Hypothyroidism: Sensitive Diagnosis and Optimal Treatment of All Types and Grades—A Comprehensive Hypothesis

Based on a Review of the Standard and "Alternative" Literature and Extensive Clinical Experience

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Abstract. The hypothesis of this paper is that hypothyroidism (in its various forms and degrees) is often undiagnosed in its grade 3 primary, secondary (pituitary), tertiary (hypothalamic), and non-thyroidal illness hypothyroidism versions; and under-treated in all versions, including its grades 1 and 2 primary hypothyroidism versions. The current standard and alternative approaches to the diagnosis and management of hypothyroidism, and their logical inconsistencies and inadequacies, are discussed. The biggest losers in this neglectful situation are elderly, memory- loss, mood-disordered, chronically fatigued, or overweight patients.

An extensive review is presented, which is then coupled with logical argument and clinical experience to clarify the hypothesis. Methods employing the *free* thyroid hormone levels (FT_4 and FT_3), by the accurate direct- and tracer-dialysis methods, respectively, and a lower normal range for the thyroid stimulating hormone level are described. These help optimize the newly-developed diagnostic strategies. Their superiority over the standard conventional and alternative approaches are suggested by inferential argument and by the author's personal experience of his own case of post-surgical (thyroglossal cystectomy) hypothyroidism—missed by the medical profession for 36 years—and his clinical experience with approximately 5,000 patients over a 19-year time period.

Diagnostic strategies and treatment methods are described which refute traditional objections to measuring the FT_3 serum level—at least in the case of the serum test done by the dialysis method—and to treating with varying combinations of both T_4 *and either* T_3 *or* T_4/T_3 combination hormone preparations. The objections about aggressive thyroid treatment causing or aggravating osteoporosis and cardiac arrhythmias are found (in the author's practice) to not only be overblown, but to be entirely non-existent when corrections are made for certain mineral, vitamin, amino acid, and sex- and growth-hormonal deficiencies.

Keywords: Absence of osteoporotic and cardiac-arrhythmic effects • Dialysis free T_3 measurement and optimal correction • Hypothyroidism • Optimal 24-hour T_3 serum level correction • Types and grades

Background

While overt hypothyroidism is easily diagnosed by physicians, the primary illness can be less apparent in its early or so-called "subclinical" stages.[4][54] Central, secondary and tertiary,[49] and non-thyroidal illness/"euthyroid-sick" syndrome[13][19][47] hypothyroidism are also overlooked by the current conventional diagnostic approach which frequently relies exclusively on the ultra-sensitive serum thyroid stimulating hormone (TSH) level. It is important to recognize that the ultra-sensitive TSH is an *indirect* test with a "normal range" that is useful for diagnosing *grades 1, 2, and 3 primary* hypothyroidism *only* (see next section, "The Grades of Primary Hypothyroidism"). In the United States, a free T_4 (FT_4) level is sometimes obtained and occasionally a total or free T_3 (FT_3) level, but a free T_3 level by the tracer-dialysis method, the only accurate indicator of this exclusively-active hormone's function, is rarely obtained. This is astounding, considering that T_3 is the "final common pathway" of the metabolism of thyroid hormones and is the main active version of the hormone.

The Grades of Primary Hypothyroidism

A patient is considered to have grade1 primary hypothyroidism when his or her serum FT_4 level (and possibly the total T_3 and/or FT_3 level) is below the normal range, and the ultra-sensitive TSH is way above its normal range.[18][25][32][33][73] Grade 2 primary

hypothyroidism is diagnosed when the FT_4 and FT_3 levels are in the lower half of their normal ranges but the sensitive TSH is elevated above its "normal range" of approximately 0.4-2.5 mIU/L.[81] Many physicians have also come to recognize a grade 3 hypothyroidism: FT_4, FT_3, and sensitive TSH all in their normal ranges but the TRH-stimulated TSH jumps up >20 points within 30 minutes. Since the advent of the ultra-sensitive TSH, it has been realized that the TRH-stimulation test of the TSH is not necessary.[46] It became apparent that a positive TRH-stimulated TSH test always results from an ultra-sensitive basal TSH in the higher part of its "normal range," and thus such a high-normal ultra-sensitive TSH level on its own signifies grade 3 hypothyroidism.[54]

Only about 5% of the physicians in the U.S. treat grade 3 hypothyroidism, and the author is proud to count himself among them because he has never had a case that did not respond positively, in numerous ways, to his correction of that state. The current conventional approach appears to be tailor-made for many unpleasant surprises; just as one example, covert/"subclinical"/grade 3 hypothyroidism can present initially as a myocardial infarction.[42]

Patients with "subclinical" hypothyroidism, who have the qualifying proposed serum thyroid hormone profile discussed above, almost always have multiple classic symptoms and signs of hypothyroidism. As one authorship has stated, "The presence or absence of symptoms, in both hypothyroidism and 'subclinical' hypothyroidism, depends more on the clinician than on the patient."[29]

In other words, even "subclinical" hypothyroid patients have symptoms (making the term a misnomer); it is just that the physician frequently does not elicit the symptoms and signs. This view is backed by the papers of Staub et al, and Zulewski et al, respectively, which clearly showed significant changes in a clinical symptom index (the Billewicz scale) in "subclinically" hypothyroid women of mean age 50, compared to age-matched controls;[62] and showed significant correlation with serum free thyroxine and TSH levels.[80]

Some physicians regard hypothyroidism as far more common than is generally acknowledged. This article will detail how patients who *are* being treated are actually under-treated because of excessive reliance on the ultra-sensitive serum TSH level for monitoring, and the use of a single thyroid hormone, thyroxine (T_4), in its treatment. Additionally, there are excessive fears of precipitating or aggravating osteoporosis. Evidence for these fears is equivocal and shared by concerns that both natural and iatrogenic hypo- *and* hyperthyroidism may cause the condition.[1][8][30][34][55][71] Apparently, under-treatment of either thyroid state is a risk factor as well.

