Reducing the Scope of Guidelines and Policy Statements in Hypothyroidism

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Abstract *Although practice guidelines and policy statements on hypothyroidism are generally effective, many patients do not respond to the prescribed treatment. Significantly, clinicians routinely face the conundrum of either following the guidelines, which are ineffective, or ethically prescribing alternative (but proscribed) treatment, which might bring and has brought severe punishment by boards of medicine or medical councils. This paper argues: (1) Current guidelines are based on (a) suppression of evidence that other scientific disciplines would routinely accept and (b) language and logic that the American Medical Association-endorsed tome, Evidence-Based Medicine: Logic and Critical Thinking in Medicine, deems unsound; (2) Reduction in scope of the hypothyroidism guidelines is based on clear definitions, sound logic, text analysis, mathematical analysis, and scientific methodology; (3) Alternative treatments, which are supported by decades of research and practice, should not be proscribed for patients with continuing symptoms of hypothyroidism; and (4) This reduction in scope allows clinicians to treat successfully and ethically. The number of people who do not respond to the prescribed treatment is estimated to be as high as 1.7 million people in the United States, 300,000 people in the United Kingdom, and millions more internationally – 90 percent of whom are women.*

Introduction

Multiple causes, mostly non-medical scientific deficiencies, combine to keep patients suffering from the continuing symptoms of hypothyroidism in spite of endocrinology directed care, diagnosis, thyroxine-only therapy, and proscriptions. Patient counterexamples demonstrate this suffering is not necessary. Patients can regain their active, attractive lives via endocrinology-proscribed replacements for the operative hormone, triiodothyronine (T3), of unacknowledged and unaddressed physiology. These proscriptions preclude proper care for up to 1.7 million Americans, 300 thousand in the UK, and millions more internationally, most of whom are women.[1]

Enforcement of medical practice guidelines and policy statements (hereafter guidelines) encourages the delivery of quality medical services. But if these directives are not correct, as many are,[2-4] their enforcement discourages quality medicine through intimidation. Then the clinicians often over-comply[5,6] with the proscription against the needed hormone replacement. When the patients' symptoms are not mitigated, clinicians often use suggested excuses for nonspecific symptoms[7] or functional somatoform disorders.[7,8] This imposition places clinicians in the position of either violating medical ethics[9] or risking severe punishment from their board of medicine or medical council.

This scenario is complicated by imprecise definition of "hypothyroidism," ignored medical science, evidence suppression by evidence-based medicine (EBM), unscientific

study conclusions, and further considerations for not banning the proscribed hormone replacement.

Scope of Review

First, this review explores the background, case law, definitions, the greater thyroid system (GTS), the lack of capability, patient counterexamples, and EBM.

Second, it examines the meta-analyses of several studies of the effectiveness of combination thyroxnine (T4) triiodothyronine (T3) studies using literature searches, subject selection, dose selection, statistical studies, and conclusions.

Third, it investigates other considerations for not banning triiodothyronine (T3) replacement therapies: medically accepted challenge, de-challenge, re-challenge (CDR) test logic, differential diagnostic protocol, serum T3 variation, heart attacks, and bone loss.

Surrounding Environment

Reducing the physiological scope of the hypothyroidism guidelines requires knowledge of influences outside of medicine, law, language, physiology, counterexamples, and EBM.

Case Law Showing the Impact of Government Enforcement of Guidelines

Medical boards/councils often discipline clinicians who do not follow the treatment standards. When clinicians run afoul of custom and medical practice guidelines, they invite investigation, fines, and loss of license.[5,6] The US Supreme Court recognized the fear of investigation and punishment in *Goldfarb v. Virginia State Bar*.[5] Even without a history of adverse action by guideline enforcers, the fear instilled was sufficient to make the guideline effectively mandatory. A clinician who treats a patient in a manner that is not prescribed by medical associations has either exceptional courage or temerity.

The study of hypothyroidism shows a few clinicians have effectively treated patients by violating medical guidelines and customs. Although an argument could be made about their temerity, it is more likely that their behavior arose from ethical feelings and a greater sense of ethics and duty to ease their patients' suffering and to change that which is contrary to the best interests of the patient.[9]

A US federal appeals court cited *Goldfarb* in a case against the American Medical Association (AMA) by chiropractors represented by *Wilk*.[6] The AMA created two policy statements. The first statement deemed any professional corporation with unscientific practitioners was unethical. The second statement declared chiropractic an unscientific profession. After years of litigation, the court found that chiropractic helped patients and was scientific. However, during the 15 years of litigation, patients suffered because the potentially enforced standard treatments were based on faulty science and opinion. This study will show an analogous situation exists today surrounding potentially enforced hypothyroidism guidelines.

