PE1463/QQQQ
Dr Henry H. Lindner submission of 27 September 2017

Dear Women and Men of the Scottish Parliament,

I am writing again at the request of the petitioners about the ineffectiveness of the current approach to the diagnosis and treatment of hypothyroidism as expressed in guidelines produced by professional medical associations (1). I will show that those guidelines are the product of false assumptions; not of the evidence. I am a physician who has diagnosed and treated hypothyroidism in over a thousand patients according to their signs and symptoms. Few have such experience in clinical thyroidology. Because I did not follow the guidelines, I was able to produce remarkable improvements in patients who would never have been diagnosed, and who were diagnosed but undertreated. Gordon B.F. Skinner, a Scottish physician, reported similar experiences and conclusions (2,3). Also, it was only by trying to help suffering patients with effective T4/T3 therapy that I came to appreciate the prevalence of dysfunctional hypocortisolism, especially among women (4). In what follows, I will argue for the following recommendations for improving the care of patients with hypothyroidism:

1. Define hypothyroidism correctly, as "insufficient T3-effect in some or all tissues of the body".
2. Endorse the patient's signs and symptoms as the only true indicators of T3-effect.
3. Endorse the free T4 (FT4) and free T3 (FT3) levels, together, as the best indicator of T3-availability.
4. Acknowledge that the TSH test is an indirect and fallible indicator of a patient's T3 status.
5. Acknowledge that effective thyroid replacement therapy produces different TSH, FT4 and FT3 levels than seen in healthy controls. No blood test can tell a physician what dose the patient needs.
6. Demand that laboratories base their FT4 and FT3 reference ranges upon healthy non-patients who have been carefully screened for hypothyroid symptoms. They must also provide separate ranges for patients on levothyroxine therapy—as informed by clinical studies. (See below.)
7. Endorse the practice of clinical thyroidology: the diagnosis and treatment of hypothyroidism according to clinical criteria first (signs and symptoms), and according to the relative FT4 and FT3 levels second. This is precisely what patients want and need.
8. Uphold a physician's right to practice clinical thyroidology and to prescribe effective T4/T3 combination therapy, including natural desiccated thyroid. This is necessary to prevent persecution by the medical board and thus remove a major impediment to the practice of clinical thyroidology.

The endocrine profession remains stuck in a simplistic laboratory-based paradigm that was invented in the 1970s. I call it the "TSH-T4 reference range paradigm". All of the thyroid research of the past 5 decades has been performed within and interpreted according to this paradigm. All evidence that contradicts the paradigm has been ignored, minimized or re-categorized. The dominance of such paradigms in our sciences was described by Thomas Kuhn (5). The TSH-T4 reference range paradigm is defined by these assumptions:

1. Hypothyroidism is an underactive thyroid gland producing low T4 levels.
2. Almost all hypothyroidism is primary (thyroid gland failure), detectable by an elevated TSH level.
3. A normal TSH test, in both untreated and treated persons, equals "euthyroidism".
4. Hypothyroidism is perfectly treated by normalizing the TSH and/or FT4 with levothyroxine (T4).

Because reliance on the TSH for diagnosis is problematic, an add-on assumption is required:

5. Hypothyroidism must be confirmed by a FT4 level that is below the laboratory's reference range.

The paradigm requires that all of the following unstated assumptions be true:

1. TSH secretion is perfect in every person—absent any obvious hypothalamic-pituitary (HP) disease.
2. Perfect TSH secretion reacts to once-daily T4 therapy exactly as it reacts to thyroid gland output: so the TSH level is also the perfect guide for therapy.
3. T4-to-T3 conversion is perfect in every person, so physicians need only to prescribe T4.
4. The FT4 reference ranges reported by laboratories represent "euthyroidism".