The conservative American College of Physicians has found enough evidence of the widespread nature of hypothyroidism to recommend that women over 50 years of age be screened for it once every 5 years[36] (since women are 9 times more likely than men to become hypothyroid). In an editorial rebuttal, renowned thyroidologist David Cooper argues for a more aggressive approach to case-finding: 5-yearly screening of women beginning at age 35 and treatment of milder degrees of hypothyroidism.[17] He cites powerful support[3][65] including that of the American Thyroid Association.[60]

A recent estimate of the widespread prevalence of primary hypothyroidism suggests a figure of 9-10% in the United States. This estimate was limited to *active, uncorrected* grades 1 and 2 primary hypothyroidism, and was based on a survey of serum TSH levels on >26,000 adults at a health fair.[53] Only about 10% of those thus identified as hypothyroid admitted to being diagnosed and treated (by definition, inadequately!) despite the long-term health risks associated with the condition. Results of the study were first presented at the October 1997 annual meeting of the American Thyroid Association held in Colorado Springs. These researchers also discovered a strong relationship between an underactive thyroid and elevated serum cholesterol levels, as other investigators also have.[20][29][34][45] T_3 is more effective than T_4 in lowering excess lipid levels and in decreasing the risk of coronary and cerebral arterial occlusion in even subtly-hypothyroid patients.[23]

"Euthyroid-Sick"/Non-Thyroidal Illness/T_3-Hypothyroidism

Another condition that is increasingly being regarded as not necessarily always free of thyroidal functional effects or of the potential benefits of treatment is the "euthyroid-sick/non-thyroidal illness/low-T_3 syndrome."[13][19][47] In this condition the FT_3 level (and sometimes the total T_3 level, the FT_4 level, or the Free Thyroxine Index—FTI or T_7) is below normal and the TSH is normal or even low-normal.[46] This is not due to pituitary or hypothalamic

problems but instead to other extrathyroidal illness. It is important not to over-treat this condition when it is present in acute cardio-arrhythmic or other severe potentially life-threatening illness because in these cases the low FT_3 (or FT_4 or FTI) may be potentially life-saving by lowering the metabolic and/or cardiac rate. However, the majority of so-called "euthyroid sick" cases these days appear to occur in chronic ambulatory conditions such as chronic fatigue syndrome, "dysmetabolic syndrome X," or depression. In these conditions, the low FT_3 function not only is *not* helpful but is actually harmful, and is helping to perpetuate the fatigued[13][19][47] or depressed state.[15][38][76]

The validity of the "euthyroid sick" syndrome was first questioned in the 1980s. It had become common for psychiatrists to find that in refractorily depressed patients who had been passed as euthyroid by endocrinologists, serum T_3 levels were low[38] and T_3 administration, more so than T_4, actually "enhanced the effectiveness of the antidepressants."[15][31][39][66][76] In 1990, Palazzo and Suter[47] also published their earlier questioning of the so-called "euthyroidism" of the "sick euthyroid" patients they were seeing in an intensive care unit in England.

Psychiatrists have known for a long time that even in the absence of diagnosed hypothyroidism low T_3 levels are actually causative factors in depression.[38] The depression is rendered refractory by the low T_3 state, and will frequently not respond to any antidepressant medication unless T_3 is used to "augment" the antidepressant medication.[15][31][39][66] In bipolar-affective-disordered/manic-depressive patients, leading psychiatrists have advocated and successfully used thyroid hormone treatment, especially supraphysiologic doses of T_4, to help reduce the frequency and severity of the moodswings.[26][61][74] In approximately one-sixth of individuals on lithium therapy, thyroid function is lowered to a frankly hypothyroid level.[6] When a more inclusive definition of hypothyroidism is used, there may be substantial numbers of other patients who should be considered to be rendered hypothyroid by lithium. So, many of the psychiatric cases who are regarded as euthyroid may in fact be cases of grade 3 primary hypothyroidism, secondary or tertiary hypothyroidism, or "euthyroid sick syndrome" hypothyroidism. The term "euthyroid sick" is now being openly disputed,[13][19][47] meaning that the T_3 used in *augmenting antidepressant treatment* may in fact be a "back-door" entry to the *thyroid* treatment of refractorily depressed hypothyroid patients,[15] until now regarded as euthyroid by the current approach to diagnosis.