Definitions and Greater Thyroid System

Two definitions of hypothyroidism are commonly used.[10] The proper definition, generally used by medical professionals, the "clinical consequences of deficient secretion by the thyroid gland," implicates the thyroid gland primarily and the rest of the hypothalamus-pituitary-thyroid (HPT) axis secondarily. The other definition, "clinical consequences of deficient thyroid hormones in the body," implicates the whole GTS, Figure 1, including the HPT axis (the upper half) and the *post-thyroid physiology* (the lower half).

Two physiologically different definitions produce confusion, misdiagnosis, and over-compliance. The first definition is the basis for thyroid function tests. But the symptom-oriented second definition is used by patients when their symptoms of hypothyroidism continue. Thus, patient-clinician conversations are confusing, aggravating, and rarely productive.

The potential for medical prosecution[5,6] forces over-compliance. Consequently, T3 is not prescribed even when needed by deficient post-thyroid physiology.

Guidelines[11-18] focus on the behavior of the thyroid gland by assaying (1) its input, the thyroid-stimulating hormone (TSH); (2) its

primary output, thyroxine (T4); and (3) its internal operation via antibodies. Often only TSH is assayed. Post-thyroid physiology is given so little attention[19-22] that the guidelines neither include nor disclaim the following:

1. Peripheral conversion sites of T4 to T3.[20]
2. Peripheral cellular hormone receptors of T3.[19]
3. Intracellular use of T3 to regulate the energy-producing respiratory cycle.[21]
4. Clearance of serum communicated hormones including T3. (Urine measurements of T3 require serum clearance.[22])

Figure 1 (p.78) shows the relationships among the thyroid-related glands and functions. Brain signals excite the hypothalamus to produce the thyroid-releasing hormone (TRH). The pituitary gland compares TRH with circulating T3 and T4 and produces the thyroid-stimulating hormone (TSH). The thyroid responds to the TSH by producing all of the thyroxine, T4, and 20 percent of the required triiodothyronine, T3. These facts are acknowledged by the endocrinology establishment, without qualification.

The peripheral conversion[20] takes in T4 from the thyroid gland and produces T3 and reverse T3 (rT3) by removing an iodine atom from the thyroxine molecule. Although 20 percent of the body's T3 is produced by the thyroid gland, 80 percent is produced elsewhere, notably the liver (60 percent). The conversion sites on the heart, brain, and other organs produce the other 20 percent.

Peripheral cellular hormone reception was discovered in 1967.[19] It accepts T3 for intracellular use. This T3 up-regulates the respiratory cycle in the mitochondria,[21] which produces energy and by-products of carbon dioxide and water from blood sugar and oxygen. The T3 and water are then cleared from the blood by the kidneys while the lungs (not shown) clear the carbon dioxide. The clearance action by the kidneys is proven by the fact that T3 can be measured in the urine.[22] (Without clearance the hormones would accumulate, and soon the body would be thyrotoxic.)

Note: these operations depend upon a delicate chemical infrastructure, which must produce T3 and T4 in precise amounts. Both T3 and T4 product descriptions, for example, list many requirements and interactions,[23,24] including adequate adrenal support. Although some have claimed that T4 is the active ingredient inside the nucleus, a prominent endocrinologist claimed the following in a 2005 Food and Drug Administration meeting: *"T3 is the active ingredient, and it's the thing that accounts for the thyroid hormone action. As I've been reminded many times, there are no intracellular events that we know that can be described by T4 at the level of the nucleus. Only T3. T4 is not the active compound. Likewise, the site of action is in the nucleus."*[25]

A mountain of evidence suggests that the symptoms of hypothyroidism are impacted by the GTS. To answer the calls from within endocrinology and medicine[26] for greater clarity, this evidence needs to be included in the discussion. As will be shown, this evidence has been suppressed.

