

PE1463/EEEE

John Midgley Submission of 31 August 2016

SUBJECT: COMMENTS ON SUBMISSION OF DOCUMENT PE1463DDDD, SCOTTISH GOVERNMENT LETTER OF 2ND AUGUST 2016 TO THYROID UK.

I am in receipt of a copy of the above communication and wish to make detailed replies to its comments. Firstly, the responses of the above to the submission by Thyroid UK generally display an unnecessarily patronising and dismissive attitude and the air of “we know best” pervades the whole of the replies. Secondly, the responses frequently misrepresent what is actually being claimed or shown by the Thyroid UK document, contain many non-sequitur arguments, use doubtful logic to justify their position and display both elementary scientific errors and a distressing ignorance of modern work in thyroidology and its consequences for improved diagnosis and treatment.

In presenting this response, I must emphasize that I am acting in this regard as an independent researcher/biochemist and not formally as an adviser to Thyroid UK, though I have been encouraged by them to write it. My credentials are a) inventor of the FT4 and FT3 tests now performed worldwide, b) winner of the Prince of Wales award for Industrial Innovation and Production in 1985, c) independent consultant for diagnostic R & D, d) archivist for the Cochrane Collaboration, and e) author and co-author of 100 + communications of topics including thyroid testing and thyroid physiology over a period of 55 years..

RESPONSE TO QUESTION 1.

The purpose of the Thyroid UK submission was precisely NOT aimed at producing a scientific survey of the type apparently desired by the correspondent and by its very nature is bound to contain more dissatisfied patients, coming as it does from a charity devoted to such patients. The casual and somewhat arrogant dismissal of the contents of the document constitutes a fundamental misrepresentation of its purpose and the refusal to engage properly with its contents is unacceptable. It is primarily concerned with ascertaining the existence of and detailing the experiences of a significant number of subjects inadequately diagnosed and treated by the medical profession; the exact numbers and proportions of the population as a whole are irrelevant to the exercise and cannot be used as an excuse to dismiss the submission out of hand. The statement “we must rely on the evidence base” is illogical since the evidence base itself is out of date, partial and unresponsive to and ignorant of the implications from newer studies.

RESPONSE TO QUESTION 2.

This answer is again irrelevant as no one has suggested that Scotland differs in significant ways from the rest of the UK in this regard. The data gathered cannot be exactly precise as regards numbers and percentages, as this would require a contribution from every person with thyroid dysfunction in the land, but this does not detract from the thrust of the submission.

RESPONSE TO QUESTION 3.

A sentence stating the obvious and irrelevant to the point of the submission. Thyroid UK was

asked by the Scottish Government to submit evidence for a listening exercise but was not formally commissioned to do so. This is nitpicking legalism.

RECOMMENDATION 1.

If this response here had any basis in fact, then it would not be the constant experience of very many patients that TSH is almost always the only test carried out in treatment control, free T4 occasionally, and free T3 almost never. As (see answers to responses below) free T3 is the most accurate assessment of control of the response to treatment (be it T4 monotherapy, T4/T3 combination or T3 alone) the use of TSH is inaccurate and frequently misleading, with unpleasant consequences for the patient. It is ironic that the test which gives the most accurate information is the test least used. Modern knowledge shows that the reference range for TSH and free T4 derived from healthy euthyroid subjects is inappropriate for patients under thyroid hormone therapy. The idea that most patients routinely receive “personalised medical attention” is completely alien to the experiences of the great majority of subjects, whose condition is merely deduced from what few biochemical tests are done, with little regard to presentation symptoms which, if the biochemical tests indicate “normality” are frequently brushed aside as being due to other problems. This attitude has led to very great wastage of money from irrelevant and useless treatment for other wrongly perceived conditions, frequent fruitless visits to the doctor, inability of sufferers to work, and diversion of others to look after such people.

RECOMMENDATION 2.

