess alcohol can also cause imbalanced blood sugar levels.
- Tropical fruit (melon, grapes, banana etc), dried fruit and fruit juices can also be very sugary, therefore only a very limited intake of these should be allowed. Instead include other fruit such as cherries, berries, apples and pears, which are less 'sweet'.
- Ensure plenty of protein, such as lean meat, chicken, fish, eggs, beans, lentils, nuts and seeds, are included with each meal. Protein helps to slow the release of sugar into the blood stream.
- Stimulants such as tea, coffee and cigarettes may provide a temporary energy boost, however these not only deplete many essential nutrients, but always reduce energy levels in the long run. Aim to drink at least 1 - 1½ litres of filtered/ bottled water throughout the day, which can include herbal teas.
- Nutrients that specifically support the adrenal glands are vitamin C, found in most fresh fruit and vegetables. Magnesium is dramatically depleted in times of stress, and symptoms of a deficiency often include fatigue, anxiety, insomnia and a predisposition to stress. Include plenty of dark green leafy vegetables, wholegrains, nuts and seeds to supply adequate levels of magnesium. The B-complex vitamins can help to support adrenal function, particularly vitamin B5, which directly supports adrenal cortex function and hormone production. Sources include wholegrains, nuts and seeds.

Lifestyle:

- Good quality sleep is of utmost importance for long-term health and regeneration. Few people can cope with less than 7 or 8 hours of sleep per night, and those who regularly undersleep are almost always less efficient, not more. To promote proper sleep, keep regular sleeping patterns and ensure the bedroom is dark enough with adequate ventilation. Do not work in the bedroom.
- Make sure that food is eaten in a relaxed environment, and chewed thoroughly to promote optimum digestion and absorption of nutrients.
- Regular exercise is very beneficial for relieving stress and decreasing negative emotions such as worry or anxiety. However in patients with significantly depleted adrenal hormones, intensive cardiovascular exercise will further deplete adrenal reserves. Gentle exercises such as yoga, pilates, swimming and brisk walking are all excellent alternatives and are often calming in themselves.
- Regular relaxation needs to be built into ones daily life. Reading, bathing, massage and listening to music can promote relaxation, but watching the TV does not! Activities such as tai chi and meditation are extremely beneficial at reducing stress.
- Counselling or other therapies may be beneficial for those having to cope in the face of severe stressors.



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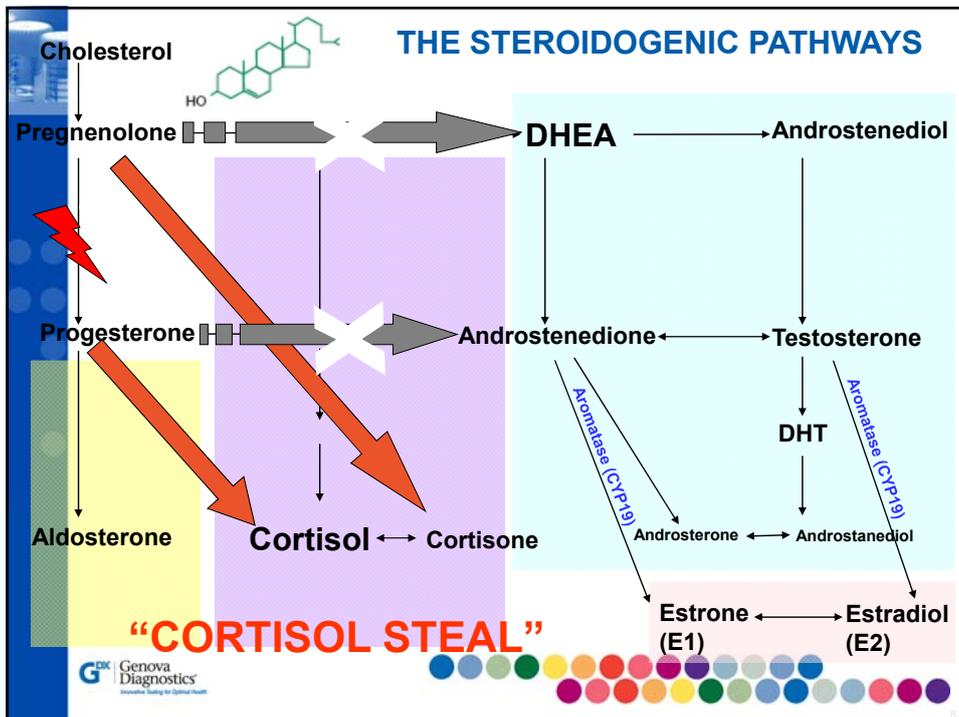
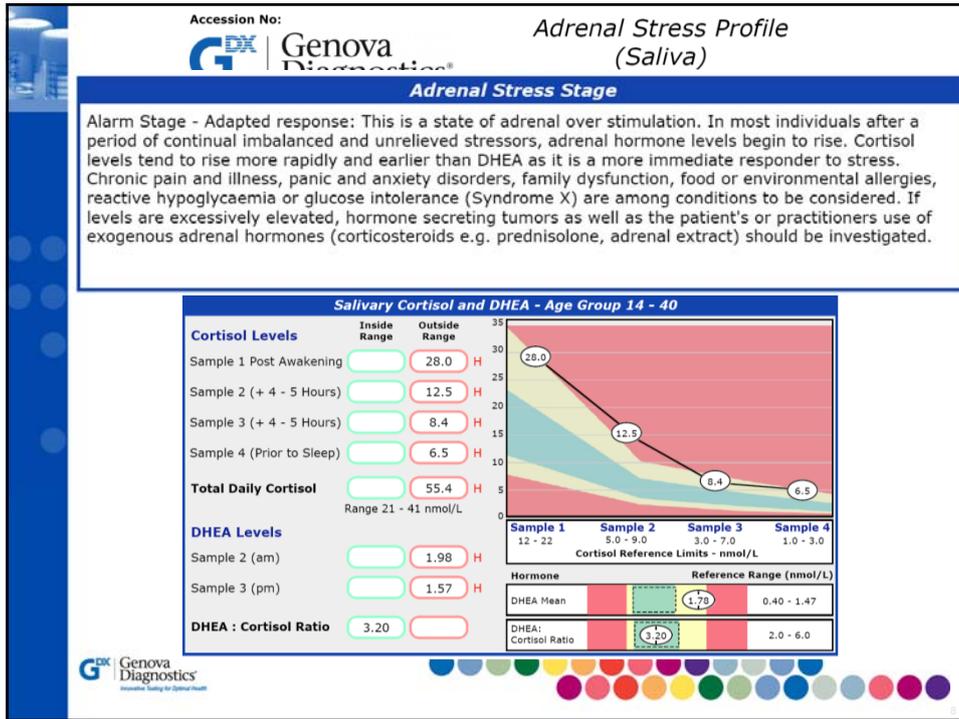
Three Stages of Selye's Stress Response. The General Adaptation Syndrome

