On the Clinical Diagnosis and Treatment of Hypothyroidism

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Current professional guidelines for the diagnosis and treatment of hypothyroidism abandon clinical medicine for a laboratory exercise: TSH and free T4 normalization. This approach is both illogical and ineffective. The TSH level is not a measure of thyroid hormone sufficiency in any given patient, either untreated or treated; reliance on the TSH produces both under- and over-diagnosis and undertreatment. Dysfunctional central hypothyroidism with a normal TSH may be more common than primary hypothyroidism, and TSH-normalizing T4 therapy neither normalizes T3 levels nor restores euthyroidism. The TSH test is useful only for investigating the cause of clinically-diagnosed hypothyroidism. The free T4 and free T3 levels are more direct indicators of thyroid suffficiency, but their reference ranges have inappropriately low lower limits due to laboratories' inclusion of unscreened persons and hypothyroid patients in their samples. A normal free T4 does not imply thyroid sufficiency. The diagnosis and treatment of hypothyroidism must clinical, guided by signs and symptoms first and by the free T4 and free T3 levels second. Every symptomatic patient with relatively low free T4 and/or free T3 levels deserves a trial of T4/T3 combination therapy titrated to obtain the best clinical response.

The ultimate test of whether a patient is experiencing the effects of too much or too little thyroid hormone is not the measurement of hormone concentration in the blood but the effect of thyroid hormones on the peripheral tissues.[1]

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1. Official TSH-T4 Reference Range Thyroidology

The active thyroid hormone, T3, is one of the most powerful molecules in the human body, affecting every system, every tissue of the body and every aspect of our well-being and health. It increases the mitochondrial energy production[2,3] thereby improving the function of every tissue and organ in the human body. It has other direct and indirect effects that we are only beginning to understand. The symptoms and signs of hypothyroidism are many and various. Hypothyroid patients may receive many different diagnoses.[4] (See Table 1.) Even mild hypothyroidism degrades a person's quality of life and long-term health; therefore its diagnosis and effective treatment is essential to the practice of medicine. What guidance do physicians now receive?

Table 1. Signs and Symptoms of Hypothyroidism

Fatigue, excessive need for sleep
Cold intolerance
Weight gain, cannot lose weight
Constipation, poor digestion
Muscle or joint aches, stiffness
Myxedema in face, lower legs
Cognitive dysfunction
Dry skin, itching
Headaches
Depression or anxiety
Elevated total and LDL cholesterol
Atherosclerosis
Hypertension
Carotenemia, yellowing of skin
Dry hair, hair loss
Slow heart rate, palpitations
Insomnia, restlessness
Heavy menses or amenorrhea
Infertility
Allergies

The American Association of Clinical Endocrinology (AACE) and American Thyroid Association (ATA) 2012 practice guidelines endorse the TSH test as the best screening test for the diagnosis of primary hypothyroidism and the best guide for its treatment.[5] The guidelines assume that almost all hypothyroidism is primary; that central hypothyroidism is rare and confined to persons with obvious hypothalamic-pituitary (HP) damage or disease. The guidelines thus assume that an anatomically-intact HP system always function perfectly to maintain optimal thyroid levels and effects. No supporting evidence or argument is offered for any of these assumptions. Regarding the actual thyroid hormone levels, the guidelines state that the free T4 (FT4) should be checked only if central hypothyroidism is suspected, and testing for free T3 (FT3) is of no value.[6] The signs and symptoms of hypothyroidism are briefly mentioned, but the guidlelines assert that clinical rating scales have been superseded by sensitive serum testing; that the physican should rely on test results and their reference ranges. Even though the guidelines rely on the TSH for screening and for treatment, they admit that the diagnosis of

hypothyroidism rests on a low FT4. Here again, no evidence or argument is offered for this use of any laboratory's FT4 range as a diagnostic range. The production and meaning of laboratory reference ranges is not even discussed. (See below.) The guidelines leave the diagnosis of hypothyroidism in the hands of laboratory scientists.

The goal of treatment of primary hypothyroidism is said to be a normal TSH. Again, no evidence or argument is provided to support the claim that normalizing the TSH restores euthyroidism in all or most patients. The evidence actually falsifies this claim. (See below.) During treatment the physician is told to ignore the "clinical criteria"—the patient's signs and symptoms. Both the thyroid hormone levels and clinical criteria are said to lack "sufficient specificity to serve as therapeutic endpoints".[7] The latter assertion is neither explained nor supported. The guidelines mention that normalizing the TSH with T4 therapy may leave the FT3 low-normal or low; but the physician should not be concerned with this deficiency of the active thyroid hormone. The guidelines warn physicians not to treat any patient, no matter how symptomatic, unless the diagnosis is "biochemically confirmed"[8]—i.e. unless the TSH is above or the FT4 below the laboratory's reference ranges.

In sum, physicians are expected to accept this TSH-T4 reference range thyroidology on faith and to ignore their patients' signs, symptoms and relative thyroid hormone levels. Thyroidology is reduced to TSH and FT4 reference range management. A patient with a normal TSH and free T4, anywhere from the bottom to the top if its range, is "euthyroid", treated or untreated, regardless of signs or symptoms of hypothyroidism. Any persisting hypothyroid symptoms in a person whose TSH and/or FT4 are normal must have another cause: chronic fatigue syndrome, fibromyalgia, depression, poor habits, obesity, etc.

There is disagreement about this paradigm even among professional bodies. The National Association of Clinical Biochemists (NACB) guidelines recognize that merely normalizing the TSH in primary hypothyroidism results in undertreatment. They advise that T4 therapy should reduce the TSH to below 2.0mIU/L and raise the FT4 into the upper third of its reference range.[9] The consensus statement by the Royal College of Physicians advises that the appropriate dose of levothyroxine is that which "restores the euthyroid state and relieves symptoms..." and that in most patients these goals will be achieved "by a dose of thyroxine resulting in a normal or slightly raised serum thyroxine concentration, a normal serum triiodothyronine concentration, and a normal or below normal serum thyroid

stimulating hormone."[10] A senior thyroidologist in the UK has written, "Some patients achieve a sense of wellbeing only if free T4 is slightly elevated and TSH low or undetectable. The evidence that this exogenous form of subclinical hyperthyroidism is harmful is lacking… and it is not unreasonable to allow these patients to take a higher dose if T3 is unequivocally normal."[11] In contrast, the authors of the UpToDate[12] article on the treatment of hypothyroidism imply that a low TSH during T4 treatment is "subclinical hyperthyroidism" with the same implications as the endogenous form. No evidence is provided to support this claim, and there is much evidence that falsifies it. (See Sect. 5.) Regarding secondary/central hypothyroidism, *The Williams Textbook of Endocrinology* acknowledges that in such cases the TSH is usually normal and FT4 often low-normal,[13] i.e. the diagnosis often is not "biochemically confirmed".

I will show that that TSH-T4 reference range thyroidology is illogical and ineffective, resulting in both under- and over-diagnosis and in an almost universal undertreatment of hypothyroidism. Since it began to be adopted in the 1970s, there has been an explosion in the number of people diagnosed with chronic fatigue syndrome, fibromyalgia and depression. While their causes are multifactorial, each of these disorders shares many symptoms with hypothyroidism and should be considered as due to hypothyroidism until proven otherwise.

2. The Illogicality of TSH-based Thyroidology

The guidelines promote the TSH test for screening and for treatment, yet defer to the FT4 to confirm both the diagnosis and treatment. So why attempt to rely on the TSH at all? In order for TSH-based thyroidology to work, all its unstated assumptions would have to be true:

1. The process of TSH secretion is always perfect unless there is known damage or disease affecting the HP system. Almost all hypothyroidism is primary.
2. The TSH level is a reliable inverse measure of thyroid levels and effects throughout the body, so a normal TSH assures thyroid sufficiency for almost all persons.
3. TSH secretion reacts to once-daily oral levothyroxine therapy exactly as it does to endogenous thyroid secretion, so normalizing the TSH always restores thyroid sufficiency.

