THYROID AUSTRALIA LTD
SUPPORT FOR THOSE WITH THYROID CONDITIONS, THEIR FAMILIES AND FRIENDS

THYROID FUNCTION TESTS AND HYPOTHYROIDISM

MEGAN STEVENS AND ALUN STEVENS

"It is extraordinary that more than 100 years since the first description of the treatment of hypothyroidism and the current availability of refined diagnostic tests, debate is continuing about its diagnosis and management."

Anthony Toft and Geoffrey Beckett BMJ 2003 (8 February); 326:295-296

Over the years we have been asked by thousands of people to explain thyroid function tests in the contexts of both diagnosis and the management of therapy. A significant proportion of these correspondents and callers have found that despite having thyroid hormone levels within the laboratory reference ranges, they still suffer debilitating symptoms. Our counselling has included providing these people with reliable information from recognised medical authorities to inform them of the nuances of thyroid testing and to provide them with a basis for discussion with their doctors.

This document is an extract of the pertinent elements of the information we have provided. It is technical in nature and may therefore not be suitable for those who have not yet developed a basic knowledge of the thyroid and hypothyroidism. We have tried to help, by including a glossary of medical terms at the end of the document and comments in [*square brackets*] throughout the text.

The information is suitable for discussing with your doctors. The quoted material is sourced from well known international authorities on the thyroid and from peer reviewed medical journals. Make your doctor aware of this if you present this material to him or her.

References are provided for all quoted material and links are provided for material which can be found on the internet. Citations are presented as Author(s), "Title", *Publication Name*, Date; Volume(Issue): Page Numbers. You will need to set up a free account to view the Lancet material on line.

Some references are repeated in a number of sections for completeness of those sections.

SECTIONS

WHO SHOULD BE SCREENED?

Lawrence C Wood MD, "Hidden Thyroid Illness: Who Should Be Screened? 1999: A New Look at an Old Question" Thyroid Foundation of America, *The Bridge*, Fall 1999, 14:3

"By age fifty, one in ten women have thyroid failure as evidenced by a simple blood test for Thyroid Stimulating Hormone (TSH). Your pituitary gland located at the base of your brain normally regulates thyroid function by producing Thyroid Stimulating Hormone. If your thyroid fails, your TSH levels rise. In contrast, the high blood levels of thyroid hormone in hyperthyroidism are associated with low TSH levels."

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John Lazarus et al, "Postnatal care and women's health"
***The Lancet*, 1 May 1999; 353:1532**

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Paul W. Ladenson MD, et al "American Thyroid Association Guidelines for Detection of Thyroid Dysfunction"
***Archives of Internal Medicine*, 2000; 160: 1573-1575**

http://archinte.ama-assn.org/issues/v160n11/ffull/isa90012.html

?The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter.?

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Sections

WHICH TESTS ARE PERFORMED?

Thyroid Function Tests

The standard Thyroid Function Tests which are performed in Australia are:

- Thyroid Stimulating Hormone (TSH)
- Free Thyroxine (Free T4 or FT4)
- Free Triiodothyronine (Free T3 or FT3)

The Medicare protocol for screening patients who have not yet been diagnosed with a thyroid function problem is to test TSH and only if the result of this test is outside the reference range to test Free T4. Medicare will only fund screening tests which satisfy this protocol. Medicare monitors doctors' and laboratories' observance of this protocol. As will be demonstrated below, this protocol limits the diagnostic effectiveness of thyroid function tests.

This protocol only applies to thyroid function tests funded by Medicare. The protocol does not apply to thyroid function tests paid for in full by the patient.

This protocol also does not apply to the testing of patients already diagnosed with a thyroid function problem. Medicare supports the testing of Free T4 and Free T3 for these patients.

Antibody Tests

Thyroid antibody tests are performed to support the diagnosis of thyroid disease. The tests that are performed in the context of hypothyroidism are for:

- Thyroid peroxidase antibodies (TPO Ab) which are sometimes referred to as Microsomal antibodies.
- Thyroglobulin antibodies (Tg Ab).

