



New horizons: thyroid dysfunction

THE ACUTE SENSITIVITY OF PATHOLOGY TESTS FOR DIAGNOSING THYROID DYSFUNCTION IS RAISING INTERESTING QUESTIONS FOR CLINICIANS. MATT JOHNSON REPORTS.

The principle is simple. Identify the symptoms that define the disease. Use the symptoms to determine the cause. Develop a test that identifies the causative factor or, at least, the physiological clues it leaves behind. Refine the test so it becomes increasingly accurate and treatments can be better targeted and managed.

It's this principle that so effectively guides the interaction of scientists, pathologists and other doctors.

But what happens when the tests become so accurate that the patient, despite a positive test, shows no symptoms?

Do you change the 'positive' value and risk normalising the disease?

Or do you commence treatment for something that may never cause a problem?

Over the past decade the sensitivity of some of the tests for thyroid dysfunction have increased their accuracy by 100-fold, and with rapid growth in the number of tests being conducted, an increasingly large number of patients are being captured in the 'abnormal' range.

Some have raised concerns that this has led to confusion – not clarity – for patients.

But others argue that identifying sub-clinical thyroid dysfunction could prove highly beneficial in the long term.

The thyroid and its hormones

Weighing about 30 grams, the two connected lobes of the thyroid gland wrap around the sides of the larynx in the throat.

The gland secretes two hormones directly into the bloodstream: tri-iodothyronine (T3) and thyroxine (T4), both of which regulate an enormous range of metabolic and growth functions. The two most common dysfunctions of the thyroid gland are hypothyroidism (decreased hormone output) and hyperthyroidism (increased hormone production), with one in 20 people estimated to experience some form of thyroid dysfunction in their lifetime.

T3 and T4 are the active hormones released by the thyroid gland, but their production is controlled by the pituitary gland located in the base of the skull. The

pituitary gland secretes thyroid-stimulating hormone (TSH).

Too little T3 or T4 in the blood prompts the pituitary to release more TSH, causing thyroid activity to increase. Too much T3 or T4 decreases the amount of TSH released by the pituitary.

Because it controls the release of T3 and T4, measuring TSH is usually the first step in investigating thyroid function. In fact, the logarithmic relationship between T4 and TSH means small changes in T4 levels normally result in very large changes in TSH levels, making TSH a very sensitive indicator of thyroid gland dysfunction.

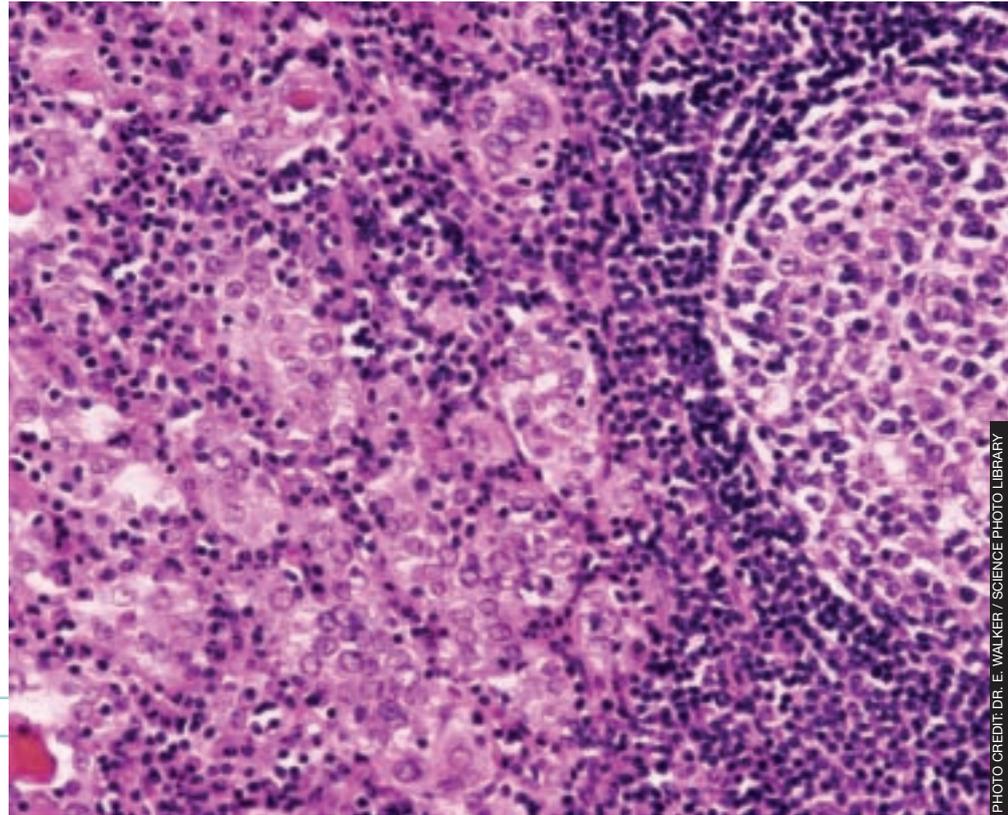
Too good to be true?