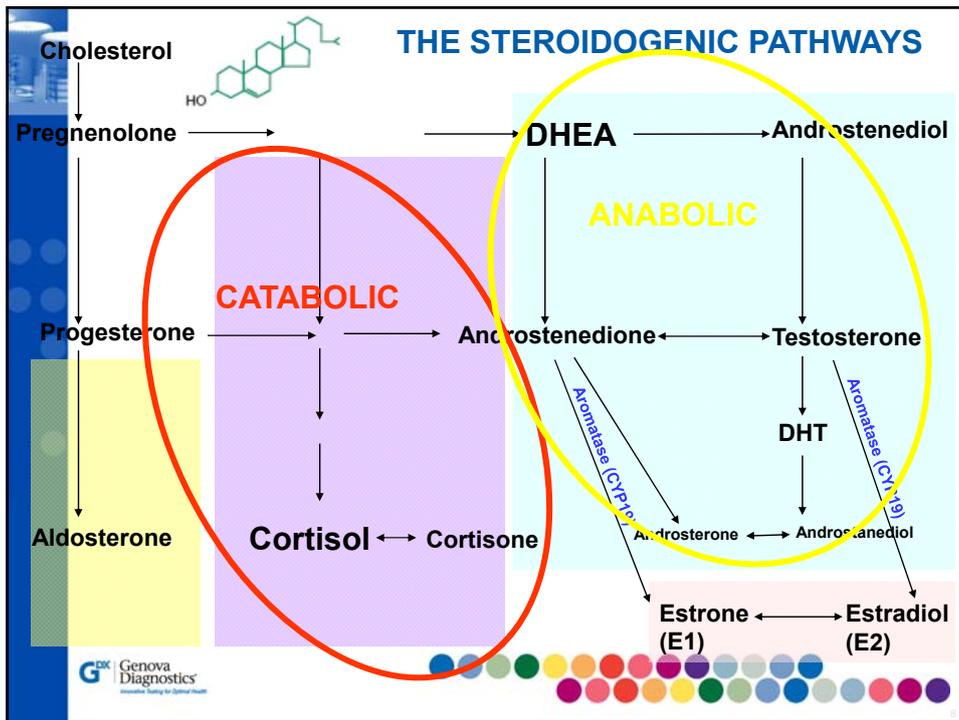
- First stage: Alarm stage – Heightened arousal and mobilisation of the body's defences in the interest of self-protection.
- Arousal: rapid increases in catecholamines and slower increases in corticosteroids



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Anabolic / Catabolic Balance

“Wear and Tear”
vs
“Rest and Recovery”

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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

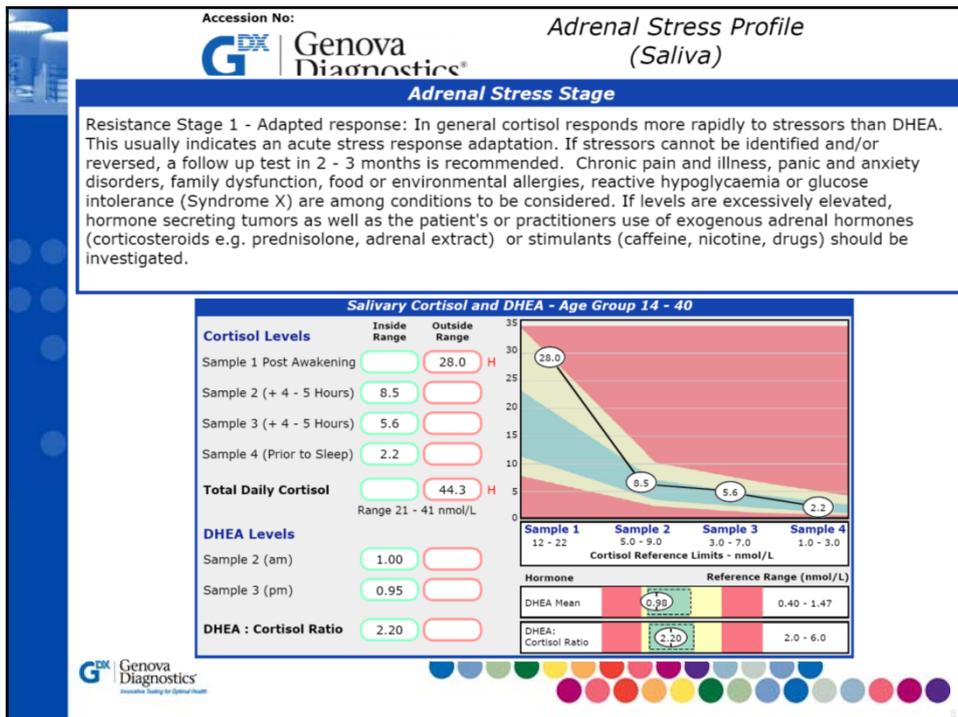
If you can't beat (resist) it, then join (adapt to) it!



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.

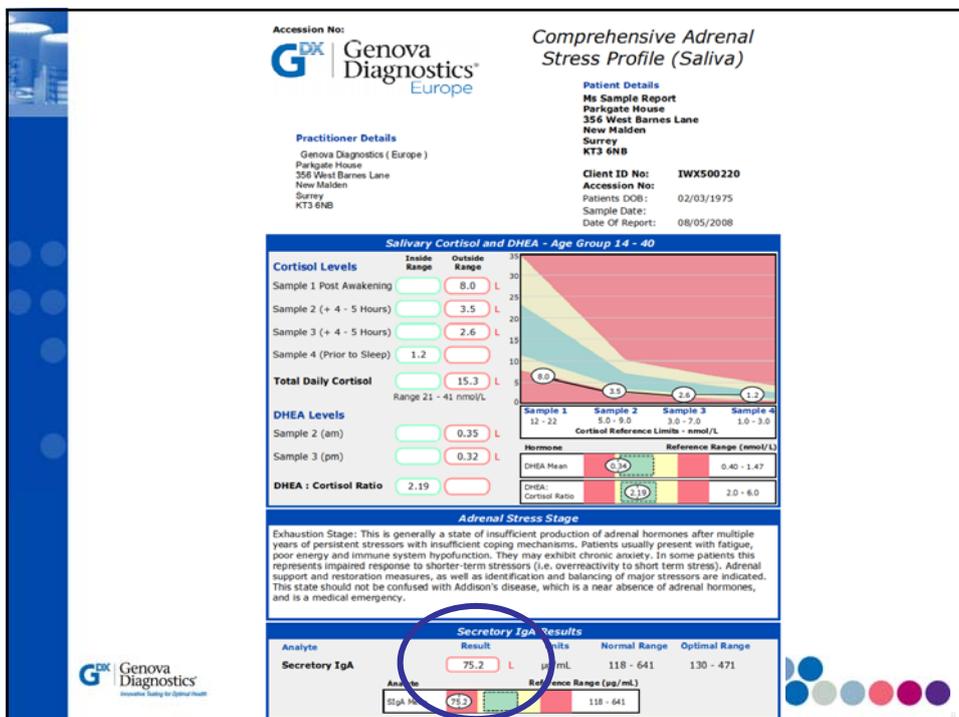
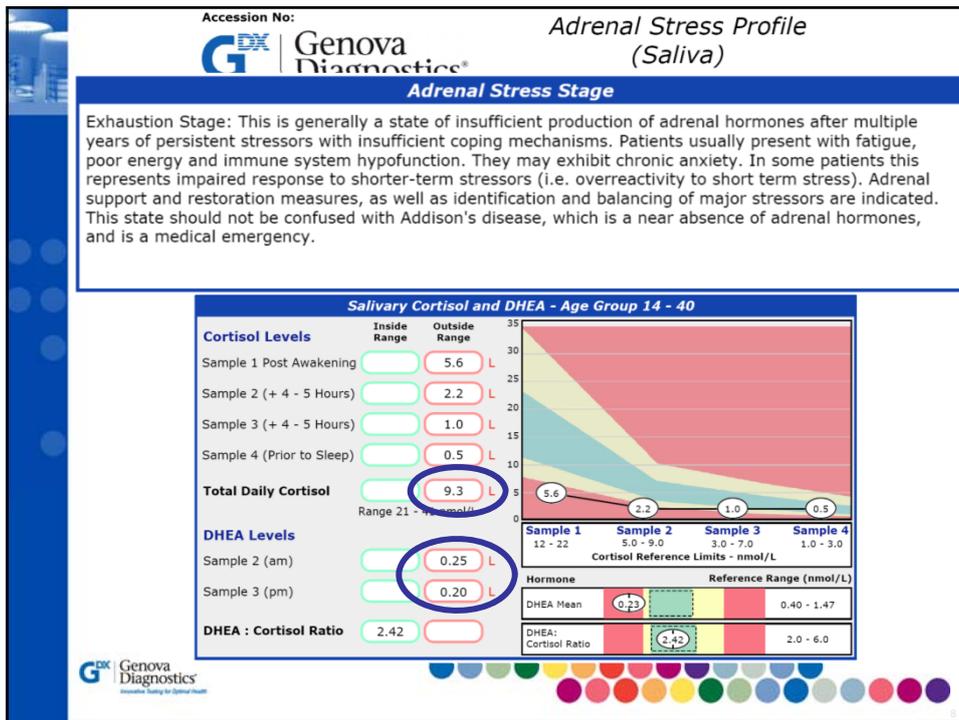