Testing for these antibodies is not governed by the Medicare protocol.

The presence of elevated levels of thyroid antibodies is highly predictive of developing thyroid disease, even when thyroid function tests produce results within the reference range – see below.

Sections

THE STANDARD INTERPRETATION OF THYROID FUNCTION TESTS

Thyroid function tests provide the primary tool for diagnosing thyroid disease and for managing doses for thyroid hormone replacement therapy. The interplay of the thyroid hormones (T4 and T3) and the regulatory hormone (TSH) provide a pattern which can be used to deduce the thyroid status of the patient. The following tables present the explanations of two authors of books for patients and a more technical overview:

RIS Bayliss KCVO MD, FRCP & WMG Tunbridge MD FRCP
***Thyroid disease: The facts*, 3rd ed., (OUP, 1998), p.22**

Free T4 level	Free T3 level	TSH level	Significance
High	High	Low	
Normal	High	Low	
Normal	Normal	Normal	
Normal or slightly high	Normal	Normal or slightly low	
Normal or low	Normal	Normal or low	
Low or normal	Normal	High	
Low	Normal or low	High	

Ridha Arem, MD
***The thyroid solution: A mind-body program for beating depression and regaining your emotional and physical health*, (Ballantine Books, 1998), p.229**

Range of TSH Level (mIU/L)	Diagnosis
>20	
4.5-20	
2.1-4.4	
0.4-2.0	
0.1-0.39	
<0.1	

LM Demers PhD FACB, CA Spencer PhD FACB, "NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease"
The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, 2002

http://www.nacb.org/lmpg/thyroid/2_thyroid.pdf

Figure 4

Fig 4. The serum TSH/FT4 relationship typical of different clinical conditions

Sections

THE IMPORTANCE OF THE INDIVIDUAL

Reference Ranges for thyroid function tests are based on statistical averages. They are not based on standards of biological activity at different levels of thyroid hormones. This is not a problem in itself provided that the circumstances of the individual are always considered.

The particular issue for thyroid patients is that an individual's thyroid hormone levels do not naturally move over the whole Reference Range. Individual thyroid hormone levels are confined to narrow personalised ranges around the so called Set Point. Being in this personal range is important.

Stig Andersen et al, "Narrow Individual Variations in Serum T4 and T3 in Normal Subjects: A Clue to the Understanding of Subclinical Thyroid Disease"
***Journal of Clinical Endocrinology and Metabolism*, 2002 March; 87(3):1068-72**

"High individuality causes laboratory reference ranges to be insensitive to changes in test results that are significant for the individual."

...

Joseph H Keffer, "Preanalytical Considerations in Testing Thyroid Function"
***Clinical Chemistry* 1996; 42(1):125-134**

"The application of population-based norms is inappropriately wide when applied to individuals. Each person has a narrow range of fluctuation of T4, even with seasonal or annual study."

Sections

REFERENCE RANGES DON'T TELL HOW YOU FEEL

Drs John P Walsh & Bronwyn G A Stuckey, "What is the optimal treatment for hypothyroidism".
***Medical Journal of Australia*, 2001; 174: 141-143**
Thyroid Australia, *Thyroid Flyer*, 2:4, Oct 2001

http://www.thyroid.org.au/Download/Flyer%202001.4%20T3.pdf

...

P Saravan, W-F Chau, N Roberts et al, "Psychological well-being of in patients on "adequate" doses of L-thyroxine: results of a large controlled community based questionnaire study"
***Clinical Endocrinology*, 2002; 57:577**

?..some patients with TSH levels within the laboratory normal range might still be hypothyroid at the cellular level for several reasons. ?

...

Drs Colin M Dayan, Ponnusamy Saravanan, & Graham Bayly, "Whose normal thyroid function is better – yours or mine?".
***The Lancet*, 3 Aug 2002; 360(9330): 353**

...

C Meier, P Trittibach et al, "Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey"
***British Medical Journal*, 2003 (8 February); 326:311-312**

...

"TSH is a poor measure for estimating the clinical and metabolic severity of primary overt thyroid failure. This is in sharp contrast to the high diagnostic accuracy of TSH measurement for early diagnosis of hypothyroidism.

