PE1463/U

SUBMISSION OF DR J E MIDGLEY TO ROUNDTABLE DISCUSSION OF 1ST OCTOBER

1. The existence of various methods for measuring free T4 and free T3 that are incompatible and inconsistent

Before the optimal procedure for diagnosing thyroid dysfunction can be discussed, measurement methods for a given analyte (in this case thyroid hormones) must be consistent, whatever their source. Over the last 50 years, the measurement of the free fraction of thyroid hormones (free T4 and free T3) has had various approaches, with degrees of validity ranging from totally absent to the sound and well-supported. The responsibility for this completely unsatisfactory situation lies chiefly with the failure of regulation (national and international) to revisit the background to the working of thyroid function tests as the understanding behind test development grows, the failure of commercial companies to fully understand the detailed knowledge and care needed to produce accurate free T4 or free T3 methods, and not least the complacency of medical thyroidology. This composite failure has led to the accretion of tests that do not agree with each other, resulting in misrepresentation and misunderstanding of how such tests work. This has caused confusion as to why certain tests are chosen in particular countries and compromised the assessment of the validity of such tests.

50 years ago, a method was derived to correct for the measurement of the total T4 or T3 in serum, thereby giving (so it was claimed) an indirect estimate of the smaller free (not protein bound) fraction that determined the thyroid status of a patient. Without going into detail, this was termed the "thyroid hormone uptake test". Derivatives of this test exist today, are licensed for sale by the regulatory authorities, and form a significant part of the sales of commercial companies to thyroid diagnosticians. Recently, attempts have been made to justify the use of such tests over more soundly based methods, apparently merely because the diagnosticians involved "liked the results". An example of such thinking is given in: Free T4 immunoassays are flawed during pregnancy. Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE, Goodwin TM. American J Obstet Gynecol. 2009 Mar;200(3):260.e1-6. doi: 10.1016/j.ajog.2008.10.042.

Unfortunately, from the outset, this approach was completely invalid from basic principles and does not (and cannot) properly derive free T4 and T3 values in the way claimed. However, such tests are still widely used, though hopefully not by laboratories regulated by the UK National Health Service. That this methodology is still permitted and used though it is known to be fatally flawed should be of concern even to those who no longer use it.

30 years ago, two new methodologies were invented (one by me) which did correspond to the physical laws governing the measurement of free hormones. As expected, there were initially some concerns in usually fairly obscure areas of thyroid

diagnosis. Nevertheless, the results with the new tests significantly advanced the field but clearly showed up the deficiencies of the original ones mentioned earlier.

Over the next 5-10 years, the new tests were continually improved and a further invention by me derived a more robust technique, which solved many of the problems earlier cited. However, once again, examples of the earlier less good tests and the better later ones are sold side by side.

Finally, today on the internet, there are offered for sale in Europe and the US, presumably permitted by regulators, free T4 and T3 tests that are clearly aimed at "point of care" (i.e. perhaps the office of a private physician) or at small independent diagnostic laboratories. They are at root totally invalid and do not give acceptable results, and misdiagnosis is a serious concern. That they have been used is evidenced in peer-reviewed publications which have employed such tests.

Such a mishmash of contradictory methodologies leads inevitably to confusion in the field and encourages a "pick and mix" attitude where tests are used not to primarily help the patient but to reinforce medical prejudices. This unscientific attitude cannot be a justifiable position to take and the medical profession has a considerable responsibility for its continuation.

Therefore I would like to suggest to the representatives of the Scottish Government that, to avoid the infiltration of faulty and invalid diagnostic tests into Scottish laboratories, private doctors offices etc, an independent regulatory body is established to monitor and proscribe the use of inadequate and faulty test procedures of the kind I have described. There is a baseline from which such regulation could be established, for example, for free T4 and free T3 tests by referring to the careful calibration studies being carried out on commercial assays by Professor Linda Thienpont of Ghent University working for the Standardisation Committee of the International Federation of Clinical Chemistry. Only those assays that, within reasonably set limits, were consistent with such standardisation should be allowed for diagnostic use in Scotland. This at a stroke would improve inter laboratory consistency of results, and hopefully better diagnosis.

One cannot hope for acceptable results with tools whose quality ranges from nonexistent to good. This situation has to be clarified and rationalized urgently, even if it means that some hospital procedures and choice of tests have to be modified. Otherwise diagnostic anarchy will continue, and the justification for the equally faulty approach of TSH-only screening will be encouraged.

2. The value of the diagnostic paradigm of log TSH versus free T4

Given the chaotic situation that exists in the diagnostic area of free T4 and free T3 tests, it is little wonder that the simpler, more easy to understand TSH test has become predominant in screening procedures even though it is strictly is not a thyroid hormone but a pituitary hormone. Additionally, the relative ease of development of reliable TSH tests, in contrast to the technical sophistication needed

to develop equivalent free thyroid hormone tests, has also encouraged their general use. For a long time it has been assumed that there exists a strong, constant arithmetical relationship between TSH and free T4 throughout the spectrum of thyroid function. This belief naturally led to two assumptions 1) that if there is such a close relationship, measuring TSH by implication indicates a corresponding Free T4 concentration (thus avoiding the need to perform what perceivedly was a more controversial test) and 2) that the use of a suitable reference range for TSH would therefore reliably discriminate patients with normal or dysfunction.