The Current Standard and "Alternative" Approaches

Three popular reference texts on the thyroid[9][10][16] point to the great functional importance of T_3 thyroid hormone. It is 9 times more physiologically active in comparison to the T_4 hormone. The T_4 hormone merely serves as a pro-hormone or pre-hormone, with the possible exception of the brain's apparent need for a significant amount of T_4 for optimal function. T_4 is transported more briskly through the choroid plexus/"blood-brain barrier" than is T_3. Thus, brain cells rely heavily on conversion of T_4 to T_3 for their functional supply of thyroid hormone.[75][76]

Despite this broad agreement on the roles of the two thyroid hormones, when it comes to hypothyroidism diagnosis, these texts often advocate only the ultra-sensitive serum TSH level and sometimes a FT_4 *or* a Free Thyroxine Index (FTI or T_7), but no FT_3 level. These experts recommend the sole use of T_4 for treatment in nearly all cases. This paper will present evidence for the inclusion of the FT_3 and FT_4 levels in all thyroid screening and monitoring. It will also support the strategy of including T_3 thyroid hormone together with T_4 in the treatment of most cases of primary, and all cases of secondary, tertiary, *and* non-thyroidal illness hypothyroidism. This is implied by Escobar-Morreale et al with their discovery of the inadequate reversal of post-ablative hypothyroidism in rats by T_4-only treatment.[24] *If the TSH, FT_4, and FT_3 levels serve any diagnostic function at all, they do so only as an integral group of tests, each of which is in a reciprocal relationship to the others*. The Escobar-Morreale study demonstrated that adding T_3 to the replacement regimen did restore euthyroidism to rat tissues.

The major theoretical and practical reasons for the T_4-only treatment approach in the past centered around the greater *stability* of the T_4 blood level in comparison to the T_3 level, which has wider diurnal and post-dose fluctuations.[12] The inaccuracy of the older tests for the T_3 hormone also contributed to this perspective. However, the diurnal variation of T_3 in the untreated human is fairly low; twice- to thrice-daily dosage of all treatment preparations containing

T_3 eliminates this objection in treated cases. Additionally, newer technology has provided the ready availability of the very accurate FT_3 and FT_4 blood levels by the dialysis methods.[63] These factors have erased the validity of the current conventional approach. They have also removed the validity of the non-specific basal-temperature-recording "alternative" diagnostic and monitoring method of Broda Barnes as described in his 1976 book,[5] even if that method was very valuable at the time when accurate T_3 testing was not available.

The traditional, cheap, older tests of thyroid function, the serum total T_4, T_3-uptake, FTI, total T_3, and T_3-by-RIA tests should be abandoned because they are inaccurate and unreliable as gauges of thyroid function.[63] Physicians in Britain, South Africa, and several other countries did so years ago. In contrast, the richest and "most medically-advanced" nation in the world is still adversely influencing people's thyroid health in a penny-wise, pound-foolish way by either sticking to these cheaper, outdated, inaccurate tests, or by limiting the blood testing to a single, indirect, fallible measure of all types of thyroid malfunction—the ultra-sensitive TSH test.

The most common conventional way to diagnose hypothyroidism is with an ultra-sensitive TSH that is elevated beyond the so-called "normal reference range." For most labs, the upper limit of the normal range varies from about 2.5 at the low end, to 4.0-5.0 mU/L at the high end. This is thought to reflect the anterior pituitary's sensing of inadequate thyroid hormone levels in the blood or in its own cells, which would be consistent with grades 1 and 2 primary hypothyroidism. This range will undoubtedly diagnose the severest grades of primary hypothyroidism but it is far too limited a measure, and large numbers of patients who have some other form or degree of hypothyroidism will be missed. This strategy will fail to detect secondary and tertiary hypothyroidism because TSH is not elevated in these conditions. (Psychiatrists and nutritional medicine practitioners find secondary and tertiary hypothyroidism to be far more common than endocrinologists think. This is because endocrinologists fail to measure the accurate T_3 level often enough to detect an abnormality.) The conventional strategy will also fail to detect the "euthyroid sick" syndrome which, by definition, has a TSH level in its normal range. And, it will miss grade 3 primary hypothyroidism unless one realizes that a TSH level in the upper half of its "normal range" identifies this condition.

Some Modern Conventional Myths About Diagnosis and Treatment

In the author's opinion, the current conventional approach is used because of the following nine errors of thought. The first four myths are widely held concerns that persist in the conventional medical community regarding *the TSH and its role in the diagnosis and treatment of hypothyroidism.* They join five other misperceptions.

The Myths.

(1) "An elevated ultra-sensitive TSH level is almost always required before a diagnosis of hypothyroidism can be made." (This myth was addressed in the previous section.)

(2) "'Over-suppression' of the TSH almost always means that excessive treatment, or hyperthyroidism *de novo*, is in place." Normally, the anterior pituitary will secrete enough TSH to maintain adequate thyroid hormone levels. When this fails to occur, either grade 1 primary or secondary hypothyroidism is considered to be present. There seem to be subtle (conventionally-termed "subclinical") failures of the anterior pituitary to produce sufficient TSH in response to low thyroid hormone levels. These failures cannot be explained solely by the traditional form of secondary hypothyroidism (secondary to a pituitary tumor or outright pituitary failure, as in Sheehan's Syndrome: postpartum hemorrhage or infarction of the pituitary gland). Secondary hypothyroidism can also be due to a TSH-specific hidden hypopituitarism. Failure to produce sufficient TSH could also be due to tertiary hypothyroidism, in which the thyrotropin-releasing hormone (TRH) from the hypothalamus fails, for poorly understood reasons, to stimulate the anterior pituitary to secrete adequate amounts of TSH.

