Controversies in the Diagnosis and Treatment of Hypothyroidism

Diagnosis of hypothyroidism: Why TSH testing may not be an accurate marker of tissue thyroid levels

Hypothyroidism is a common disorder characterized by an inadequate cellular thyroid effect to meet the needs of the tissues. Typical symptoms of hypothyroidism include the following: fatigue, weight gain, depression, cold extremities, muscle aches, headaches, decreased libido, weakness, cold intolerance, water retention, premenstrual syndrome (PMS), and dry skin. Low thyroid causes or contributes to the symptoms of many conditions, but the deficiency is often missed by standard thyroid testing. This is frequently the case with such conditions as depression, hypercholesterolemia (high cholesterol), menstrual irregularities, infertility, PMS, chronic fatigue syndrome (CFS), fibromyalgia, fibrocystic breasts, polycystic ovary syndrome (PCOS), hyperhomocysteinuria (high homocystine), atherosclerosis, hypertension, obesity, diabetes, and insulin resistance.

The TSH test is generally considered the most sensitive marker of peripheral tissue levels of thyroid. We believe this view, however, is incorrect. Most endocrinologists and other physicians erroneously assume that, except for unique situations, a normal TSH is a clear indication that the person's tissue thyroid levels are adequate (symptoms are not due to low thyroid). But a more thorough understanding of the physiology of hypothalamic-pituitary-thyroid axis and tissue regulation of thyroid hormones exposes as clearly erroneous the widely held belief that the TSH is an accurate marker of the body's overall thyroid status.

The TSH is inversely correlated with pituitary T3 levels; but with physiologic stress (1-32), depression (33-38), insulin resistance and diabetes (28,39,116,117), aging (30,40-49), calorie deprivation (dieting)(27, 50-57), inflammation (5-8,22,108,109-111), PMS (58,59), chronic fatigue syndrome and fibromyalgia (60,61), obesity (112,113,114), and numerous other conditions (1-32), increasing pituitary T3 levels are often associated with diminished cellular and tissue T3 levels and increased reverse T3 levels in the rest of the body (1-62) (see pituitary diagram). The pituitary is both anatomically and physiologically unique, reacting differently to inflammation, chronic calorie reduction (dieting) and physiologic stress than every other tissue in the body (1-20,50-52,62,63). During physiologic stress or dieting there is a reduced conversion of T4 to T3 and an increase in the formation of the anti-thyroid reverse T3 in tissues throughout the body except for the pituitary, where local mechanisms to increase pituitary T3 levels (1-63).

Triac/Tetrac

Physiologic stress, depression, emotional stress and chronic dieting also result in the abnormal stimulation other mechanisms that reduce cellular thyroid activity but is not detected by standard blood tests. This abnormal metabolic pathway converts T4 into a substance called tetraiodothyroacetic acid (Tetrac) and T3 into a substance called triiodothyroacetic acid (Triac) (128-132). The levels of Tetrac and Triac increase two to twelve-fold with dieting or physiologic stress (129-132). Both these substances are selectively taken up by the pituitary and suppress TSH production but have no effect in the rest of the body (128,129,134-137). Everts et al found that Triac is twice as potent as T3 at suppressing TSH secretion and 20 times more potent than T4 at suppressing TSH secretion (137). Thus, with physiologic or emotional stress, chronic dieting, depression and inflammation, the pituitary T3 levels do not correlate with T3 levels in the rest of the body--the TSH does not rise despite significant cellular hypothyroidism. This is another reason that the TSH is not a reliable or sensitive marker of an individual's true thyroid status if such common conditions are present and is another reason that a TSH cannot be relied upon as an accurate marker for tissue thyroid status.

Serum levels of thyroid hormones

Due to the differences in the pituitary's response to physiological stress, depression, dieting, aging, and inflammation as discussed, most individuals with diminished tissue levels of thyroid will have a normal TSH (1-63). Doctors are taught that if active thyroid (T3) levels drop, the TSH will increase. Thus, endocrinologists and other doctors tell patients that an elevated TSH is the most useful marker for diminished T3 levels and that a normal TSH indicates that their thyroid status is "fine." The TSH, however, is merely a marker of pituitary levels of T3 and not of T3 levels in any other part of the body. Only under ideal conditions of total health do pituitary T3 levels correlate with T3 levels in the rest of the body, making the TSH a poor indicator of the body's overall thyroid status. The relationship between TSH and tissue T3 is lost in the presence of physiologic or emotional stress (1-32), depression (33-38), insulin resistance and diabetes (28,39), aging (30,40-49)(see thyroid hormones and aging graph), calorie deprivation (dieting)(50-57), inflammation (5-8,22), PMS (58,59), chronic fatigue syndrome and fibromyalgia (60,61), obesity (112,113,114), and numerous other conditions (1-63). In the presence of such conditions, the TSH is a poor marker of active thyroid levels and thyroid status of an individual, and a normal TSH cannot be used as a reliable indictor that a person is euthyroid (normal thyroid) in the overwhelming majority of patients (see serum thyroid hormones graph)

Numerous studies have shown that using the TSH as a measure of thyroid function will miss 20-95% of patients with low thyroid depending on the condition (1-63). One study exemplifying the failure of the TSH to detect hypothyroidism is a study published in the Journal of Rheumatology that evaluated the incidence of hypothyroidism in patients with fibromyalgia (60). They found that through the use of thyrotropin releasing hormone (TRH) testing, which is a more accurate measure of thyroid function, all of the patients with fibromyalgia were hypothyroid despite the fact that standard thyroid function tests, including TSH, T4 and T3, were in the normal range.

They found that these patients tended to have low normal TSH levels that averaged 0.86 vs 1.42 in normals with high normal free T4 and low normal T3 levels so doctors erroneously feel these patients are on the high side of normal because of the low normal TSH and high normal T4.

A study published in the *New England Journal of Medicine* investigated the incidence of hypothyroidism in women with premenstrual syndrome (PMS) with TRH testing and iodine uptake scans as well as measuring of TSH, T4, T3, T3U, thyroid antibodies. The study found that 94% of patients with PMS had thyroid dysfunction (tissue hypothyroidism) compared to 0% of the asymptomatic patients. 65% of the hypothyroid patients had thyroid tests in "normal" range and could only be diagnosed by TRH testing (missed by the usual thyroid function tests). They found that all PMS patients had complete resolution of symptoms with thyroid treatment even though the standard blood tests were "normal" (38).

A study published in the *American Journal of Psychiatry* also investigated thyroid function in women with PMS with the use of TRH testing. The study found 70% of women with PMS had abnormal TRH testing, showing thyroid dysfunction despite having normal TSH levels (120).

A study in the *Journal of Endocrinology and Metabolism* examined the accuracy of using the TSH to identify hypothyroidism in obese individuals (113). The study found that while the TSH levels were not significantly different between normal weight and obese individuals, obese individuals were shown to have significant thyroid dysfunction when the more accurate TRH testing was done and 36% of obese patients had severe thyroid dysfunction not detected by standard TSH testing.

Similarly, a study published in the journal *Psychoneuroendocrinology* also evaluated the accuracy of TSH to detect hypothyroidism in obese patients by testing the TSH as well as performing the gold standard TRH testing on obese, healthy and hypothyroid individuals (125). It was found that in obese individuals the TSH failed to detect hypothyroid patients 40% of the time.

A large study published in the *Journal BMC Endocrine Disorders* evaluated the accuracy of TSH testing in 2570 women attending a reproductive endocrine clinic for menstrual irregularities or infertility (121). The study found that the TSH was a very poor indicator of abnormal thyroid function as over half the women with a TSH between 2 and 4 mIU/L, which would be interpreted as indication of normal thyroid function, were shown to be hypothyroid when the more accurate and sensitive TRH testing was done.

A study published in *The Lancet* performed thyroid biopsies in patients with chronic fatigue and found that 40% of these patients had lympocytic thyroiditis, with only 40% of these being positive for TPO or antithyroglobulin antibodies or having an abnormal TSH and thus, the thyroid dysfunction would have gone undetected in the majority of patients if the biopsy had not been done (122,123). This study also demonstrated that because the TSH is a poor indicator of thyroid function, it also does not predict whose symptoms will respond to thyroid replacement. The authors state, "After treatment with thyroxine, clinical response was favorable, irrespective of baseline TSH concentration (12)."

As with many other studies, this study demonstrates that many fatigued patients or those with chronic fatigue syndrome potentially have thyroiditis and hypothyroidism that is not detectable by standard auto-antibody and TSH testing and that such patients will likely respond to thyroid replacement regardless of their baseline thyroid function tests. The authors recommend the use of the term subchemical hypothyroidism for hypothyroidism not detected by standard TSH testing and that the TSH should not be relied upon to accurately detect thyroid dysfunction in chronically fatigued patients.

A study in published in the *British Medical Journal* examined the accuracy of using the TSH as a marker for adequate thyroid replacement (124). The study found that the TSH was very poor indicator of optimal thyroid replaced and that a suppressed TSH was not an accurate indictor of over-replacement. It was shown that 80% of the time a suppressed TSH was not an indication of hyperthyroidism or over-replacement and the authors discourage the reliance on the TSH for optimal dosing.

Other studies confirm the fact that standard thyroid function tests (TSH, T4 and T3) cannot be used to rule out central hypothyroidism as occurs with numerous conditions discussed above, as they are generally undifferentiable from euthyroid (normal thyroid) individuals. One such study clearly demonstrating this fact was published in the *Journal of Clinical Endocrinology and Metabolism*; it was determined how often central hypothyroidism that was confirmed with TRH testing went undetected by standard thyroid function tests (119). The authors found that 92% of patients with central hypothyroidism would have remained undiagnosed using baseline thyroid function tests. The authors conclude. "…most prior studies have failed to accurately identify many cases of central or mixed hypothyroidism because of diagnostic criteria that require a T4 or FT4 value below the normal range in addition to a low TSH value. However, patients with central hypothyroidism most often have normal TSH values and T4 or FT4 levels within the low part of the normal range (119)."

Another study published in the Journal of Endocrinology and Metabolism determined accuracy of second and third generation (highly sensitive) TSH testing being able to differentiate those with untreated hyperthyroidism (high thyroid) from those with very low thyroid tissue thyroid due to physiologic stress. The study found that a suppressed TSH was found in both conditions and was unable to differentiate high tissue thyroid levels from those with low tissue thyroid levels (127).

Value of Serum T4

The suppression of TSH with physiologic and emotional stress and illness suppresses the production of T4 (1,2,9,64-68), which would tend to lower serum T4 levels. In the presence of such conditions, however, there are competing effects that result in an increase in serum T4 while further reducing tissue levels of T3 levels, making serum T4 (or free T4) a poor marker of tissue thyroid level, as is the case with

the TSH. Such effects include a suppression of tissue T4 to T3 conversion (misleadingly increasing serum T4 levels) (1-68,76) with an increased conversion of T4 to reverse T3 (12,14,18,35,36,41,59,69-74,85) and an induced thyroid resistance with reduced uptake of T4 into the cells (misleadingly increasing serum T4 levels) (16,1976-84) in all tissues except for the pituitary (84). Although all such effects reduced intracellular T3 in all tissues except for the pituitary, the serum T4 level can be increased, decreased or unchanged. Consequently, serum T4 levels frequently do not correlate with tissue T3 levels and, as with the TSH, the serum T4 level is often misleading and an unreliable marker of the body's overall thyroid status (see serum thyroid levels in stress and illness).