Three Stages of Selye's Stress Response. The General Adaptation Syndrome

- 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

Genova Diagnostics



Accession No: GDX Genova Diagnostics Europe

Practitioner Details: Genova Diagnostics (Europe), Parkgate House, 250 West Barnes Lane, New Malden, Surrey, KT3 6NB

Adrenal - Thyroid Profile

Patient Details: Ms Sample Report, Parkgate House, 250 West Barnes Lane, New Malden, Surrey, KT3 6NB

Client ID No: ZWXS00220
Accession No: Patients DOB: 20/03/1975
Sample Date: 09/12/2008
Date Of Report: 09/12/2008

Salivary Cortisol and DHEA - Age Group 14 - 40

Sample	Time	Output	Range
Sample 1	Post Awakening	9.2	L
Sample 2	(+ 4 - 5 Hours)	4.0	L
Sample 3	(+ 4 - 5 Hours)	2.5	L
Sample 4	(Prior to Sleep)	1.0	L
Total Daily Cortisol		16.7	L
Range 21 - 41 nmol/L			

DHEA Levels

Sample	Time	Output	Range
Sample 2	(am)	0.30	L
Sample 3	(pm)	0.32	L
DHEA : Cortisol Ratio		1.86	L
Range 1.0 - 1.47			

Adrenal Stress Stage

Exhaustion Stage: This is generally a state of insufficient production of adrenal hormones after multiple years of persistent stressors with insufficient coping mechanisms. Patients usually present with fatigue, poor energy and immune system hypofunction. They may exhibit chronic anxiety. In some patients this represents impaired response to shorter-term stressors (i.e. over-reactivity to short term stress). Adrenal support and restoration measures, as well as identification and balancing of major stressors are indicated. This state should not be confused with Addison's disease, which is a near absence of adrenal hormones, and is a medical emergency.

Urinary T3 (FTV) Results

Analyte	Result	Units	Normal Range
Triliodothyronine (T3)	128	nmol/mol creatinine	147 - 591
Urinary T3	0.05	nmol/mol	147 - 591

Commentary

ADDITIONAL TEST RESULTS

DEVIATIONS FROM THE NORMAL CORTISOL RHYTHM

The Morning cortisol level is below the normal range. Morning cortisol may be a good indication of peak adrenal gland function since they represent peak cyclic activity. Low morning cortisol levels suggest a degree of adrenal hypofunction.

The noon cortisol level is below the normal range. Noon cortisol levels may be a good indication of adaptive adrenal gland function since they represent the adrenal glands' response to the demands of the first few hours of the day. Low noon cortisol levels suggest a degree of adrenal hypofunction with decreased adaptive response.

A low afternoon cortisol is suggestive of suboptimal adrenal functioning.

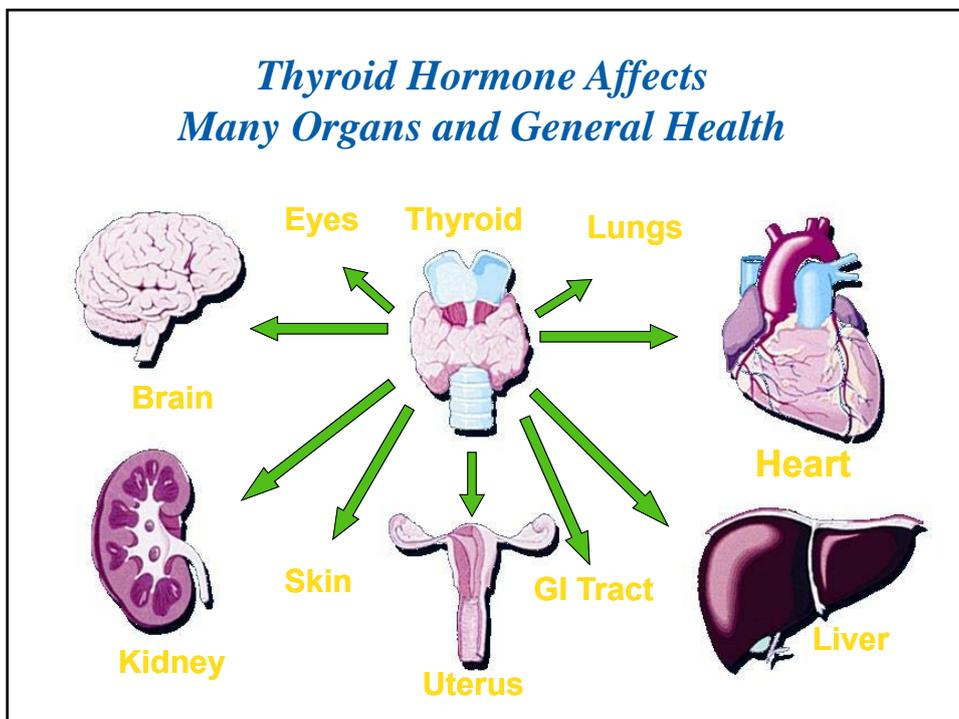
DEVIATIONS IN DHEA PRODUCTION

Decreased DHEA levels may be seen in thyroid disorders, cardiovascular disease, obesity, reduced immunity, rheumatologic diseases, and excess cortisol production, or with administration of pharmacological doses of glucocorticosteroids. Low levels are indicative of a lowered capacity to endure physiological or psychological stress/trauma/injury, and may present with abnormal immune response, with increased incidence of autoimmune disease.

URINE T3 COMMENTARY

Triiodothyronine (Free T3, or FT3) represents the biologically active fraction of total T3, the majority of which is bound by protein carriers in the serum and is therefore inactive. T3 is 3-5 times as physiologically active as T4, and 80% of the circulating T3 is from the peripheral conversion of T4 predominately in liver and kidney. A low urinary FT3 suggests a hypothyroid state. This can result from inadequate production of T4 in the thyroid gland or from impaired peripheral conversion from T4, consistent with a relative shift away from T3 production and toward reverse T3 production, an adaptive change thought to conserve energy expenditure. (Serum T4 and/or TSH levels can provide a fuller picture.) Decreased T3 production has been observed in states of severe caloric restriction, systemic inflammatory conditions, and/or prolonged or severe stress. The enzyme necessary for the conversion of T4 into T3 (5'-deiodinase) is selenium dependent. Conversion may be impaired by a selenium deficiency or by the presence of the heavy metal selenium antagonists such as mercury, cadmium and lead. Hypothyroidism may induce signs and symptoms such as fatigue, depression, low body temperature, weight gain, constipation, changes in menstrual function, myxedema, decreased memory and concentration, muscle and joint pain, hair loss, and/or possible goiter.