(3) "Because the new ultra-sensitive TSH test is a very sensitive and accurate *test* for measuring *the TSH level*, this new test for TSH is always or usually the correct yardstick by which to measure *the function of the thyroid hormones T_4 and T_3."* This is an unconscious, unintentional "sleight of hand." The assumptions are that if the ultra-sensitive TSH is low-normal, adequate amounts of T_4 are being converted to T_3 in the pituitary receptors; and that if the ultra-sensitive TSH is below normal, excessive amounts of T_3 are being formed from T_4 in those receptor cells. There does not appear to be any evidence

that the pituitary gland—or any organ or tissue for that matter—can convert T_4 to T_3 at any greater rate than that which is reflected in the serum FT_3 level. Anyone who routinely measures the serum FT_3 level will observe that it is often *low*, even when the TSH level is low-normal or below normal, and even in the absence of identifiable pituitary or hypothalamic disease. Some of these cases are so-called "euthyroid sick"/non-thyroidal illness syndrome cases, and some are subtle secondary or tertiary hypothyroid cases without known disease involvement of either the pituitary or the hypothalamus. Other cases may be any combination of these two forms of hypothyroidism, or of non-thyroidal illness hypothyroidism, or of grade 3 primary hypothyroidism.

The TSH is an *indirect* gauge of T_4 and T_3 activity; *it depends on its own integrity of function and not only on the relative highs and lows of the two thyroid hormone levels*. Most of us realize this truth when there is known hypopituitarism or hypothalamic malfunction. But, we don't recognize that it is *also* true in subtle/occult pituitary and hypothalamic failure, and in the hypothyroidism that is now increasingly recognized as a frequent accompaniment of non-thyroidal illness or the "euthyroid sick" syndrome.[13][19][47] It is incorrect to state that the FT_4 and FT_3 levels are inconsequential. High or high-normal levels would indicate that the high or high-normal TSH is not even due to hypothyroidism but to lab error, stress, a spurious high TSH, or some other condition. This is another example of why it is *always* necessary to measure FT_4 and FT_3. Measuring the TSH level can occasionally be eliminated with a patient who over-suppresses the TSH even when FT_4 and FT_3 are *not* elevated. But in my opinion, FT_4 and FT_3 can *never* be dispensed with.

(4) "The normal range of TSH is approximately 0.4-4.2 mIU." Where is the evidence for this range? *Many* patients with TSH levels of 1.0-4.5 (and low-ish-normal FT_4 and FT_3 levels) have classic hypothyroid symptoms—and they *virtually always* respond to thyroid hormone treatment with dramatic resolution of these symptoms and a quantum leap in their sense of well-being, mood, energy, bowel function, memory, etc.[82] Sometimes, patients with these mild degrees of thyroid hypofunction can be taken off the thyroid treatment after 3-12 months without relapsing. Perhaps the treatment, which causes a period of rest for the thyroid gland and which is known to reduce autoimmune antibodies,[70] enables the gland to recover at least temporarily.

(5) "It is not necessary to measure the FT_3 level because FT_4 usually converts adequately to FT_3." This is simply not true. (Many of the myths involve the FT_4 and FT_3 serum levels and the "inappropriateness" of T_3 in the treatment of hypothyroidism.) FT_4 *often*—more often than not, at least in depressed and chronically fatigued hypothyroid patients—*does not* convert sufficiently to FT_3,[15][22][31][38][76] neither in humans nor in laboratory rats.[24] Routine measurement of FT_3 (by the accurate dialysis method) *whenever* screening for, or monitoring treatment of, hypothyroidism will quickly confirm this.

(6) "It is not a good idea to treat with a combination of T_4 and T_3 because the FT_3 level is so unstable and inconsistent that one cannot obtain useful information from measuring it, potentially leaving the patient open to the wrong dosage [usually too much] of T_3." All that is required to invalidate this objection is to *always* prescribe a dosage for any T_3-containing preparation that is to be taken *twice- to thrice-daily*. Taking the two split doses *after* breakfast and dinner assists in stabilizing the FT_3 level by slowing its absorption and thereby extending its duration of action. There seems to be no appreciable fluctuation of the FT_3 level when this simple dosing regimen is implemented. The 3x-daily regimen does not require after-food administration as the 8-hourly repetition of the T_3 easily maintains a consistent serum level.

(7) "The 'euthyroid sick'/non-thyroidal illness syndrome should never be treated with any thyroid hormone because it never involves a malfunction of the thyroid gland or hormones that may cause any symptoms." Once again, this is not accurate. Chopra[13] expands on this, and Palazzo and Suter's letter suggested that at least some "euthyroid sick" patients, even acutely ill ones in an intensive care unit, do *not* have adequate thyroid function. They believe the patients would probably benefit from increasing their thyroid hormone levels, especially T_3.[47] Finally, Leslie DeGroot has also joined the questioning of the prevailing dogma on this issue.[19]

(8) "T_4 is the only hormone that should be used in treatment; one should *never* prescribe a combination of thyroid hormones." Why not? If that is the only way to optimize *both* the FT_4 and FT_3 serum levels—and that is *usually* the case—what is wrong with treating with two thyroid hormones? The gland itself secretes both. The fact that it usually requires the prescribing of both hormones to optimize the

serum levels of T_3 and T_4, taken within the context of the rare use of that treatment approach, certainly gives one pause about the adequacy of the treatment of most patients in the U.S. (and in countries where no form of T_3 is even available such as, at last report, Australia, Israel and Spain!).

(9) "Keeping both the FT_4 and FT_3 levels at the high end of their normal ranges will cause osteoporosis." This concern was merited 30-50 years ago when much higher doses of thyroid hormone were used in the treatment of most cases of hypothyroidism. This author, however, has not observed this complication in over 19 years of his more aggressive approaches to treatment.[82] In fact, his treatment-optimized hypothyroid osteoporotic patients' bone density scans not only don't deteriorate from one year to the next but almost invariably *improve*, by statistically significant percentages, without the use of elindronate, calcitonin, or any other drugs. This means that actual "overtreatment" of hypothyroidism would have to be more substantial than is currently thought. Concurrent correction of other factors such as deficiencies of vitamins, minerals, other hormones, and amino acids seems to maintain and extend bone density even in the presence of optimal or "aggressive" treatment of hypothyroidism.