Current best method to diagnosis

With increasing knowledge of the complexities of thyroid function at the cellular level, it is becoming increasingly clear that TSH and T4 levels are not the reliable markers of tissue thyroid levels as once thought, especially with chronic physiologic or emotional stress, illness, inflammation, depression, and aging. The TRH test is a reliable method but because such testing is expensive, burdensome and requires trained personnel and multiple blood draws, it is not practical to use in a clinical setting. While there are limitations to all testing and there is no perfect test, obtaining free triiodothyronine, reverse triiodothyronine, and triiodothyronine/reverse-triiodothyronine ratios can be helpful to obtain a more accurate evaluation of tissue thyroid status and may be useful to predict those who may respond favorably to thyroid supplementation (1,11,12,14,18,35,36,41,59,69-74,85) (see serum thyroid levels in stress and illness). Many symptomatic patients with low tissue levels of active thyroid hormone but normal TSH and T4 levels significantly benefit from thyroid replacement, often with significant improvement in fatigue, depression, diabetes, weight gain, PMS, fibromyalgia, and numerous other chronic conditions (86-99).

With an understanding of thyroid physiology, it becomes clear why a large percentage of patients treated with T4 only preparations continue to be symptomatic. Thyroxine (T4) only preparations should not be considered the treatment of choice and are often not effective in conditions associated with reduced T4 to T3 conversion, reduced uptake of T4 or increased T4 to reverse T3 conversion. As discussed above, with any physiologic stress (emotional or physical), inflammation, depression, inflammation, aging, or dieting, T4 to T3 conversion is reduced and T4 will be preferentially converted to reverse T3 (12,14,18,35,36,41,53,69-74,85), which acts a competitive inhibitor of T3 (blocks T3 at the receptor) (100-104), reduces metabolism (100,103,104), suppresses T4 to T3 conversion (101,103), and blocks T4 and T3 uptake into the cell (105).

While a normal TSH cannot be used as a reliable indicator of global tissue thyroid effect, even a minimally elevated TSH (above 2) demonstrates that there is diminished intra-pituitary T3 level and is a clear indication (except in unique situations such as a TSH secreting tumor) that the rest of the body is suffering from inadequate thyroid activity because the pituitary T3 level is always significantly higher than the rest of the body and the most rigorously screened individuals for absence of thyroid disease have a TSH below 2 to 2.5 (106,121). Thus, treatment should likely be initiated in any symptomatic person with a TSH greater than 2. Additionally, many individuals will secrete a less bioactive TSH; so for the same TSH level, a large percentage of individuals will have reduced stimulation of thyroid activity, further limiting the accuracy of TSH as a measure of overall thyroid status. Reduced bioactivity of TSH is not detected by current TSH assays used in clinical practice.

Due to the lack of correlation of TSH and tissue thyroid levels, as discussed, a normal TSH should not be used as the sole reason to withhold treatment in a symptomatic patient. A symptomatic patient with an above average reverse T3 level and a below average free T3 (a general guideline being a free T3/reverse T3 ratio less than 2) should also be considered a candidate for thyroid supplementation (13,14,18,69-76,85-106). A relatively low sex hormone binding globulin (SHBG) and slow reflex time can also be useful markers for low tissue thyroid and levels and can aid in the diagnosis of tissue hypothyroidism (93,107,115).

A study published in the *Journal of Clinical Endocrinology and Metabolism* assessed the level of hypothyroidism in 332 female patients based on a clinical score of 14 common signs and symptoms of hypothyroidism and assessments of peripheral thyroid action (tissue thyroid effect). The study found that the clinical score and ankle reflex time correlated well with tissue thyroid effect but the TSH had no correlation with the tissue effect of thyroid hormones (118). The ankle reflex itself had a specificity of 93% (93% of those with slow relaxation phase of the reflexes had tissue hypothyroidism) and a sensitivity of 77% (77% of those with tissue hypothyroidism had a slow relaxation phase of the reflexes), making both the measurement of the reflex speed and clinical assessment a more accurate measurement of tissue thyroid effect than the TSH.

Croxson et al in *Journal of Endocrinology and Metabolism* found that the Achilles reflex relaxation time (ARRT) was a better marker of tissue peripheral T3 levels than TSH and T4 levels. The ARRT correlated with T3 levels and was able to correctly detect low tissue T3 levels in chronically dieting individuals while the TSH and T4 failed to detect dramatically low tissue and serum T3 levels. The inadequacy of standard TSH and T4 testing was demonstrated in that such failed to detect the dramatic reduction in tissue levels of T3 in all of the patients (119).

A combination of the serum levels of TSH, free T3, free T4, reverse T3, anti-TPO antibody, antithyroglobulin antibody, and SHBG should be used in combination of with clinical assessment and measurement of reflex speed and basal metabolic rate to most accurately determine the overall thyroid status in a patient. Forgoing treatment based on a normal TSH without further assessment will result in the misdiagnosis or mismanagement of a large number of hypothyroid patients who may greatly benefit with treatment. Simply relying on a TSH to determine the thyroid status of a patient demonstrates a lack of understanding of thyroid physiology and is not evidence-based medicine (see Why my Doctor Doesn't Know All of This). In patients with elevated or high normal reverse T3 levels, T4 only preparations should not be considered adequate and T3 containing preparations, in particular timed released T3, should be considered the treatment of choice.

Understanding Local Control of Thyroid Hormones: (Deiodinases Function and Activity)

To accurately assess thyroid function, it must be understood that deiodinase enzymes are essential control points of cellular thyroid activity that determine intracellular activation and deactivation of thyroid hormones. This local control of cellular thyroid levels is mediated through three different deiodinase enzymes present in different tissues in the body; type I deiodinase (D1) and type II deiodinase (D2) increase cellular thyroid activity by converting inactive thyroxine (T4) to the active triiodothyronine (T3) while type III deiodinase (D3) reduces cellular thyroid activity by converting T4 to the anti-thyroid reverse T3 (reverse T3) (1-9) (see deiodinase figure).

The activity of each type of deiodinase enzyme changes in response to differing physiologic conditions, and this local control of intracellular T4 and T3 levels results in different tissue levels of T4 and T3 under different conditions. Because it is the activity of these deiodinases and transport of T4 and T3 into the cell that determines tissue and cellular thyroid levels and not serum thyroid levels, serum thyroid hormone levels may not necessarily predict tissue thyroid levels under a variety of physiologic conditions.

Deiodinase type I (D1)

D1 converts inactive T4 to active T3 throughout the body, but D1 is not a significant determinant of pituitary T4 to T3 conversion, which is controlled by D2 (1,7,10). D1 but not D2 is suppressed and down-regulated (decreasing T4 to T3 conversion) in response to physiologic and emotional stress (11-22);

depression (23-45); dieting (46-51); weight gain and leptin resistance (47-91); insulin resistance, obesity and diabetes (91-99); inflammation from autoimmune disease or systemic illness (11,100,102-115); chronic fatigue syndrome and fibromyalgia (121-125); chronic pain (116-120); and exposure to toxins and plastics (126-134). In the presences of such conditions there are reduced tissue levels of active thyroid in all tissues except the pituitary. The reduced thyroid tissue levels with these conditions is often quoted as a beneficial response that lowers metabolism and thus does not require treatment, but there is no evidence to support such a stance while there is significant evidence demonstrating it is a detrimental response (135-142).

In addition, D1 activity is also lower in females (143,144), making women more prone to tissue hypothyroidism, with resultant depression, fatigue, fibromyalgia, chronic fatigue syndrome, and obesity despite having normal TSH levels.

Deiodinase type II (D2)

Thyroid stimulating hormone (TSH) is produced in the pituitary and is regulated by intra-pituitary T3 levels, which often does not correlate or provide an accurate indicator of T3 levels in the rest of the body. Using the TSH as a indicator for the body's overall thyroid status assumes that the T3 levels in the pituitary directly correlate with that of other tissues in the body and that changes directly correlate with that of T3 in other tissue of the body under a wide range of physiologic conditions. This, however, is shown not to be the case; the pituitary is different than every other tissue in the body.

Due to a unique make-up of deiodinases in the pituitary, it will respond differently and often opposite to that of every other tissue in the body. Numerous conditions result in an increase in pituitary T3 levels while simultaneously suppressing cellular T3 levels in the rest of the body, making the pituitary, and thus the TSH, a poor indicator for tissue thyroid levels in the rest of the body under numerous physiologic conditions.

In addition to having a unique make-up of deiodinases, the pituitary also contains unique membrane thyroid transporters and thyroid receptors. As opposed to the rest of the body that is regulated by both D1 and D3, the pituitary contains little D1 and no D3 (136); so pituitary T3 levels are determined by D2 activity (1,7,10), which is 1000 times more efficient at converting T4 to T3 than the D1 enzyme present in the rest of the body (1,10,46,145,146) and is much less sensitive to suppression by toxins and medications (147). In the pituitary, 80-90% of T4 is converted to T3 (4,148,149) while only about 30-50% of T4 in the peripheral tissue is converted to active T3 (149,150). This is due to the inefficiency of D1 and the presence of D3 in all tissues of the body except the pituitary that competes with D1 and converts T4 to reverse T3 (7).

Additionally, D2 also has an opposite response from that of D1 to physiologic and emotional stress, depression, both dieting and weight gain, PMS, diabetes, leptin resistance, chronic fatigue syndrome, fibromyalgia, inflammation, autoimmune disease, and systemic illness. D2 is stimulated and up-regulated (increased activity) in response to such conditions, increasing intra-pituitary T4 to T3 conversion while the rest of body suffers from diminished levels of active T3. This causes the TSH to remain normal despite the fact that there is significant cellular hypothyroidism present in the rest of the body.

Thus, the pituitary levels are under completely different physiologic control and T3 levels will always be significantly higher than anywhere else in the body (2,151-158). Consequently, if the TSH is elevated, even mildly, it is clear that many tissue of the body will be deficient in T3; but due to the different physiology, a normal TSH cannot be used as a reliable indicator for normal T3 levels in the rest of the body.

Different thyroid levels and conditions will have different effects on the T3 levels in the pituitary than in the rest of the body, resulting in different T3 levels in the pituitary and the rest of the body, making the TSH unreliable under numerous circumstances. For instance, as the levels of T4 declines, as in hypothyroidism, the activity of the D2 increases and is able to partially compensate for the reduction in serum T4 (3,159-167). On the other hand, with reduced T4 levels, the activity and efficiency of D1 decreases (168-173) resulting in a reduction in cellular T3 levels while the TSH remains unchanged due to the ability of the pituitary D2 to compensate for the diminished T4.

As stated above, this lack of correlation of TSH and peripheral tissue levels of T3 is dramatically worsened in numerous conditions. These include chronic emotional or physical stress, chronic illness, diabetes, insulin resistance, obesity, leptin resistance, depression, chronic fatigue syndrome, fibromyalgia, PMS, and both dieting and weight gain. In such conditions, tissue levels of T3 are shown to drop dramatically out of proportion with serum T3 levels (8,9,100-103,174-176). While serum T3 levels may drop by 30%, which is significant but still may be in the so-called "normal range," tissue T3 may drop by 70-80%, resulting in profound cellular hypothyroidism with normal serum TSH, T4, and T3 levels (8,11,100-103,146,174). Consequently, in the presence of such conditions, the TSH is a poor indicator for peripheral thyroid levels and a normal TSH should not be considered a reliable indicator for an individual being euthyroid (normal thyroid), especially in the presence of symptoms consistent with thyroid deficiency.

Doctors in the thyroid division of the department of Medicine at Brigham and Women's Hospital and Harvard Medical School investigated how the pituitary's unique deiodinase makeup responds differently than the tissues of the rest of body and how the pituitary is a poor indicator for thyroid levels in the rest of the body. In their review published in *Endocrine Reviews*, the authors state, "The approximately 1000-fold lower Km of D2 than D1 [D2 is 1000 times more efficient] may give this enzyme a major advantage in terms of extrathyroidal T3 production... The free T3 concentration in different tissues varies according to the amounts of hormone transported and the activity of the tissue deiodenases. As a result, the impact of the plasma thyroid hormones on target tissues is not the same in every tissue" (1).