Lack of Compatibility

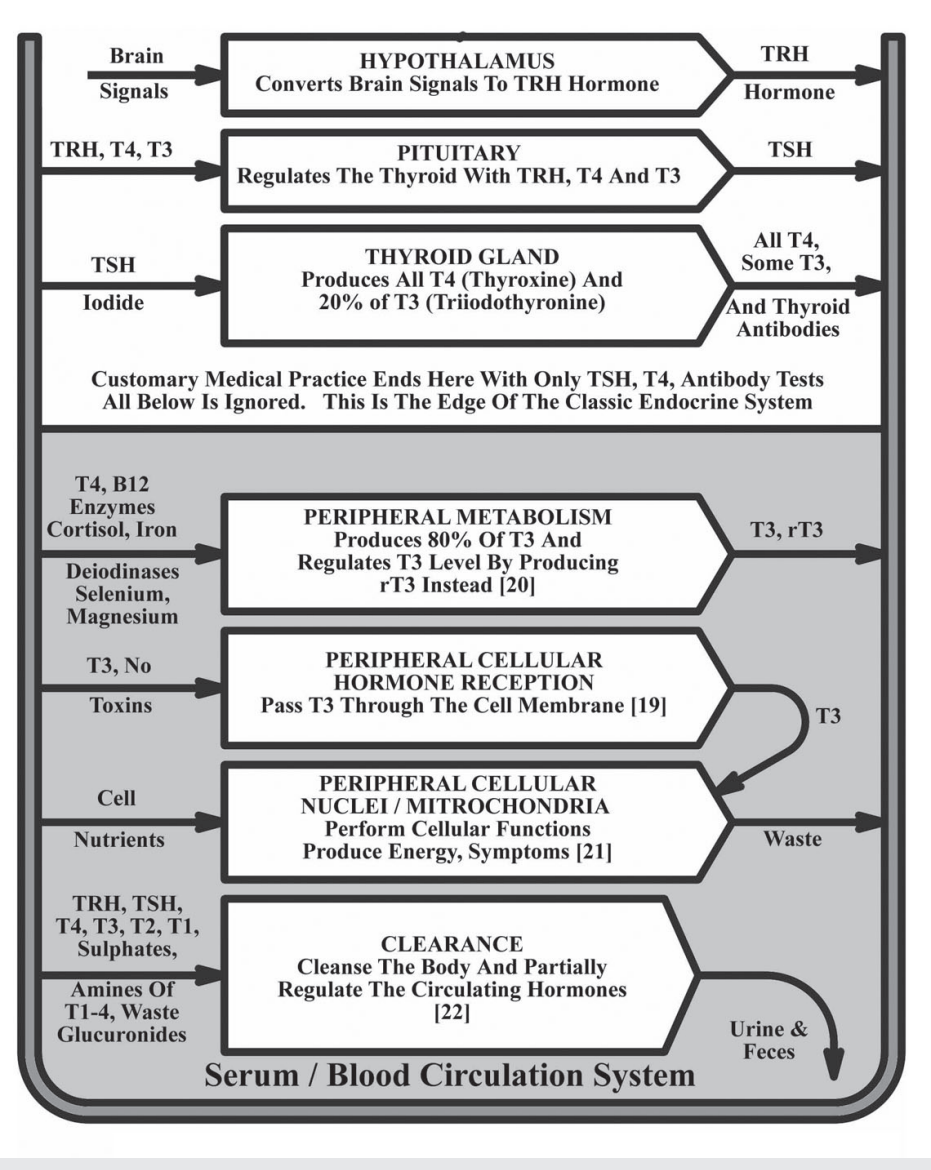
The lack of recognition of the post-thyroid physiology and lack of appreciation for the effects of post-thyroid deficiencies creates a compatibility issue between established hypothyroidism care and the care for post-thyroid deficiencies. These deficiencies reduce the connection between thyroid function and symptoms of hypothyroidism. This disconnection diminishes the value of thyroid function tests and begs the question: Should we be concerned for chemical hyperthyroidism (primarily over-suppressed TSH) without clinical hyperthyroidism? This lack of compatibility was observed:

"*It is of special interest that some patients with severe biochemical hypothyroidism had only mild clinical signs, whereas other patients with minor biochemical changes had quite severe clinical manifestations. Thus, we assume that tissue hypothyroidism at the peripheral target organs must be different in the individual patient.*[27]

Inadequate Diagnostics

Post-thyroid or tissue deficiencies are not only not assayed but dismissed, and their as-

Figure 1. Greater Thyroid System



says often proscribed. But the post-thyroid physiology should be assayed because it separates the thyroid diagnostics from the production of symptoms by several functions. For example, if only TSH is assayed, then there are four functions between the pituitary gland and the production of symptoms: the thyroid gland, peripheral conversion of T4 to T3, peripheral cellular hormone reception of T3, and mitochondria use of T3 plus clearance by the kidneys. If TSH and T4 is assayed, then three functions are ignored: peripheral conversion, peripheral cellular hormone reception, and mitochondria plus clearance by the kidneys.