Reported By: NRA



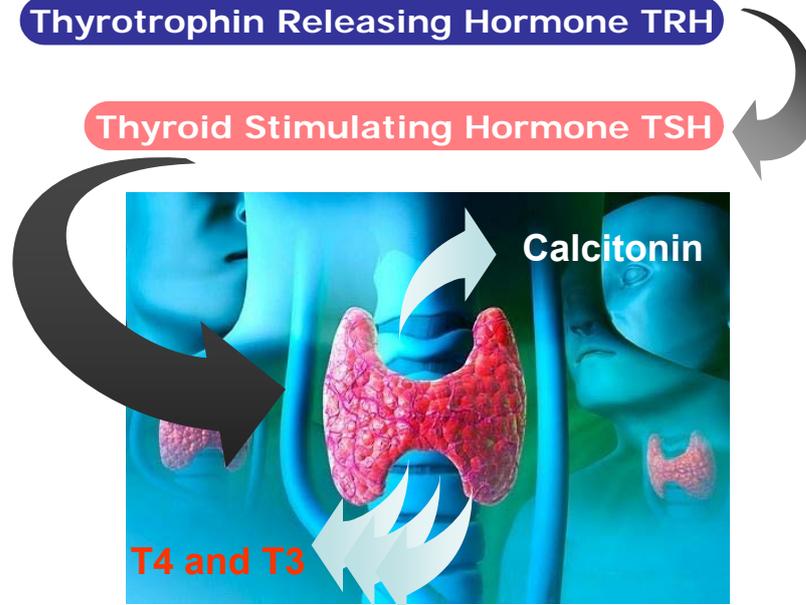
Who Has Thyroid Disease?

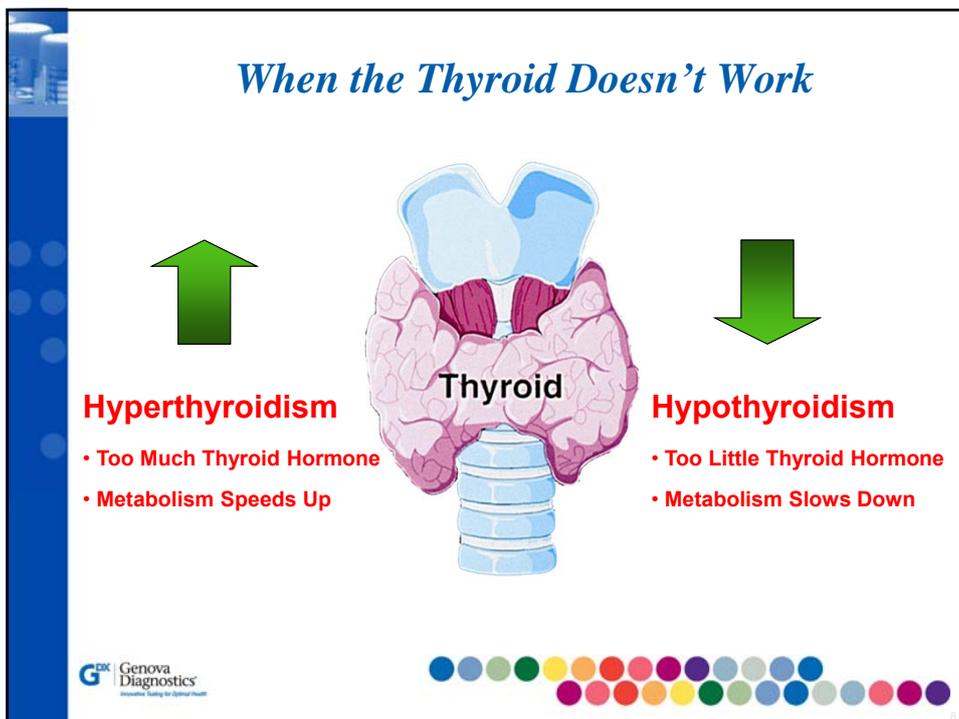
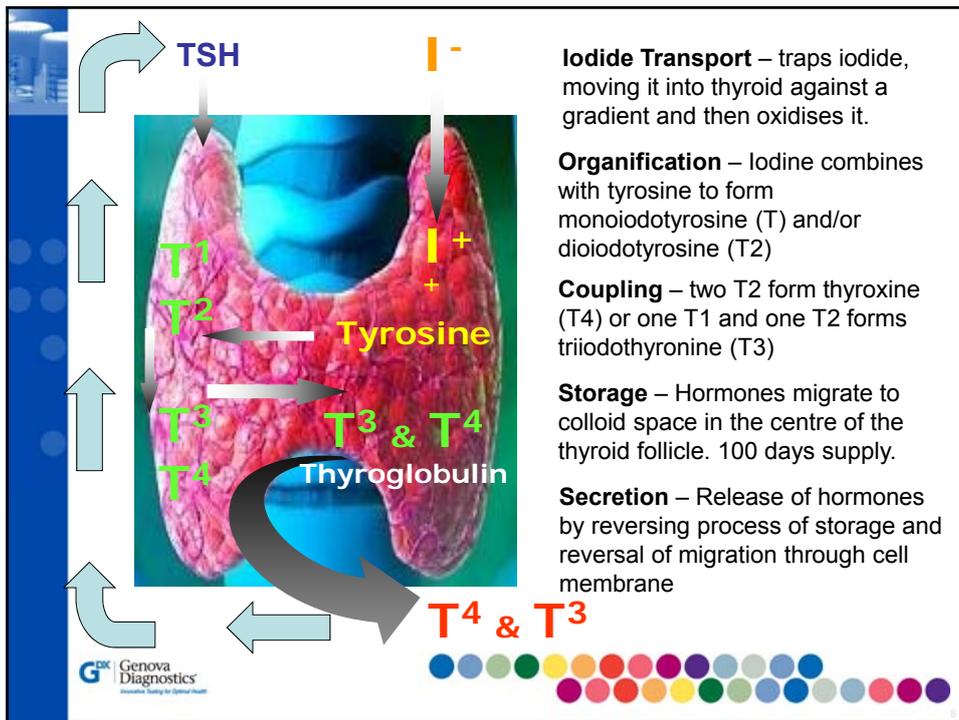
- 27 million Americans have overactive or under-active thyroid glands, but more than half remain undiagnosed.
- More than 8 out of 10 patients with thyroid disease are women.
- Women are 5 to 8 times more likely than men to suffer from hypothyroidism.
- 15 to 20 % of people with diabetes and their siblings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



Thyrotrophin Releasing Hormone TRH

Thyroid Stimulating Hormone TSH





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 → T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency

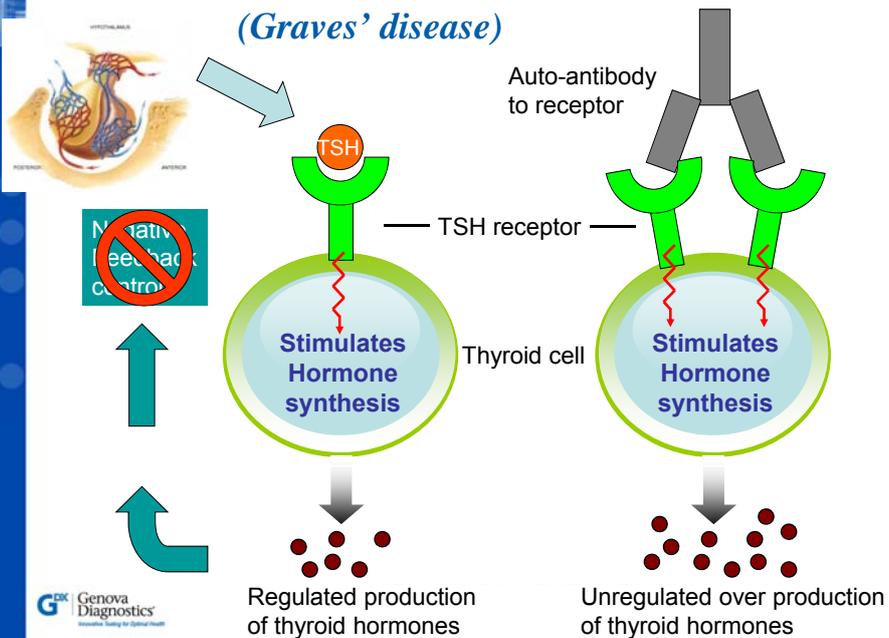


Anti – TG & Anti – TPO Antibodies

- 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)