In the journal *Endocrinology*, Lim et al. measured peripheral (liver) and pituitary levels of T3 in response to induced chronic illness. They found that pituitary T3 and TSH levels remained unchanged while the peripheral tissues were significantly reduced. The authors summarize their findings by stating,

"The reduction in hepatic nuclear T3 content and T3-Cmax in the Nx2 rats is consistent with the presence of selective tissue deficiency of thyroid hormones. The pituitary, however, had normal T3 content, suggesting a dissociation in thyroid hormone-dependent metabolic status between peripheral tissue (liver) and the pituitary. This explains the failure to observe and increase in serum TSH level, a manifestation of reduced intracellular rather than serum T3 concentration…Most interesting, we found that, in contrast to the liver, the pituitary of the Nx rats was not deprived of thyroid hormone. This finding offers a convincing explanation of the failure to observe an increase of serum TSH when illness or stress-induced reduction of hepatic T4 5'-monodeiodination causes a fall in serum t3 concentration (11)."

In the *New England Journal of Medicine*, Larsen et al. summarize the fact that the pituitary has a unique composition of deiodinases that is not present in any other tissue in the body, making the pituitary T3 levels, and thus the TSH, a poor indicator for tissue T3 in the rest of the body -- stating that the TSH cannot be reliably used as a marker of thyroid status in the rest of the body (148).

> "Changes in pituitary conversion of T4 to T3 are often opposite of those that occur in the liver and kidney under similar circumstances. The presence of this pathway of T3 production indicates that the pituitary can respond independently to changes in plasma levels of T4 and T3…Given these results, it is not surprising that a complete definition of thyroid status requires more than the measurement of the serum concentrations of thyroid hormones. For some tissues, the intracellular

T3 concentration may only partially reflect those in the serum. Recognition that the intracellular T3 concentration in each tissue may be subject to local regulation and an understanding of the importance of this process to the regulation of TSH production should permit a better appreciation of the limitations of the measurements of serum thyroid hormone and TSH levels (148)."

Deiodinase type III (D3)

The pituitary is the only tissue that does not contain D3 (7), which converts T4 to reverse T3 and competes with D1 that converts T4 to T3 (8,9,11,23,24,92,104,178-183). Reverse T3 is a competitive inhibitor of T3, blocking T3 from binding to its receptor and blocking T3 effect (184-189), reduces metabolism (184,187,188), suppresses D1 and T4 to T3 conversion (147,185,187,190-192), and blocks T4 and T3 uptake into the cell (183,193), all reducing intracellular T3 levels and thyroid activity. Because many tissues may have abundant D3 levels while the pituitary is uniquely void of D3 (7), the inhibitory effects on the peripheral tissues causing hypothyroidism are not reflected by TSH testing.

Reverse T3 is present in varying concentrations in different tissues and with different individuals (1,12,61,62,151,179-183,194-196). It is up-regulated with chronic physiologic stress and illness (1,195,196) and is an indicator for reduced T4 to T3 conversion and low intracellular T3 levels even if the TSH is normal (104,177-179,182,184,193,195,196).

Because increased serum and tissue level of reverse T3 will result in a blocking of the thyroid receptors, even small increases in reverse T3 can result in a significant decrease in thyroid action and result in severe hypothyroidism not detected by standard blood tests (184-189). Because any T4 given will contribute to more reverse T3, T4-only preparations should not be considered optimal thyroid replacement in the presence of high or high-normal reverse T3 levels (197-201) while T3 can be significantly beneficial (52,53,121-124,201-215).

Stress

Chronic physiologic stress results in decreased D1 activity (11,12,13-17,234) and an increase in D3 activity (1,195,196), decreasing thyroid activity by converting T4 into reverse T3 instead of T3 (1,195,196,216,234). Conversely, D2 is stimulated, which results in increased T4 to T3 conversion in the pituitary and reduced production of TSH (11,16,18-22,234). The increased cortisol levels seen with stress also contribute to physiologic disconnect between the TSH and peripheral tissue T3 levels (16,18-20). This stress induced reduced tissue T3 level and increased reverse T3 results in tissue hypothyroidism and potential weight gain, fatigue, and depression (12,13,194,217-219). This vicious cycle of weight gain, fatigue, and depression that is associated with stress can be prevented with supplementation with timed-released T3 (25,26,52,121-124,199,201-215,220,221) but not T4 (52,197-199,201,222,223).

The reduced immunity from chronic stress has been thought to be due to excess cortisol production; but the associated reduction in tissue thyroid levels are shown to play a larger role in the decreased immunity seen with stress, and thyroid supplementation is shown to reverse the stress induced reduction in immunity (217).

As with stress, treatment with prednisone or other glucocorticoid will suppress D1 and stimulate D3, reducing T4 to T3 conversion and increasing T4 to reverse T3, causing a relative tissue hypothyroidism that is not detected by TSH testing (12,18-21,194,218,224). This low cellular thyroid level certainly contributes to the weight gain and other associated side-effects with such treatment. Thus, in stressed patients or those treated with corticosteroids, there are reduced tissue T3 levels that are not reflected by the TSH level, making the TSH an inappropriate marker for tissue levels of T3.

Depression

Many depressed and bipolar patients have undiagnosed thyroid dysfunction as the underlying cause or major contributor to their depression (23-38). The dysfunction present with these conditions includes down regulation of D1 (reduced T4 to T3 conversion) and reduced uptake of T4 into the cell, resulting in increased serum T4 levels with low intracellular T3 levels (24-26,30,31,35,39-45) and upregulated D3, resulting in elevated reverse T3 (23,24,30,31), which blocks thyroid effect (147,184-194) and is an indicator of reduced transport of T4 into the cell (183,193). Additionally, studies show that depressed patients have reduced T4 transport across the blood brain barrier due to a defective transport protein, transthyretin, resulting in significantly reduced thyroid levels in the brains of depressed patients despite "normal" serum levels and standard thyroid tests (23,39,40) as well as a reduced TSH response to TRH (28-31,43-50).

It is not surprising that T4 and T4/T3 combinations may have some benefit in depression; but due to the suppressed T4 to T3 conversion from suppressed D1(24-26,30) and reduced uptake of T4 into the cell and brain (25,31,39,40), timed-released T3 is significantly more beneficial than T4 or T4/T3 combination supplementation (25,41,202,225-227).

In the *International Journal of Neruopsychopharmacology*, Posternak M et al. published a double blind placebo control trial of 50 patients with normal thyroid function as defined by a normal TSH (1.5 +/- 0.8). The patients were randomized to receive 25 mcg of T3 or placebo in addition to antidepressant therapy (221). The study found almost a 2-fold increase in response rate with T3 and a 4.5 times greater likelihood of experiencing a positive response at any point over a six-week period with the addition of T3. Side effects were higher in placebo group on 10/11 criteria including a significant increase in nervousness with the placebo group.

Kelly T et al. investigated the effectiveness of T3 for the treatment of biopolar disorder in who patients had failed to adequately respond to an average of 14 medications used to treat their bipolar disorder. The average dose of T3 used was 90.4 mcg (range 13 mcg-188 mcg). The medication was found to be well tolerated and 84% experienced significant improvement and 33% had a full remission. Again, this is in patients who had not previously responded to numerous medications. One patient who was switched to T4 for cost reasons experienced a return of symptoms, which resolved with the reintroduction of T3. The authors concluded, "Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression… (227)." The authors thanked several doctors who encouraged them to go beyond the traditional 50 mcg of T3 because it has helped so many of their patients.

With over 4000 patients, The Star*D Report is the largest trial comparing antidepressant effectiveness for depression. It found that 66% of patients fail to respond to antidepressants or have side-effects severe enough to discontinue use. Of those who do respond, over half will relapse within one year (228). The trial found that T3 was effective even when other medications -- such as citalopram (Celexa), bupropion (Wellbutrin), sertraline (Zolft), venlafaxine (Effexor), or cognitive therapy – were not. It was shown to be 50% more effective, even with the less than optimal dose of 50 mcg, under direct comparison with significantly less side effects than commonly used therapeutic approaches with standard antidepressants. The authors included a case study to exemplify the effectiveness of T3, especially when other medications are not:

> "Ms. "B," a 44-year-old divorced white woman, became depressed after losing her job as a secretary in a law firm. She initially sought treatment from her primary care physician and then entered the STAR*D study. Ms. B met criteria for major depressive disorder and generalized anxiety disorder. Her baseline QIDS-SR score was 16. After 12 weeks on citalopram, her QIDS-SR score was 10 [minimal response]. She was then randomly assigned to augmentation with buspirone; she soon experienced gastrointestinal distress,

> and she stopped taking buspirone after 6 weeks. She elected to try one more augmentation agent and was randomly assigned to T3 augmentation. When she started T3 augmentation, her QIDS-SR score was 12. After 4 weeks, she felt that her mood and energy had lifted substantially. She felt better able to make decisions, organize, and prioritize and felt that she was able and ready to look for another job. "I felt as if my brain suddenly had oxygen," she said, "and everything became clearer." After 12 weeks, Ms. B felt back to normal, and her QIDS-SR score was 0 [complete resolution of symptoms] (228)."

With an understanding of thyroid physiology and associated dysfunction that is present in depressed patients, it is clear that timed-released T3 supplementation should be considered in all depressed and bipolar patients despite "normal" serum thyroid levels. Additionally, straight T4 should be considered inappropriate and suboptimal therapy for replacement in such patients.

Pain

Chronic pain will significantly suppress D1 and upregulate D2, resulting in a reduction in tissue T3 without a change in TSH. Thus, the significant cellular hypothyroidism is not detected by serum TSH and T4 testing (116-119). This cellular hypothyroidism, which again is undiagnosed by standard blood tests, increases the risk of the associated fatigue and depression seen with chronic pain (116,117,229).

Narcotic pain medication can, of course, alleviate pain and thus potentially improve the diminished tissue T3 levels seen with chronic pain; but narcotics also suppress D1 but not D2, so such treatment is ineffective at reversing the suppressed tissue T3 levels (116-118,229). Thus, for those with significant chronic pain or using significant amounts of narcotic pain medicine, it must be understood that such a condition is associated with low tissue thyroid levels not detected by standard blood tests. Tolerance to the inhibitory effect of narcotics on TSH secretion and T4 to T3 conversion does not occur (116,119). Expert pain specialists understand this and recommend T3 supplementation to patients with significant pain or on narcotic pain medications (229).

Dieting

Acute or chronic dieting can result in a significant decrease in intracellular and circulating T3 levels by up to 50% (46,47,51,90), which significantly reduces basal metabolic rate (number of calories burned per day) by 15-40% (48,230,232). With chronic dieting, the thyroid levels and metabolism often do not return to normal levels; the body stays in starvation mode for years with significantly reduced metabolism despite the resumption of normal food intake, making it very difficult to lose or maintain lost weight (48).

A study by Araujo RL et al. published in *American Journal of Physiology, Endocrinology and Metabolism* found that 25 days of calorie restriction (dieting) significantly reduced D1, resulting in reduced T4 to T3 conversion with a 50% reduction in T3. This dramatic reduction in T3 was associated with an increase in D2, so there was no increase in TSH but rather a decrease from an average of 1.20 ng/ml to 0.7 ng/ml, demonstrating the fact that the TSH is a poor marker for tissue T3 levels, especially in a chronically dieting patient (47).

Fontana et al. found that T3 levels were significantly decreased by 25% in chronically dieting individuals compared to non-dieting individuals with no difference in TSH and T4 (thus undetected by TSH and T4 testing). This clinically significant reduction in T3 levels, potentially causing inability to lose weight or regaining of lost weight, fatigue, and depression, remained in the normal range despite the significant decline, demonstrating the weakness and unreliability of the common use of population references ranges that consider 95% of the population as "normal" (49).