...

H Al-Adsani, LJ Hoffer and JE Silva, "Resting Energy Expenditure is Sensitive to Small Dose Changes in Patients on Chronic Thyroid Hormone Replacement"
***Journal of Clinical Endocrinology and Metabolism*, 1997; 82:1118-1125**

http://jcem.endojournals.org/cgi/content/full/82/4/1118

..

"... it should be recognised that only 20-25% of resting energy expenditure is thyroid hormone dependent in humans, as this is the maximum reduction seen in individuals with profound hypothyroidism."

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Sections

SHOULD YOU BE TREATED?

The most important first step. Does the test result indicate that you have hypothyroidism and need to be treated? The standard interpretation is the starting point, but there is much more that must be considered:

MPJ Vanderpump, WMG Tunbridge et al, "The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey"
***Clinical Endocrinology*, 1995, 43:55-68**

"A logit model [*logarithmic probability model*] indicated that increasing values of serum TSH above 2 mU/L at first survey increased the probability of developing hypothyroidism which was further increased in the presence of anti-thyroid antibodies."

"The current study has demonstrated that the presence of anti-thyroid antibodies or raised serum TSH alone was associated with a highly significant raised risk of developing hypothyroidism at twenty years. It has also demonstrated that, independent of age, the higher the serum TSH above 2 mU/L, the greater is the prognostic significance for the development of overt hypothyroidism in subjects with or without anti-thyroid antibodies."

[***Note**: This is the Whickham Study which is referred to in a number of the references.*]

Drs Anthony D Toft & Geoffrey J Beckett, "Thyroid function tests and hypothyroidism",
***British Medical Journal*, 8 February 2003, 326:296-7**

"It is the exquisite sensitivity of the thyrotroph that led to the use of serum TSH measurements as a first line test of thyroid function

...

?There is also the difficulty of interpreting a serum concentration of TSH in isolation.?

...

Michael T McDermott & E Chester Ridgway, "Clinical perspective: Subclinical hypothyroidism is mild thyroid failure and should be treated",.
***Journal of Clinical Endocrinology and Metabolism*, 2001, 86(10): 4585-4590**

?We believe that mild thyroid failure is a common disorder that frequently progresses to overt hypothyroidism.?

...

Christian Meier et al, "TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind, placebo-controlled trial (Basel Thyroid Study)"
***Journal of Clinical Endocrinology and Metabolism*, 2001, 86(10): 4860-4866**

"... we demonstrate by this double blind study that SCH [*subclinical hypothyroidism*] has negative clinical and metabolic effects in affected patients. Physiological, TSH-guided, L-thyroxine treatment can improve LDL-C [*Low Density Lipoprotein Cholesterol – the 'Bad' cholesterol*] and total cholesterol levels and clinical signs and symptoms of hypothyroidism, and thereby may reduce morbidity and mortality in patients with this common syndrome."

LM Demers PhD FACB, CA Spencer PhD FACB," NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease"
The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, 2002

?Over the last two decades, the upper reference limit for TSH has steadily declined from ~10 to approximately ~4.0-4.5 mIU/L. ?

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Dr Lawrence C Wood, "TSH: A new "normal"?: New guidelines from the National Academy of Clinical Biochemistry (NACB)".
Thyroid Federation International, *Thyrobulletin*, Spring 2002; 5(1): 9

"Dr. Carole Spencer from USC Medical Center recently reviewed new research indicating that the normal range for TSH is actually much lower than the range presently accepted in virtually all medical laboratories.?

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Prof Jim Stockigt, "Subclinical hypothyroidism or Mild thyroid failure: How important is early diagnosis and what treatment is optimal?"
Sigma Pharmaceuticals, March 2001; Thyroid Australia, *Thyroid Flyer*, Jul 2001; 2(3)

http://www.thyroid.org.au/Information/Stockigt.html

"When we have normal population data for serum TSH we need to log-transform [*plot the graph on a logarithmic scale*] the values in order to get the familiar bell-shaped curve that defines a normal distribution."