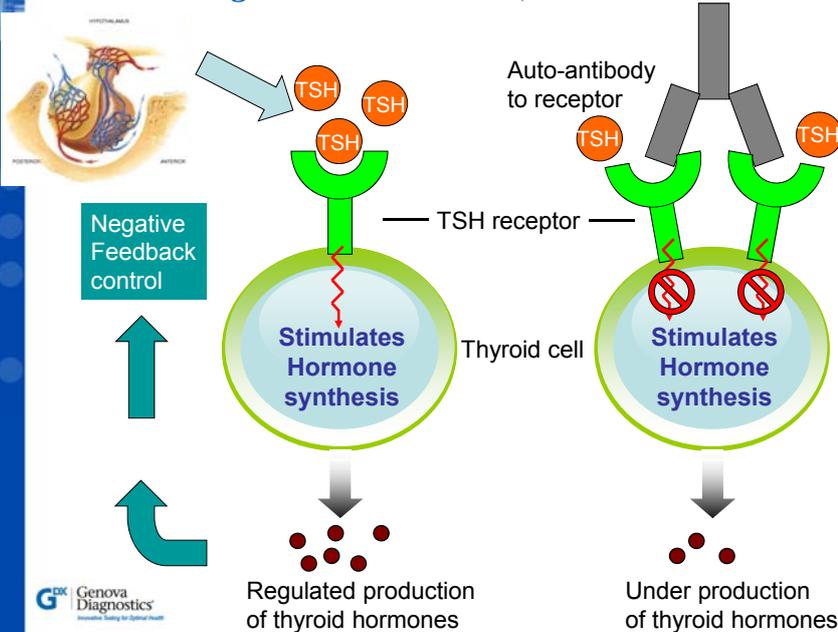


Hashimoto's Thyroiditis

- 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).



Blocking Auto-antibodies (Hashimoto's disease)



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)



Commentary

THYROID INTERPRETATION GUIDELINES

Primary Hypothyroidism is PROBABLE. The likelihood increases if serum tryglycerides are elevated (>4.52) and the total cholesterol levels are increased (>6.22)

Some of the clinical signs of hypothyroidism include:

1. Difficulty losing weight
2. Mentally sluggish, reduced initiative
3. Easily fatigued, sleepy during the day
4. Sensitive to cold, poor circulation (cold hands and feet)
5. Chronic constipation
6. Excessive hair loss and / or coarse hair
7. Morning headaches, wear off during the day
8. Loss of lateral 1/3 of eyebrow
9. Seasonal sadness

PROBABLE auto-immune thyroid disease.

Thyroiditis is the most common thyroid condition, leading to either hypothyroidism (Hashimoto's and sub-acute thyroiditis) or hyperthyroidism (Grave's disease). Hypothyroidism due to thyroiditis is the most common. Thyroiditis can present with normal, elevated, or decreased levels of thyroid hormone at any time.

Hashimoto's and Grave's disease the levels of auto-antibodies are significantly elevated. With sub-acute thyroiditis, the levels are usually normal or slightly increased. Viral infection has been implicated in the etiology of sub-acute thyroiditis, including mumps virus, coxsackievirus and adenoviruses. Bacteria also implicated include: Staph aureus, Srep pneumoniae & Srep pyogenes.

Peripheral Thyroid Function

Analyte	Value	Optimal Range	Reference Range
FREE T3	4.4	3.4 - 6.0	2.8 - 6.5 pmol/L
FREE T4 : FREE T3 RATIO	2.36 L	3.0 - 5.0	3.0 - 5.0

Thyroid Auto Immunity

Analyte	Value	Optimal Range	Reference Range
THYROGLOBULIN :	110 H	<40	0 - 40 IU/ml
PEROXIDASE (MICROSOMAL)	385 H	<35	0 - 35 IU/mL

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

Case # 2 Mary
46 Y/O Female

Measured Values	Result	Reference Range
Total Cholesterol	6.78 H	<=5.17 mmol/L
Total HDL (HDL2, 3)	0.90 L	>=1.03 mmol/L
Total LDL (LDL, Lp(a), IDL)	5.22 H	<=3.36 mmol/L
Total Triglycerides	4.52 H	<=2.26 mmol/L
Total VLDL (VLDL1, 2, 3)	0.62	<=0.78 mmol/L
Calculated Values		
Non-HDL Cholesterol (LDL+VLDL)	5.84 H	<=4.14 mmol/L
Total Cholesterol : HDL Ratio	7.5 H	<=4.8



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. So proper uptake is essential.
- Depression: 1/3 of depressed individuals may have unrecognised hypothyroidism.
- Loss of memory and thinking ability.



Accession No: **Total Thyroid Screen**

Genova Diagnostics Europe

Patient Details
Mary

Practitioner Details
I W D L Genova Diagnostics
Parkgate House
356 West Barnes Lane
New Malden
Surrey
KT3 6NB

Client ID No: IWX500220
Accession No:
Patients DOB: 46 Years
Sample Date: 16/03/2006
Date Of Report: 18/12/2007

Case # 2 Mary
46 Y/O Female

• She had had multiple tests for under-active thyroid always 'normal', by thyroid specialists.

• Normal Ranges ?
• Hypothyroid ?

Central Thyroid Regulation & Activity			
Analyte	Result	Optimal Range	Reference Range
TOTAL THYROXINE (T4)	76.0 *	77 - 150	58 - 154 nmol/L
THYROID STIMULATING HORMONE	2.69 *	1.0 - 2.0	0.4 - 4.0 mIU/L
FREE THYROXINE (T4)	10.4 *	12 - 20	10 - 22 pmol/L

Peripheral Thyroid Function			
Analyte	Result	Optimal Range	Reference Range
FREE T3	4.4 *	3.4 - 6.0	2.8 - 6.5 pmol/L
FREE T4 : FREE T3 RATIO	2.36 L	3.0 - 5.0	3.0 - 5.0

Thyroid Auto Immunity			
Analyte	Result	Optimal Range	Reference Range
THYROGLOBULIN :	110 H	<40	0 - 40 IU/mL
PEROXIDASE (MICROSOMAL)	385 H	<35	* 0 - 35 IU/mL

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, that 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

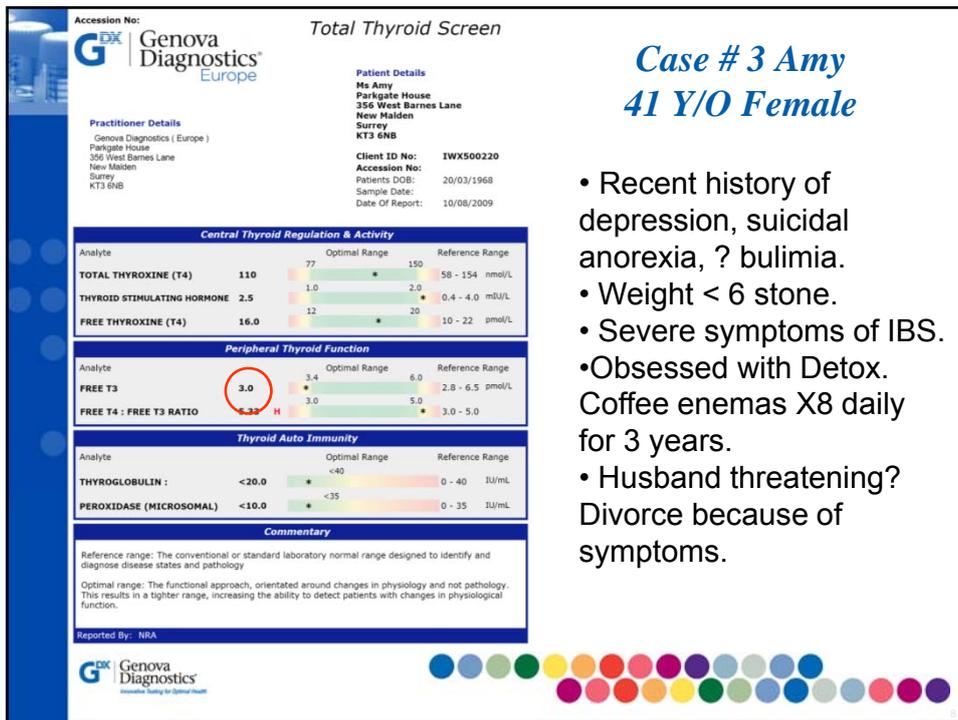
- Failure of Control (secondary or tertiary)
- Primary Failure
- Failure of Conversion of T4 → T3
- Receptor Uptake Failure (resistance)
- Adrenal Insufficiency