A study by Leibel et al. published in the journal *Metabolism* found that individuals who had lost weight in the past had a significantly lower metabolism than those of same weight who had not gained or lost significant weight in the past (48). The metabolism in the weight reduced patients was 25% less than an equal weight person who did not lose or gain significant weight in the past and equal to someone who weighed 60% less than they did. Additionally, the reduction was shown to be present years later.

This 25% percent reduction in metabolism equates to an approximate deficit of 500-600 cal per day. Thus, if the previous overweight person is to maintain the reduced weight he or she lost, he or she must either eat 600 cal per day less compared to a person of same weight who has not had a weight problem or must jog about 1 ½ hours per day to maintain the lost weight. This equates to approximately a pound per week of weight gain, explaining why weight is so quickly gained without continued very strict dieting. So many people who have difficulty keeping weight off don't eat excessively but are continually told they are eating too much or they need to exercise more by people who have never had a weight problem. They are made to feel it is a character issue and that nobody believes how how little food they actually consume. Unless the physiologic thyroid dysfunction is corrected, any diet and exercise strategy is doomed.

Croxson et al. in *Journal of Endocrinology and Metabolism* found that individuals with a history of intense dieting had dramatic reductions in T4 to T3 conversion with an intracellular deficiency of T3. The inadequacy and inaccuracy of standard TSH and T4 testing was demonstrated, as such testing failed to detect the dramatic reduction in tissue levels of T3 in all of the patients (50).

Insulin resistance/diabetes/metabolic syndrome/obesity

As with leptin resistance, it has been shown in numerous studies that insulin resistance, diabetes, or metabolic syndrome have associated significant reduction in T4 to T3 conversion, an intracellular deficiency of T3, and an increased conversion of T4 to reverse T3, further reducing intracellular T3 levels (91,100,92,94,147,184-193,235). Additionally, the elevated insulin will increase D2 activity and suppress TSH levels, further decreasing thyroid levels and making it inappropriate to use the TSH as a reliable marker for tissue thyroid levels in the presence of elevated insulin levels as occurs with obesity, insulin resistance, or type II diabetes (91-99,233).

Pittman CS et al. found that normal individuals had a 77% conversion of T4 to T3, while diabetic individuals had a 45% conversion of T4 to T3 and increased T4 to reverse T3. Improvement in glucose levels only slightly increased T4 to T3 conversion to 46% (93).

Islam S et al. investigated the T4 to T3 conversion in 50 diabetic patients compared to 50 non-diabetic controls. There was no difference in TSH and free T4 levels, but the diabetic individuals had significantly decrease free T3 levels ($p = 0.0001$) that averaged 46% less than controls. The FT3/FT4 ratio was 50% less in diabetic patients versus controls. The TSH failed to elevate despite the fact that serum T3 was approximately half of normal (92). Saunders J, et al. also found that diabetics had approximately a 50% reduction in T3 levels and significantly increased reverse T3 levels and decreased T3/reverse T3 ratios (94).

In the *International Journal of Obesity*, Krotkiewski, et al. published the results of their investigation of the impact of supplemental T3 on cardiovascular risk in obese patients to partially reverse the reduced T4 to T3 conversion seen with obesity (53). Seventy obese patients with "normal" standard thyroid function tests were treated with 20 mcg of straight T3 for six weeks. While the dose was not high enough to completely reverse the reduced T4 to T3 conversion seen with obesity, there was a significant reduction in a number of cardiovascular risk factors, including cholesterol and markers for insulin resistance. There were no side-effects in any of the patients. The authors conclude, "T3 may be considered to ameliorate some of the risk factors associated with abdominal obesity, particularly in some subgroups of obese

women with a relative resistance to thyroid hormones possibly dependent on decreased peripheral deiodination of thyroxine (T4) (53)."

Thus, replacement with timed-released T3 preparations to normalize the reduced intracellular T3 levels is appropriate in such patients despite so-called "normal" levels while, on the contrary, T4-only preparations do not address the physiologic abnormalities of such patients and should be considered inappropriate replacement for obese patients or those with insulin resistance, leptin resistance, or diabetes, as they do not address the physiologic abnormalities in this group.

Leptin

The hormone leptin has been found to be a major regulator of body weight and metabolism. The body secretes leptin as weight is gained to signal the brain (specifically the hypothalamus) that there are adequate energy (fat) stores. The hypothalamus should then stimulate metabolic processes that result in weight loss, including a reduction in hunger, an increased satiety with eating, an increase in resting metabolism, and an increase in lipolysis (fat breakdown). New research has found that this leptin signaling is dysfunctional in the majority of people who have difficultly losing weight or are unable to lose weight (54-58).
The problem is not in the production of leptin; studies show that the majority of overweight individuals who are having difficulty losing weight have a leptin resistance, where the leptin is unable to produce its normal effects to stimulate weight loss (54-58). This leptin resistance is sensed as starvation, so multiple mechanisms are activated to increase fat stores, rather than burn excess fat stores (54-83).

Leptin resistance is shown to suppress D1 and stimulate D2, resulting in reduced cellular T3 but a reduction in serum TSH (47,84-89). A study by Cettour-Rose et al. published in *American Journal of Physiology, Endocrinology and Metabolism* demonstrated that physiologic reversal of leptin resistance restored deiodinase activity except in the presence of elevated reverse T3 (86). Thus, in the presence of elevated leptin level (above 10) there is a reduction of cellular T3 and a suppression of TSH, making the TSH an unreliable indicator of thyroid status, especially when combined with an elevated reverse T3. Thus, for anyone who has difficulty losing weight, a leptin level above 10 demonstrates that low intracellular thyroid levels is contributing to this difficulty, especially if combined with a high normal or elevated reverse T3 (above 150).

Exercise

It has been shown that women or men who perform more than moderate exercise, especially when associated with dieting, have reduced T4 to T3 conversion and increase reverse T3, counteracting many of the positive effects of exercise in women including weight loss (236,237). Consequently, T3 and reverse T3 levels should be evaluated in individuals who exercise and/or diet to better determine cellular thyroid levels, as TSH and T4 would not necessarily reflect tissue levels in such patients.

Iron deficiency

Iron deficiency is shown to significantly reduce T4 to T3 conversion, increase reverse T3 levels, and block the thermogenic (metabolism boosting) properties of thyroid hormone (238-242). Thus, iron deficiency, as indicated by an iron saturation below 25 or a ferritin below 70, will result in diminished intracellular T3 levels. Additionally, T4 should not be considered adequate thyroid replacement if iron deficiency is present (238,239,241,242).

Inflammation associated with common conditions

The inflammatory cytokines IL-1, Il-6, C-reactive protein (CRP), and TNF-alpha will significantly decrease D1 activity and reduce tissue T3 levels (105-113). Any person with an inflammatory condition -- including physical or emotional stress (243-248), obesity (248-252), diabetes (248,249,253), depression (254-257), menopause (surgical or natural) (258), heart disease (248,259,260), autoimmune disease (lupus, Hashimoto's, multiple sclerosis, arthritis, etc) (114,115,164,265), injury (266), chronic infection (261,262) or cancer (267-269) -- will have a decreased T4 to T3 conversion in the body and a relative tissue hypothyroidism. The inflammatory cytokines will, however, increase the activity of D2 and suppress the TSH despite reduced peripheral T3 levels; again, making a normal TSH an unreliable indicator of normal tissue thyroid levels (105-113)

There is a direct inverse correlation between CRP and reduced tissue T3 (112,270), so individuals with elevated CRP (greater than 3 mg/l) or other inflammatory cytokines will have a significant reduction in cellular T3 levels. The suppression of intracellular T3 levels correlates with the degree of elevation of CRP, despite serum thyroid tests being "normal" (112,270). Thus, if any inflammation is present, which is found in numerous clinical and subclinical conditions (as above), the body will have lower cellular T3 levels that are often inadequate for optimal functioning; but the pituitary will have increased levels of T3, resulting in a lowering of the TSH that would potentially be inappropriately interpreted as an indication of "normal" thyroid levels.

Thus, any person with an inflammatory condition will have diminished tissue levels of T3 potentially severe enough to cause symptoms, but these symptoms will not be detected by standard thyroid testing. Additionally, due to the reduced T4 to T3 conversion induced by the inflammation in these conditions, effective treatment must include T3 (combination or, ideally, timed-released T3). Also, due to the inflammatory suppression of TSH, not only is a normal TSH necessarily an indication of euthyroidism (normal thyroid), but also a suppressed TSH is not necessarily an indication of excessive thyroid with treatment. Rather, free T3 and reverse T3 levels along with clinical parameters should be used to determine optimal replacement doses of thyroid.

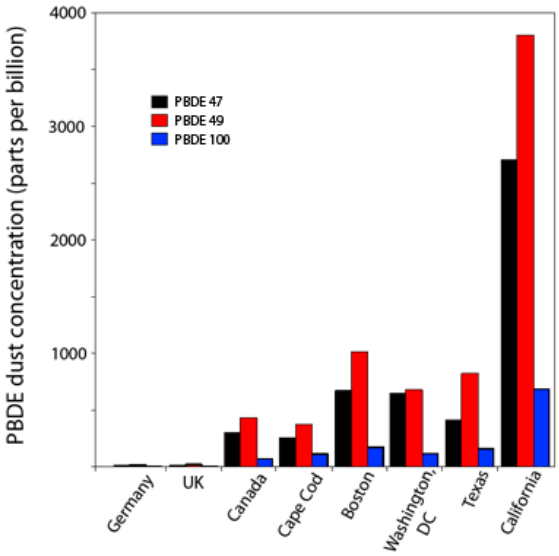
Additionally, inflammation will stimulate D3, producing more reverse T3, further causing cellular hypothyroidism not detected by TSH testing by suppressing intracellular T4 to T3 conversion and blocking the T3 receptor inside the cell (271).

Environmental toxins

Numerous toxins, including plastics such as Bisphenol-A, pesticides, mercury, and flame retardants such as PBDE, are shown to block tissue thyroid receptors and reduce T4 to T3 conversion with resultant low tissue levels of thyroid that are not detected by standard blood tests (126-134,283). In addition to being 1000 times more efficient at converting T4 to T3 (1,145), D2 is 100 to 1000-fold less sensitive to suppression by toxins or by mineral or hormonal deficiencies (1,2-5,145,224,273,274). Thus, the D1 in the body is suppressed by toxins, pesticides, and plastics at levels that are hundreds to thousands times lower than required to suppress the D2 in the pituitary. This is proving to be a major problem for the population in general; levels of plastics and other toxins commonly found in individuals (toxins that are considered "normal" exposure) result in reduced levels of T3 in all tissues with the exception of the pituitary, which is resistant to the effect of toxins. Because the pituitary is relatively unaffected, the reduced tissue thyroid levels are not detected by standard TSH testing.

For instance, Bisphenol-A, which is ubiquitous in the environment and large amounts of which can leach into food and liquids from plastic water bottles and the lining of aluminum cans, is shown to significantly block thyroid activity in all tissues except the pituitary, potentially contributing to or causing weight gain, fatigue, and depression but not detected by TSH testing (128,129,132,133,275). Levels of a number of

thyroid blocking toxins, including bisphenol-A and PBDE's, are significantly higher in individuals in the United States (PBDE's being especially high in California)(275,276), resulting in reduced T3 effect in all tissues in almost all individuals in the United States compared to the rest of the world that is not detected by standard thyroid testing. This is potentially a significant contributor to the epidemic of obesity and depression in the US.