Exemplars of "Alternative" Approaches

Broda Barnes's book *Hypothyroidism: The Unsuspected Illness*[5] is used by many natural medicine physicians in the U.S. in their approach to hypothyroidism. The book suggests that 64 diseases are caused or aggravated by hypothyroidism (mostly undiagnosed), and that hypothyroidism afflicts approximately 40% of the population. The 40% figure seems high. But, if successfully treated grades 1 and 2 primary, all grade 3 primary, subtle forms of secondary and tertiary, and many cases of non-thyroidal illness hypothyroidism are added to the 10% of the population found in the health fair survey[53] previously mentioned who are either untreated or inadequately treated grades 1 and 2 primary hypothyroidism cases, the figure must surely jump to at least 20%—of which only a small percentage is being treated.

Two further controversial "alternative" physicians have also more recently become associated with a focus on T_3. The first is Dennis Wilson, MD, of Florida.[77] In the early 90s, he noticed that many patients with chronic fatigue and other similar symptoms had low basal body temperature, *a la* Broda Barnes, and low T_3 levels (actually low total T_3 levels, a less accurate depictor of the T_3 status than the FT_3 level, especially by the tracer-dialysis method). He dubbed this condition "Wilson's Syndrome." (The name is inappropriate because it is easily confused with Wilson's Disease, a disorder of copper metabolism named after a different physician a long time ago). Wilson treated his patients with a slightly longer-acting form of T_3 and reported that most of them improved significantly. He contended that the T_3 could often be discontinued after a few months and some of the patients would not relapse into the low T_3 state. This was presumably because the supply of T_3 had broken the "vicious cycle" of the low T_3 level causing a breakdown in peripheral conversion of T_4 to T_3. (It is possible that the action of 5'deiodinase is dependent on a certain threshold amount of T_3.) However, some patients—perhaps most—needed to stay on the T_3 treatment.

Other physicians find that these patients then have high-normal, above-normal, or way-above-normal FT_3 levels, and subnormal or low-normal FT_4 levels.[83] This would appear to be almost as unfortunate as the converse situation, commonly found in a conventionally-treated hypothyroid patient, in which the FT_4 level may be in or above the normal range but the FT_3 level is at or below the low end of its normal range. We say "almost as unfortunate" because T_3 carries out 90% of the thyroid function.[12] Having at least adequate T_3 would appear to be more important than having T_4 at an adequate serum level *if one has to choose between the two* (which, of course, is not the case). But, as mentioned previously, the cells of the brain may require the availability of plenty of T_4 for conversion to T_3, since T_4 is transported more briskly through the "blood-brain barrier." On the other hand, Escobar-Morreale et al showed that, at least in the rat, *some* additional T_3 needs to be available directly for optimal brain cell function to occur.[24]

The other physician currently promoting a controversial "alternative" approach to the management of hypothyroidism and thyroid hormone resistance is John C. Lowe, DC of Texas. He has, particularly, found high doses of T_3 very beneficial in cases of euthyroid fibromyalgia.[44] Because the patients were euthyroid and their symptoms were relieved by supraphysiologic T_3 dosages that did not produce thyrotoxicosis, the researchers concluded that the

patients had peripheral resistance to thyroid hormone. Lowe has found that a substantial percentage of these euthyroid cases are improved or put into remission by T_3 therapy. He uses T_3-only therapy with euthyroid patients, but with primary and central hypothyroid patients, he generally uses T_4/T_3 combination preparations with either desiccated hog tissue or synthetic hormones. One of his research partners, Richard Garrison, MD, until his untimely death in 2007, was engaged in a Veterans' Administration approved study on the effects of T_3 in Gulf War Syndrome, a condition thought to be related to chronic fatigue syndrome and fibromyalgia (which are often present in the same patients). He was using hyaluronic acid, which has been found to be a marker for fibromyalgia[79] and hypothyroidism,[84] as a gauge of the improvement, if any, brought about by T_3 in Gulf War Syndrome.

Presentation of the Hypothesis

The current conventional and "alternative" approaches do not allow for optimal, comprehensive diagnosis and treatment. The author proposes a new approach that is more logical and perspicacious, and which imitates the basic physiology of thyroid function. This approach includes attention to grade 3 primary hypothyroidism, subtle non-obvious forms of secondary/pituitary and tertiary/hypothalamic central hypothyroidism, and many cases of non-thyroidal illness hypothyroidism. The author submits that most cases treated by the current standard approach are in fact under-treated, and he proposes a logic-supported treatment approach that eliminates this situation.

Sensitive Diagnosis

Although this is not a report of any actual findings on his part, it is fair to say that the author has observed dramatic clinical improvement in thousands of patients whose thyroid status was previously regarded as normal (based on the older tests or on a single TSH level, or a combination of the two) when he has boosted patients' free T_3 levels, and often the FT_4 levels as well. This new approach always utilizes the FT_3 and FT_4 diagnostically, as well as the ultra-sensitive TSH serum level. The TSH is given the new normal NACB (National Academy of Clinical Biochemistry) reference range[81] of 0.4-2.5 mU/L, but levels between 1.0-2.5 mU/L are also considered for treatment as cases of grade 3 primary hypothyroidism, secondary, tertiary, or non-thyroidal illness hypothyroidism if the FT_4 and FT_3 levels are no higher than the lower quarter of their reference ranges. Readings between 0.01 and 0.40 are tolerated in patients who have other causes for a low TSH level, as discussed above. Understandably, the suppression of a TSH that was not elevated without treatment is not going to be in the low end of its normal range on optimal FT_4 and FT_3, but will be well below that level and possibly even as low as 0.01 mU/L.