It is with good reason that these assumptions are never stated: they are illogical, unphysiological, and/or falsified by scientific studies and the daily reality of clinical practice. The first and fatal problem with TSH thyroidology is its illogicality. The level of a pituitary stimulating hormone is not a reliable measure of hormone levels or end-organ effects. Indeed, in no other case do we try to use a pituitary hormone as a surrogate inverse measure of hormone levels or effects. We do not use luteinizing hormone (LH), follicle-stimulating hormone, or adrenocorticotropin levels to diagnose or to treat gonadal or adrenal hormone deficiencies. Dysfunctional LH production is the most common cause of male hypogonadism, and LH is typically suppressed with therapy. We hormone deficiencies by symptoms, signs, and free hormone levels. We then check the level of the pituitary hormone level to find the cause of the hormone deficiency. A high pituitary hormone level implies that the primary gland is dysfunctional; a normal or low level implies that the HP system itself is dysfunctional. Thyroidology should be no different.

Using the TSH as a surrogate measure of T3 effect in a given patient is as illogical as insisting that one's home-heating thermostat is working perfectly even as one's house is getting colder and colder. Even if the TSH is elevated, it is a compensatory mechanism. The increased stimulation of the dysfunctional thyroid gland may indeed work to maintain thyroid levels and effects. It is true, as with other pituitary stimulating hormones, that there is a correlation between TSH and FT4 levels due to the presence of primary hyper- and hypothyroidism in the population. However, this correlation does not imply that the TSH level is a reliable inverse measure of thyroid hormone levels or effects in any given patient, particularly when it is in or near its reference range.

The reliance on the TSH is also inconsistent with what we know about the complexity and fallibility of the entire system of HP function, thyroid gland function, T4-to-T3 conversion, and T3-effector mechanisms. Dysfunction can occur at any level. The HP system itself is extremely complex, certainly far more complex than the thyroid gland and therefore much more likely to be dysfunctional. It is part of the brain and is affected by inputs from many regions of the brain and by many neurotransmitters, environmental chemicals, drugs, illnesses,[14] stress, and other factors. All its proteins are subject to genetic mutation. Indeed, a number of mutations and other molecular disorders including the secretion of an inactive form of TSH have been associated with dysfunctional central hypothyroidism.[15,16,17] Like LH

and growth hormone, TSH production declines with age. The TSH response to response to low FT4 levels declines by 80% between ages of 20 and 80.[18]

Even if we had some independent way of knowing that HP function was perfect in a given patient, the TSH level still would tell us only about the response of the HP system to circulating T4 and T3, not about T3-effects in other tissues of the body. The HP system differs from other tissues; it more sensitive to circulating T4. The brain and pituitary gland have higher levels of the deiodinase D2 compared to other tissues, so they convert T4 to T3 more avidly.[19,20] The central nervous system has no D1, but many other tissues in the body do and D1 is a major determinant of T3 production in the body. The production and activity of D1, D2, and D3 are variously affected by many factors.[21] There are also four different thyroid hormone receptors[22,23] and at least ten different active transport systems with variable tissue distribution.[24,25,26] All of these proteins are subject to single nucleotide polymorphisms[27,28] that can affect TSH secretion, the response of the thyroid gland to TSH, T4-to-T3 conversion and action of T3 in various tissues. Local factors ultimately determine tissue and cellular thyroid levels and effects. Peripheral thyroid hormone resistance may be more common than realized.[29] To reduce all of thyroidology to TSH or even T4 management is to ignore both the known and unknown complexities of the endocrine system.

Case reports of various diseases and damage to the HP system are interesting, but do not imply that all central hypothyroidism (CH) is associated with abnormal imaging studies. There are many reports of persons with CH whose imaging studies are normal,[30,31,32] and I see such patients frequently. They have a dysfunctional central hypothyroidism, usually of hypothalamic origin. Normal aging blunts the TSH response to TRH,[33] and 2.5% of the elderly have a low FT4 index with an inappropriately normal TSH and no evidence of any HP abnormalities.[34] I assert that a more sensitive clinical approach to case-finding using signs, symptoms, and meaningful FT4 and FT3 reference ranges, (Sect. 2.) will reveal that dysfunctional CH is much more common than primary hypothyroidism. Consider that even in cases of CH due to obvious damage or disease the TSH is usually normal and the FT4 frequently low-normal.[35,36] There are various degrees of CH in such cases. Logically, in less severe cases of dysfunctional CH, both the TSH and FT4 will usually be normal. Thus a patient who has hypothyroid symptoms, a normal TSH, and a low-normal or low FT4 and/or FT3, and whose symptoms resolve with thyroid optimization has CH by definition. Many

cases of CH, and all cases of dysfunctional CH are undiagnosable with the AACE/ATA guidelines.

This reliance on the TSH is supported by some specious arguments and rationalizations. The TSH is said to be the best test of thyroid sufficiency due to its sensitivity. The latest generation of the TSH test is indeed sensitive to lower TSH levels than could be measured by earlier tests. The TSH test is also sensitive in that it responds in a logarithmically-amplified degree to changes in serum FT4. However, neither of these facts implies that the TSH is the right test.

This "Immaculate TSH" doctrine has corrupted all of thyroidology, including most clinical studies. Researchers routinely equate a normal TSH with euthyroidism, leading to ambiguous results and false interpretations. Consider the conflicting studies on "subclinical hypothyroidism" where the TSH is elevated but the FT4 and FT3 are normal. They can be anywhere from the bottom to the top of their ranges, with vastly different clinical implications. A high TSH with mid-range FT4 and FT3 levels and no symptoms is not hypothyroidism at all. On the contrary, if both FT4 and FT3 are low-normal the patient may be severely hypothyroid; even fall into a myxedema coma.[37]

The daily result of the AACE/ATA guidelines is that physicians can only diagnose "subclinical hypothyroidism" which is often not hypothyroidism, and primary hypothyroidism. They cannot diagnose dysfunctional central or mixed central/primary hypothyroidism where the TSH and FT4 are normal. They cannot even diagnose the majority of cases of CH caused by disease or damage of the HP system, until that pathology becomes evident in some other way. When they do diagnose hypothyroidism, they simply normalize the TSH in primary hypothyroidism and the FT4 in central hypothyroidism, practices that have been repeatedly shown to result in undertreatment. (See below.)

The diagnosis and treatment of hormone deficiencies must instead proceed according to known physiological principles. We first determine that a hormone deficiency may exist based upon clinical criteria. This is first-rank evidence—of actual end-organ hormone effect. Then we search for less direct second-rank evidence, i.e., for rather low free hormone levels in the serum. If we diagnose a hormone deficiency, we then check the level of the pituitary stimulating hormone in order to determine the cause of the deficiency or excess.

3. The Problem with the FT4 and FT3 Reference Ranges

In thyroidology, the reliance on the TSH has produced a unique problem with the reporting of the thyroid hormone levels. Laboratory reports create confusion first of all because they contain a mixture of physician-adjudicated diagnostic ranges and 95%-inclusive population ranges. The nature of the range is usually not indicated. Among the diagnostic ranges are fasting serum glucose, Hgb A1C, 25-OH Vitamin D and lipid panels. Physicians are beginning to think that all ranges ar diagnostic. Endocrine reference ranges, however, are just population ranges. They are mere statistics that include 2 standard deviations from the mean—the middle 95%—almost all—of some group of "apparently healthy" adults. The subjects are usually laboratory employees and their friends and relatives. They are screened for medications and diseases, but not for symptoms of hormone deficiency. The limits represent the 2.5^{th} and 97.5^{th} percentile levels of this essentially unscreened group. Only those with levels below the 2.5^{th} percentile are defined as "low". In practice, this means that a physician will tell a symptomatic patient with hormone levels near the bottom of the range, say at the 5^{th} percentile, that he/she has a sufficient hormone level when in fact 95% of unscreened adults have higher levels.

Using a 95%-inclusive unscreened population reference range as a diagnostic range may work if one's goal is only to detect overt disease or damage of the endocrine system, which are rare. It fails, however, to detect any level of hormone deficiency that affects more than 2.5% of that population. HP and glandular dysfunction are known to occur due to age-related deterioration of the endocrine system, chronic stress, unhealthy lifestyles, obesity, environmental toxins, genetic abnormalities, etc. It is highly likely that a population that is not screened for symptoms will contain more than 2.5% of persons with suboptimal hormone levels. For evidence of this one need only look at the breadth of the endocrine reference ranges. The lower and upper limits for many hormones differ by factors of 2 up to 5—surely these cannot represent sufficient, let alone optimal levels. One can double, triple or even quintuple a person's low-normal hormone level and still be within the range. Such an intervention would produce remarkable changes in the person's physiology. Individuals also vary greatly in their hormonal needs.