This reply is misleading in that the cutoff of 10 mU/L for TSH is presently used by most medical practitioners as a statistical action point whether there are symptoms of thyroid dysfunction or not. It is certainly the primary role of a doctor to do no harm, but harm can be caused equally by acts of omission as well as commission. The elementary error made here is that patients must conform to a “statistical determination” of their condition rather than a personal assessment of their individual needs. Some patients may show signs of overt hypothyroidism with TSH values at 4 and above, and there is evidence that values for TSH above 2.5 are indicating that the thyroid, though not actually in failure, is under strain. In such cases it is incumbent on a responsible practitioner to be aware of the possibility if not the certainty of problems that may arise in the future if the situation persists or worsens, and take appropriate action in reassessment at a later time. It is now acknowledged that the intervention level for TSH is progressively decreasing. Why the foot-dragging if it has been known for so long that 10 mU/L is too high a cutoff point? And if a value of 10 mU/L is now considered too high, where is the instruction to doctors to abide by the lower limits and where are the admissions of error that too high a cutoff has caused unnecessary distress to patients in the past? Such attitudes cannot be

casually swept under the carpet as if they did not matter. An example of bad science being reluctantly relinquished in the face of overwhelming evidence.

The diagnosis of subclinical hypothyroidism based solely on a slightly raised TSH is also incorrect. When all three parameters, free T3, free T4 and TSH are combined in a multivariate analysis a significant proportion of so-called subclinical hypothyroid subjects rejoin the normal range. The fact that thyroid expression can be altered by nonthyroidal disease is well-known and the fact that a patient is showing symptoms of such a disease should preclude a thyroid test until the patient recovers.

RECOMMENDATION 3.

This reply encapsulates the unacceptably sweeping powers given to the clinical chemistry laboratory in the tests it chooses to do, and the diagnosis emanating from the results. The clinical chemist has not seen the patient and has no knowledge of their detailed presentation to the doctor. This attitude has reduced the patient's diagnosis to determining it by an anonymous set of numbers which are either in or out of the respective normal ranges, which themselves are uncertain and vary significantly from laboratory to laboratory. And this means the entirely arbitrary highlighting of results by an automated machine. Medical practice must reconsider the importance of presentation of the patients themselves as opposed to statistical assignments made entirely from an inadequate number of tests and dictation to the doctor by those not intimately concerned with the patient. This response is entirely at odds with the response given for Recommendation 1.

RECOMMENDATION 4.

This is an illogical argument. It is demonstrably the case that biochemists take it upon themselves to refuse to carry out tests in complete ignorance of all the patient's presenting symptoms. See the response above in Recommendation 3. Rather than being rare, such refusals are common, not based on the patient as much as simplistic analysis and the cost of performing the requested tests.

RECOMMENDATION 5.

The statement here presents the reader with a muddle. What trial is being referred to and what did it indicate? There is need for more research, but this uncertainty should not inhibit the testing for DIO₂ if poor conversion of T4 to T3 is suspected in therapy.

RECOMMENDATION 6.

The use of TSH within the reference range as an indicator of optimal treatment for thyroxine or even T4/T3 combination therapy is now discredited. The relationship between TSH and thyroid hormone levels is not the same in treatment as in the euthyroid untreated state. Furthermore, there is no convincing evidence that inevitably a suppressed TSH will over the long term give a significant risk of further problems. The studies purporting to show increased risk of osteoporosis or atrial fibrillation arising from this are fatally flawed as will be explained later. Similarly the

trials examining the value of T4 only or combined T4/T3 therapy are also confounded as will also be explained later. Furthermore, the outcome of therapy can be a balance between good perception of health now against vague and minor (1 extra episode per 1000 patient years) increased risk of adverse events later in life. If a patient has to suffer inadequate treatment with long term misery, against such small future perils, it is clear what most subjects would prefer. Once again harm is being done by acts of omission rather than commission. It is for this reason that regrettably many patients divorce themselves from perceived current medical practice and self-medicate. Informed discussion between doctor and patient is therefore lost in these cases.

RECOMMENDATION 7.

Here is more confused thinking. If a patient displays symptoms indicative of thyroid dysfunction, but the biochemical parameters are in the reference range then according to the current ideas the patient cannot by definition be dysfunctional. This is a case of shoehorning a patient into a category based on chemistry alone and not on presentation, a wholly unsatisfactory state of affairs. This elevates reliance on statistical measurement above common sense. Statistics basically are measures of probability not certainty and the limits of reference ranges are not to be treated as goalposts but wider areas where normality shades into abnormality..

RECOMENDATION 8.