Nothing should be presumed perfect in biology. These assumptions are not just improbable; they are illogical and/or contradicted by the evidence. (See below.) They are nothing but the wishful thinking of a few influential physicians in the 1970s (6,7,8,9). They hoped to simplify the diagnosis and treatment of hypothyroidism to TSH and FT4 tests and their reference ranges. In fact physicians know better than to try to use pituitary hormone levels, follicle-stimulating hormone (FSH) or adrenocorticotrophic hormone (ACTH), to diagnose or treat hypogonadism or adrenal insufficiency. They know that in these deficiencies, HP dysfunction is common, and the pituitary hormone levels are of no help to guide therapy. They diagnose and treat these deficiencies based upon signs, symptoms and end-hormone levels. They check the pituitary hormone level only to determine the cause of the deficiency. The TSH should be used only in this way. To rely on the TSH as a surrogate indicator of T3-effect is illogical. It is like insisting that one's home-heating thermostat is working perfectly even as the house gets colder and

colder. Indeed the guidelines' authors know that the TSH test is misleading in many circumstances (it has "pitfalls"). Yet they still endorse it as the "best test". Consider: How were the TSH's pitfalls discovered, and how can a physician avoid all pitfalls in all cases? There is only one way: by attending to the best indicators of T3-status—the signs and symptoms first, and relative FT4 and FT3 levels second.

The guidelines state that neither the patient's signs and symptoms nor relative FT4 and FT3 levels can be used to diagnose hypothyroidism, and "do not have sufficient specificity to serve as therapeutic endpoints". They have it backwards: it is the TSH and FT4 tests and reference ranges that are insensitive and non-specific indicators of the patient's' T3 status. The guidelines thus violate one of the important guiding principles in medicine. Clinical medicine is "the study and practice of medicine in relation to the actual patient; the art of medicine as distinguished from laboratory science" (10). Because of the tremendous complexity of the body and the great differences among individuals, physicians must attend to the patient's condition first and to laboratory test results second. In thyroidology what ultimately matters is the amount of T3 effect within cells, and there is no blood test for this. The practical result of these anti-clinical guidelines is that physicians, including endocrinologists, completely ignore the patient's signs and symptoms and rely solely on the TSH test. This naturally produces widespread underdiagnosis and undertreatment; not to mention many dissatisfied patients. Thus in recent decades thyroid patient advocacy organizations have multiplied as have personal websites that oppose the TSH-T4 paradigm. Most patients at these sites testify that their quality of life was not restored until a physician treated them in spite of their "normal" TSH and FT4 levels, and/or with sufficient T4/T3 therapy to eliminate their symptoms regardless of their TSH level. Because such care is so hard to obtain, many patients resort to self-diagnosis and treatment.

My experience corresponds to these patients' reports. I find that most persons who are suffering from insufficient T3-effect do not have an elevated TSH. Their hypothyroidism is caused by insufficient TSH production (central partial hypothyroidism) and/or by some form of partial thyroid resistance (11). A large percentage of the population have one or more variants of their deiodinase enzymes that cause reduced T4-to-T3 conversion and hypothyroid symptoms in spite of "normal" thyroid tests (12). Almost every patient that I have seen who is on TSH-normalizing T4 therapy (TSHT4Rx) has had persisting hypothyroid symptoms, some to the point of incapacitation. Studies show that TSHT4Rx does not eliminate hypothyroid symptoms (13,14,15,16). It produces lower FT3 levels than in healthy controls (17,18). It produces the same low 24-hour urine T3 levels as in untreated hypothyroid patients (19).

Because the TSH test can mislead, the guidelines fall back upon the FT4 test to diagnose hypothyroidism. Amazingly, the guidelines' authors say nothing about the nature of their definitive test's reference range. They apparently assume, as do most

physicians, that the hormone ranges on laboratory reports represent "the most normal of normals"— perfect hormone sufficiency. In fact, these ranges are just broad statistical measures (2 standard deviations from the mean) that include the middle 95% of a group of "apparently healthy" persons. The subjects are not screened for signs or symptoms of insufficient hormone effect—so they actually just represent the entire population. It is thus by design that 95% of all hormone tests come back as "normal". Only the lowest 2.5% are "low". If you're at the 5th percentile, if 95% of persons have higher levels, you are still "normal". This misunderstanding of the ranges corrupts all of endocrinology, but there is an additional, unique problem with the FT4 and FT3 ranges. Since laboratories are told that a normal TSH is "euthyroidism", many include physician-ordered tests done on clinic and hospital patients, if the patient's TSH is normal (20). So the FT4 and FT3 ranges at most labs are thyroid patient ranges. This illegitimate practice further reduces the symptom-unscreened lower limits for FT4 and FT3, causing more underdiagnosis. (See table.) The resulting FT4 and FT3 ranges are extremely broad; the lower limit is less than half the upper limit. Such a broad population range cannot identify major deviations from a person's usual thyroid levels (21). Consider that a person will experience significant changes if his/her usual FT4 and/or FT3 levels are halved or doubled—yet may still test as "normal".