Causes of Hypothyroidism Failure of Conversion

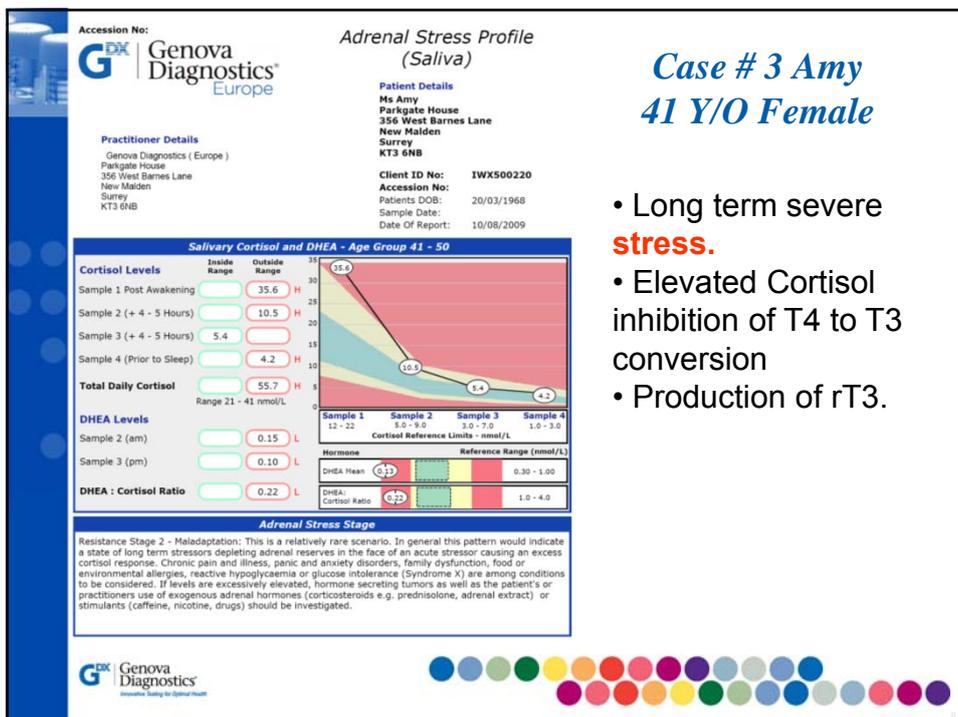
Cortisol ↓ DHEA ↓ Failure T4 → T3
Cortisol ↑ C:D Ratio ↑ Excess T4 → rT3
Deiodinase Enzymes ↓ Failure T4 → T3





**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.

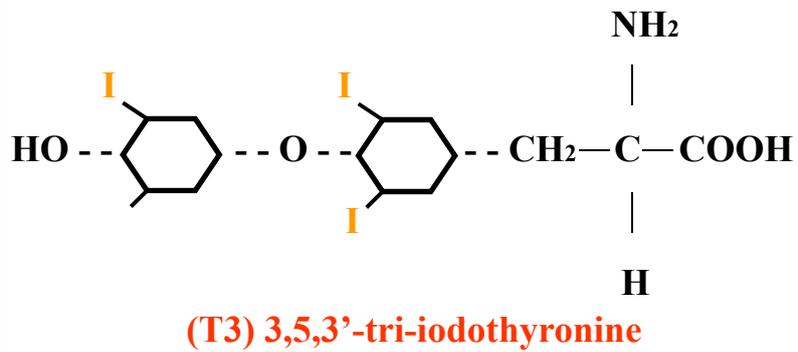


**Case # 3 Amy
41 Y/O Female**

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

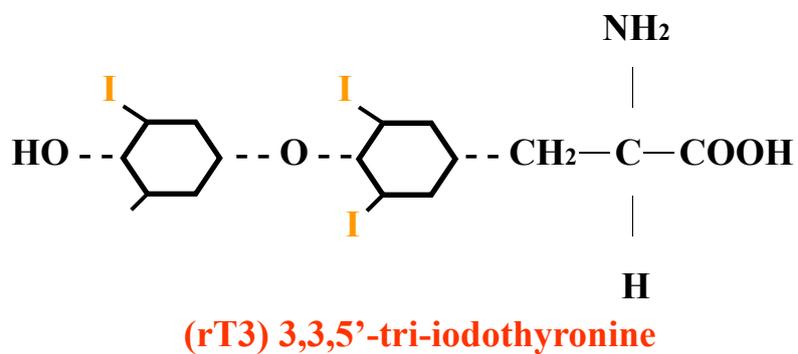
Structure of Thyroid Hormones

Take away one **iodine** atom and we have:



Structure of Thyroid Hormones

Take away a different **iodine** atom and we have:



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



Factor Associated
With ↓ T3 & ↑ rT3

Reduced T3

- Immune activation
IL-6, TNF- α , IFN
- High Cortisol
- High Catecholamines
- High Free Radicals

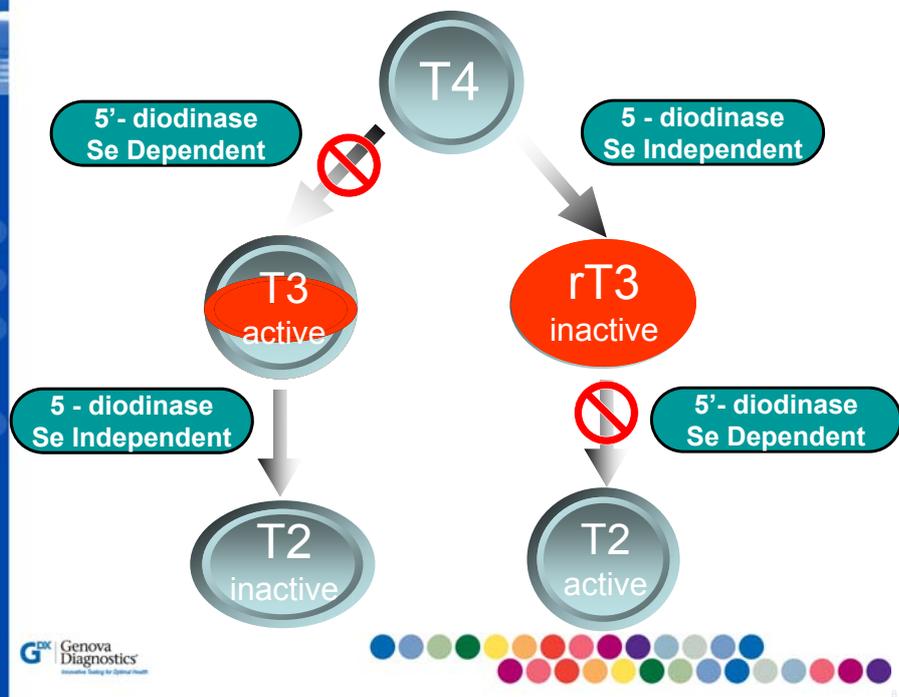
Increased rT3

- Aging
- Fasting
- Stress
- Prolonged Illness
- Toxic Metal Exposure
- Diabetes (IDDM)



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 ?