The statement that trials do not support patient reports of benefits from liothyronine or NDT is fatally flawed. The reason is that the human race contains a range of possibilities. This is as true of thyroid function as any other metabolic process. Thus within the euthyroid untreated ranges for TSH, FT4 or FT3 there exists a progressive change in thyroid control from those with the lowest free T3 to those with the highest values within the range. In the event of future thyroid dysfunction, subjects will respond to treatment differently, according to their original position in the euthyroid range. The majority of subjects will respond favourably to thyroxine therapy being in the middle of the range. At the two edges of the range however there will be two groups, those with very efficient conversion of T4 to T3 and on the other hand those with poor conversion. These form minorities of approximately 10% at each end of the range. Therefore if trials comparing T4 only and combined T4/T3 therapy are conducted irrespective of the positioning of subjects in the original euthyroid range, there will be a large majority who will be indifferent, a small minority (the good converters) who may easily be overdosed and suffer adverse symptoms with combined therapy, and poor converters who will prefer combined therapy, but are too small a minority to have any statistical power in influencing the overall results. It is in this way that all trials so far carried out are fatally flawed in their outcomes and are frankly not worth the paper they are written on. Prior stratification of patients according to conversion efficiency (FT4/FT3 ratio on T4 monotherapy) should first have been done, so as to provide a well-controlled and well-performed trial with meaningful results.

Some of the response here seems to be an attempt to “blind by science”. We are well aware of the intricacy of such matters as active membrane transport of hormones, intracellular metabolism (ubiquitination and nuclear transcription). Interesting as these topics are for an academic they have little bearing on the basic needs for intelligent diagnosis and treatment of patients, needs which are far from being met by present day protocols.

RECOMMENDATION 9.

The recommendations of both the British Thyroid Association and American Thyroid Association are based on past evidence that no longer holds water. Recently the leading US scientists Dr A Bianco and J Jonklaas of the US have publicly expressed their doubts as to appropriateness of the uniform use of thyroxine monotherapy and have questioned currently held positions against combined therapy in a significant proportions of patients. A comment on the last sentence in this paragraph has already been addressed.

RECOMMENDATION 10.

Unfortunately too many doctors take a censorious attitude against those patients who have despairingly opted to self medicate, and feel insulted that their expertise has been brought into question.

RECOMMENDATION 11.

If a patient has greater knowledge about their condition and treatment options than the doctor, the doctor should refrain from making derogatory remarks and dismissing the patient as a troublemaker, as too often happens. Thyroid dysfunction is a sufficiently common ailment for doctors to be much more aware of the options for treatment, as opposed to the force fed inadequate advice they have to swallow from out-of-date authorities..

RECOMMENDATION 12.

There is copious evidence in the peer-reviewed literature that different brands of thyroxine tablets, though nominally containing the same amount of thyroxine, display significantly different bioavailability. The recommendation for a subject on thyroxine is to maintain the same brand if at all possible. Also some examples contain fillers, whose ingredients can upset some people.

RECOMMENDATION 13.

If only this happy suggestion were the norm and not the exception.

RECOMMENDATION 14.

Once again this misses the point that a doctor should do no harm regarding acts of omission being as important in this regard as acts of commission.

RECOMMENDATION 15.

This suggestion fails to convince, in that patients are referred to an out of date, badly researched

document from the British Thyroid Foundation which contains many factual errors and false assumptions.

RECOMMENDATION 16.

If only the desired activities posted here were actually carried out routinely.

RECOMMENDATION 17.

See previous comments on this matter.

RECOMMENDATION 18.

One hopes that clinicians do in fact always abide by these rules.

RECOMMENDATION 19.

Subclinical hypothyroidism is not simply a matter of elevated TSH when other parameters fall within their reference ranges. Modern studies have shown that simple-minded univariate analysis eg using TSH alone misdiagnoses a significant fraction of those who have been so designated. A revisitation for education in the use of statistics and statistical interpretation by the relevant authorities is urgently needed.

RECOMMENDATION 20.

Such studies could not be carried out validly by randomized clinical trials. For one thing, a significant number of potential subjects have removed themselves from being chosen for any trial, through self medication, absenting themselves from possible selection. As these are heavily represented by subjects requiring additional T3, any attempt at a clinical trial fairly and randomly selecting a typical patient group under direct medical supervision is immediately invalidated.