Testosterone

Low testosterone in men will result in a lowering of D1 activity without changing pituitary D2 (143). Thus, a drop in testosterone will result in lower tissue levels of T3 without producing an elevation of TSH (143,144). Environmental factors, including pesticides, plastics, and other pollutants, have resulted in a significant decrease in the average testosterone levels for men, so most men will have, at least, a relative deficiency of testosterone (277). Major laboratories have, unfortunately, reduced the "normal" range of free testosterone to maintain the 95 percentile as normal, the result being that many abnormally low levels will now be considered normal.

In particular, the majority of male diabetics and those with insulin resistance will have suppressed testosterone level that is in the low or low-normal range, which further suppresses D1 and tissue T3 levels and perpetuates the weight gain or inability to lose weight -- worsening of these conditions (278-280).

Growth hormone

Growth hormone deficiency reduces T4 to T3 conversion and increases reverse T3 while supplementation with growth hormone improves T4 to T3 conversion and reduces reverse T3 (194,233,281,282). The age-associated decline in growth hormone certainly contributes to the reduced T3 levels with age not detected by TSH and T4 testing (see thyroid hormones and aging graph).

Individual variations in deiodinase

The relative amounts of D1, D2, and D3 vary in different tissues among different individuals (284) and under varying conditions (8,11,12-21,23-26,28-45,100-103,116-120,126-129,146,174-176,216,224,229,), resulting in hundreds of possible symptoms with hypothyroidism; some people have one symptom, some have a few, and some people have many, depending on the relative level of T3 in each tissue. Unfortunately, serum thyroid levels often do not accurately reflect intracellular tissue levels or levels in a particular tissue.

Summary:

With an improved understanding of thyroid physiology that includes the local control of intracellular activation and deactivation of thyroid hormones by deiodinases, it becomes clear that standard thyroid tests often do not reflect the thyroid status in the tissues of the body, other than the pituitary. This is especially true with physiologic and emotional stress, depression, dieting, obesity, leptin insulin resistance, diabetes, chronic fatigue syndrome and fibromyalgia, inflammation, autoimmune disease, or systemic illness. Consequently, it is inappropriate to rely on a normal or low TSH as an adequate or sensitive indicator of normal or low tissue levels of T3 in the presence of any such conditions, making the TSH a poor marker for the body's overall thyroid level.

In order to be appropriately and thoroughly evaluated for thyroid dysfunction and obtain optimal treatment, it is important that patients find a thyroidologist who understands the limitations of standard thyroid testing and can clinically evaluate patients by taking an extensive inventory of potential signs and symptoms that may be due to low tissue thyroid levels despite normal standard thyroid tests. The free T3/reverse T3 ratio can be valuable in evaluating potential deiodinase dysregulation and measuring the speed of the relaxation phase of the muscle reflex, and the basal metabolic rate can also be helpful additions in the evaluation of tissue thyroid levels.

Thyroid Hormone Transport and Cellular Energy

Thyroid hormone transport is an extremely important topic. It must be clearly understood by any physician who hopes to accurately evaluate an individual's thyroid status and to appropriately treat thyroid dysfunction. Unfortunately, only a small fraction physicians and endocrinologists understand even the basics of thyroid transport, because what they have learned in medical school and continue to be taught regarding this topic is incorrect. When one understands the physiology involved with thyroid hormone transport, it becomes clear that standard blood tests, including the TSH and T4 levels, cannot be used to accurately determine intracellular and tissue thyroid level in the presence of a wide range of common conditions, including chronic and acute dieting, anxiety, stress, insulin resistance, obesity, diabetes, depression and bipolar disorder, hyperlipidemia (high cholesterol and triglycerides), chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases (Alzheimer's, Parkinson's and multiple sclerosis), migraines, cardiomyopathy, and aging.

Serum thyroid levels are, of course, commonly used as an indication of cellular thyroid activity. In order to have biological activity, the T4 and T3 must, however, cross the cellular membrane from the serum into the target cells. It follows that the activity of these transport processes may have an important influence on the regulation of biological activity of the thyroid hormones. For about two and half decades it was assumed that the uptake of thyroid into the cells is by simple diffusion and that the driving force for this diffusion is the concentration of the free hormones in the serum. This "free hormone" or "diffusion hypothesis" was formulated in 1960 and assumes the concentration of free hormones (free T4 and free T3) in the serum determines the rate and extent of uptake into the cell and thus intracellular thyroid hormone concentration.

This hypothesis and mechanism of thyroid uptake into the cell has been shown to be totally incorrect (1-43). It has clearly been shown that the rate-limiting (most important) step in the determination of thyroid activity is the rate of thyroid hormone transport into the cell (5,20,41,44,45) and that this transport has nothing to do with diffusion, but rather it is energy

requiring active transport (1-43,45,46,47,48-64,65,66,67). The incorrect "diffusion hypothesis," however, continues to be taught in medical school and is believed to be true by most physicians and endocrinologists (see thyroid transport graph).

Conditions associated with abnormal thyroid transport

It is important to note that because this transport of thyroid hormones into the cell is energy dependent, any condition associated with reduced production of the cellular energy (mitochondrial dysfunction) will also be associated with reduced transport of thyroid into the cell, resulting in cellular hypothyroidism despite having standard blood tests in the "normal" range. Conditions associated with reduced mitochondrial function and impaired thyroid transport include: insulin resistance, diabetes and obesity (68,69,70,71,106); chronic and acute dieting (4,51,66,72,112,113,114,115,116,117,118); diabetes (69,73,74,75,76); depression (73,77,78,79); anxiety (73,80); bipolar depression (73,77,81,82); neurodegenerative diseases (73,83,84,85,86,87); aging (73,74,88-100); chronic fatigue syndrome (73,101,102); fibromyalgia (73,103,104); migraines (73); chronic infections (73); physiologic stress and anxiety (73,79); cardiovascular disease (73,99,104,105,108); inflammation and chronic illness (73,109,110,111); and those with high cholesterol and triglyceride levels (58,60,72,106,107). Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present (1-107).

The exact cause of the inhibition of the transport of thyroid is unknown, but it is clear that there are a number of substances that are produced by the body in response to dieting and physiologic stress that negatively effect thyroid hormone transport (5,41). This is clearly shown by studies where cell cultures are incubated with the serum from physiologically stressed or dieting individuals; there is shown to be a dramatic reduction of the uptake of T4 by the cells that correlates with the degree of stress (41,42).

Additionally, it has been clearly shown that there are different transporters that are specific and necessary for the transport of T4 and T3 into the cell where they have their effect. The transporter for T4 is much more energy dependent (it requires more energy) than the transporter for T3 (see figure 1) (5,40,41,49,52,53,66). Even slight reductions in cellular energy (mitochondrial function) results in dramatic declines in the uptake of T4 while the uptake of T3 is much less affected (5,41,62,67). Thus, the conditions listed above have, in particular, an impaired transport of T4 that results in cellular hypothyroidism. This cellular hypothyroidism is not detected by serum T4 levels because the less T4 transported into the cell and the lower the cellular level of T4, the higher the serum T4 level. The TSH will also not detect such cellular hypothyroidism because the pituitary has completely different transporters that are not energy dependent and increase transport activity, while the rest of body has impaired thyroid transport (see thyroid transport graph).

Pituitary thyroid transport determines TSH levels

As discussed previously, the pituitary is different than every cell in the body with different deiodinases and different high affinity thyroid receptors. It is also shown to have unique thyroid transporters that are different than those in the rest of the body (1,17,43,50,52,55,59,60,61). The pituitary thyroid hormone transporters are shown not to be energy dependent and will maintain or increase the uptake of T4 and T3 in low energy states, while this is not the case for

transporters in other parts of the body that have significantly reduced transport (1,17,22,43,50,52,55,59,60,61).

The transporters for T4 and T3 in the pituitary are also not inhibited by numerous environmental toxins and substances produced by the body during physiologic stress and calorie reduction that inhibit thyroid transport into other cells in the body, including bilirubin and fatty acids. Thus, the reduced uptake of T3 and T4 and subsequent intracellular hypothyroidism that occurs throughout the body from numerous conditions stated above is not reflected by TSH testing because thyroid uptake in the pituitary cells is not effected, making the TSH a poor marker for cellular thyroid in any tissue other than the pituitary (1,43,55).

Even common medications, including benzodiazepines such as diazepam (Valium), lorazapam (Atavan) and alprazolam (Xanax), are shown to inhibit T3 uptake into the cells of the body but have no effect on transport of T3 into the pituitary (61).

This difference in pituitary thyroid transport was investigated by Germain et al. This study demonstrated that with calorie restriction (dieting), pituitary T3 content is independent of the rest of the body. The dramatically reduced serum T4 and T3 levels seen with dieting are associated with an increase in pituitary T3 receptor saturation (percent of activated T3 receptors), which results in a decrease in TSH even when serum levels were reduced by 50% (55).

Studies show that numerous conditions are associated with reduced transport of thyroid into the cells, which can lead to dramatic cellular hypothyroidism and symptoms that are not detected by standard blood tests because the TSH will be normal and serum T4 may actually increase due to reduced uptake into the cells (54). Most physicians and endocrinologist are unaware of the importance of the difference of this rate-limiting step in cellular thyroid activity in the pituitary and the rest of the body. Physicians are often quick to declare a person with numerous symptoms of low thyroid as having “normal” thyroid function based on a normal TSH and T4 level.

Wassen FS et al states in the *Journal of Endocrinology* that “These observations lend further support to the view that thyroid hormone transport into the pituitary is regulated differently than that in the liver (50).” As stated, the T4 level may be high normal. This high-normal T4 and low-normal TSH often leads an endocrinologist to erroneously make a diagnosis of “normal” or “high-normal” thyroid level while a patient is in fact suffering from low cellular thyroid levels (see thyroid transport graph).

Stress

Chronic emotional or physiologic stress can cause the significant reduction of T4 into the cells of the body while the pituitary is unaffected. A study published in the *Journal of Clinical Endocrinology and Metabolism* studied the effect of adding serum from different groups of individuals to cell cultures and measured the amount of T4 uptake from the serum into the cell. The study found that the serum from those with significant physiologic stress inhibited the uptake (transport) of T4 into the cell while the serum from non-physiological stress had no effect, demonstrating that serum T4 levels are artificially elevated in physiologically stressed individuals and that serum T4 and TSH levels are poor markers for tissue thyroid levels in stressed individuals (4).

A number of studies have shown that significant physiologic stress reduces cellular uptake T4 and T3 by up to 50% (63,64,109,110,111). Arem et al found that with significant physiological stress, tissue levels of T4 and T3 were dramatically reduced by up to 79% without an increase in TSH. Additionally, when comparing the T4 and T3 levels in different tissues in different individuals, there is significant variation. This large variation of T4 and T3 levels in different tissues (not reflected by TSH or serum T4 and T3 levels) explains the wide range of symptoms that are due to tissue specific hypothyroidism not reflected or detected by standard blood tests, including TSH and T4 (56).

A confirming study published in the *Journal of Clinical Endocrinology and Metabolism* also found that serum from non-stress individuals had no effect on T4 cellular uptake, while those with significant physiologic stress had up to a 44% reduction in T4 uptake into the cell (42). It was shown that the free T3/reverse T3 ratio was the most accurate marker for reduced cellular uptake of T4 (42).

A number of substances have been identified that are produced in response to physiologic stress or calorie reduction. These include 3-carboxy-4-methyl-5-propyl-2-furna propanoic acid (CMPF), indoxyl sulfate, billirubin and fatty acids (1,3,57,58,60). The addition of these substances to cell cultures in concentrations comparable to those seen in patients results in a 27%-42% reduction in cellular uptake of T4 but has no effect on T4 or T3 uptake into the pituitary (1,17,57,58,60)(see thyroid transport graph).