Case # 3 Amy 41 Y/O Female



Comprehensive Thyroid Assessment



Patient: Amy

Order Number: 90080181

DOB: 41 years

Completed: June 13, 2007

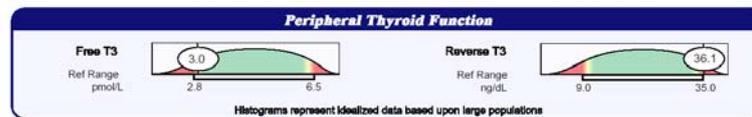
Sex: F

Received: June 08, 2007

MRN: 0001054579

Collected: June 04, 2007

Route Number: A074786



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



REVIEWS

Novel insights into thyroid hormones from the study of common genetic variation

Colin M. Dayan and Vijay Panicker

Abstract | Effects of thyroid hormones in individual tissues are determined by many factors beyond their serum

- 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.

quently a high specificity for thyroid hormones) are summarized in Table 1. The activity of these transporters in any given tissue is likely to be a key factor in determining

Competing interests
The authors declared no competing interests.

(THR), and tissue-specific differences in the distribution and levels of the different isoforms of THRs, as well as of retinoic acid and other regulator molecules, represent another level of local variation. Figure 1 summarizes the key steps between thyroid hormone release and its effects in individual tissues.

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Colin M. Dayan, University of Bristol, Clarendon Building, Wilks House, Bristol BS1 2PT, UK.
E-mail: c.dayan@bristol.ac.uk

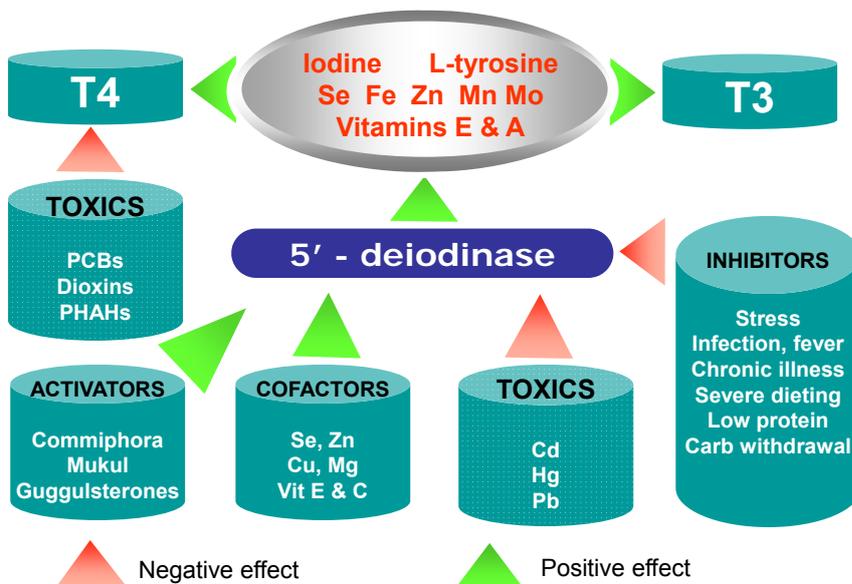


Table 3 | Association of deiodinase SNPs and serum thyroid hormone parameters

SNP	Free T ₄ level	T ₃ or free T ₃ level	T ₃ :T ₄ ratio	rT ₃ level	TSH level
<i>In the DIO1 gene</i>					
rs11206244 ¹³⁻¹⁶	Increased	Decreased	Decreased	Increased	No effect seen
rs12095080 ^{13,14}	No effect seen	Increased	Results of association not published	rT ₃ :T ₄ ratio decreased	No effect seen
rs2235544 ¹⁵	Decreased	Increased	Increased	Decreased	No effect seen
<i>In the DIO2 gene</i>					
rs225014 ^{13-15,17-19}	No effect seen	No effect seen	No effect seen	No effect seen	No effect seen
rs12885300 ¹⁷	Decreased ^a	No effect seen	Increased ^a	Decreased ^a	No effect seen
<i>In the DIO3 gene</i>					
rs945006 ¹³	No effect seen	No effect seen	No effect seen	No effect seen	No effect seen

^aEarly, not replicated findings. Abbreviations: rT₃, reverse T₃; SNP, single nucleotide polymorphism.

- Convincing evidence indicates a role of type 1 iodothyronine deiodinase (D1) in determining the serum T4:T3 ratio
- Preliminary evidence suggests associations between D2 variants and hypertension, psychological well-being and response to T3 or T4 treatment.



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 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.



Adrenal & Thyroid Connection

- 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.



Adrenal & Thyroid Connection

- Thyroxine 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.



Adrenal & Thyroid Connection

- The 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.





CLINICAL RESEARCH

Thyroid Insufficiency. Is TSH Measurement the Only Diagnostic Tool?

W. V. BAISIER MD,¹ J. HERTOGHE MD^{2†} AND W. ECKHAUT MD³

- **Results:** A score of the 8 main symptoms of hypothyroidism, serum thyroxine radio-immunoassay (T4-RIA), serumT4-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.

hormone (TSH) test, even the third generation procedure, as well as the serum free thyroxine (T4) test, correlate poorly with the clinical status of the thyroid diseased patient. Therefore, we are interested in showing that another test, the 24 h urine free triiodothyronine (T3) test, correlates well with the symptoms of thyroid disease. We started by composing a list of generally accepted symptoms upon which to rely as an objective base reflecting the clinical status of the patient. We soon noticed that, from this extended list, a small series of the most frequently seen symptoms could be isolated. As a test for the reliability of our views, we compared this restricted list of main symptoms before and after



Accession No:



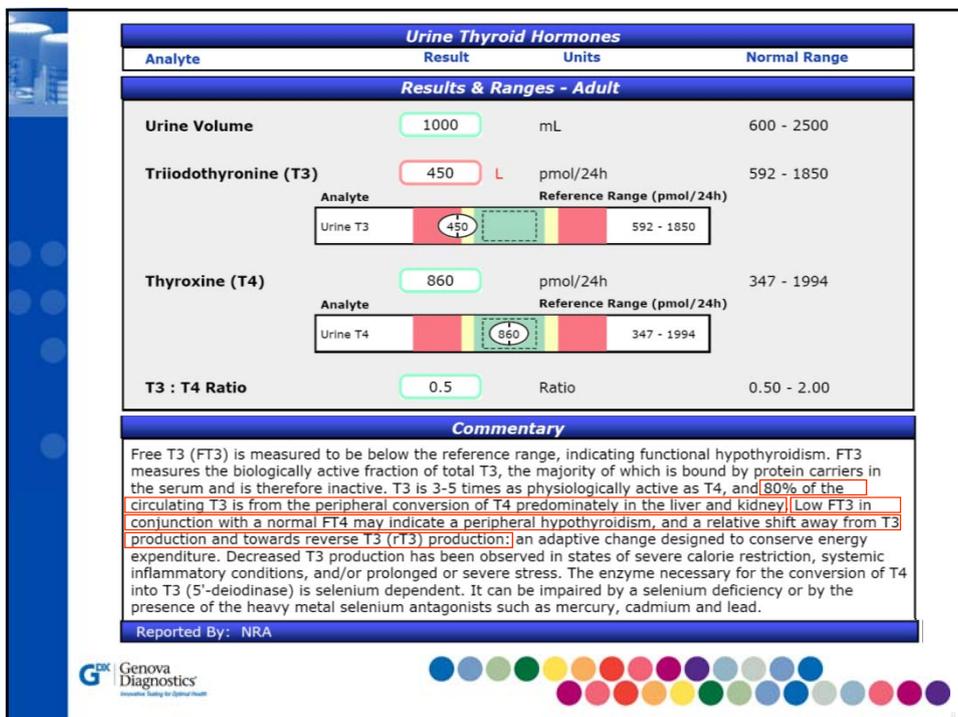
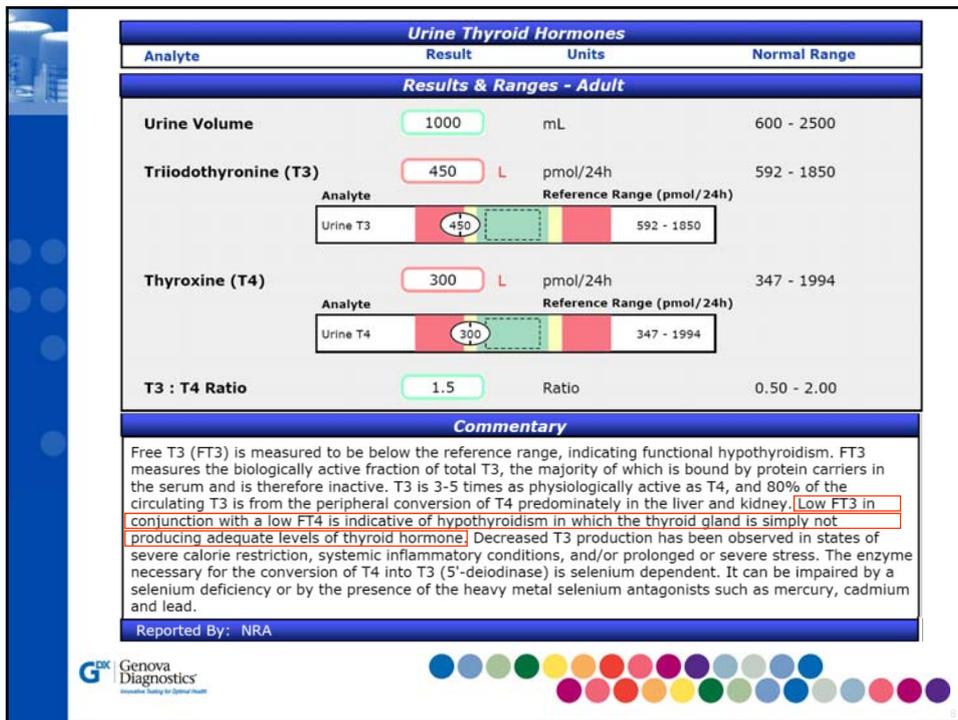
Thyroid Hormones
24 Hour Urine

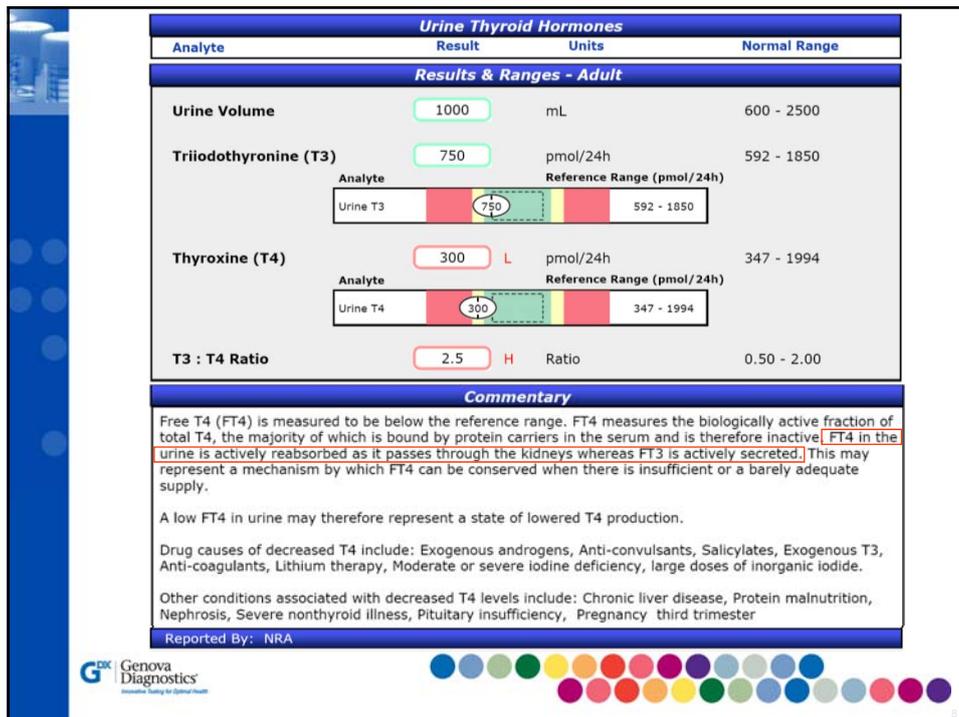
Commentary

The diagnosis of hypothyroidism is usually made almost exclusively from measurements of TSH and T4 levels found in blood tests. However this method is thought to be largely ineffective at diagnosing cases of mild hypothyroidism, more accurately termed 'thyroid dysfunction'. Hormone levels in urine, assesses tissue exposure to thyroid hormones over a 24-hour period. The urine thyroid test therefore serves as a valuable tool for detecting those patients that are suffering from thyroid dysfunction that may otherwise go undetected through standard blood tests.

Urine Thyroid Hormones			
Analyte	Result	Units	Normal Range
Results & Ranges - Adult			
Urine Volume	1000	mL	600 - 2500
Triiodothyronine (T3)	890	pmol/24h	592 - 1850
	Analyte	Reference Range (pmol/24h)	
	Urine T3	592 - 1850	
Thyroxine (T4)	1060	pmol/24h	347 - 1994
	Analyte	Reference Range (pmol/24h)	
	Urine T4	347 - 1994	
T3 : T4 Ratio	0.8	Ratio	0.50 - 2.00
Commentary			
The diagnosis of hypothyroidism is usually made almost exclusively from measurements of TSH and T4 levels found in blood tests. However this method is thought to be largely ineffective at diagnosing cases of mild hypothyroidism, more accurately termed 'thyroid dysfunction'. Hormone levels in urine, assesses tissue exposure to thyroid hormones over a 24-hour period. The urine thyroid test therefore serves as a valuable tool for detecting those patients that are suffering from thyroid dysfunction that may otherwise go undetected through standard blood tests.			
Reported By: NRA			







Thyroid Patient Advocacy UK Dismissal of all other assays?

- 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.



Available online at www.sciencedirect.com

ScienceDirect
Phytomedicine 15 (2008) 16–22
www.elsevier.de/plymed

ELSEVIER

Phytomedicine

Lycopus europaeus (Gypsywort): Effects on the thyroidal parameters and symptoms associated with thyroid function

A.-M. Beer^{a,*}, K.R. Wiebelitz^a, H. Schmidt-Gayk^{b,†}

- 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.

*Corresponding author. Tel.: +49 2324 396487; fax: +49 2324 396497. E-mail address: andrea.beer@klinik-blumenstein.de (A.-M. Beer).
†Deceased.

ably by the reduction of the beta-receptor density in the heart. In these experiments with low oral doses of *Lycopus* extract TSH and thyroid hormone levels

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Innovative. Scaling for Optimal Health.



Check list

- Thyroid function
- Adrenal function
- Sex hormones
- Comprehensive Digestive Stool Analysis
-‘leaky gut’ & dysbiosis, malabsorption
- Food allergies and intolerances
- Poor liver detoxification.

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To quote just one patient:

(Thyroid Patient Advocacy (TPAUK.com))

“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.”

Thank You!