In thyroidology, since we have no reliable test of T3 levels and effects within the tissues and cells of the body, the best laboratory indicators of thyroid status are the FT4 and FT3

levels in the serum. Most physicians trust that these ranges are adjudicated or based upon carefully screened populations. However, the FT4 and FT3 reference ranges or not even 95%-inclusive unscreened population ranges; they are hypothyroid patient ranges, contaminated by the inclusion of physician-ordered TSH-normal test panels. How does this occur? Every commercial FT4 kit comes with a manufacturer's suggested reference range. This range is usually based on the testing of 120 or more "apparently healthy" persons with screening for symptoms. Each laboratory using the kit has to produce its own reference range and has the option of either using the manufacturer's range, the published literature, tests done on their own population, or some combination of these.[38] Rather than identify, screen, and test 120 or more healthy persons to produce their FT4 and FT3 ranges, laboratories typically save time and money by adjusting the manufacturer's reference range using their own physician-ordered thyroid panels in which the TSH was normal.[39] They thus produce ranges that include untreated and treated hypothyroid patients. This is yet another way in which the immaculate TSH doctrine has corrupted thyroidology.

The effect of this practice is again seen in the breadth of the ranges. Whereas studies of adult non-patients, without screening for symptoms, yield a 95%-inclusive FT4 range of around 1.0 to 1.6ng/dL (12.9–20.6pmol/L),[40,41,42,43] most laboratories report much broader FT4 ranges, typically having lower limits of only 0.6 to 0.8ng/dL (7.7 to 10.3pmol/L) and upper limits of 1.8 to 2.2ng/dL (23.2 to 28.4pmol/L). The best explanation for these broader limits is that the lower limits are reduced by the inclusion of patients with untreated central/mixed hypothyroidism, and the upper limits raised by the inclusion of levothyroxine-treated primary hypothyroidism patients, who require higher FT4 levels to normalize their TSH. The results of this careless laboratory practice are devastating for hypothyroid patients. Many symptomatic persons have FT4 levels below 1.0ng/dL and normal TSHs, warranting a diagnosis of CH. They would be diagnosed with the use of a reasonable unscreened population range. However, if a range were produced using careful screening, if all persons with any signs or symptoms of hypothyroidism were excluded, including those with elevated cholesterol levels, the resultant FT4 lower limit would certainly be higher, probably around 1.2ng/dL (15.5pmol/L). One could also argue that the reference range should be based only on 25 to 35 year-old subjects, as the decline in hormone levels with aging is deleterious and not adaptive. However, even with a tighter FT4 reference range, the

clinician must still use clinical judgment since any reference range, no matter how tight, is just an arbitrary statistical treatment of some population. Persons differ in their need for thyroid hormone,[44,45] their conversion of T4 to T3, their sensitivity to T3, and in other mechanisms required for thyroid hormone action. The 5th or even 50th percentile may not be sufficient for some.

4. T3 and the Ineffectiveness of TSH-Normalizing T4 Therapy

Once-daily oral thyroid hormone replacement is an unphysiological intervention in the functioning of a very complex system. In contradiction to the AACE/ATA guidelines, most studies of TSH-normalizing T4 therapy (TSHT4Rx) show that it does not restore clinical euthyroidism in most persons. Patients receiving TSHT4Rx continue to have signs and symptoms of hypothyroidism. They display significant impairment in psychological well being compared to controls of similar age and sex.[46] They have decrements in health status, psychological function, working memory, and motor learning compared to euthyroid controls.[47] They have poor performance on various domains of neurocognitive functioning, and levels of wellbeing significantly lower than those of the general population.[48] They are twice as likely to be taking anti-depressant medications.[49] They have persistent endothelial dysfunction,[50] and an increased risk of cardiovascular morbidity.[51] They have higher hypothyroid index scores and higher BMIs than euthyroid controls.[52] They have 21% greater fat mass than controls.[53] After thyroid ablation, patients on TSHT4Rx gain weight (avg. 4kg), whereas those who receive TSH-suppressive therapy do not.[54] Patients on TSH-normalizing doses of either T4 or T4/T3 have much worse scores than euthyroid controls on various measures of mentation and mood.[55] Women on T4 therapy have more depression and anxiety than women not taking T4, and their symptoms are worse with higher TSH levels within the range.[56]

The corrupting effect of TSH-based thyroidology is seen in studies of the treatment of subclinical hypothyroidism (SH) and their interpretation. When patients with SH do not benefit from low T4 doses that normalize the TSH, physicians conclude that SH produces no symptoms and should not be treated. For instance, in one study the SH patients had FT4 and FT3 levels only slightly lower in the ranges than healthy controls. When these patients were given low-dose T4, the TSH was normalized, but the FT3 levels did not rise compared to placebo. Since there was no improvement in cognitive function with treatment, the authors

concluded that there is no cognitive impairment in SH.[57] A better conclusion is that normalizing the TSH with low doses of T4 does not restore euthyroidism, and the failure to raise the T3 level is a useful marker of under-treatment. In another study, increasing the patients' doses of T4 lowered their TSH from mid-range to low-normal but had no effect at all on their symptoms. The authors concluded that merely normalizing the TSH to any point within the range is sufficient.[58] A better conclusion is that the TSHT4Rx is similarly ineffective at any TSH level within the range. Since neither a normal TSH nor FT4 guarantees euthyroidism, and since merely normalizing the TSH with T4 constitutes inadequate treatment in most patients, we must reinterpret every study and review that was based upon TSH-T4 reference range endocrinology.

The use of the TSH to guide treatment was definitively tested in the late 1980's. In the only rigorous study of clinically-guided T4 therapy, four experienced clinicians adjusted the T4 doses of 148 hypothyroid patients based on clinical criteria, using physical signs and symptoms as quantified with the Wayne index.[59] For the patients they judged to be clinically euthyroid, the treated TSH reference range was <0.1-13.7mIU/L (conventional range: 0.35-5.0mIU/L). The treated FT4 range was nearly 50% higher than the conventional range (12-36pmol/L vs. 9-25pmol/L), and the treated FT3 range was virtually identical to the conventional range (3.0-8.6 vs. 2.9-8.9pmol/L). With T4 replacement therapy, TSH proved to be the least accurate measure of euthyroidism and FT3 the most accurate. The authors concluded that "biochemical tests of thyroid function are of little, if any, value clinically in patients receiving thyroxine replacement". There has never been a comparable study that has contradicted the authors' findings or conclusion.

5. Why TSH-Normalizing T4 Therapy does not Work

As the above study suggests, the explanation for the inadequacy of TSHT4Rx is found in the T3 levels. The serum T3 level reflects the amount of T4-to-T3 conversion throughout the body and therefore the T3 levels in the tissues. Patients with untreated primary hypothyroidism (PH) are much less symptomatic if their FT3 is normal rather than low.[60] TSHT4Rx produces lower T3 levels than in healthy controls.[61,62,63,64,65,66,67] After thyroidectomy, with no thyroidal T3 production, the restoration of pre-operative T3 levels requires T4 doses that either suppress the TSH[68] or produce T4 levels 40% higher than before surgery.[69] In patients with subclinical hypothyroidism, TSHT4Rx can actually lower

the T3 compared to pretreatment levels.[70] On TSH-suppressive T4 therapy, a FT4 that is 66% higher than controls produces the same total T3 level and no symptoms of hyperthyroidism.[71] T4-treated patients have the same 24-hour urine FT3 levels as untreated hypothyroid patients.[72] Patients feel better when their TSH is suppressed below the range and their FT4 and FT3 are in the upper half of their ranges. The FT4 dose they require is 50mcg greater than that which normalizes their TSH response to thyrotropin-releasing hormone.[73] The inability of TSHT4Rx to raise FT3 levels or produce clinical euthyroidism has led some investigators to recommend adjusting T4 therapy based upon the T3 level.[74,75]

Why are T3 levels and effects so low in TSHT4Rx? First, there is no guarantee that the treated patient has perfectly vigorous TSH production to start with, in which case using the TSH to determine treatment must result in undertreatment. Aging is accompanied by a reduction in HP function, and middle-aged adults are the most frequent recipients of thyroid replacement and most often included in studies. A degree of HP dysfunction appears to be widespread—as indicated by the low lower limits seen in laboratory FT4 reference ranges that include TSH-normal symptomatic patients.