Symptom-unscreened FT4 ranges:	
Blood donors/non-patients:	1.0 to 1.65ng/dL
Clinic/hospital patients:	0.8 to 1.8ng/dL
Symptom-unscreened FT3 ranges:	
Blood donors/non-patients:	2.5 to 4.3pg/ml
Clinic/hospital patients:	2.0 to 4.4pg/ml

What should the TSH, FT4 and FT3 levels be in persons who are well-treated on T4 therapy? Only one study attempted to answer that question. Four experienced clinicians adjusted the T4 doses of 148 long-term primary hypothyroidism patients based upon clinical criteria alone—signs and symptoms (22). For those patients judged to be clinically euthyroid, the resultant reference ranges were as shown in the table. The TSH treatment range was least like the conventional population range. The TSH was low or suppressed in half of the clinically-euthyroid patients. The FT4 treatment range was 50% higher than the conventional range. Only the FT3 treatment range was nearly identical to the conventional range. If T4 monotherapy is to be guided by any test, it should be the FT3. Laboratories should report these ranges for persons on T4 therapy, pending more studies.

Clinical vs. Conventional Ranges	
TSH:	<0.1-13.7 vs. 0.35-5mIU/L
FT4:	12-36 vs. 9-25pmol/L
FT3:	3.0-8.6 vs. 2.9-8.9pmol/L

The primary impediment to effective thyroid replacement therapy is physicians' belief that a low TSH with treatment indicates thyrotoxicosis. However, once-daily thyroid replacement therapy with T4 or T4/T3 is an unnatural intervention into a complex system. We cannot expect the HP system to react to it exactly as it does to the thyroid gland's own output. In fact it overreacts to the unnatural peak levels. Many studies have shown that, in primary hypothyroidism, the T4 doses required to relieve symptoms and reverse metabolic changes often produce a low TSH. The Royal College of

Physicians acknowledges that a correct dose of T4 may produce a "normal or below normal serum (TSH) concentration" (23). Others have stated, "Some patients achieve a sense of wellbeing only if free T4 is slightly elevated and TSH low or undetectable. The evidence that this…is harmful is lacking…and it is not unreasonable to allow these patients to take a higher dose if T3 is unequivocally normal" (24). However, due to the guidelines' endorsement of the TSH to guide treatment, physicians refuse to prescribe T4 or T4/T3 doses that produce a low TSH. Indeed, once the TSH is normal, the physician attributes the patient's signs and symptoms to another cause. Since the paradigm is anti-clinical, it is immunized against clinical failure.

The professional associations' guidelines recommend against prescribing T4/T3 combination therapy claiming that the existing studies show insufficient benefit over T4 monotherapy. However, the T4/T3 doses were not adjusted by clinical criteria. They were either TSH-normalizing doses or the product of arbitrary T3-for-T4 substitutions. Still, they did show that T4/T3 therapy is safe and beneficial, often produces better results, and is usually preferred by patients. The guidelines also recommend against prescribing natural desiccated thyroid (NDT), based upon no evidence. NDT is simply a convenient T4/T3 combination. Pharmaceutical-grade porcine NDT tablets meet the same standards for consistency of T4 and T3 content as do synthetic T4 and T3 tablets. NDT was the standard therapy until the 1970s. Recent studies have shown that NDT is safe and has advantages over T4 monotherapy (25,26,27). T3-containing regimens are not dangerous; they are simply more effective T4 monotherapy. What matters is the dose.

Clinical thyroidology is actually much simpler than the TSH-T4 laboratory-based scheme—and it actually works. The physician simply needs to attend to the patient's signs and symptoms first and foremost. If the patient has signs and symptoms consistent with hypothyroidism, and especially if the FT4 and/or FT3 are relatively low, the physician should offer the patient a trial of gradually-increasing T4 or T4/T3 doses adjusted by clinical criteria. Together, they can see whether the therapy eliminates the signs and symptoms without producing evidence of overdosing. If persistent benefits are obtained, the trial confirms that the patient was suffering from hypothyroidism. If a higher dose brings no benefits and/or causes problems, it should be lowered. This is the rational and ethical way to practice thyroidology.