Since these functions can be deficient (or excessive clearance) they can diminish the T3 up-regulation of the respiratory cycle, reduce the body's energy production, and increase the production of symptoms.

Obviously with the dismissal of post-thyroid assays, clinicians attempting to care for patients with the continuing symptoms of hypothyroidism do not have sufficient information. This lack of information makes the existence of counterexamples reasonable.

Counterexamples

Science has long recognized counterexamples as valuable clues. Counterexamples bring attention to outliers and encourage the reexamination of hypotheses. Consider Earnest Rutherford. In 1911 at his suggestion, Hans Geiger and Ernest Marsden created a simple experiment, shooting alpha particles through a gold foil. As predicted, most of the alpha particles traveled straight through the foil. However, to their great surprise, they discovered that a very tiny percentage was deflected. A small fraction was deflected at very large angles. The counterexamples–the one in 10,000 electrons that did not fit the theory–forced Rutherford to reexamine a cherished paradigm. By paying attention to counterexamples, Rutherford and his colleagues ushered in a new era for atomic physics.

Counterexamples are an integral part of sciences because all sciences are based upon observations, which are not exhaustive. Existing outliers may not be noticed initially and may become a counterexample later.[28,29] Indeed, the lack of counterexamples is the best evidence of good science.[30] Contrary to medicine, the proscription of all T3-containing therapies has many patient counterexamples.

Evidence-Based Medicine

EBM promotes meta-analyses of randomized clinical trials as the most truthful, and hence the highest form of evidence. Consequently, lower forms of evidence, including counterexamples,[31,32] are routinely dismissed: *If the study wasn't randomized, we'd suggest that you stop reading it and go on to the next article*.[31]

Meta-Analyses on Combination T3-T4 Therapies

Meta-analyses or reviews examine a facet of medicine. These reviews start by searching literature and examining the selected literature for subject selection and continue with experimental methods, data analyses, and conclusion. All of these must logically support the current medical guidelines on hypothyroidism. They do not.

Literature Search and Selection

The literature searches taken by three meta-analyses[33-35] considered only 11, 9, and 9 studies respectively out of more than 500 relevant studies.[33] Thus, the investigations were reduced by 98 percent. Among the studies *not* considered were:

1. Post-thyroid physiology.[19-22]
2. Warnings that T4-only therapy failed to mitigate the symptoms of hypothyroidism in some patients;[36]
3. Verification of euthyroid hypometabolism, finding symptoms similar to hypothyroidism, and consequential production of patient counterexamples;[37]
4. Studies disagreeing with the meta-analyses' conclusions;[38,39]
5. T3 being more active than T4,[40] which suggests the meta-analyses examined a special situation, subjects whose post-thyroid physiology was *not* deficient; and
6. Study and proper treatment of patients failed by endocrinology, finding symptoms similar to hypothyroidism, and consequential production of patient counterexamples.[22]

The dismissal of applicable literature renders the analysis and conclusions of the meta-analyses dubious as demonstrated in the following three sections.

Subject Selection in T3/T4 Study RCTs

The first logical basis for the study conclusion is subject selection. The subject selections of most hypothyroidism studies are those with thyroiditis and/or thyroid destruction by surgery or radioiodine therapy.[33] Therefore, all of these subjects need T4. There is no note of subjects with post-thyroid deficiency and consequently would require T3.

Dose Selection in T3/T4 Study RCTs

The second logical basis for a conclusion is the actions taken, i.e., the doses given to the subjects. Most subjects received T3 below its adult starting dose of 25 mcg/day.[23] The subjects in RCTs received T3 in some ratio to the withdrawn T4. The various RCTs used T4:T3 ratios of 14:1, 10:1, and 5:1. Subsequent research by the US National Institutes of Health (NIH) found the therapeutic equivalence was 3:1.[41] Thus, most of the subjects were under treated with the T3/T4 combination. In light of the NIH finding, the conclusion that T3 therapy is never needed is invalid.