...

David S Cooper, M.D., "Subclinical hypothyroidism"
***New England Journal of Medicine*, 2001 (July 26); 345(4): 260–265**

"Given the high rate of conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating antithyroid antibodies, it makes sense to treat asymptomatic persons with positive antibody tests even if they have normal serum lipid [*cholesterol*] levels. However, because an elevated serum thyrotropin [*TSH*] level is associated with an increased risk of overt hypothyroidism even in the absence of antithyroid antibodies, positive antithyroid-antibody titers should not be the sole criterion for therapy. It is also reasonable to treat subclinical hypothyroidism in pregnant women and in women who have ovulatory dysfunction with infertility."

American Association of Clinical Endocrinologists, "New Campaign Urges People to "Think Thyroid" at Critical Life Stages and Get Tested", Thyroid Awareness Month 2001, Jan 2001

"AACE encourages patients whose TSH is outside the normal range (.5-5.0 µU/ml) to see an endocrinologist for treatment and thyroid disease management. Even though a TSH level between 3.0 and 5.0 µU/ml is in the normal range, it should be considered suspect since it may signal a case of evolving thyroid underactivity."

Prof A P Weetman, "Fortnightly review: Hypothyroidism: screening and subclinical disease"
***British Medical Journal*, 19 Apr 1997; 314: 1175**

...

Drs Colin M Dayan, Ponnusamy Saravanan, & Graham Bayly, "Whose normal thyroid function is better – yours or mine?"
***The Lancet*, 3 Aug 2002; 360(9330): 353**

"A typical (statistical) reference range for thyroid-stimulating hormone (TSH) in many laboratories is around 0.2-5.5 mU/L. However, the 20-year longitudinal Whickham survey indicated that individuals with TSH values greater than 2.0 mU/L have an increased risk of developing overt hypothyroidism over the next 20 years."

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Summary

- The Reference Ranges for the TSH test currently being used routinely are too wide at the upper end. There is clear evidence that adverse medical outcomes occur at TSH levels within the current reference ranges.
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- ...
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- ...
- The consequences of not treating mild thyroid failure can be significant. There are risks to under treatment and non-treatment just as there are risks to over treatment.

Sections

ARE YOU BEING OPTIMALLY TREATED?

Having been diagnosed, people with hypothyroidism generally need to take supplemental thyroid hormone for the rest of their lives. How do they know when they are taking the dose that is optimal for them:

RIS Bayliss, KCVO, MD, FRCP & WMG Tunbridge, MD, FRCP
***Thyroid disease: The facts*, 3rd ed., (OUP, 1998), p.100**

"Most patients with thyroid deficiency feel at their best when the dosage of thyroxine raises their free thyroxine level towards the upper end of the normal range, or even a little above it. This usually reduces the thyroid stimulating hormone (TSH) level towards the bottom of the normal range or even a little below it, but not so low as to be undetectable. The total daily dose in an adult with no functioning thyroid tissue at all is usually 0.15-0.2 mg. Occasionally the dose may need to be 0.25 mg."

Drs Anthony D Toft & Geoffrey J Beckett, "Thyroid function tests and hypothyroidism"
***British Medical Journal*, 8 February 2003; 326: 296-7**

http://bmj.com/cgi/content/full/326/7384/295?ijkey=CFlqXBks53nhU

?The other difficulty in interpreting serum TSH concentrations is to decide what value should be aimed for in patients taking thyroxine replacement. It is not sufficient to satisfy the recommendations of the American Thyroid Association by simply restoring both serum T4 and TSH concentrations to normal...?

...

Prof A P Weetman, "Fortnightly review: Hypothyroidism: screening and subclinical disease"
***British Medical Journal*, 19 Apr 1997; 314: 1175**

"...even within the reference range of around 0.5-4.5 mU/l, a high thyroid stimulating hormone concentration (>2 mU/l) was associated with an increased risk of future hypothyroidism. ..."

...