The TSH test currently used in Australia is a chemiluminescence immunoassay that is highly automated, extremely accurate and takes less than 20 minutes to complete. Blood in the collection tube is centrifuged to separate the plasma and the tube goes directly into a machine for analysis.

Perry Giannopoulos, senior hospital scientist at SydPath, says the accuracy of

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– Dr Graham Jones



Light micrograph of a section through a thyroid gland with the autoimmune disorder Hashimoto's disease

PHOTO CREDIT: DR. E. WALKER / SCIENCE PHOTO LIBRARY

the chemiluminescence method is now almost too good.

“Over the past 30 years we’ve moved through different assays. The original radio-immunoassays measured down to a lower limit of about one. When we moved to enzyme-immunoassays, that limit improved to 0.1 – and now, these third-generation chemiluminescence assays are 10 times better again,” she says.

The improvements in accuracy with each generation of assays has been the key factor in allowing doctors to make the distinction between true hyperthyroidism and the non-specific changes in thyroid results in people with other illness.

But the increased accuracy has raised concerns that the clinical aspects – the signs and symptoms – of hypo- and hyperthyroidism have been downgraded, with many patients now returning abnormal results but showing no symptoms.

One article published in the BMJ (2000;320:1332–4) described this as having led to “chaos” in the diagnosis of hypothyroidism.

And some have noted that the concept of “sub-clinical hypothyroidism”

and using TSH concentrations above 2 mIU/L to suggest an increased risk of hypothyroidism mean half the population fall into this category.

But to Dr Graham Jones, SydPath’s staff specialist in chemical pathology at St Vincents Hospital in Sydney, the increased testing accuracy is a positive virtue.

He contends the significance of borderline values will only be borne out in longer-term studies that now, at least, can be based on very precise data.

“It may be that identifying these sub-clinical patients allows them to be treated and never develop more serious symptoms, but the outcome studies will take time to do,” he says.

In the short term Dr Jones sees the accuracy as providing better answers for doctors and their patients.

“The symptoms of hypothyroidism such as lethargy and weight gain are so common that TSH testing is often required to exclude thyroid disease, and with the current tests, you’ll arrive at the right answer nearly all the time.”

Chemical pathologist and endocrinologist Professor Creswell

SYMPTOMS OF HYPOTHYROIDISM

Too little T4 and T3 causes the metabolism to slow down too much.

The symptoms include:

- lethargy and fatigue
- sensitivity to cold
- unusual weight gain
- depression
- confusion
- hair loss
- dry skin
- constipation
- goitre.

Eastman agrees it will take years to determine how many of these sub-clinical patients will develop clinical signs, but says the increased accuracy of the test is already allowing doctors to identify and treat high-risk patients.