Implications of the Statistical Analyses of the Studies

The third logical basis for a conclusion is the analysis of the data. All three meta-analyses[33-35] used basic statistical analyses, which find mean and standard deviation. These averaging techniques mute the recognition of the low occurrence rate phenomenon.[42] Those with post-thyroid deficiencies have a low occurrence rate.[1] Thus, their impact on the study is minimized. Consequently, their support of the conclusion is also limited.

Conclusion of Meta-analyses of T3/T4 Study RCTs

The good news for the majority of patients is the meta-analyses[33-35] do support the T4-only therapy for deficient secretion by the thyroid gland. The bad news for endocrinology is there is no factual support in the meta-analyses to apply the T4-only therapy to post-thyroid physiology because the meta-analyses:

1. Ignore approximately 98 percent of relevant literature, including studies[19-22,35-41] and patient counterexamples;[22,37,43]
2. Do not reconcile their conclusions with contradictory facts;
3. Select subjects who probably did not have post-thyroid deficiencies;
4. Provide combination therapies of lower therapeutic value than T4-only therapy; and
5. Use statistical methods that reduce the impact of low occurrence rate phenomenon.

Since the meta-analyses do not support the T4-only therapy for the post-thyroid physiology, unqualified proscriptions for T3-containing therapies in practice guidelines are not valid. This reduction in scope of sciences is not unique. The scope of Newtonian physics, the study of motion, was limited by Einstein's Theory of Relativity because Newtonian physics does not account for the limiting effects of traveling near the speed of light.

Reduction in Scope Specifics

With the above, when logic and critical thinking is applied to practice guidelines, they are found in error and consequently lacking truth when applied to post-thyroid deficiencies.

Text Analysis

The texts of guidelines[11-18] must support the proscription of T3-containing therapies. However, a text analysis[44] finds none address the potential for post-thyroid deficiencies causing the symptoms of hypothyroidism. They only consider the thyroid gland and possibly functionally preceding glands.

Illogical Proscriptions

A recent hypothyroidism statement[18] and a recent guideline[12] have become more restrictive as shown by the 12 quotations below. Each one is rebutted using principles found in AMA endorsed *Evidence-Based Medicine: Logic and Critical Thinking in Medicine*:[45]

1. *Patients with suspected primary hypothyroidism should only be diagnosed with blood tests including measurement of TSH.*[18] Two questions immediately arise:

a. If the patient's TSH is below the hypothyroidism level, as it would be with euthyroid hypometabolism,[37] can primary hypothyroidism be suspected from their common symptoms? This is not clear.[26,45]

b. Who will suspect primary hypothyroidism, the clinician or the medical council/ board? The potential for discipline[5,6] is not clear.[26,45]

2. *Patients with primary hypothyroidism should be treated with T4 using levothyroxine tablets alone*[18] is a requirement based upon suppressed evidence[45] for coexisting post-thyroid deficiencies[19-22,36-40] and consequently oversimplifies the prescription.[45]

3. *There is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests within the reference ranges*.[18] This position is refuted by the greater activity of low serum T3,[40] the existence of euthyroid hypometabolism,[37] the proper care of endocrinology's failures,[22] medical science,[19-22,36-40] and the experiences of patient counterexamples.[22,37,43] "No indication" stems from the suppression of evidence.[45]

4. *In patients with suspected primary hypothyroidism there is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests initially within the normal range*.[18] This position is also refuted by the existence of euthyroid hypometabolism[37] and is an oversimplification and a suppression of evidence.[45]

5. *The College does not support the use of thyroid extracts or thyroxine and T3 combinations without further validated research published in peer-reviewed journals.*[18] This position is unassailable only if the evidence found in peer-reviewed journals, numerous papers, and T3 therapies is suppressed.[45]

6. *Clinical scoring systems should not be used to diagnose hypothyroidism*.[18] However, clinical scoring has demonstrated the existence of non-thyroid problems,[27] but salient evidence is ignored and suppressed.[22,45]