Prof Jim Stockigt, "Subclinical hypothyroidism or Mild thyroid failure: How important is early diagnosis and what treatment is optimal?"
Sigma Pharmaceuticals, March 2001; Thyroid Australia, *Thyroid Flyer*, Jul 2001; 2(3)

http://www.thyroid.org/au/Information/Stockigt.html

"When we have normal population data for serum TSH we need to log-transform [*plot the graph on a logarithmic scale*] the values in order to get the familiar bell-shaped curve that defines a normal distribution."

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Drs John P Walsh & Bronwyn G A Stuckey, "What is the optimal treatment for hypothyroidism"
***Medical Journal of Australia*, 2001; 174: 141-143**
Thyroid Australia, *Thyroid Flyer*, 2:4, Oct 2001

http://www.thyroid.org.au/Download/Flyer%202001.4%20T3.pdf

"There is evidence that individuals have different set points in the relationship between serum thyroxine [*T4*], T3 and TSH concentrations. ..."

...

Douglas S Ross, M.D., "Ask the doctor: When an individual is put on thyroid hormone therapy, is it best to be in the low part of the TSH normal range, or just somewhere in the normal range?"
Thyroid Foundation of America, *The Bridge*, Spring 2002, 17(1)

...

Drs Anthony D Toft & G J Becket
***The Lancet: Correspondence*, 2 Mar 2002; 359(9308): 797**

Comments in response to J V Parle et al, "Prediction of all-cause and cardiovascular mortality in elderly people from one low

serum thyrotropin result: A 10-year cohort study", The Lancet, 358, 15 Sep 2001:

"Unfortunately … confusion [is caused] by using the … findings to justify that patients taking thyroxine-replacement therapy should not have a suppressed serum thyrotropin [*TSH*] concentration. ...?

...

P B S Fowler
***The Lancet: Correspondence*, 2 Mar 2002; 359(9308): 797**

Comments in response to J V Parle et al, "Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: A 10-year cohort study", The Lancet, 358, 15 Sep 2001:

?My colleagues and I have studied the effect of long-term thyroxine on bone-mineral density and serum cholesterol in 30 patients followed up for 12·7 years.

...

A course needs to be steered between osteoporosis, with the possible increase of pathological fractures, and potentially fatal coronary artery disease.?

LM Demers PhD FACB, CA Spencer PhD FACB, "NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease"
The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, 2002

http://www.nacb.org/lmpg/thyroid_lmpg_pub.stm

"It is now well documented that hypothyroid patients have serum FT4 values in the upper third of the reference interval when the L-T4 replacement dose is titered [*adjusted*] to bring the serum TSH into the therapeutic target range (0.5-2.0 mIU/L)."

"…Also, as shown in Figure 2, serum TSH values are diagnostically misleading during transition periods of unstable thyroid status, such as occurs in the early phase of treating hyper- or hypothyroidism or changing the dose of L-T4. Specifically, it takes 6-12 weeks for pituitary TSH secretion to re-equilibrate to the new thyroid hormone status. These periods of unstable thyroid status may also occur following an episode of thyroiditis, including post-partum thyroiditis when discordant TSH and FT4 values may also be encountered."

Figure 2

Fig 2. The lag in pituitary TSH reset during transition periods of unstable thyroid status following treatment for hyper- or hypothyroidism.

"Guideline 2. Thyroid Testing for Ambulatory Patients

Patients with stable thyroid status:

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Patients with unstable thyroid status:

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"Guideline 23. Levothyroxine (L-T4) Replacement Therapy for Primary Hypothyroidism

- L-T4, not desiccated thyroid, is the preferred medication for long-term replacement therapy for hypothyroidism.
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- ...?

C Meier, P Trittibach et al, "Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey"
***British Medical Journal*, 2003 (8 February); 326:311-312**

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"TSH is a poor measure for estimating the clinical and metabolic severity of primary overt thyroid failure. This is in sharp contrast to the high diagnostic accuracy of TSH measurement for early diagnosis of hypothyroidism.