Dieting

In a highly controlled study, Brownell et al found that after repeated cycles of dieting, weight loss occurred at half the rate and weight gain occurred at three times the rate compared to controls with the same calorie intake (118). Chronic and yo-yo dieting, frequently done by a large percentage of the population, is shown to be associated with reduced cellular T4 uptake of 25%-50% (3,49,112,114,115,116). Successful weight loss is doomed to failure unless the reduced intracellular thyroid levels are addressed, but this reduced cellular thyroid level is generally not detected by standard laboratory testing unless a free T3/reverse T3 ratio is done.

In a study published in the *American Journal of Physiology-Endocrinology and Metabolism*, Van der Heyden et al studied the effect of calorie restriction (dieting) on the transport of T4 and T3 into the cell (49). It was found that dieting obese individuals had a 50% reduction of T4 into the cell and a 25% reduction of T3 into the cell due to the reduced cellular energy stores, demonstrating that in such patients standard thyroid blood tests are not accurate indicators of intracellular thyroid levels. This also demonstrates why it is very difficult for obese patients to lose weight; as calories are decreased, thyroid utilization is reduced and metabolism drops. This will, however, not be detected by standard TSH, T4 and T3 testing (a free T3/reverse T3 can aid in the diagnosis of reduced uptake of thyroid hormones and intracellular hypothyroidism). Additionally, there are increased levels of free fatty acids in the serum with chronic dieting, which further suppresses T4 uptake into the cells and further cellular hypothyroidism (106,72,57,58,114).

Many overweight individuals fail to lose weight with dieting. While it is always assumed they are doing a poor job of dieting, it has been shown, however, that chronic dieting in overweight individuals results in increased levels of NEFA, which suppresses T4 uptake into the cells (3).

This suppressed T4 uptake results in reduced intracellular T4 levels and subsequent T4 to T3 conversion and a reduced metabolism (3,112,114,115,116)(see thyroid transport graph).

Reverse T3

TSH and serum T4 levels fail to correlate with intracellular thyroid levels. Additionally, the free T3 will also tend to be less accurate with reduced cellular energy. This artificial elevation of T3 due to be reduced uptake into the cell is generally offset by a reduced T4 to T3 conversion due to reduced uptake and T4 and subsequent conversion to T3, making T3 a more accurate marker than the TSH or T4 with physiologic stress. Also, the transporter for reverse T3 (rT3) is similar to T4 in that it is energy dependent and has the same kinetics as the T4 transporter (6,41,45,62,66,67). This property (among others) makes it the most useful indicator of diminished transport of T4 into the cell (45).

Thus, a high reverse T3 demonstrates that there is either an inhibition of reverse T3 uptake into the cell and/or there is increased T4 to reverse T3 formation. These always occur together in a wide range of physiologic conditions and both cause reduced intracellular T4 and T3 levels and cellular hypothyroidism. Thus, reverse T3 is an excellent marker for reduced cellular T4 and T3 levels not detected by TSH or serum T4 and T3 levels. Because increased rT3 is a marker for reduced uptake of T4 and reduced T4 to T3 conversion, any increase (high or high normal) in rT3 is not only an indicator of tissue hypothyroidism but also that T4 only replacement would not be considered optimal in such cases and would be expected to have inadequate or sub-optimal results. A high reverse T3 can be associated with hyperthyroidism as the body tries to reduce cellular thyroid levels, but this can be differentiated by symptoms and by utilizing the free T3/reverse T3 ratio, which is proving to be the best physiologic marker of intracellular thyroid levels (see Diagnosis of low thyroid due to stress & illness Graph).

Treatment

Levothyroxine (T4)-only replacement with products such as Synthroid and Levoxyl are the most widely accepted forms of thyroid replacement. This is based on a widely held assumption that the body will convert what it needs to the biologically active form T3. Based on this assumption, most physicians and endocrinologists believe that the normalization of TSH with a T4 preparation demonstrates adequate tissue levels of thyroid. This assumption, however, had never been directly tested until two studies were published (119,120). The first study investigated whether or not giving T4 only preparations will provide adequate T3 levels in varying tissues. Plasma TSH, T4 and T3 levels and 10 different tissue levels of T4 and T3 were measured after the infusion of 12-13 days of thyroxine.

This study demonstrated that the normalization of plasma TSH and T4 levels with T4-only preparations provide adequate tissue T3 levels to only a few tissues, including the pituitary (hence the normal TSH), but almost every other tissue will be deficient. This study demonstrated that it is impossible to achieve normal tissue levels of T3 by giving T4 only preparations unless supra-physiological levels of T4 are given. The authors conclude: “It is evident that neither plasma T4 nor plasma T3 alone permit the prediction of the degree of change in T4 and T3 concentrations in tissues…the current replacement therapy of hypothyroidism [giving T4] should no longer be considered adequate…(119).”

The second study compared the plasma TSH, T4 and T3 levels and 13 different tissue levels of T4 and T3 when T4 or T4/T3 preparations were utilized (120). This study found that a combination of T4/T3 is required to normalize tissue levels of T3. The study found that the pituitary was able to maintain normal levels of T3 despite the rest of the body being hypothyroid on T4 only preparations. Under normal conditions it was shown that the pituitary will have 7 to 60 times the concentration of T3 of other tissues of the body; and when thyroid levels drop, the pituitary was shown to have 40 to 650 times the concentration of T3 of other tissues. Thus, the pituitary is unique in its ability to concentrate T3 in the presence of diminished thyroid levels that are not present in other tissues. Consequently, the pituitary levels of T3 and the subsequent level of TSH are poor measures of tissue hypothyroidism, as almost the entire body can be severely hypothyroid despite having a normal TSH level (120).

These studies add to the large amount of medical literature demonstrating that pituitary thyroid levels are not indicative of other tissues in the body and showing why the TSH level is a poor indicator of a proper thyroid dose. These studies also demonstrate that it is impossible to achieve normal tissue thyroid levels with T4 preparations such as Synthroid and Levoxyl. It is no surprise that the majority of patients on T4 preparations will continue to suffer from symptoms of hypothyroidism despite being told their levels are "normal." Patients on T4 only preparations should seek out a physician who is well-versed in the medical literature and understands the physiologic limitations and inadequacy of commonly used thyroid preparations.

The dramatic reduction of T4 cellular uptake with a wide variety of conditions (T3 being less affected) also explains why T4 preparations are often associated with poor clinical response and continued residual symptoms that the unknowing physician assumes is not due to low thyroid, because serum levels look "good" if the physician does not understand the potential effects of reduced thyroid hormone transport. As stated by Hennemann G et al in *Endocrine Reviews*: "Even a small decrease in cellular ATP concentration results in a major reduction in the transport of T4 (and rT3) but only slightly affects T3 uptake (5)." This makes it inappropriate to use T4-only preparations if treating any condition associated with the following: reduced mitochondrial function or ATP production, which includes insulin resistance, diabetes and obesity 68,69,70,71,106); chronic and acute dieting (4,51,66,72,112,113,114,115,116,117,118); diabetes (69,73,74,75,76); depression (73,77,78,79); anxiety (73,80); bipolar depression (73,77,81,82); neurodegenerative diseases (73,83,84,85,86,87); aging (73,74,88-100); chronic fatigue syndrome (73,101,102); fibromyalgia (73,103,104); migraines (73); chronic infections (73); physiologic stress and anxiety (73,79); cardiovascular disease (73,99,104,105,108) and inflammation and chronic illness (73,109,110,111); Likewise, high cholesterol, fatty acids or triglyceride levels also selectively inhibit T4 transport into the cell as opposed to T3 (57,58,60,72,106,107,114), making T4-only preparations physiologically inappropriate for individuals with high cholesterol or triglycerides or who are chronic dieters, which dramatically increases serum free fatty acids (72). It is not surprising that T3 has been shown to be superior in such patient populations.

Fraser et al investigated the correlation between tissue thyroid activity and serum blood tests (TSH, free T4 and T3) and published their results in the *British Medical Journal*. The study authors concluded that "The serum concentration of thyroid stimulation hormone is unsatisfactory as the thyrotrophs in the anterior pituitary are more sensitive to changes in the concentration of thyroxin in the circulation than other tissues, which rely more on triiodothyronine (T3)." They found a suppressed or undetectable TSH was not an indication or a reliable marker of over replacement or hyperthyroidism. They state,

> It is clear that serum thyroid hormone and thyroid stimulating hormone concentrations cannot be used with any degree of confidence to classify patients as receiving satisfactory, insufficient, or excessive amounts of thyroxine replacement…The poor diagnostic sensitivity and high false positive rates associated with such measurements render them virtually useless in clinical practice…Further adjustments to the dose should be made according to the patient's clinical response (121).

The positive predictive value of the TSH, which is the likelihood that as suppressed TSH indicates over replacement or hyperthyroidism, was determined to be 16%. In other words, a suppressed TSH is not associated with hyperthyroidism or over-replacement 84% of the time, making it an inaccurate and inappropriate marker to determine appropriate replacement dosing. Additionally, the TSH becomes an even worse indicator the optimal replacement dose in the following situations: if a person has insulin resistance or obesity (68,69,70,71,106); is a chronic dieter (4,51,66,72,112,113,114,115,116,117,118); has diabetes (69,73,74,75,76); has depression (73,77,78,79); has bipolar depression (73,77,81,82); has a neurodegenerative diseases (73,83,84,85,86,87); is of older age (73,74,88-100); has chronic fatigue syndrome (73,101,102); has fibromyalgia (73,103,104); migraines (73); has a chronic infections (MT63)(73); is stressed or anxious (73,79,80); has heart failure or cardiovascular disease (73,99,104,105,108); suffers from migraines (73); has inflammation or a chronic illness (73,109,110,111); or has high cholesterol or triglyceride levels (57,58,60,72,106,107,114).

In a study published in the *British Medical Journal*, Meir et al also investigated the correlation of TSH and tissue thyroid effect. It was shown that the TSH level had no correlation with tissue thyroid levels and could not be used to determine a proper or optimal thyroid replacement dose. The authors concluded that "TSH is a poor measure for estimating the clinical and metabolic severity of primary overt thyroid failure. ... We found no correlations between the different parameters of target tissues and serum TSH." They stated that signs and symptoms of thyroid effect and not the TSH should be used to determine the proper replacement dose (122).

Alevizaki et al also studied the accuracy of using the TSH to determine the proper thyroid replacement dose in T4 treated individuals. The study found that such a practice of using the TSH, although common, results in the majority of tissues being hypothyroid, except for the pituitary. They conclude, "TSH levels used to monitor substitution, mostly regulated by intracellular T3 in the pituitary, may not be such a good indicator of adequate thyroid hormone action in all tissues (123)."

In a study published in the *Journal of Clinical Endocrinology and Metabolism*, Zulewski et al also investigated the accuracy of TSH to determine proper thyroid replacement. The study found that the TSH was not a useful measure of optimal or proper thyroid replacement, as there was no correlation between the TSH and tissue thyroid levels. Serum T4 and T3 levels had some correlation, with T3 being a better indictor than T4. In contrast, a clinical score that involved a thorough assessment of signs and symptoms of hypothyroidism was shown to be the most accurate method to determine proper replacement dosing. The authors also agreed that it is improper to use the TSH as the major determinant of the proper or optimal doses of thyroid replacement, stating "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 [symptoms] (124)."

Conclusion

The most important determinant of thyroid activity is the intra-cellular level of T3, and the most important determinant of the intracellular T3 level is the activity of the cellular thyroid transporters (1-67). Reduced thyroid transport into the cell is seen with a wide range of common conditions, including insulin resistance, diabetes, depression, bipolar disorder, hyperlipidemia (high cholesterol and triglycerides), chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases (Alzheimer's, Parkinson's and multiple sclerosis), migraines, stress, anxiety, chronic dieting and aging (1-43,46,49,51,52,53,58,60,66,68,69,72-118).