7. *Tests such as clinical assessment of reflex relaxation time, cholesterol, and muscle enzymes should not be used to diagnose hypothyroidism*.[12] This statement is not clear[26,45] since the definition[10] of "hypothyroidism" is not stipulated. Also, these tests, as well as basal temperature[46] and basal metabolism rate, indicate post-thyroid deficiencies. Although not definitive, these tests provide a viable rationale for further examination.[46]

8. *Serum total T3 or assessment of serum free T3 should not be done to diagnose hypothyroidism*.[12] This guidance is not clear[10,26,45] and suppresses the evidence of potential T3 deficiency.[45]

9. *Thyroid hormones should not be used to treat symptoms suggestive of hypothyroidism without biochemical confirmation of the diagnosis*.[12] This guidance ignores the potential for euthyroid hypometabolism[22,37] or any other post-thyroid physiology deficiency, which often require indirect testing of cellular energy production.[21] Again evidence is suppressed and clarity is lacking.[26,45]

10. There is no evidence to support using desiccated thyroid hormone in preference to T4 monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism.[12] This stunning assertion contradicts a study of treating endocrinology's failures[22] and decades of successful prescription of desiccated thyroid.[46] Evidence has been suppressed again.[45]

11. The evidence does not support using T4 and T3 combinations to treat hypothyroidism.[12] The suppression evidence in meta-analyses per EBM[33-35] makes this fallacious[45] position possible.

12. *Patients with hypothyroidism should be treated with T4 monotherapy*[12] has two problems. Since the definition[10] of "hypothyroidism" is not stipulated, the statement is not clear.[26,45] Furthermore, this statement does not consider the potential for coexisting deficiencies in the post-thyroid physiology, which requires T3 replacement.

The 12 rebuttals above stem from medical practice's refusal to address the role of post-thyroid physiology. Far from being based on all available evidence, the guidelines governing the diagnosis and treatment of hypothyroidism ignore hundreds of studies, papers, and anecdotal evidence that stretch back approximately 100 years.

Absurdity

The T3-hormone basis of the post-thyroid physiology[19-21,40] plus counterexamples[22,28-30-,37,43] makes proscriptions against T3-containing therapies for post-thyroid deficiencies absurd, since the philosophy of hormone replacement is to replace the deficient hormone.[47] But, the enforcement[5,6] of guidelines makes this absurdity mandatory. This situation invites this admonition: *No legislature directs courts to follow the plain meaning of a statute when it leads to absurd results*.[48]

Further Considerations for Not Banning T3

The prescription of T3 containing hormone replacements is also adversely influenced by opinion and false diagnostics. These

misconceptions must be defeated to allow clinicians the freedom to properly treat post-thyroid deficiencies.

Challenge, De-Challenge, Re-challenge (CDR) Testing

A heightened form of counterexamples is the medically accepted CDR (challenge, de-challenge, re-challenge) test.[49] Consider a woman who tested negative for hypothyroidism but benefitted from T3 treatments. She was so fatigued that she found minimal household chores exhausting. Her clinician noted that the thyroid was low but in the normal range. Soon afterwards she fainted, fell, and broke her leg. The emergency room clinician, concerned about the possibility of myxedema coma, recognized the thyroid-related problem and prescribed T3.

1. Challenge: In the emergency room she was too weak to lift her ankle-to-hip cast, so she had to be admitted. Ten days after receiving T3, her vitality returned and she could be released.
2. De-challenge: After twenty years of receiving T3, the woman's new clinician refused to prescribe T3, and her symptoms quickly returned.
3. Re-challenge: She found another clinician who did prescribe T3, and her symptoms disappeared.

This woman apparently suffered from euthyroid hypometabolism.[37] This far-from-isolated example powerfully contradicts the meta-analyses[33-35] claim that T3 is ineffective. This example also claims T3 is effective for some patients.

Excuses for Failure versus Differential Diagnostic Protocol

When the T4-only therapy fails, clinicians offer excuses that the patient has "non-specific symptoms" or "functional somatoform disorders."[7,8] But, these excuses are not properly based because these untestable diagnoses can only be made after all physical possibilities have been eliminated. This is a fundamental requirement of the logic of differential diagnoses. Obviously, the process of elimination is only successful if *all* of the potential unknown causes are eliminated by testing. The completeness of the list of unknown causes depends upon the state of medical science.[50] These excuses are improper since medical science discloses the four post-thyroid functions[19-22] shown in the gray area of the GTS, Figure 1, which are *not* currently tested, directly or indirectly.