“Before we had a highly sensitive TSH test, there were a group of people who had normal T4 and T3 levels and were not



identified as being at risk of developing hyperthyroidism because we were unable to measure subnormal TSH levels,” he says.

“But if you become more selective and look at the high-risk patients in this group – those older patients with long-standing goitre and with cardiovascular disease – you are now much more likely to treat these people on their biochemical

SYMPTOMS OF HYPERTHYROIDISM

Too much T4 and T3 causes the metabolism to speed up too much, and ultimately damages the heart and liver and leads to death.

Symptoms of an overactive thyroid include:

- rapid pulse
- tremor (shaking) of the hands
- sweating
- sensitivity to heat
- weight loss (despite a high appetite)
- agitation and anxiety
- fatigue
- diarrhoea
- bulging eyes
- goitre.

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evidence of subclinical hyperthyroidism than wait for clinical signs. It’s a judgment at this stage, but you have to make a lot of judgments in clinical practice.”

The increased accuracy has also seen a trend towards treating some patients identified with sub-clinical hypothyroidism.

Other thyroid tests

“There is certainly some conflicting data whether treating sub-clinical patients delays the development of clinical signs,” Professor Eastman says, “but it certainly shows improvements in cardiac function and lipid levels, and it means patients with elevated cholesterol are much more likely to be treated earlier rather than later.”

In most circumstances, TSH is the only thyroid function test ordered for patients, but if the result is outside the normal range, a T4 level can also be requested.

Much of the T3 and T4 produced by the thyroid is bound to other molecules and is not available to act on its target cells, so Australian laboratories measure ‘free’ T3 and T4. That is, the active amount of the hormones.

Free T4 (FT4) is also commonly used to monitor the effectiveness of treatment and is typically measured every few weeks in the early stages.

Thyroid antibody tests can be used to support the diagnosis for patients who have returned abnormal TSH or FT4 results, or who are displaying clinical signs of thyroid disease but have returned normal tests.

Only 10% of healthy individuals will have positive thyroid antibodies, with a higher prevalence among the elderly.

Thyroid peroxidase antibodies (TPOs) – the predominant thyroid microsomal antibody (TMA) component – and thyroglobulin antibodies (TGAs) are regularly produced in thyroid disease.

The specific test for TPOs is quantitative, can be fully automated and

may easily be linked to other thyroid testing strategies; hence there is a worldwide trend towards TPO analysis, a trend which Kate McGill, senior operations manager of immunochemistry at St Vincent’s Hospital in Sydney, would also like to see adopted.

“TMA and TGA tests are ‘old fashioned’; they’re manual, time consuming and only semi-quantitative,” says Ms McGill, comparing the tests to the more expensive TPO test. “Although it may be difficult to justify TPO on cost grounds, in every other way, TPO is the method of choice for thyroid antibody testing as part of a strategy for thyroid disease investigation.”

The thyroid gland requires iodine to produce T3 and T4, and how much of the substance the thyroid absorbs from the blood is an accurate measure of thyroid activity.

Injecting a small amount of radioactive iodine allows pathologists to scan the thyroid and measure the uptake to determine the cause and help plan treatment.

The diagnosis of thyroid nodules, autoimmune hyperthyroidism and thyroid cancer can all be assisted by the scan, which uses a specialised nuclear imaging camera to take pictures of the thyroid gland from three different angles over 20 minutes.

Associate Professor Judith Freund, director of nuclear medicine and bone densitometry at the St Vincent’s Clinic in Sydney, says the accuracy of other thyroid tests has improved so much that the thyroid uptake test is only really used now in Australia for diagnosing sub-acute thyroiditis and in therapy for thyrotoxicosis.

“The test also helps us decide how much iodine therapy a patient requires, and if certain treatment will not be effective because their iodine uptake is too low,” she says. 🔥