This high incidence of reduced cellular thyroid transport seen with these conditions makes standard thyroid tests a poor indicator of cellular thyroid levels in the presence of such conditions. The pituitary has different transporters than every other tissue in the body; the thyroid transporters in the body are very energy dependent and affected by numerous conditions while the pituitary is minimally affected. Because the pituitary remains unaffected, there is no elevation in TSH despite wide-spread tissue hypothyroidism, making the TSH an inaccurate marker for tissue T3 levels under the numerous conditions listed above (1,3,4,17,22,43,50,52,55,59,60,61).

The reduced thyroid transport seen with these conditions results in an artificial elevation in serum thyroid levels (especially T4), making this a poor marker for tissue thyroid levels as well (5,40,41,49,52,53,62,66,67). An elevated or high-normal reverse T3 is shown to currently be the best marker for reduced transport of thyroid hormones and an indication that a person has low cellular thyroid levels despite the fact that standard thyroid tests such as TSH, free T4, and free T3 are normal (6,32,41,45,62,66,67,125-172)(see Diagnosis of low thyroid due to stress & illness Graph).

The intracellular T3 deficiency seen with these conditions often results in a vicious cycle of worsening symptoms that usually goes untreated because standard thyroid tests look normal. Additionally, it is not surprising that T4 preparations are generally ineffective in the presence of such conditions, while T3 replacement is shown to be beneficial, with potentially dramatic results (71,74,75,76,80,81,82,86,97,98,99,100,101,102,103,104,105,173-198). In the presence of such conditions, it should be understood that significant intracellular hypothyroidism may exist that remains undiagnosed by standard blood tests (the freeT3/reverse T3 ratio may aid in the diagnosis). Thus, more appropriated testing beyond standard thyroid function tests should be considered and supplementation with T3 should be considered with such patients.

Why Doesn't My Doctor Know All of This?

A question often raised by patients is: "Why doesn't my physician know about the inaccuracies and limitations of standard thyroid tests?" The reason is that the overwhelming majority of physicians (endocrinologists, internists, family practitioners, rheumatologists, etc.) do not read medical journals. When asked, most doctors will claim that they routinely read medical journals, but this has been shown not to be the case. Many reasons exist, but it comes down to the fact that doctors do not have the time -- they are too busy running their practices. The overwhelming majority of

physicians rely on what they have learned in medical school and on consensus statements by medical societies, such as the Endocrine Society, the American Association of Clinical Endocrinologists or the American Thyroid Association, to direct treatment decisions.

Historically, relying on a consensus statement to treat or not to treat a particular patient has been shown to result in poor care and, as such, society consensus statements and practice guidelines are considered to be worst level of evidence in support of a particular therapy or treatment. A number of organizations, including the World Health Organization and others, have ranked the strength and accuracy of various types of evidence used in the medical decision process. In all scoring systems, the highest strength of evidence is randomized control trials and meta-analyses, with lower scores for other types of evidence. All grading systems place consensus statements and expert opinion by respected authorities (societies) as the poorest level of evidence, because historically they have failed to adopt new concepts and treatments based on new knowledge or new-found understanding demonstrated in the medical literature (1-6).

For instance, a recent study published in the 2009 *Journal of American Medical Association* studied the evidence supporting the practice guidelines and consensus statements published by the American College of Cardiology and the American Heart Association. It was found that only 11% of the recommendations, practice guidelines and consensus statements were based on quality evidence and over half were based on poor quality evidence that was little more than the panel's opinion. The review also found that even the strongest (Class 1) recommendations, which are considered medical dogma, cited as a legal standards and often go unquestioned as medical fact, were only supported by high quality evidence 19% of the time and not revised based on new evidence (6).

Guidelines are often out-of-date even before they are published. Additionally, once a guideline is published, there is major resistance to making needed changes or revisions as new information becomes available. They are often inappropriately used to define "proper" treatment for decades to come (22,26-28). Groups such as the Endocrine Society, the American Association of Clinical Endocrinologists and the American Thyroid Association have a long history of publishing guidelines and recommendations that are not supported by the medical literature and fail to adjust or abandon recommendations when new understanding and knowledge contradicts their recommendations, including those that state that a normal TSH adequately rules out thyroid dysfunction, despite massive amounts of literature that demonstrate this not to be the case or that T4 only replacement is adequate for most patients. A doctor who simply follows outdated society treatment guidelines that relies on a simple laboratory test and ignores the clinical aspects of a patient is not practicing evidence-based medicine. (1-7,22). Such doctors may be adequate as lab technicians, but as doctors and clinicians they fall short (1-7). This method of practice is consistently rebuked as improper and poor medicine, but has become the standard used by a large percentage of endocrinologists and physicians who feel medicine can be related to simply reading "normal" or "abnormal" in a laboratory column.

Discussing the lack of scientific basis of most medical society's consensus statements and treatment guidelines in *Internal Medicine News*, Dr. Diana Petritti, states,

> "Expert opinion and consensus statements can be quite misleading when used as the basis for a practice. Expert opinions imply that there is something that the experts know that clinician doesn't know. I don't think it's always appreciated that it's only opinion.

> There is a tendency to make guidelines and recommendations seem authoritative. I believe that physicians think that there is a great deal more behind authoritative recommendations than there might be when you lift the lid of the box and see what's underneath (8)."

There has been significant concern by health care organizations and medical experts that physicians are placing too much reliance on consensus statements that over generalize and may not apply to a particular patient and for failing to learn of new information presented in medical journals (1-3,6-23). Thus, physicians are showing a lack the ability to translate this new information into treatments for their patients. The concern is that doctors fail to practice evidence-based medicine, erroneously relying on what they have previously been taught and on "expert" societies instead of changing treatment philosophies based on new information as it becomes available. This is especially true for endocrinological conditions, where physicians are very resistant to changing old concepts of diagnosis and treatment -- despite overwhelming evidence to the contrary -- because it is not what they were taught in medical school and endocrinology residency.

This concern is particularly clear in an article published in the *New England Journal of Medicine* entitled "Clinical Research to Clinical Practice: Lost in Translation" (9). The article was written by Claude Lenfant, M.D., Director of National Heart, Lung and Blood Institute, and it is well supported. He states that there is great concern that doctors continue to rely on what they learned 20 years before and are uninformed about scientific findings. According to Dr. Lenfant, medical researchers, along with public officials and political leaders, are increasingly concerned about physicians' inability to translate research findings in their medical practice to benefit their patients. He says that very few physicians learn about new discoveries from reading medical journals or by attending scientific conferences; thus, they lack the ability to translate new knowledge in the field into enhanced treatments for their patients. He states that a review of past medical discoveries reveals how excruciatingly slow the medical establishment is to adopt novel concepts, noting that even simple methods to improve medical quality are often met with fierce resistance.

> "Given the ever-growing sophistication of our scientific knowledge and the additional new discoveries that are likely in the future, many of us harbor an uneasy, but quite realistic suspicion that this gap between what we know about disease and what we do to prevent and treat them will become even wider. And it is not just recent research results that are not finding their way into clinical practice; there is plenty of evidence that 'old' research outcome have been lost in translation as well (1)."

Dr. Lenfant discusses the fact that the proper practice of medicine involves the combination of medical knowledge, intuition and judgment and that physicians' knowledge is lacking because they don't keep up with the medical literature. He states that there is often a difference of opinion among physicians and reviewing entities, but that judgment and knowledge of the research pertaining to the patient's condition is central to the responsible practice of medicine. "Enormous amounts of new knowledge are barreling down the information highway, but they are not arriving at the doorsteps of our patients (9)."

These thoughts are echoed by physicians who have researched this issue as well, such as William Shankle, M.D., Professor, University of California, Irvine. He states,

> "Most doctors are practicing 10 to 20 years behind the available medical literature and continue to practice what they learned in medical school….There is a breakdown in the transfer of information from the research to the overwhelming majority of practicing physicians. Doctors do not seek to implement new treatments that are supported in the literature or change treatments that are not (10)."

This view is echoed by the Dean of Stanford University School of Medicine who states that in the absence of translational medicine the delivery of medical care would remain stagnant and uninformed by the tremendous progress taking place in science and medicine (11).
This concern has also received significant publicity in the mainstream media.

An example is an article by Sidney Smith, M.D., former president of the American Heart Association, published in 2003 in the *Wall Street Journal* entitled *Too Many Patients Never Reap the Benefits of Great Research*. Dr. Smith is very critical of physicians for not seeking out available information and applying that information to their patients, arguing that doctors feel the best medicine is what they've been doing and thinking for years. They discount new research, Dr. Smith says, because it is not what they have been taught or practiced, and they refuse to admit that what they have been doing or thinking for many years is not the best medicine. He states, "A large part of the problem is the real resistance of physicians…; many of these independent-minded souls don't like being told that science knows best, and the way they've always done things is second-rate *(12)."* The National Center for Policy Analysis also expresses concern for the lack of ability of physicians to translate medical therapies into practice (13).

A review published in *The Annals of Internal Medicine* found that there is clearly a problem of physicians not seeking to advance their knowledge by reviewing the current literature, believing proper care is what they learned in medical school or residency and not basing their treatments on the most current research. The review found that the longer a physician is in practice, the more inappropriate and substandard the care (14). Thus, it is not a surprise that the scientific evidence as expressed in the literature is often opposite to what is continually repeated as dogma by most physicians and those considered to be "experts."

Another example is a study published in the *Journal of the American Medical Informatics Association* (15). In reviewing the study, the National Institute of Medicine reports that there is an unacceptable lag between the discovery of new treatment modalities and their acceptance into routine care: "The lag between the discovery of more effective forms of treatment and their incorporation into routine patient care averages 17 years (16)." In response to this unacceptable lag, the Business and Professions Code passed an amendment relating to the healing arts. This amendment -- CA Assembly Bill 592; An Act to Amend Section 2234.1 of the Business and Professions Code -- states: "Since the National Institute of Medicine has reported that it can take up to 17 years for a new best practice to reach the average physician and surgeon, it is prudent to give attention to new developments not only in general medical care but in the actual treatment of specific diseases, particularly those that are not yet broadly recognized [such as the concept of tissue hypothyroidism, chronic fatigue syndrome and fibromyalgia] (17)."

The Principals of Medical Ethics adopted by the American Medical Association in 1980 states that a physician shall continue to study, apply, and advance scientific knowledge, make relevant information available to patients, colleagues, and the public (18). This has, unfortunately, been replaced with a goal of being able to make rapid decision on a patient's thyroid status based

review the normal or abnormal column on the lab results for a single test. This despite the fact that hundreds of studies document the inaccuracy of the TSH.

Signs, symptoms, history and the physical exam are typically considered to be irrelevant if the TSH is normal. This method is vehemently defended. Also, the current insurance reimbursement system in the United States fosters this thinking, as the worst physicians are financially rewarded by insurance companies as they are able to see many patents per day as opposed to a doctor does an thorough evaluation of thyroid function, which takes more time. While it is true that the best physicians are continually fighting to provide cutting edge treatments and superior care that the insurance companies deem not medically necessary, even these physicians eventually get worn down and are forced to capitulate to the current system that promotes substandard care.

This was clearly demonstrated in a study published in the March 2006 edition of *The New England Journal of Medicine* entitled Who is at Greater Risk for Receiving Poor-Quality Health Care. The study found that the majority of individuals received substandard, poor-quality care, and that there was no significant difference among different income levels or whether or not the individual was covered by insurance. It used to be the case that only those in low socioeconomic classes without insurance received poor-quality care. But insurance company restrictions on treatments and diagnostic procedures have made the same poor care afforded to those of low socioeconomic status the new standard-of-care for society at large (19). An example of this is a physician's failing to spend the time to adequately assess a potential hypothyroid patient and instead simply does a TSH test.