Serum T3 Variation - An Alleged T3 Danger

Endocrinology claims T3 treatment is dangerous because it creates excessive variation of T3 in the serum or blood.[7] On the basis of this claim, testing on human subjects has been proscribed because it would be unethical.[51] However, the claim that T3 has a half-life[23] suggests the exponential decay analysis associated with radioactive material can be used. The goal of this analysis (see Appendix 1 for a mathematical derivation) is to demonstrate that the T3 variation is well within the variation allowed by the "normal" range for serum T3 and potentially as low as the circadian variation.[52] Then by appropriate titration, the variation is always within the normal range.

The "normal" range maximum-to-minimum ratio is 2.5:1. A strong circadian variation is 1.2:1.[52] The analysis results for various half-lives versus numbers of treatments per day are shown in **Table 1** (p.83). It is quite possible by taking T3 a few times a day to have a variation substantially less than the "normal" range and can be as low as circadian variation, particularly since the half-life for T3 is often claimed to be 2.5 days.[23] This analysis is consistent with the successful use of T3 by patient counterexamples. Please note that therapy requirements must also be met.[23,24]

T3 Treatment's Alleged Heart Attack Danger

Excessive T3 has also been associated with heart attacks. A long-term study of 1,569 patients treated properly with establishment-dismissed desiccated thyroid showed a significantly lower rate of heart attacks than found in the five thousand sub-

Table 1. Maximum to Minimum Ratios (R) for Various Half-Lives and Doses Per Day

T3 Half-Life (Days) (h)	Max/Min Ratio for n=1 Dose per Day	Max/Min Ratio for n=2 Doses per Day	Max/Min Ratio for n=3 Doses per Day	Max/Min Ratio for n=4 Doses per Day
0.75	2.52	1.587	1.361	1.26
1.0	2.0	1.414	1.26	1.189
1.5	1.587	1.26	1.167	1.122
2.0	1.414	1.189	1.122	1.091
2.5	1.32	1.149	1.097	1.072

ject Framingham study.[46] Based upon the Framingham study, there should have been 22 heart attacks among the 1,569 patients instead of only four. Furthermore, patients who quit taking desiccated thyroid had heart attacks more often, nominally at the Framingham rate.

The improper prescription for T3 must also be considered since the GTS is dismissed and not tested. Among the nonspecific symptoms of hypothyroidism are those of fatigue[53] and low body temperature.[54] There is doubt that needs rectifying.

T3 Treatment's Bone De-Calcification

Bone de-calcification has been associated with hyperthyroidism and associated excessive T3 levels. However, excessive serum T3 levels are an indirect measure of intracellular behavior. As Figure 1 demonstrates, there are still more factors to consider, such as peripheral cellular hormone reception and the chemistry required for intracellular operation. A study found cellular receptor defects could produce bone loss even when the subject/patient has normal hormone levels.[55] Again, the embedded assumption by endocrinology that *post-thyroid physiology* never fails[7] creates incorrect paradigms and guidelines. In any case, valid or informed consent requires an answer to living an active, attractive life with calcium supplements or remaining fatigued and almost lifeless. That choice should be obvious.

Conclusion

And if no randomized trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there. [32]

The following factors contribute to the misdiagnosis of millions of patients, mostly women, who suffer from the symptoms of hypothyroidism in spite of therapy.[1] Taken together, they are a breath-taking indictment of the hypothyroidism practice. Patients suffering from the untreated chronic symptoms of hypothyroidism are not suffering for the lack of scientific medical facts. They are suffering from endocrinology's cavalier disregard of the basics of science:

1. Overemphasis on the thyroid gland and preceding glands
a. The overemphasis has focused testing on thyroid gland deficiencies and has ignored the potential impact of post-thyroid deficiencies.
b. Physiologically different definitions for "hypothyroidism" blur this distinction and create confusion.
c. The ignored post-thyroid physiology rationalizes the existence of patient counterexamples as shown by the GTS.
d. Post-thyroid functions must be considered in differential diagnostics.
e. The existence of post-thyroid physiology reduces the valid application of excuses for failing to mitigate the symptoms of hypothyroidism.