A significant number of patients have a TSH level below 1.0 but their FT_3 and possibly FT_4 will be below normal. These are cases of secondary/pituitary or tertiary/hypothalamic central hypothyroidism,[49] or of "euthyroid sick"/non-thyroidal illness syndrome.[46] These individuals should receive supplemental thyroid hormone therapy, especially if they have serious conditions like depression, chronic fatigue syndrome, obesity, or early dementia that are dependent on good thyroid hormone function for their reversal. There are far too many of these extremely vulnerable patients to ever believe that the TSH alone is an adequate screening tool.

In both diagnostic screening and treatment monitoring since 1989, measuring both the FT_3 and FT_4 serum levels on all patients usually shows a large disparity between the two measures.[82] Unless patients had life-threatening or cardiac-arrhythmic illnesses (in which low T_3 serum levels may have been life-saving by keeping their metabolism and/or heart rate low), including T_3 in their treatment invariably enabled patients to lose their classic hypothyroid symptoms just as described in the literature[4][21][22]___ something study patients had not been able to do with T_4-only treatment even when the FT_4 level had been pushed to the maximum or beyond.[15] In most cases, it is important for both FT_4 and FT_3 levels to be optimized with whatever combination of T_4 and T_3 is necessary in treatment. This objective necessitated the use of both T_3- and T_4-containing preparations in the management of the vast majority of all hypothyroid patients. Gelenberg reported the same phenomenon in a psychiatric newsletter.[31]

There are currently four categories of hypothyroidism that are often not being diagnosed as such and therefore go untreated:

(1) grade 3 primary hypothyroidism;
(2) subtle secondary/pituitary hypothyroidism without identifiable pituitary tumor or disease;
(3) subtle tertiary/hypothalamic hypothyroidism (in

depression, chronic fatigue, and other chronic illnesses); and

(4) many cases of non-thyroidal illness/"euthyroid sick" syndrome hypothyroidism (in which the low FT_3 and sometimes FT_4 levels are counter-productive and not life-saving).

The remaining categories, grades 1 and 2 primary hypothyroidism, are usually diagnosed and treatment is embarked upon, but these patients are very often under-treated mostly due to excessive concerns about cardiac arrhythmias and osteoporosis/osteopenia being caused or aggravated by high-normal thyroid replacement. In most of the studies that suggest these concerns, researchers did not perform the accurate dialysis free T_3 test—or *any* T_3 test.

A 1999 paper by Bunevicius et al shows the superiority of T_4 plus T_3 over T_4-only treatment of 33 hypothyroid patients in a double-blind crossover study.[11] The fourth author, Arthur Prange, is one of the several American psychiatrists who have published articles on the great benefit of T_3 in refractorily depressed patients.[33][74] It is likely that the benefit of the combination approach used in the 1999 study would have been even greater if the FT_3 and FT_4 levels had both been optimized, rather than a fairly arbitrary amount of the previous T_4 treatment simply being substituted by a functionally equivalent amount of T_3. Nevertheless, this is a landmark paper. The Bunevicius study, and those of Escobar-Morreale et al,[24] Chopra,[13] DeGroot,[19] Saravanan et al,[56] Appelhof et al,[2] and the present paper, as well as the popular books by Arem[4] and Shames and Shames,[59] and the lay patient-advocate view by Mary Shomon on the website Thyroid.About.com, should all help to revolutionize the treatment of hypothyroidism—despite the cautionary editorial in the same issue of the *New England Journal of Medicine* that published the Bunevicius paper.[68]

Further evidence of the shift toward including T_3 in the assessment and treatment of the various forms of hypothyroidism is provided by yet another paper published in 1999. The multi-center Italian study, "Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism," reported that "both FT_4 and FT_3 serum levels . . . are necessary for a more accurate disclosure of over- or under-treated patients."[27]

Even Toft, one of the giants of thyroidology in the modern era and who initially reacted so negatively to the publication of the Bunevicius et al paper, largely showed himself to be open to a reassessment of the idea of the addition of T_3 to T_4 treatment. In an abstract published in April 2002, he stated, *inter alia*, the following: "The first treatment for hypothyroidism, introduced at the end of the 19th century, was animal thyroid extract which contained both T_3 and T_4. Because of variable potency it was widely replaced by synthetic T_4, from the 1960s, in high doses of 200-400 ug daily to compensate for the lack of T_3. The development of TSH assays showed that a dose of T_4 of 100-150 ug daily was usually adequate to restore serum TSH to normal [*sic*]. Because a suppressed serum TSH has been shown to be a risk factor for osteoporosis, atrial fibrillation, and most recently for excess cardiovascular mortality, there is a consensus that the correct treatment of hypothyroidism is a dose of thyroxine which restores euthyroidism and maintains both T_4 and TSH in their respective reference ranges. However, a significant minority of patients only achieve the desired sense of well-being if serum TSH is suppressed. Furthermore, patients rendered hypothyroid following treatment of thyrotoxicosis, and taking a dose of T_4 which maintains a normal TSH, gain more weight than those who do not become hypothyroid. Studies in hypothyroid rats suggest that it is only possible to restore universal tissue euthyroidism using a combination of T_3 and T_4. Patients in whom long-term T_4 therapy was substituted by the equivalent combination of T_3 and T_4 scored better in a variety of neuropsychological tests. *It would appear that the treatment of hypothyroidism is about to come full circle*."[69] (Italics mine.)