In addition, the HP feedback control system evolved to interact with the thyroid gland and its continuous production of thyroid hormones, not to tell doctors how to prescribe unphysiological once-daily oral T4 therapy. The brain and pituitary have high levels of D2 and convert T4-to-T3 more avidly than other tissues. The higher T4 peaks and 24hr serum T4 levels on T4 therapy appear to over-suppress the TSH relative to the thyroid effect obtained. When hypothyroid patients are given a single dose of 50mcg T4, their TSH drops by 25 to 50% but their T3 and T4 levels do not change.[76] In many patients with subclinical hypothyroidism, the TSH can be normalized with T4 doses of only 25 to 50mcg, well below the average full replacement dose for a 70kg person of 145mcg/day.[77]

Reducing the TSH with T4 therapy does not guarantee an increase in T3 levels or affects in the body. The reduction in the TSH causes a proportional reduction in thyroidal T4 and T3 production. In addition, reducing the TSH level also reduces the T4-to-T3 conversion throughout the body. The T4/T3 ratio in PH with a high TSH is double that in CH, when FT4 levels are similar.[78] Since approximately 75% of T3 in the serum is produced peripherally from T4-to-T3 conversion,[79] this correlation between TSH and T3 strongly suggests causation. In thyroidectomized dogs receiving T4 replacement therapy, TSH-

injections raised serum T3 levels to a peak at 12 hours and simultaneously lowered T4 levels.[80] The suppression of TSH with T4 therapy in PH and CH further reduces T4-to-T3 conversion.

The 40 to 50% higher FT4 levels seen in T4-treated PH patients with vigorous TSH secretion suppress peripheral T4-to-T3 conversion by another mechanism. D2 in skeletal muscle is the source of ≈72% of peripheral T3 production.[81] D2 action is suppressed by higher FT4 levels and induced by lower levels, whereas D1 in the liver and kidneys is induced by higher and suppressed by lower FT4 levels.[82] D2 suppression also explains why T4 doses that further increase already supraphysiological levels of T4 do not produce proportionate increases in FT3 levels.[83]

Reverse T3 (RT3) is another part of the explanation. About 40% of T4 produced in the body is usually converted to RT3. This is part of a natural buffering mechanism to prevent excess thyroid effect in the body. It probably evolved in the setting of frequent starvation which characterized much of pre-human and human evolution. RT3 inhibits T4-to-T3 conversion.[84] On T4 therapy, RT3 levels are higher than in controls, and are 50% higher than with T4/T3 combination therapy that produces the same TSH level.[85] In my experience, many persons on T4 have high RT3 levels, further reducing its effectiveness and leaving them symptomatic.

The peak levels seen with oral thyroid replacement may also play a role in over-suppression of the TSH. Endogenous T4 and T3 production are essentially constant over 24hrs, whereas oral dosing delivers the entire day's hormone into the circulation within a few hours. With once-daily T4 therapy, peak FT4 levels are 13% to 36% higher, and peak FT3 levels are 8% higher at 3hrs than at the 24hr. trough.[86,87,88] The 24hr. trough FT4 level is higher in most T4-treated patients than in controls. It appears that these unphysiological T4 peaks and levels produce excessive T3 levels in the HP system due to its avid T4-to-T3 conversion, leading to an excessive and prolonged suppression of TSH production compared to endogenous production. In humans, little variation is seen in TSH levels with daily full replacement doses of T4 or T3,[89] suggesting that the T4 peaks have a long-lasting effect. In rats, rapid T3 infusions suppress the TSH levels for only 7 hours, whereas rapid T4 infusions suppress the TSH for over 22 hours.[90] Only a continuous T4/T3 infusion produces tissue thyroid sufficiency equal to controls without suppressing the TSH.[91] It's possible that this

sensitivity to T4 peaks in the serum is an evolutionary adaptation to the occasional excess thyroid hormone ingested by carnivores, in order to avoid hyperthyroidism and its increased caloric requirements.[92]

Often TSHT4Rx doesn't even produce mid-range FT4 levels. In my experience, it can even leave FT4 levels low in the range and FT3 levels low. These patients typically remain quite hypothyroid. In patients with known CH, where the TSH cannot be used to guide treatment, merely normalizing the FT4 is insufficient.[93] It leaves the FT3 below the range in one-half of the patients.[94] The nearly universal weight gain with CH ("hypothalamic obesity") is iatrogenic; the addition of T3 to T4 therapy produces marked weight loss and resolution of hypothyroid symptoms.[95] In CH most guidelines recommend keeping the FT4 above the middle of the laboratory's reference range. Some experts recommend keeping the FT4 near the upper limit of the range and FT3 in the upper half of the range,[96] and others recommend monitoring clinical indices of thyroid action.[97] Shouldn't we give patients with PH the same consideration? Shall we continue to doom them to inadequate treatment because of our faith in their TSH level?

6. The Unfounded Fear of TSH-Suppressive Therapy

Due to the official endorsement of the TSH as the "best test", physicians assume that a low TSH level with T4 monotherapy must have the same physiological implications as a low TSH due to endogenous production. Scientific papers routinely refer to a low TSH on T4 therapy as "subclinical hyperthyroidism". Therefore physicians avoid any TSH suppression because they believe it will cause all the problems of hyperthyroidism: cardiac dysfunction, atrial fibrillation, bone loss, and muscle wasting.

However, we know this is not the case. There is an extensive literature describing the clinical and laboratory findings with TSH-suppressive T4 therapy given to patients who have had thyroid cancer. These studies consistently show no abnormalities or long-term negative consequences as long as the T4 dose is titrated to avoid signs or symptoms of thyrotoxicosis. Patients on physician-monitored TSH-suppressive T4 therapy do not have any increase in cardiovascular disease, dysrhythmias, fractures, or mortality compared to those with normal TSH values.[98,99] The benign effects of TSH-suppressive T4 therapy contrast sharply with the thyrotoxicosis seen in persons with similarly low TSH values caused by endogenous production. One study of endogenous "subclinical hyperthyroidism" found that patients had

both symptoms and signs of thyroid excess even thought their TSH was only slightly low at 0.15mIU/L. Both their FT4 and FT3 were in the upper thirds of their ranges,[100] a pattern not seen with TSHT4Rx. In overt hyperthyroidism, FT3 levels are high.[30] Calorimetry studies of energy expenditure in patients receiving TSH-suppressive therapy after thyroidectomy showed no increase in metabolism compared with the pre-surgical state.[101]

TSH-suppressive therapy is feared because it is known that excessive thyroid effect in the heart can lower the systolic time intervals[102] and produce a hyperkinetic heart with increased heart rate, excessive cardiac contractility, impaired diastolic relaxation, and thickening of the heart muscle. These changes increase cardiac work, which can be disadvantageous if cardiac blood flow is severely compromised. They also can cause a reduction in exercise tolerance. In one study, a downward adjustment the T4 dose in TSH-suppressive therapy to increase the TSH to 0.01-0.1mIU/L produced a normalization of all echocardiographic and ergometabolic signs of thyroid hormone excess.[103] In a study of athyreotic patients with suppressed TSH levels, they had no cardiac symptoms and their cardiovascular studies were similar to controls. The authors concluded that in the absence of symptoms of thyrotoxicosis, patients treated with TSH-suppressive doses of T4 may be followed clinically without specific cardiac laboratory studies. The explanation for the lack of thyrotoxic effect was again found in the FT3 level. The FT4 was above the upper limit of the range but the FT3 was identical to that of the healthy controls.[104]