Most physicians will satisfy their required amount of continuing medical education (CME) by going to a conference a year, usually at a highly desirable location that has skiing, golf, boating, etc. Physicians are rarely monitored as to whether or not they actually showed up for the lectures or went skiing instead. One must also understand that the majority of conferences organized by medical societies are in fact sponsored by pharmaceutical companies. These payments by pharmaceutical companies are called unrestricted grants, so that the society has free reign to do what they want with the money and thus can claim there is no influence of lecture content by the companies. The problem, however, is that if the society wants to continue getting these "unrestricted" grants, they must think twice about providing content that the sponsoring pharmaceutical company might disapprove of. Consequently, ground breaking research that goes against the status quo and does not support the drug industry receives little attention.

Although medical societies profess to operate for the public good, there is significant concern that the medical societies not only use guidelines and recommendations to further their own economic interests, but they also use the opportunity to "sit in judgment of their competitors" (20-23,29). They are putting their interests above those of patients and are not aligned with the best interest of patients or the general public (20-23,29). Potential resolutions of this problem has been discussed in a number of medical journals, including Journal of the American Medical Association (22,29). It is states that practice guidelines, such as those published by the Endocrine Society and the American Thyroid Association stating that the TSH should be the sole means to diagnosed low thyroid, have evolved into marketing and opinion pieces that have less to do with the proper treatment of patients and more about expanding the societies' influence in a competitive marketplace (22,29). A review article published in the 2009 American Family Physician by Lin recommends that family physicians should avoid using such "opinion" or "consensus-based" guidelines all together and argues that good guidelines offer flexibility,

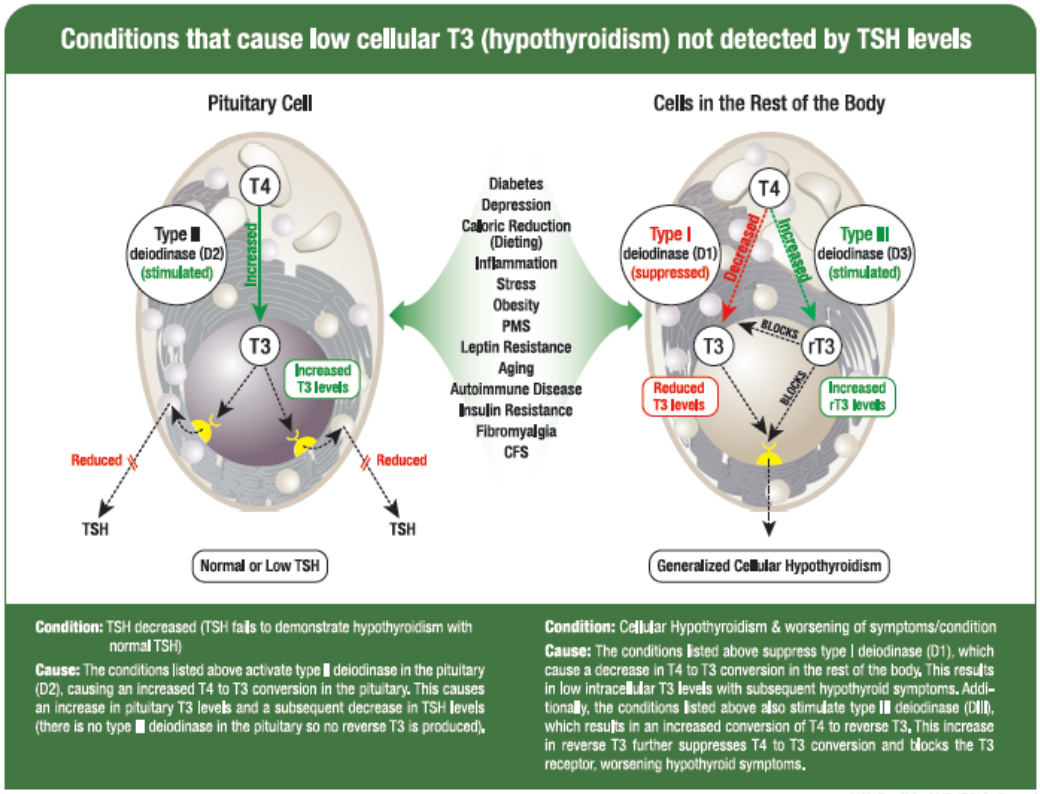
incorporate patients wishes and emphasis patient-oriented outcomes such as quality of life over laboratory results and other surrogate markers (31).

Evidence-based medicine involves the synthesis of *all* available data when comparing therapeutic options for patients. Evidence-based medicine does not mean that data should be ignored until a randomized control trial of a particular size and duration is completed. A physician who tries to avoid the need of being a physician and is fine with just being a technician or health care provider will adamantly defend the "one-size fits all" method of diagnosis and treatment. But the best doctors who truly practice evidence-based medicine and not merely the perception of such will not rely on consensus statements to best provide their patients. In a review article of evidence-based medicine by Toriello HV, et al, the authors emphasize that "Evidence-Based medicine is the integration of research evidence with both clinical expertise and patients' specific values and circumstances (30)." It is not relying on the old dogma of a consensus statement. Instead of relying on old dogma, the best physicians will seek out and translate both basic science results and clinical outcomes to decide on the safest, most efficacious treatment for their patients. Further, the best physicians will continually assess the current available data to decide which therapies are likely to carry the greatest benefits for patients and involve the lowest risks.

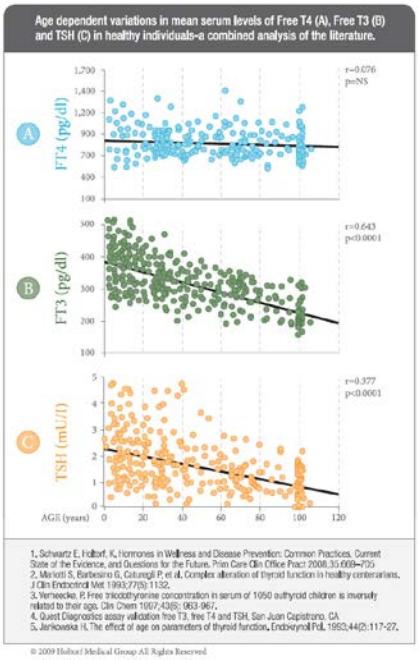
Additionally, and essential component of informed consent requires that in the absence of medical certainty, patients have the opportunity to choose among medically indicated treatments (20). Thomas May from the Medical College of Wisconsin's Center for the Study for the Study of Bioethics addressed the question of patient choice when there is medical controversy regarding the treatment. May concluded that it is vital to preserve choice and allow the individual whose life is most affected by that choice, the patient, to exercise autonomy of decision (24). This is in total agreement with the American Medical Association's code of ethics, which states: "The principle of patient autonomy requires that competent patients have the opportunity to choose among medically indicated treatments and to refuse any unwanted treatments (25)." Choice can only be preserved by understanding and acknowledging divergent viewpoints on treatment options and providing those treatment options (20,24,25).

Graphs:

Pituitary Diagram:



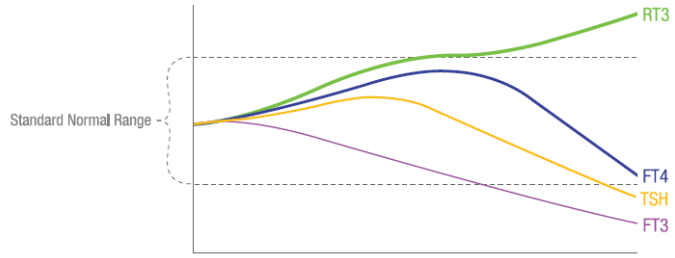
Thyroid Hormones and Aging:



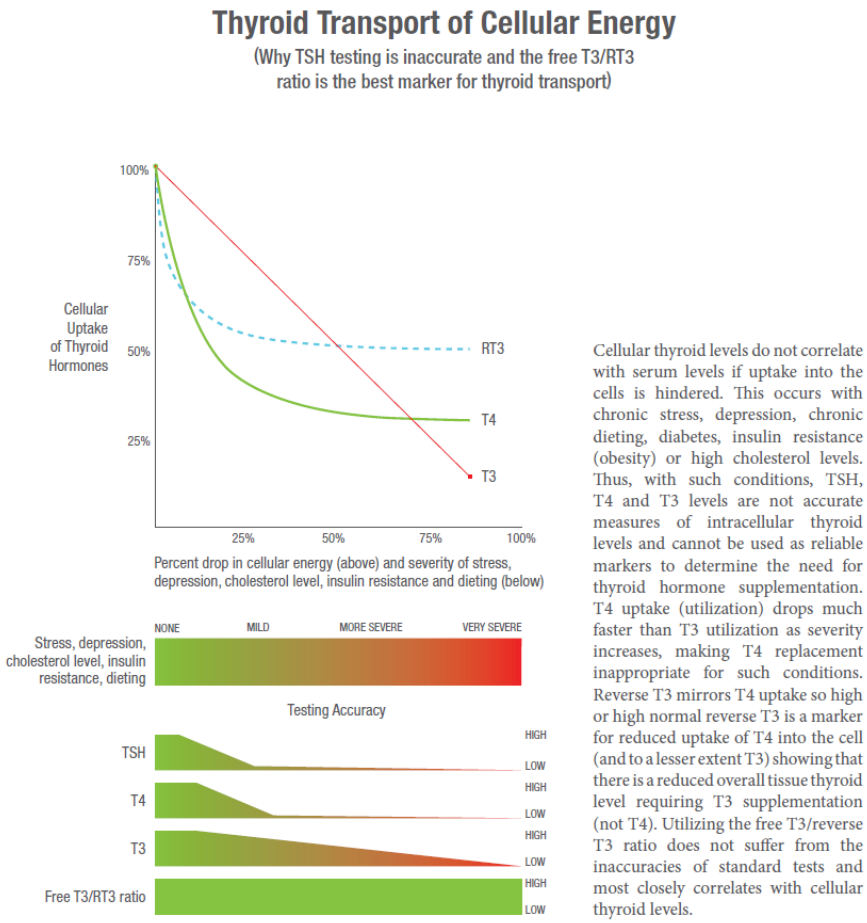
Serum thyroid levels in stress and illness:

Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions)

Demonstrates why TSH levels lack the accuracy to detect cellular levels and the free T3/reverse T3 ratio is the most accurate method to determine cellular thyroid levels in the presence of physiologic stress, illness, depression or obesity.



Severity of illness/depression stress/calorie reduction	none	mild	moderate	severe
Normal aging	young	middle	older	elderly
Tissue hypothyroidism (diminished tissue T3 level)	none/mild	mild/moderate	moderate/severe	severe
Inaccuracy of TSH and T4 levels	none	potentially significant	significant	substantial
Diminished utilization of T4	none/mild	mild/moderate	moderate/severe	severe



Cellular thyroid levels do not correlate with serum levels if uptake into the cells is hindered. This occurs with chronic stress, depression, chronic dieting, diabetes, insulin resistance (obesity) or high cholesterol levels. Thus, with such conditions, TSH, T4 and T3 levels are not accurate measures of intracellular thyroid levels and cannot be used as reliable markers to determine the need for thyroid hormone supplementation. T4 uptake (utilization) drops much faster than T3 utilization as severity increases, making T4 replacement inappropriate for such conditions. Reverse T3 mirrors T4 uptake so high or high normal reverse T3 is a marker for reduced uptake of T4 into the cell (and to a lesser extent T3) showing that there is a reduced overall tissue thyroid level requiring T3 supplementation (not T4). Utilizing the free T3/reverse T3 ratio does not suffer from the inaccuracies of standard tests and most closely correlates with cellular thyroid levels.

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Diagnosis of Hypothyroidism: Why TSH testing may not be an accurate marker of tissue thyroid levels

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