Toward the end of 2003 there was a rash of papers, in the *Journal of Clinical Endocrinology and Metabolism* in October[57][72] along with an editorial by Kaplan et al,[40] and an article in the *Journal of the American Medical Association* in December,[14] "showing" that the substitution of T_3 for some of the T_4 in T_4-treated hypothyroid patients produced no benefit. But, these study patients' T_4 and T_3 serum levels were even less optimized than those of the 33 patients in the Bunevicius et al 1999 paper.[11] In addition, they often ended up on a lower total daily intake of thyroid hormone (T_4 and T_3 combined) than they had originally been receiving when T_4-only was their treatment. This is no way to try to prove the futility of T_3 treatment—not only for primary hypothyroidism patients but even less so for patients who have one of the other types of hypothyroidism (eith-

er as the sole cause of their hypothyroidism or as an additional cause of their total hypothyroid picture). In these latter types of hypothyroidism there is a strong tendency for the dialysis free T_3 level to lag behind the dialysis free T_4 level. This is partly because of a lack of TSH (which drives the conversion of T_4 to T_3), but may also be due to peripheral interference with the 5'-deiodinase conversion of T_4 to T_3.

It is telling that the Kaplan et al editorial[40] indicated a marked note of despair that an ideal treatment for all the symptoms of hypothyroidism will ever be found! Considering the flawed assumptions on which the editorial and the articles were based, it is not at all surprising to me that optimal treatment is an elusive goal to these researchers and opinion-makers! If they would simply switch their focus from "optimizing" TSH to truly optimizing the dialysis free T_4 and free T_3 serum levels, they would achieve, as I have, this laudable goal in virtually all their patients.

The holy grail publication pendulum has already started to swing back toward evidence for the efficacy of the addition of T_3 to T_4 treatment. We see this in two articles published in the first half of 2005, Saravanan et al[56] in February (697 primary hypothyroid patients) and Appelhof et al[2] in May (141 primary hypothyroid patients). The Appelhof paper compared the outcomes for two different ratios of T_4 to T_3, 5:1 and 10:1. It is notable that the patients receiving the higher amounts of T_3 reported the most satisfaction with their results, especially in weight loss. Unfortunately, both studies were still operating under the flawed assumption that whatever amount of T_3 was added to any patient's treatment, an equivalent amount of T_4 had to be subtracted. Using my approach, the T_4 dosage would have been increased in many patients due to its level still being suboptimal. Because of the feedback loop: $T_3 \rightarrow TSH \rightarrow T_4$, the addition of T_3 would have actually lowered the total amount of T_4 available, thus requiring additional amounts.

Optimal Treatment

The issue is: What is the best substance with which to treat these patients? The approach being advocated here, used successfully since 1989 in over 5,000 patients,[82] has the goal of optimizing the free serum levels of *both* the T_3 and T_4 thyroid hormones (measured by the dialysis methods). The physician should use in treatment whatever combination of both thyroid hormones produces this result (and that includes T_4 alone). This is true regardless of whether the treatment results in a TSH level below its normal range. If such a result occurs, it simply means that the patient's TSH feedback loop is not functioning properly, or else it would not be suppressed below normal when the T_4 and T_3 thyroid hormone levels are *not elevated*!

Unless the FT_3 level in a new case is significantly higher than the FT_4 level, it is not optimally helpful to treat with T_4-only replacement. If the patient has a high TSH level (TSH drives T_4-to-T_3 conversion) and still cannot directly produce enough T_3 from his or her gland and from the conversion of T_4 to T_3 peripherally, then that patient will not convert enough T_3 from T_4-only treatment after the TSH level drops.

The conventional approach to the treatment of hypothyroidism assumes that T_4-only preparations convert peripherally to T_3 in fairly standard amounts and at fairly standard rates. If that does not occur, it is considered to be because of extrathyroidal illness "which is of no concern to the physician charged with correcting *thyroid* dysfunction." But, the clinical experience of always measuring free T_3 and free T_4 serum levels shows that the assumed scenario is not true for the majority of patients. At least 80% of my patients have required some T_3 in treatment (always prescribed for 2 or 3 times/day dosage) in addition to T_4 for their free T_3 and free T_4 serum levels to be optimized.

Consistent measuring of both the FT_3 and FT_4 blood levels in all hypothyroid patients who are on *T_4-only therapy* will very rapidly dispel the myth of adequate conversion (as well as the myth of "extrathyroidal causes" of low T_3 levels). A certain *minority* of hypothyroid patients do convert enough T_4 to T_3 at a sufficient rate for T_4-only treatment to be effective in producing an adequate FT_3 serum level. However, as I said above, the majority of patients require some combination of T_3 and T_4 to optimize FT_3 and FT_4 levels. Once these levels are optimized, the patients' health and performance improve.