Perhaps the main reason given for avoiding any TSH-suppression is the fear of producing atrial fibrillation (AF). It is true that higher thyroid hormone levels, even with the ranges, are associated with increased automaticity and trigger activity in the pulmonary vein myocytes which are known to initiate paroxysmal AF.[105] Any increase at all in thyroid hormone levels or effects increases the likelihood of AF in a susceptible person; it does not require overtreatment. In untreated patients, the risk of AF rises from 3% at the bottom of the FT4 range to 7% at the top of the range.[106] Thus the decision to increase a patient's thyroid levels and effects with supplementation always entails a risk of producing AF if he/she is susceptible. Other risk factors for AF include obesity, sleep apnea, and alcohol use. The clinician must weigh the risk of AF in a minority against the benefits of optimal thyroid levels and effects for the majority. Refusing to diagnose hypothyroidism, or treating it with ineffective TSHT4Rx in order to avoid triggering AF is not ethically justifiable. The patient

should be informed of the risk and their consent documented. Fortunately, AF induced by thyroid replacement therapy usually resolves with a reduction in FT4 levels, except in older patients with significant underlying heart disease.[107]

Most physicians believe that TSH-suppressive thyroid replacement therapy causes bone loss and eventually osteoporosis. What is true is that thyroid hormone increases the metabolic rate of all tissues throughout the body, including the rate of bone turnover. If the person is in a net bone-catabolic state, then faster bone turnover speeds bone loss. In such persons hypothyroidism slows bone loss. Hypothyroid females treated with T4 lose bone within the first month, while still hypothyroid, and continue to lose bone over the following 6 months.[108] This occurs because most women enter a bone-catabolic state at around age 30,[109] probably due to declining estrogen, progesterone, testosterone, DHEA, and growth hormone levels. A review of 21 studies of TSH-suppressive therapy and bone density found that only postmenopausal women were at risk for reduced bone density.[110] Estrogen replacement therapy prevents bone loss in women on TSH-suppressive T4 therapy.[111] In elderly men a mean thyroxine dose of 130mcg/day has no effect on bone density.[112] They apparently have sufficient testosterone and estradiol to prevent bone loss. In adolescent females, TSH-suppressive T4 therapy can even increase bone mineral density compared to controls.[113] Here again, the solution is not to keep all patients hypothyroid, but to correct the hormonal or other conditions that have put the patient in a bone-losing state.

Muscle wasting is a problem seen only in endogenous hyperthyroidism where both FT3 and FT4 levels are 2 or more times the upper limit of their ranges. Anti-thyroid therapy that raises the TSH to an average of just 0.01mIU/L and lowers the FT3 and FT4 to high within the ranges eliminates muscle breakdown.[114] Muscle-wasting is not a relevant concern with physician-monitored thyroid replacement therapy. As with bone loss, muscle loss with higher thyroid hormone levels is a matter of increased metabolic rate. Muscle is broken down for gluconeogenesis if the diet does not supply sufficient calories.

7. The Benefits of Optimal Thyroid Levels and Effects

The benefits of treating overt hypothyroidism are well-known. Less well known are the benefits of having higher thyroid hormone levels within the broad ranges and, similarly, of lower TSH levels and higher FT3 levels on T4 therapy. Consider again that the upper and lower limits of the reported FT4 ranges differ by a factor of 2.5 to 3.5, and the FT3 ranges by

a factor of 2. Surely there can be marked physiological differences within these broad ranges. The association of hypothyroidism with atherosclerosis is well known, and logically this should also hold for variations within the ranges. Higher thyroid levels ameliorate several risk factors for coronary artery disease. Lowering the TSH to less than 2.0 mIU/L with T4 therapy is associated with lower cholesterol, homocysteine, and CRP levels than simply normalizing the TSH.[115] Patients with subclinical hypothyroidism have elevated lipid levels compared to controls and to eliminate the difference requires TSH-suppressing T4 doses.[116] A lower FT4 level within the range is associated with hypercoagulability.[117] In persons referred for coronary angiography, those with FT3s in the upper third of the range have half the incidence of severe atherosclerosis as those with FT3s in the lower third.[118] A T4 dose of 150mcg/d prevents progression of coronary artery atherosclerosis, whereas a dose of 100mcg/d allows progression.[119]

The negative health and quality-of-life consequences of obesity are well-documented. Optimal thyroid levels help prevent weight gain and promote weight loss. In untreated persons, body mass index and weight gain are associated with lower FT4 values within the range,[120] as are four of the five components of the metabolic syndrome.[121] Lower FT3 levels within the range are also an independent predictor lower metabolic rate and of weight gain.[122]

Optimal, not just normal thyroid levels are also beneficial for cognitive function, mood, and well-being. In elderly persons, higher T4 levels within the range were associated with better cognitive function[123] and lower risk of cognitive decline.[124] Lower thyroid hormone levels and higher TSH levels within the ranges have been associated with depression or a worse prognosis for remission of depression.[125,126,127,128] There are many studies in which T3 therapy alleviated depression in persons with normal thyroid function tests (TFTs).[129,130,131,132,133,134,135] Those who respond are more likely to have T4 levels in the lower third of the range.[136] In T4-treated PH patients, higher FT4 and lower TSH levels within the ranges are associated with psychological well-being.[137] Persons with lower FT4 levels within the range have more complaints of myalgia and muscle weakness and have lower muscle strength.[138] 80% of persons with hypothyroid symptoms but normal TFTs experience improved mood and energy on an average levothyroxine dose of 125mcg/day.[139]

Ignoring the abundant objective evidence for the physiological and psychological benefits of having higher free hormone levels within the ranges, some claim that those with normal TFTs who experience subjective improvement on thyroid replacement therapy must have a "thyrotoxic euphoria". This *ad hoc* diagnosis is inconsistent with the evidence of physiological benefits given above, and with the fact that patients feel worse, not better when they have excessive thyroid hormone levels. Studies of endogenous hyperthyroidism, TSH-suppressive therapy, and fixed T3-for-T4 substitution show that excessive thyroid supplementation reduces one's quality of life. When symptomatic persons and asymptomatic controls, all with normal TFT's, were given 100mcg of T4 daily, the controls experienced thyrotoxic symptoms and their T3 and T4 levels increased more within the ranges than those who had hypothyroid symptoms.[140] Likewise, a group of patients with endogenous "preclinical hyperthyroidism" (low TSH with high-normal FT4) displayed the same negative, undesirable symptoms as a group of hyperthyroid patients.[141] Hormones are not drugs. There is no substitute for diagnosing and treating according to clinical criteria. A level of thyroid hormone supplementation that makes an individual feel and function better and produces no signs or symptoms of excess should be considered beneficial and necessary until proven otherwise.

8. The Greater Efficacy of T4/T3 Combination Therapy

The elevation of the TSH in the face of thyroid gland dysfunction is a compensatory mechanism, stimulating more hormone production and greater T4-to-T3 conversion throughout the body. TSH and TRH also directly induce mitochondrial biogenesis and activity.[142,143] Lowering the TSH levels with thyroid replacement therapy interferes with these homeostatic mechanisms, reducing both thyroidal T4 and T3 production and T4-T3 conversion throughout the body. When resorting to replacement therapy, the physician bears the responsibility of fully restoring and optimizing T3 levels and effects throughout the body. It is thus only logical that thyroid replacement therapy should include T3.

The effects of T4, T3 and combination therapy on various tissues were revealed in an elegant series of experiments performed on rats. The investigators determined both serum and *post mortem* tissue levels of T4 and T3 in rats receiving continuous infusions of various combinations of the two hormones. A T3-only infusion failed to restore T3 levels in all tissues—illustrating the importance of T4 and peripheral T4-to-T3 conversion.[144] A

continuous T4-only infusion also failed to restore serum and tissue T3 levels to those of controls in all tissues until T4 levels were raised into the supraphysiological range and TSH was suppressed.[145] The addition of T3 to a T4 infusion in the same ratio produced by the rat's thyroid gland (1:6) allowed a normalization of both serum and tissue levels of both hormones without suppressing TSH.[146] The human thyroid produces T3 and T4 in a lower 1:14 ratio.[147] If we could give T4 and T3 by continuous infusion, mimicking thyroidal production, we might be able to use this ratio and might only need to normalize the TSH. However, it is clear that once-daily oral therapy produces a relative over-suppression of TSH production, and therefore of T3 production thoroughout the body, so we need to provide more T3.