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H Al-Adsani, LJ Hoffer and JE Silva, "Resting Energy Expenditure is Sensitive to Small Dose Changes in Patients on Chronic Thyroid Hormone Replacement"
***Journal of Clinical Endocrinology and Metabolism*, 1997; 82:1118-1125**

http://jcem.endojournals.org/cgi/content/full/82/4/1118

...

"... it should be recognised that only 20-25% of resting energy expenditure is thyroid hormone dependent in humans, as this is the maximum reduction seen in individuals with profound hypothyroidism."

...

JA Romijn, JWA Smit and SWJ Lamberts, "Intrinsic imperfections of endocrine replacement therapy",
***European Journal of Endocrinology* (Oct 2003); 149:91-97**

The authors review the successes and shortcomings of replacement therapies for endocrine conditions. In particular, they focus on the experiences of that group of patients who have continuing vague complaints and decreased quality of life. In their view it is likely that these complaints may be explained by imperfections of the replacement therapy in not completely mimicking the natural endocrine function. They also express concern that these subtle signs of imperfection may result in treating doctors mislabelling the complaints.

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Summary

- In the early stages of therapy and at later stages following changes in dose, TSH is potentially unreliable as an indicator of the adequacy of therapy. Free T4 is more accurate in these periods.
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- ...
- It is important that the intrinsic shortcomings of hormone replacement be recognised, that the complaints of patients be accepted and appreciated and that the patients not be mislabelled.

Sections

GLOSSARY

ATD	Autoimmune Thyroid Disease
Central hypothyroidism	Hypothyroidism caused by a pituitary malfunction
Euthyroid	'Normal' thyroid function. Neither too high nor too low.
FT3	Free T3 or Free Tri-iodothyronine The fraction of T3 in serum which is not bound to transport proteins.

FT4	Free T4 or Free Thyroxine. The fraction of T4 in serum which is not bound to transport proteins.
HDL	High Density Lipoproteins. HDL is one of the components of cholesterol as measured by blood tests. HDL is regarded as the 'Good' cholesterol.
LDL	Low Density Lipoproteins. LDL is one of the components of cholesterol as measured by blood tests. LDL is regarded as the 'Bad' cholesterol.
LDL-C	Low Density Lipoprotein Cholesterol
Levo	Left Handed. This term denotes a particular folding of the molecule. Most biologically active molecules are left handed with the right handed variants being far less active or not active at all. The biologically active forms of T4 and T3 are left handed.
Lipid	Fatty organic molecules. In the context of blood tests the term usually refers to cholesterol and related compounds.
L-T3	Levotriiodothyronine See 'Levo'. In the context of this article L-T3 has the same meaning as T3.
L-T4	Levothyroxine. See 'Levo'. In the context of this article L-T4 has the same meaning as T4.
L-thyroxine	Levothyroxine. See L-T4.
mean	Average
median	Half the individuals in a sample are below this point and half above it.
mg	Milligram. One thousandth of a gram. 1 mg = 1000 µg
µg	Microgram. Also abbreviated as mcg. One millionth of a gram.
RAI	Radio Active Iodine
Rx	Therapy or treatment.
Serum	Blood
Set Point	The specific combination of T4, T3 and TSH levels that are maintained by each person.
Somatic	Relating to the body.
Thyroid hormone resistance	A genetic condition in which the patient's cells do not respond normally to thyroid hormone.
Thyrotroph	The cells in the pituitary that produce Thyroid Stimulating Hormone.
Thyrotropin	Thyroid Stimulating Hormone.
Titer	Also Titre. The standard of strength in a volumetric measurement. A high titer implies more is present.
Titrate	The practice of adjusting the dose (in this case of thyroxine) to produce a desired result.
TPO Ab	Thyroid peroxidase antibodies

Sections

Megan Stevens MA is the founding President of Thyroid Australia. She was diagnosed with Hashimoto's Disease in 1994. Her desire to ensure that others do not experience the problems she did in obtaining reliable information led her to found Thyroid Australia with other like minded people.

Alun Stevens MSc FIAA is the Secretary of Thyroid Australia. He is an actuary and physicist. He does not have a thyroid condition himself. He just lives with one – and its owner (see above).

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