Answers to Question 4.

a) For the majority of patients T4 monotherapy is an adequate treatment. However the control of such treatment by monitoring TSH is misguided and recently shown to be incorrect. As stated above, the relationship between TSH, FT4 and FT3 in treated patients is quite different from the euthyroid panel from which the reference range used to diagnose is derived. It therefore follows that placement of TSH values even below the reference range is not necessarily harmful either in the short or long term.

b) If individuals on T4 therapy remain dissatisfied with their treatment, even if normal TSH levels are found, it should not therefore be automatically assumed that the

dissatisfaction is due to matters other than thyroid dysfunction. This is a too ready fall back position by clinicians educated by present guidelines.

c) No one is suggesting that combined therapy with T4 and T3 should be routinely used on patients. Only a minority will benefit and some others may find the treatment unsatisfactory compared with T4 only. Intelligent diagnosis, knowledge of the FT4/FT3 relationship under T4 monotherapy, and use of FT3 tests as a controlling diagnostic, would readily identify those subjects who would most probably benefit.

d) The risks of long term combined therapy if well controlled, have been greatly overblown. Indeed the studies purporting to show such possibilities are themselves fatally flawed for the following reasons. Nearly all studies have used the invalid TSH-centred criterion as a base-point for comparing the outcomes for those with within-range TSH and those with low or undetectable TSH. This is wrong for the following reasons. 1) the human race comprises individuals with significantly different set points defining their healthy state. By this is meant the particular concentrations of TSH, FT4 and FT3 that typify their health. 2) An individual's parameters do not span the whole range in their lifetime but maintain their own narrow limits within the respective ranges. In the event of dysfunction later, adequate FT3 may only be attained in some individuals by suppression of T4, and in others may not be attainable at all unless T3 supplementation is given in addition to T4. 3) Thus within the population, there will be outcomes ranging from those originally healthy with lower FT3 who are sensitive to therapy in whatever form and with whom it is more difficult to prevent over-supplementation, those who are robust to T4 monotherapy, and those who require additional T3 to regain health. In the absence of any FT3 measurements, the different sensitivities of the various groups to adverse long term outcomes are submerged in a non-discriminatory general study of unselected subjects. That is why, as is the case for the trials on combined T4/T3 therapy, the studies on the adverse outcomes of long term TSH suppression are invalidated by their lack of FT3 data and confounding of subject states vis a vis conversion, resulting FT3 levels and accompanying outcomes..

d) There may be no convincing evidence for the use of NDT and other diagnostic procedures but there is no convincing evidence against either.

NDT was used successfully for many years before the advent of T4 and problems encountered arose from the inability to measure serum T4 and T3 accurately rather than problems with the material per se. If the discipline has set its face against doing the studies then no advance can be made in determining the matter. However T4/T3 combinations, preferably with slow-release T3, should suffice.

e) Allegations have been made 1) that the T4 and T3 content of NDT is nonphysiological and thereby its use could be harmful and 2) that the control of its content is inadequate. Both allegations are ill-founded and contrary to demonstrable fact. In the first case, T4 monotherapy is even more non-physiological as regards hormone supply compared with that of the working thyroid. The unjustified and untested assumption has been made by proponents of monotherapy that virtually all patients' biochemistry will adequately convert T4 to T3 according to their particular

needs. This has been directly demonstrated to be incorrect. Secondly, NDT production is governed by eg the US Pharmacopeia, and reading the control protocol shows adequate methods for such control of hormone content (i.e. T4 relative to T3 and amounts of each). There have been further unsupported allegations of frequent batch failure, but far more recalls have been made for T4 tablets over a period. The alleged nonphysiological ratio of T4 to T3 in the preparations is also misleading as the body will use proffered hormone as it wishes i.e converting T4 to T3 to augment the T3 offered.

GENERAL CONCLUSION

These replies to the Letter are not intended as a direct rebuff to the sender. They are directed at the advising bodies whose knowledge base is out of date, whose conclusions are inaccurate, and whose reference points and assertions are often unsubstantiated by peer reviewed literature or rely on discredited studies that do not prove the points they are trying to make. There is no evidence of an open-minded approach to solving the dilemmas in thyroid diagnosis and treatment, merely a stubborn denial that refuses to consider that fundamental errors might have been, and are being made to the detriment of patients' health.