We are fortunate to have many studies that compare various T4/T3 combinations with T4-only therapy. These studies provide abundant detailed clinical data on the effects of substituting various amounts of T3 for T4. In all but four of fourteen studies, the authors concluded that T4/T3 combination therapy offered no advantage, however the studies comprise a mixed bag of undertreatment and overtreatment, and one can come to a very different conclusion upon reviewing the data. Statistical conclusions can be misleading. If one-half of the patients demonstrated improvement and one-half deteriorated, the result is no overall benefit. There is a 3-fold range in the relative potency of T3 to T4 in different subjects treated with both hormones,[148] so any fixed combination is going to have different effects in different persons. Arbitrary substitutions can produce over-replacement in some persons and under-replacement in others. Persons with some degree of hypocortisolism will not tolerate sufficient thyroid replacement.

The T4/T3 combination studies were created and interpreted according to TSH-FT4 reference range paradigm. They usually involved arbitrary substitutions of some amount of T3 for the treated patients' T4 dose. In only one study, the first, was the T4/T3 dose adjusted by clinical criteria. In many studies the doses of T4 and/or T3 were adjusted to maintain a normal or specific target TSH. From looking at the detailed results of these studies one can draw the following conclusions: (See **Appendix**)

1. Patients on TSH- or T4-normalizing doses of T4 usually have higher symptom scores than controls, as noted in other studies. They are undertreated.

2. Arbitrary substitutions of some amount of T3 for T4 can produce under- and over-replacement in a significant number of patients.
3. At any given TSH level, T4/T3 combination is more effective than T4 monotherapy, both in objective scales and signs and in patient preference.
4. Low TSH levels on therapy are usually associated with better clinical effects, both with T4 and with T4/T3 combination therapy, but some patients do not tolerate TSH-suppressive doses of either therapy.
5. Persons with a low-normal or suppressed TSH level on T4 experience the greatest improvement with adding T3 to their regimen, less improvement is seen when TSH levels are higher in the range.
6. There is no support for the contention that T3 therapy is dangerous or causes problems due to the fluctuations in free T3 levels, even with once-daily therapy.

The T4/T3 combination studies support the hypothesis that the addition of T3 to T4 therapy is beneficial for most if not all patients, and they illustrate the need for clinical thyroidology—for the adjustment of either T4 or T4/T3 combination therapy to produce optimal clinical effects for each patient, without regard for the TSH level. The benefit of adding T3 is greatest when the TSH is lowest, consistent with the fact that TSH stimulates T4-to-T3 conversion throughout the body. In its absence supplemental T3 is needed.

Some persons may require more T3 relative to T4 than others, or even exclusive T3 therapy. Around 16% of the population has a genetic polymorphism of their deiodinase 2 gene producing impaired T4-to-T3 conversion. They have lower quality of life scores on T4 therapy and significant improvement with the addition of T3 to their regimen.[149] There may be many other such polymorphisms. Many patients diagnosed with fibromyalgia have a form of hypothyroidism that responds well to T3-only therapy.[150,151,152]

9. Clinical Diagnosis and Therapeutic Trial

Neither diagnosis nor treatment can be left up to the laboratory. The physician is responsible to consider the complexity of the hormonal system and to use his/her judgment. Due to the almost exclusive reliance on the TSH, most physicians now have no experience with either the clinical diagnosis or treatment of hypothyroidism. The diagnosis of any disease or disorder is rarely 100% certain. In most cases the diagnosis is a theory. The

physician weighs all the evidence and creates the best theory to explain the signs and symptoms. Tests may support or weaken the theory. The ultimate test is a therapeutic trial. A positive response greatly strengthens the theory, and the sustained elimination of signs and symptoms strengthens it even more. Clinical thyroidology requires listening to the patient's symptoms, querying them for the presence of other thyroid-related symptoms, and looking for physical signs. The physician should also look for any other medical causes that may explain the symptoms. A frequently-overlooked problem that can mimic hypothyroidism is iron deficiency. It is very common in women and appears, among its many effects, to interfere with thyroid levels and effects.[153] Studies show that non-anemic women with fatigue and ferritin levels under 50 mcg/L experience improved energy[154,155] and mental function[156] with iron replacement therapy.

Initial thyroid testing should include a FT4, FT3 and TSH level. The TSH is not needed for initial testing, but it is inexpensive and readily available. It provides immediate evidence of HP function and prevents the patient from needing an additional blood draw to investigate the cause. Thyroid antibody testing should be reserved for determining the cause of primary hypothyroidism. The other labs test of some interest is the lipid profile. Elevated total and LDL cholesterol levels should be considered a possible sign of hypothyroidism. In my experience, T4/T3 thyroid optimization therapy reliably produces marked declines in total and LDL cholesterol levels.

Diagnosis requires clinical suspicion. While there are classical signs and symptoms of hypothyroidism, some persons may have only one symptoms, or symptoms that are not classical. If the patient has some combination of symptoms and/or signs of that could be due to hypothyroidism, and has relatively low FT4 and/or FT3 levels, then the physician should offer the patient a trial of thyroid optimization therapy, regardless of the TSH level. The greater the number of hypothyroid symptoms and the lower the FT4 and FT3 levels, the more certain is the diagnosis and the response to therapy. Certainly, any person with fatigue, myalgias and arthralgias, depression, and/or cognitive dysfunction with no other obvious cause and with relatively low thyroid hormone levels should be offered a trial of thyroid hormone optimization. The physician whould see if higher thyroid levels and effects will ameliorate the patient's symptoms and signs. If the patient experiences no benefits or feels worse, then either they do not have hypothyroidism, or they have hypothyroidism and

some degree of adrenal insufficiency (hypocortisolism). It is well-known that thyroid replacement worsens adrenal insufficiency, but what is not appreciated is that this fact applies to all degrees hypocortisolism, not only to cases of obvious Addison's disease or known HP disease.

As a tertiary specialist, the majority of patients who consult me with symptoms of hypothyroidism have normal TSH levels—untreated or treated. I find that the FT4 is usually the most sensitive test of thyroid status in an untreated person,[157] Untreated symptomatic patients usually have a relatively low FT4 level between 0.8 and 1.2ng/dL (unscreened population range 1.0-1.6ng/dL) and a mid-range or low-in-range FT3 level. The FT3 less sensitive because it is often maintained, in the face of rather low FT4 levels, by TSH elevation and enhanced peripheral T4-to-T3 conversion. A low-normal or low FT3 occurs when the FT4 is very low, when compensatory mechanisms are not working, or when the person has some other metabolic problem (euthyroid sick syndrome). A person with both a low-normal FT4 and low-normal FT3, treated or untreated, can be markedly hypothyroid. All TSH-normal symptomatic patients who respond to a trial of supplementation have, by definition, some degree of dysfunctional central hypothyroidism. They may also have an inadequate response of their thyroid gland to TSH—mixed central/primary hypothyroidism.

T4-only therapy may be sufficient for some at an optimal dose that produces sufficient T3 levels and effects, but questioning of TSHT4Rx patients often reveals persisting hypothyroid symptoms: the need to nap every afternoon, constipation, cold intolerance, inability to lose weight with effort, poor memory and concentration, high cholesterol levels, etc. In patients who remain symptomatic on T4, the FT4 is usually mid-range, sometimes low-normal, and FT3 levels are low-normal or low. The RT3 is often high-normal or high.

In my experience, TSH-normal patients, untreated or treated, with hypothyroid symptoms and rather low thyroid hormone levels usually respond well to effective treatment. Others have reported the same.[158] There have been no real studies. Symptomatic patients with normal TFTs were given a fixed dose of 100mcg of T4. This dose decreased the TSH to a lower point within range, increased the free T4 only slightly, and did not significantly raise the FT3. The authors concluded that treating such patients brings no benefits.[159] Such inadequate trials tell us nothing about the benefits of thyroid optimization. The question is, what constitutes a trial of effective thyroid replacement therapy?

10. T4/T3 Thyroid Optimization Therapy

Having dismissed the current TSH-based treatment of hypothyroidism, it behooves me to describe the practice of clinical thyroid optimization. I have 9 years experience with optimizing T4/T3 dosing according to clinical criteria and free hormone levels, without regard to the TSH, in nearly a thousand patients. I have found that with T4/T3 combination therapy, as with T4 therapy, one should start with a relatively low T4/T3 dose and increase it gradually until sufficient benefits are achieved, or until signs and symptoms of overdosing appear indicating a need to reduce the dose. Some clinical symptoms and signs of overdosing are listed in Table 2., many others may be seen. Simply put, if the patient feels persistently worse in any way rather than better, then that dose, at that time, is excessive for that patient and should be lowered, at least temporarily. Frequently patients will later need and benefit from doses they did not tolerate earlier. The thyroid dose usually must be increased a few times in the first 3yrs of treatment, especially with TSH-suppressive therapy, as thyroid levels on the same dose will fall in the first years.[160] This is probably due to the gradual atrophy of the thyroid gland and down regulation of D2 and D1.