The progressive development of more sensitive TSH tests has led to a basic diagnostic misunderstanding. Increased sensitivity by itself does not necessarily equate to increased utility. Though sensitive TSH no doubt has its use in detection of subclinical conditions, it does not appear to me to have significantly altered its value in some other areas, such as hypothyroidism and T4-therapy. Even in hyperthyroidism, free T4/T3 is as sensitive as TSH in detection. A more considered role for TSH is required, where its limitations are acknowledged, and other tests are given greater priority.

Recent evidence from several groups including my own has cast doubt on beliefs of a strong TSH-free T4 relationship (Midgley JE, Hoermann R, Larisch R, Dietrich JW (2013). "Physiological states and functional relation between thyrotropin and free thyroxine in thyroid health and disease: In vivo and in silico data suggest a hierarchical model". *Journal of Clinical Pathology* **66** (4): 335–42. doi:10.1136/. Firstly, there is not a constant and significant relationship between TSH and free T4 throughout the thyroid functional spectrum. Strong correlations occur in primary thyroid-based hypothyroidism (underfunction) and probably also in hyperthyroidism, but there is virtually no correlation between the two parameters in the euthyroid (normal function) region. Each functional region appears to have its own unique expression of control mechanisms.

TSH reference ranges appear to be related to matters such as age and a statistical approach to TSH testing (that is, rigid adherence to a particular reference range, however carefully devised) seems to be diagnostically counterproductive. Accordingly, the elevation of the diagnostic status of TSH to a standalone initial screening procedure is in my opinion very mistaken. Professors Hoermann and Dietrich are also of the opinion that TSH is not a statistical parameter that can be used in such a mechanistic way.

The matter of diagnosis of hypothyroid patients on T4 or T4/T3 therapy is one of the greatest importance in this regard. Whilst it may be that a majority of such subjects (probably those who are only mildly to moderately dysfunctional) may attain “normal” functioning with TSH values within the reference range, a significant number do not. In this regard it must be remembered that in measuring TSH, one is employing a parameter at two stages removed from the actual active hormone governing body health in general (that is free T3). To assume a meaningful relation between free T3 and TSH given the biochemical distance between them and the potential for

regulatory variation between individuals is to me far too great an assumption, and one I believe does not hold.

Two classes of patients who may not be well served by monitoring of TSH levels are those with little or no thyroid reserve and patients with deficient conversion of T4 to T3. Patients with less background knowledge may suffer poorer quality of life if the paradigm of "TSH within the reference range" is the touchstone of diagnosis and they feel obliged to obey the practitioner's advice. In the latter cases, T4 therapy could be raised in vain (suppressing TSH and leading to wrong action to reduce dose) without any significant elevation of the active hormone free T3 to normal levels.

Recent work has also cast doubt on the value of using TSH to assess quality of life (QoL). A study (Klaver et al, Thyroid) involving almost 10000 patients did not find any strong correlation of TSH concentrations with QoL. Another study in progress by Dr Johannes Dietrich indicates that different aspects of QoL relate to various thyroid hormone levels, with free T4, free T3 and T3 correlating well with vitality for example. TSH had a much smaller role to play in this regard, agreeing with the other study mentioned. This is a further indication that the role of TSH in restoring good QoL is very restricted and that other parameters play more important roles, justifying their measurement in diagnosis.

3. What thyroid hormone medication should hypothyroid subjects be given and how should they be diagnosed?

It must be admitted that for a large number of hypothyroid subjects, simple T4 monotherapy appears to give a satisfactory QoL. I mentioned earlier that these may predominate in the group with mild to moderate dysfunction, where there is at least a modicum of residual endogenous glandular activity. However a very significant minority (judged by some doctors to be as much as 25%) do not fare well. I have mentioned such groups in another contribution.

Professor R Hoermann and Dr H Lindner have given copious reasons why TSH-screening diagnosis is not a satisfactory approach from a diagnostic viewpoint and as a nonmedically qualified person, I defer to their expertise in diagnostic procedures as shown by their contributions. However, if TSH cannot be reliably used in diagnosis in this minority, another stratagem should be sought. I would suggest that, whether therapy is by T4 alone, or a T4/3 combination, TSH should be limited to detection of undertreatment and noncompliance (failure to take the pills). It should not be used to monitor adequate treatment or overtreatment. For this, I believe free T3 should be the test of choice. I conducted the first clinical trial of a valid free T3 test in 1983, involving a multicentre trial of thousands of patients. I have the document still. It showed that for almost 1000 subjects on T4 therapy, free T3 was very effective in distinguishing correct from overtreatment, even though at that time the parameters for initial diagnosis were insensitive TSH, free T4 and patient presentation. The trial supported the protocol I suggested above.

Free T3 is by definition a direct expression of the metabolic support given by the hormone to the tissues generally, and therefore should more accurately reflect the general wellbeing of the patient. Free T4 is valuable for diagnosis, but it should be realised that for some patients, even on T4 monotherapy, adequate FT3 cannot be attained until free T4 levels are either high-normal or slightly above normal. Titration of adequate free T3 by manipulating T4 dosage should in my opinion be the diagnostic aim, together with QoL satisfaction expressed by the subject.