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1. Garber JR, Cobin RH, Gharib H, et al.; American Association Of Clinical Endocrinologists And American Thyroid Association Taskforce On Hypothyroidism In Adults. Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18(6):988-1028. https://www.aace.com/files/hypothyroidism_guidelines.pdf
2. Skinner GRB, *Diagnosis and Management of Hypothyroidism*. Birmingham: Louise Lorne; 2003.
3. Skinner GRB, Holmes D, Ahmad A, Davies A, Benitez J. Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients, J Nutr Environ Med 2000;10:115-124. doi: 10.1080/13590840050043530
4. Lindner, HH. Cortisol Deficiency. http://www.hormonerestoration.com/Cortisol.html
5. Kuhn T. *The Structure of Scientific Revolutions*. Univ. of Chicago; 1962.

6. Evered D, Young ET, Ormston BJ, Menzies R, Smith PA, Hall R. Treatment of Hypothyroidism: A Reappraisal of Thyroxine Therapy. Br Med J. 1973;3(5872):131-134. PubMed Abstract
7. Stock JM, Surks MI, Oppenheimer JH. Replacement dosage of L-thyroxine in hypothyroidism. A re-evaluation. N Engl J Med. 1974;290(10):529-533. PubMed Abstract
8. Saberi M, Utiger RD. Serum Thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. J Clin Endocrinol Metab. 1974;39(5):923-927. PubMed Abstract
9. Maeda M, Kuzuya N, Masuyama Y, Imai Y, Ikeda H. Changes in serum triiodothyronine, thyroxine and thyrotropin during treatment with thyroxine in severe primary hypothyroidism. J Clin Endocrinol Metab. 1976;43(1):10-17. PubMed Abstract
10. Stedman's Medical Dictionary. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006.
11. Tjørve E, Tjørve KM, Olsen JO, Senum R, Oftebro H. On commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues. Med Hypotheses. 2007;69(4):913-921. PubMed Abstract
12. Gereben B, Zavacki AM, Ribich S, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev. 2008;29(7):898-938. PubMed Abstract
13. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57(5):577-585. PubMed Abstract
14. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid. 2007;17(3):249-258. PubMed Abstract
15. Wekking EM, Appelhof BC, Fliers E, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005;153(6):747-753. PubMed Abstract
16. Pearce EN. The Poor Health-Related Quality of Life Associated with Hypothyroidism Is Not Completely Reversed by 6 Months of Levothyroxine Treatment. Clinical Thyroidology. 2016;28(7):200-202. doi:10.1089/ct.2016%3B28.200-202 .
17. Woeber KA. Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. J Endocrinol Invest. 2002;25(2):106-109. PubMed Abstract
18. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Is pituitary TSH an adequate measure of thyroid hormone-controlled homoeostasis during thyroxine treatment? Eur J Endocrinol. 2013;168(2):271-280. PubMed Abstract
19. Baisier WV, Hertoghe J, Eeckhaut W. Thyroid Insufficiency. Is TSH Measurement the Only Diagnostic Tool? J Nutr Environ Med. 2000;10(2):195-113. doi: 10.1080/13590840050043521
20. Roche Diagnostics GmbH, Reference Intervals for Children and Adults, Elecsys Thyroid Tests, 2009. (no longer avail. at Roche.com) Reposted by author.
21. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068-72. PubMed
22. Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986;293(6550):808-810. PubMed Abstract
23. Vanderpump MPJ, Ahlquist JAO, Franklyn JA, Clayton RN, on behalf of a working group of the Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. BMJ. 1996;313(7056):539-544. PubMed Central
24. Toft AD, Beckett GJ. Thyroid function tests and hypothyroidism. BMJ. 2003;326(7384):295-296. PubMed Abstract
25. Baisier WV, Hertoghe J, Eeckhaut W. Thyroid insufficiency. Is thyroxine the only valuable drug? J Nutr Environ Med. 2001;11(3):159-166. doi: 10.1080/13590840120083376
26. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study. J Clin Endocrinol Metab 2013;98:1982-90. PubMed Abstract
27. Pepper GM, Casanova-Romero PY. Conversion to Armour Thyroid from levothyroxine improved patient satisfaction in the treatment of hypothyroidism. J Endocrinol Diabetes Obes 2014;2(3): 1055. http://www.jscimedcentral.com/Endocrinology/endocrinology-2-1055.pdf