Table 2. Signs and Symptoms of an Excessive Thyroid Dose

Any increase in malaise or fatigue
Heat intolerance
Excessive sweating
Irritability, inability to relax
Hand tremor
Fatigue
Lower exercise tolerance
Pressured speech
Pupillary dilatation
Insomnia
Palpitations or rapid heart rate
Frequent premature atrial or ventricular contractions

For persons already on TSHT4Rx who are symptomatic, one can simply add 5mcg of T3. Depending on the patient's medical situation, one can increase the T3 dose by 5 mcg every 2 weeks up to 15mcg before testing. T3 has a half-life less than 24hrs, so steady-state concentrations are reached within 1 week and most effects felt within 2 weeks. What should be the ideal proportion of T4/T3 for oral thyroid replacement? Even though the human thyroid excretes T4 and T3 in a ratio of 14:1, once-daily oral replacement requires a lower ratio (more T3) due to the over-reduction in TSH and in T4-to-T3 conversion throughout the body. This fact explains the popularity and efficacy of natural dessicated thyroid (NDT) products. Those of porcine origin contain T4 and T3 in a 4:1 ratio. 60mg of NDT contains 38mcg of T4 and 9mcg of T3. The lower T4/T3 ratio assures sufficient availability of T3, the active thyroid hormone. NDT is a fixed T4/T3 combination product that

is readily available, convenient, inexpensive, and contains T2 which has metabolic activity.[161,162,163] Fortunately, NDT has finally been compared to T4 therapy in a randomized, double-blind, crossover study. The differences favored NDT. There were no adverse effects with either treatment.[164]

I have found it most efficient to begin otherwise healthy patients on NDT at 30mg daily upon awakening and to increase the dose by 30mg every week or two up to 120mg. I then wait 6 to 8 weeks to test and adjust the dose by symptoms, signs and the FT4 and FT3 levels. Blood should be drawn in the morning, prior to taking morning dose. On NDT in contrast to T4 therapy, FT4 levels will remain relatively low and FT3 levels relatively high. FT3 levels are high at their peak 3 hrs post dose and fall gradually to the 24hr trough. Most persons who are well replaced on once-daily NDT therapy will have, at the 24 hr. trough, a FT4 of around 1.1 to 1.3 ng/dL, a FT3 that is in the upper third of range or even slightly high, and a suppressed TSH. A high FT3 during the day, and even at the 24hr trough is acceptable as it compensates for the rather low amount of FT4 in the serum and low T4-to-T3 conversion with TSH-suppression. FT4 circulates in amounts 500 times greater than FT3. Excessive NDT dosing may produce a FT4 that is high in the range and a FT3 that is also high-normal or high at the 24 hr trough. The RT3 level can be helpful in detecting overtreatment. When the NDT dose is excessive, the body will protect itself by converting more of the T4 into RT3. A normal RT3 on NDT therapy provides some reassurance that the dose is not excessive. However, FT4 and FT3 levels are only second-rank indicators of end-organ effect. the primary determinant of optimal dosing must always be the patient's signs and symptoms.

Some patients will require doses that produce high free thyroid hormone levels, and a few will require T3-only therapy. On T3 only, laboratory tests are completely useless as the FT3 must be above the range at all times, including at the 24 hr. trough. Superphysiological T3 levels are necessary at all times to compensate for the absence of the much more abundant T4. Once-daily AM dosing with T3 or NDT generally works fine, but there are some patients will do better with splitting the dose. Some persons may do better with a higher T4/T3 ratio and others with a lower T4/T3 ratio. Different T4/T3 ratios can be obtained by using levothyroxine and liothyronine, or by adding one of these to NDT.

There is no substitute for clinical thyroidology. The physician must work with the patient to find the most effective thyroid replacement regimen that eliminates the symptoms and

signs of hypothyroidism without producing any clinical evidence of overdosing. I never cease to be amazed at how consistently thyroid optimization helps patients, and at the many and various improvements that patients report. I believe that physicians will obtain much satisfaction from restoring their patients' quality of life and functionality by diagnosing and effectively treating their hypothyroidism.

Appendix: Review of T4/T3 Studies

Taylor 1970:[165] Thyroidectomized patients were treated with T4/T3 in ratios of 9:1, 4:1, and 3.3:1. Only the 3.3:1 ratio produced both optimal clinical effects and a normal protein-bound iodine (PBI) level—a reflection of total T4 plus total T3. Patients generally felt better on T4/T3 combination therapy.

Comment: This is the only study that adjusted both the doses and ratios of T4 and T3 to optimal clinical effect, not to the TSH, which was not available at the time. The optimal combination had a much lower T4/T3 ratio (3.3:1) than that produced by the human thyroid gland (estimated at 10:1 to 14:1). With the 9:1 ratio, clinical euthyroidism was not achieved without elevation of the PBI. This suggests that oral therapy requires a lower T4/T3 ratio than thyroidal production to compensate for the reduced production of T3.

Smith 1970:[166] Each 100mcg of T4 was replaced with 80mcg T4 plus 20mcg T3. Given the T4/T3 oral equivalence ratio of 1:3.3, this was a nearly 50% dose increase. Combination treatment predictably produced negative effects in many patients, yet half of the subjects noted no preference for either treatment, and 1 in 5 preferred the combination.

Comment: This was a case of excessive T3-substitution in patients already taking rather high-doses of T4.

Cooke 1982:[167] An open-label T3 add-on study of depressed patients on T4 therapy whose TSH levels were low-normal. 15 to 50mcg of T3 was added to the patient's T4 dose. There was objective and subjective improvement in mood in 7 of 9 patients.

Comment: Adding T3 to a patient's TSH-normalizing T4 dose improves mood.

Bunevicius 1999:[168] Half of the subjects were on suppressive therapy for thyroid cancer with very low or undetectable TSH levels. The avg. TSH was 0.8mIU/L. 50mcg of the usual T4 dose was replaced by 12.5mcg of T3, an equipotent 4:1 substitution producing a 10:1 ratio.

The average TSH decreased slightly from 0.8 to 0.5mIU/L. There were improvements in fatigue and some cognitive tests. Patients preferred combination therapy over T4 by 10:1.

Comment: With substitution, FT4 and FT3 levels were more similar to those of normal persons. The positive results of this study indicate that T3 may be especially helpful when a patient is on TSH-suppressive T4 therapy and thus has less T4-to-T3 conversion.

Walsh 2003:[169] 50mcg of the patients' T4 dose was replaced with 10 mcg of T3 (a 5:1 under-substitution). With combined treatment, the TSH rose from 1.5 to 3.1mIU/L. The trough FT3 level did not change and remained relatively low at 3.5pmol/L (range: 3.0-5.5pmol/L). There was no improvement in scales and some deterioration seen in the general health questionnaire. More patients preferred T4 than combination treatment. In the subgroup whose TSH did not rise by more than 0.99mIU/L, more preferred combination therapy. On combination therapy, the SHBG was lower and cholesterol higher, indicating reduced thyroid effect.

Comment: The 5:1 substitution produced undertreatment as indicated by the increase in TSH, deterioration in scales, and patient preference. Those whose TSH rose the least favored combination treatment, suggesting that at a given TSH level, T4/T3 therapy is more effective.

Sawka 2003:[170] Patients had depressive symptoms. They were given half their usual dose of T4 plus 12.5mcg of T3 twice daily. The dose of T3 was adjusted to maintain nearly equal TSH concentrations in both groups. At baseline, the T4 group was more undertreated as indicated by an avg. TSH of 2.2mIU/L compared 1.75 mIU/L for the study group. With study treatment, the avg. TSH in the T4 group declined by 0.5mIU/L, but rose by 0.1mIU/L in the T4/T3 group. There were improvements in both groups, but greater improvements in the T4/T3 group, especially in cognitive functioning, role-physical, and social functioning scales.