2. Errors of EBM
a. Reliance on EBM encourages and condones the suppression of most medical studies.
b. This suppression of evidence, especially counterexamples, runs counter to good scientific practices and necessarily leads to false inferences and conclusions.
c. The statistical analysis used in hypothyroidism meta-analyses mute the existence of counterexamples since their occurrence rate is low.
d. Strikingly, the muting of counterexamples also does not support the absolute nature of the T4-only guidelines.

3. Coerciveness of the guidelines
a. Guidelines are effectively mandatory, placing clinicians in a difficult position when the T4-only therapy fails. They must choose between their medical ethics and the potential loss of their career.
b. Clinicians who understandably refuse to violate the guidelines are left to make excuses that are not supported by medicine's differential diagnostic protocol and probably medical science.
c. Most clinicians misdiagnose their suffering patients and/or prescribe treatments that do little to alleviate symptoms and nothing to cure the disease.
d. Consequently, millions of people around the world, mostly women, suffer unnecessarily.

There are solutions to the unnecessary suffering by patients with chronic symptoms of hypothyroidism. The easy solution is to reduce the scope or medical jurisdiction of hypothyroidism guidelines to not encompass post-thyroid deficiencies. The more difficult solution is to embrace the GTS and produce guidelines that help clinicians to successfully diagnose and treat patients with post-thyroid dysfunctions.

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Competing Interests

The author declares that he has no competing interests.

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Appendix 1 - Exponential Decay Analysis

T3 allegedly has a half-life, which would make exponential decay analysis applicable. *Half-life* is the time for decay to reduce a level by half. The half-life for T3 in humans is about a day, but can be 1.5 days[23] or as long as 2.5 days.[23] For example, if the half-life is a day and the pill T3 effective level is P, then shortly after taking the pill, the T3 level goes up by P. A day later, that pill's contribution to the T3 level is only P/2. Another day later, that pill's contribution to the T3 level is down by another half to P/4. Another day, that pill's contribution to the T3 level is down by another half to P/8, etc.

Now suppose the patient takes one dose per each half-life time. Then the T3 level shortly after taking a pill is P + P/2 + P/4 +P/8 + P/16 + . . . Adding the terms finds this level is close to 2P. If the doses have been taken for seven or more half-lives the value is within 1%. Just before taking the pill, the T3 level is P/2 + P/4 +P/8 + P/16 + . . . It is P less or just about P. The maximum-to-minimum ratio is then 2P:P or 2:1.

But the common medical practice is to prescribe three doses of T3 per day. In general, this requires a reducing factor, f, to be one-half to be raised to a fractional power, or a root of a half. Consider the effective strength of a pill, P, again. Suppose that d is the number of times the pill has to be taken to reach a half-life. Then $P f^d = 0.5$ P. Dividing both sides by P yields $f^d = 0.5$. Taking the d^{th} root of both sides yields $f = 0.5^{1/d}$ or the d^{th} root of a half. Now, if n is the number of doses per day and h is the half-life time in days, then nh = d. Then the factor, $f = 0.5^{1/nh}$ i.e., the nh^{th} root of a half.

When the second pill is taken the first pill has the strength of Pf^2. When the third pill is taken, the first pill has the strength of Pf^2 and so on. The T3 level, T, shortly after taking a pill is

$T = P + Pf + Pf^2 + Pf^3 + Pf^4 + Pf^5 + \ldots$
$= P(1 + f + f^2 + f^3 + f^4 + f^5 + \ldots)$

Then by this algebraic approximation,

$1 = (1 - f)(1 + f + f^2 + f^3 + f^4 + f^5 + \ldots)$
$T = P / (1 - f)$

The maximum-to-minimum ratio, R, is T divided by T-P and substituting

$$R = T / (T - P) = (P / (1 - f)) / ((P / (1 - f)) - P)$$

Now dividing both the numerator and denominator by P and multiplying by (1 - f) simplifies R to 1/f: $R = (1/(1 - f)) / (1/(1 - f) - 1) = 1 / (1 - (1 - f)) = 1 / f$

By substituting $0.5^{1/nh}$ for f, $R = 1 / 0.5^{1/nh} = 2^{1/nh}$ which is the nh root of 2. For example, for nh = 3, R is the cube root of 2. Then, Table 1 is produced by evaluating $R = 2^{1/nh}$ for various values of doses per day, n, and half-life lengths, h.