Optimizing both the FT_3 and FT_4 levels usually requires: a combined T_4/T_3 preparation, separate T_4 and T_3 preparations, or a combination of T_4 *and* a T_4/T_3 preparation. Desiccated whole hog thyroid (e.g., Armour Thyroid) is a good, relatively inexpensive starting point for the fixed combination T_4/T_3 treat-

ment. Since it contains the short-acting T_3 hormone, it should always be prescribed to be taken *after* breakfast *and* supper (in the twice-daily regimen) to reduce the rapidity of onset and prolong the duration of action. The major shift in thinking for most physicians is to recognize that desiccated thyroid hormone should be taken *not* just once a day, but twice daily after meals. An alternative would be dosages taken three times daily (every 8 hours) without regard to meal times. If desiccated thyroid alone does not optimize both hormones' free levels, additional T_4 (or less often T_3) treatment can be added in order to achieve the goal. If synthetic thyroid hormones are used exclusively, an estimated amount of T_4 would be taken once daily along with an estimated amount of T_3 to be taken twice daily after breakfast and supper (or as described above, every 8 hours without regard to meal times).

Once optimal T_4 and T_3 hormone replacement has been achieved, the ultra-sensitive TSH remains useful as a gauge of optimal thyroid function only if it is still in the low end of its normal range, or it may go below the low end of the range (down to 0.01 mU/L). If this occurs, thyroid function will have been optimized by the yardstick of both the TSH level *and* the dialysis FT_4 and FT_3 levels. As one who has both a personal and a perfectionist interest in *optimal* thyroid function rather than "normal" function, my view is that the only satisfactory optimization is the one just described. It remains to be decided, in certain rare cases in which the TSH needs to be suppressed below 0.01 mU/L for the dialysis FT_4 and FT_3 levels to be optimized, whether to accept suboptimal free T_4 and free T_3 levels or a sub-0.01 mU/L TSH level. My own preference would be for the latter, except in frail or cardiac-arrhythmic patients.

Monitoring Treatment

The TSH, FT_3, and FT_4 serum levels are measured 4-8 weeks after treatment has begun. The interval depends on whether T_4-only or some combination of T_4 and T_3 is being used. Because the longer half-life of T_4 necessitates a longer period before its "steady state" (and that of the T_3 it is converted to) is reached, the TSH, FT_4, and FT_3 levels should only be obtained after 6-8 weeks of continuous treatment if T_4-only is used. After testing and according to the results, doses of thyroid hormones are then adjusted.

In order to optimize hormone replacement in otherwise healthy young or middle-aged patients, FT_3 and FT_4 levels should be near the upper end of the laboratory normal reference ranges (the upper one-third). Lower levels (in the middle one-third of the ranges) should be the goal for cardiac-arrhythmic and/or elderly or frail patients. Once stabilized, the levels need only be checked annually or semi-annually unless clinical indicators demand earlier re-testing.

A small number of large or overweight thyroid hormone resistant patients, *usually women*, may need up to 6-9 grains of Armour Thyroid per day (or the equivalent of thyroxine, counting 0.1 mg of T_4 as 1 grain; or a combination of the two). These patients seem to represent some form of thyroid hormone resistance syndrome.[51]

Patients who already take Armour Thyroid in once/day dosages should be advised to split their doses immediately according to the twice- to thrice-daily formula described in several sections above. After the splitting, the only change will be in their FT_3 levels. If patients have been on the same daily intake of the combined T_4/T_3 treatment for at least 5 weeks before the splitting of the doses, their serum FT_3 levels can be measured 48-72 hours after the splitting (T_3 needs only 48 hours to achieve its steady state level).

Testing the Hypothesis

The above diagnostic criteria and treatment methods should be applied to a large clinical trial using excellent measures of patients' actual functioning in their lives (including jobs and relationships, and social and leadership qualities). In this way, the hypothesis could be tested and assessed to be true or false.

Implications of the Hypothesis

It goes without saying that undiagnosed, untreated, and under-treated cases of hypothyroidism would cause massive morbidity, mortality, and suffering. If found to be true, the hypothesis would lead to the following conclusions: Many of the hyperlipidemias,[17][23][29][34] myocardial infarctions,[28][41][42][64] affective disorders,[18][22][32][33][38] dementias,[35][37] obesities, hair losses, peripheral neuropathies,[48] and some psychoses;[43][50] and in many cases, conditions such as hypertension,[28][41][64] chronic fatigue,[67] impotence,[7][52][78] immune sup-

pression,[58] and chronic constipation, could easily be ameliorated. Furthermore, if thyroidologists, endocrinologists, and other physicians were to incorporate the principles of the hypothesis, *millions* of patients would improve the diminished quality of life that they currently lead.

Serious Thoughts About Iodine

It is well known that the original cause of most cases of hypothyroidism was iodine deficiency. In an effort to deal with that issue in a public health, cost effective manner, iodized salt was substituted for non-iodized salt on all our grocery store shelves. This measure has taken the edge off the extent of the iodine deficiency of yesteryear—although not by any means completely, as good measurements of both organic and inorganic iodine levels in patients' blood or urine would show. But has anyone in thyroidology stopped to recognize that we have actually substituted many *more* cases of autoimmune thyroiditis/primary hypothyroidism for the relatively fewer cases of iodine deficiency hypothyroidism that existed previously?

Could the mechanism for this phenomenon be that we used the wrong form of iodine—inorganic instead of organic—as a food supplement, and that this harsh form of iodine actually damages the thyroid tissue enough to trigger our immune systems to react against it? I believe this is a question that, at the very least, deserves serious consideration and investigation. I have laid out this case to David Brownstein, Guy Abraham, and Jorge Flechas, and also to the Past-President of The Endocrine Society, Len Wartofsky. To date, none of them has responded.

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