Comment: The T4 group received a higher effective dose, explaining their improvements in the scales. In spite of a slight increase in TSH, the T4/T3 group had greater improvements across the board. In their commentary, the authors ignored the differences in pre- and post-study TSH levels and the greater improvements in the study group. Patients were not asked which treatment they preferred.

Clyde 2003:[171] The patients' usual dose of T4 was reduced by 50mcg and they were given 7.5mcg of T3 twice daily. This was an approximately equipotent 3.3:1 substitution. The T4 dose was adjusted in both groups to keep the TSH between 0.5 and 3.5 mIU/L. The resultant TSH was slightly lower in both groups (≈2.0 mIU/L). Both groups improved in most scales with no substantial overall differences between them. Total cholesterol and LDL did decrease in T4/T3 group and increase in the T4 group.

Comment: A study of TSH-normalizing therapy with a relatively high TSH on replacement. All study patients were under-replaced on TSHT4Rx at the beginning of the study as demonstrated by FT4 levels below the midpoint of range and FT3 levels near bottom of the range, and at the end of study, both groups still had worse hypothyroid quality-of-life ratings than controls (54 vs. 40). In this study there was little difference between these two under-replaced groups with similar TSH levels. Patients were not asked which treatment they preferred.

Siegmund 2004:[172] 5% of the patients' T4 dose was substituted mcg for mcg with T3 (5 to 8mcg T4 was replaced by 5 to 8mcg T3). The avg. TSH of 1.72mIU/L declined to 1.5mIU/L in the T4 group and to 0.5mIU/L in the T4/T3 group. The FT4 was 22pmol/L at baseline--high normal (range 10-25pmol/L). Some patients became overdosed on combination therapy. Mood was significantly impaired in 1/3rd of those whose TSH was completely suppressed (<0.02mIU/L). Removing these patients from the Beck Depression Inventory (BDI) scales revealed an improvement from 7.8 to 4.07 for the combination group compared to 6.9 in the T4 control group. Even including the 1/3 of subjects who had negative reactions, the BDI and some other subjective and objective scales improved on the T4/T3 combination.

Comment: A 1:1 substitution study, essentially a T3 add-on study. Patients were already on a relatively high-dose of T4 with FT4 levels near the upper limit of the range. The add-on T3 caused negative symptoms in 1/3rd of the subjects—skewing the overall results. Because those patients had lower TSH levels, the authors concluded that combination therapy can cause subclinical hyperthyroidism, even though their FT4 and FT3 levels were similar to the rest. They blamed the impaired well-being on fluctuations in T3 levels; when the only finding they attempted to relate to T3 fluctuations was a greater suppression of the TSH. The authors ignored the fact that the negative reactions of a subset of patients with this T3 add-on therapy produced the bulk of the undesirable results. The lesson of the study is that

Individual tolerance for thyroid replacement therapy varies greatly. There is no substitute for clinical T4 or T4/T3 dose adjustment.

Escobar-Morreale 2005:[173] A low average T4 dose of 100mcg was replaced with 75mcg of T4 + 5mcg of T3, a 5:1 under-substitution. In an 8-week T3 add-on period, all patients received 87.5mcg + 7.5mcg T3, a 1.7:1 over-substitution. TSH levels were 1.95mIU/L on 100mcg T4, 2.65mIU/L on low-dose combination therapy, 1.09mIU/L on the add-on combination therapy. Patients preferred T4/T3 combinations over T4 alone by a ratio of 9:1. The visual analog scale for depression for all treatment groups was higher than that of controls, and showed improvement only in the add-on combination group

Commentary: Another TSH-normalizing study in which most patient were under-replaced. T4/T3 combination therapy produced objective improvements and was preferred by patients.

Appelhoff 2005:[174] Patients had low-normal TSH levels. The T4 dose was reduced and T3 added to produce an overall T4/T3 ratio of 10:1 or 5:1. Study medication was preferred to usual treatment by 29.2, 41.3, and 52.2% in the T4, 10:1 ratio, and 5:1 ratio groups, respectively. The median endpoint TSH values in the three groups were 0.64, 0.35, and 0.07mIU/L. Objective testing revealed no differences except for a mean body weight change of +0.1, -0.5, and -1.7kg, respectively. Those who preferred the addition of T3 had suppressed TSH levels (0.35 and 0.07 mIU/L) and lost more weight.

Commentary: These patients were already on a relatively high dose of T4 compared to most (avg. TSH 0.64mIU/L). Even so, equipotent substitution (1mcg of T3 for 3.3mcg of T4) produced subjective improvement, and superpotent substitution (3mcg of T3 for 5mcg of T4) produce greater reported improvement and weight loss. Notice also that no deleterious effects were noted with the suppression of the TSH to 0.07mIU/L.

Rodriguez 2005:[175] 10mcg of T3 was substituted for 50mcg of T4; an inadequate 1:5 substitution and an effective reduction in dose. The avg. baseline TSH was 1.9mIU/L. Some symptom scores worsened as the TSH increased to 2.7mIU/L in the substitution group. Even so, 12 preferred the substitution treatment compared to 7 for the standard treatment.

Comment: A 5:1 T4/T3 substitution increased both TSH values and symptom scores. In spite of this more patients preferred the T4/T3 combo than T4 only. This indicates that T3 has benefits that are not reflected in the TSH level.

Slawik 2007:[176] TSH was not followed as patients had central hypothyroidism. Patients were on low-dose T4 therapy (1.1mcg/kg/d). They were randomized and crossed-over to receive 1.6 mcg/kg/d of T4 or 1.44mcg/kg/d plus 0.16mcg/kg/d of T3. Given a T4/T3 potency of 3.3/1, the T4/T3 combo produced a higher T4-equivalent dose. Both the higher BW-adapted T4 dose and the combination therapy reduced hypothyroid symptoms, but the combination therapy produced greater reductions in muscle CK and ankle reflex time. There was no increase in any negative symptoms (i.e. thyrotoxicity) on the T4/T3 combination.

Comment: A higher, more appropriate T4 dose produced high-normal or high FT4 levels and eliminated most hypothyroid symptoms and signs. The addition of T3 with a slightly lower amount of T4 brought more improvements without signs or symptoms of overdosing. Interestingly, T4 levels did not decline with the reduction in T4 dose in the T4/T3 group, indicating a reduction in T4-to-T3 conversion when sufficient T3 is supplied.

Nygaard 2009:[177] TSH normalizing-study performed on Hashimoto's patients on T4 therapy with low-normal TSH levels (≈0.1mIU/L). 20mcg T3 was substituted for 50mcg T4, a 1:2.5 over-substitution) then the T4 dose was adjusted to keep the TSH low-normal. The resultant TSH in the T4/T3 group was slightly lower than T4 group. (0.7 vs. 0.9mIU/L). Significant improvements were seen in the T4/T3 group in 7 of 11 measures of quality of life, anxiety and depression. There was an average weight loss of 3.3lbs on combination therapy and patients preferred combination therapy by a ratio of 3.3:1.

Comment: More benefit seen than in most T4/T3 studies because the T3 dose (20mcg) was higher and the treatment TSH was near the bottom of the range. There was no difference in adverse effects between treatment arms. The T4/T3 ratio was ≈4:1, similar to that of natural dessicated thyroid (NDT). This is more evidence that at the same low-normal TSH, 4:1 T4/T3 combination therapy is superior to T4 therapy.

Hoang 2013:[178] A TSH-normalizing study in which patients on T4 were randomized to receive NDT (Armour Thyroid) then crossed over. The TSH levels were slightly higher than in Nygaard study. The average NDT dose was equivalent to only 50mcg T4 and 12mcg T3; far

lower than in Nygaard. In T4-treated patients, the RT3 level was at the top of the range, with NDT it was reduced to mid-range. The patients on NDT lost 3lbs on average, and 49% of patients preferred NDT vs. 19% for T4. There were non-significant trends towards improved quality of life and better neuropsychological test scores, especially among those who preferred NDT. There were no adverse effects noted with either treatment. The equivalent potency ratio of T4 to NDT to produce a similar TSH level was 1.5mcg T4 ≈ 1mg NDT.

Commentary: This is the only randomized TSH-normalizing study of NDT vs. levothyroxine. The differences favored NDT. There were no adverse effects with either treatment.

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