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HYPOTHYROIDISM REDEFINED

At first sight there could hardly be a more simple disorder to diagnose and treat than hypothyroidism. Now that we have robust assays and reliable preparations of thyroxine in tablet size sufficiently small to tailor doses to an individual's requirement, what issues remain? **~Weetman, 1997**

Background and Summary: Our collective understanding of hypothyroidism has evolved beyond simply an issue of normal vs. abnormal laboratory values. Yet, when confronted with signs and symptoms that suggest hypothyroidism, controversy exists as to which course of action to take. Subclinical hypothyroidism (ScH) serves as an example. In ScH, thyroid stimulating hormone (TSH) elevation reflects a ***"logarithmically amplified"*** increase in stimulation directed at an underperforming thyroid gland (Andersen et al., 2002). The signs and symptoms that follow suggest that, although normal, the levels of T3 and T4 are not *"truly normal"* for the individual. Addressing this issue, one team of investigators write: *"The condition may be **clearly** associated with somatic symptoms, depression, memory and cognitive impairment, subtle neuromuscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of total and LDL cholesterol, and an increased risk of atherosclerosis."* Continuing, *"Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are **not truly normal** for that individual."* (McDermott and Ridgeway, 2001, emphasis added) Both ScH and overt hypothyroidism are seldom discussed in context with the hallmark "rat studies" conducted by Escobar-Morreale et al in the mid 1990s, although they are clearly relevant. In these studies, thyroidectomized rats were studied to determine if giving T4 alone would translate into normal thyroid hormone levels within the principle tissues of the body. Even in the face of normal plasma T3 and T4 levels, all tissues analyzed were abnormal, prompting the following statement**:** ***"****We have recently shown that it is not possible to restore euthyroidism completely in all tissues of thyroidectomized rats with T4 alone."* These studies also demonstrated *"Combined replacement therapy with T4 and T3 (in proportions similar to those secreted by normal rat thyroid) completely restored euthyroidism in thyroidectomized rats at much lower doses of T4 than those needed to normalize T3 in most tissues when T4 alone was used.* ***If pertinent to man, these results might well justify a change in the current therapy for hypothyroidism****."* (Escobar-Morreale et al., 1996, emphasis added) The lessons of ScH, and

the failure of T4 to correct subtle thyroid hormone abnormalities in clinical practice, clearly indicate that the "rat studies" are indeed pertinent to man. **Normal levels of thyroid hormone do not necessarily translate into normal tissue levels if the balance between T3 and T4 is inappropriate for the individual in question**. The treatment of ScH and overt thyroid failure with T4 supplementation is not expected to mimic the proportional release of T3 and T4 that would ordinarily occur from a normally functioning thyroid gland. It is by its very nature a disproportional increase in T4 to a *"supranormal"* level **(**Hennemann et al., 2004**), relying on increased peripheral T4-to-T3 conversion to correct the hypothyroid state**. Little thought is given to the cellular response to T4 excess, an excess that is intentionally given to the patient when T4 alone is used in the treatment of hypothyroidism. The cellular response to T4 excess, creating a subtle form of hypothyroidism, will be clearly elucidated in this presentation.

Briefly: In response to T4 excess, cellular D3 (Deiodinase III) expression is elevated above normal, with the goal of preventing an excessive cellular T4 uptake and subsequent excessive cellular T4-to-T3 conversion. However, **this elevation in D3 activity, although purposeful and protective for the cell that performs this task, lowers regional T3 availability. Consequently, elevated D3 activity at the cellular level routinely lowers plasma T3 concentrations on the order of 20%**, as seen when T4 is customarily given in the treatment of hypothyroidism (Escobar-Morreale et al., 1996). This reduction in regional T3 availability may negatively affect certain cells that are unable to adjust for the actions of other cells (see Bianco et al., 2002). **The degree of T4 excess can be associated with the degree of reverse T3 (rT3) elevation** (Franklyn and Shephard, 2000)**.** It is an understanding of the dynamic played by D3 and D2 (Deiodinase II) at the cellular level that allows us to redefine hypothyroidism. Although hypothyroidism can certainly be defined by abnormal thyroid hormone levels, **hypothyroidism can best be characterized by thyroid hormone levels at the cellular level that are not appropriate for the individual**. This situation can best be identified by evaluating the individual's rT3 status. **An elevated rT3 level strongly suggests the existence of T4 excess and the existence of an imbalance between T3 and T4.**

Conclusion: T4 excess created in the conventional treatment of hypothyroidism creates a subtle form of hypothyroidism at the cellular level, a form that can typically be identified by rT3 elevation. ***rT3 elevation signals T4 excess at the cellular level and the existence of this subtle form of hypo-thyroidism*.** This presentation is an effort to bring these issues to the forefront and to promote the use of slow-release T3, not just for the formally hypothyroid patent but also for the "euthyroid" patient presenting with signs and symptoms suggesting hypothyroidism. Also discussed is the role played by rT3 as a *"dynamic"* regulator of D2 activity. And in this role, the actions of rT3 are essential and beneficial. And in this respect, rT3 is an active hormone.

The clinical spectrum of hypothyroidism is diverse, multisystem, and easily overlooked for months or years. Mild cases of thyroid dysfunction are a familiar occurrence in practice, often discovered incidentally by virtue of abnormal thyroid function tests obtained in patients with few or nonspecific symptoms. (Felz and Forren, 2004)

Introduction

> *Hypothyroidism is usually perceived as associated with lowered production of thyroid hormones (THs) . . . , but impaired effect of THs in peripheral (adipose and muscle) tissues should also result in (or contribute to) clinical symptoms consistent with the hypothyroidism diagnosis.* ***~Tjorve et al., 2007, emphasis added***
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> *At normal serum T3 concentration, the contribution from serum T3 alone results in an approximate 50% TR [thyroid hormone receptor] occupancy in most tissues.* ***~Gereben et al., 2008***
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> *The deiodinases also modulate the thyroid status of individual tissues in response to iodine deficiency, hypothyroidism, or hyperthyroidism.* ***Cells lacking the capacity to adjust the rate of activation or inactivation are most affected****, as their thyroid status will be determined by plasma free T3 concentration.* ***~Bianco et al., 2002, emphasis added***
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> ***Plasma T3 concentrations*** *in patients receiving T4 treatment with normal plasma T4 and TSH concentrations* ***are only 80% of those in normal individuals****.* ***~Escobar-Morreale et al., 1996, emphasis added***

Our collective understanding of hypothyroidism has evolved beyond simply an issue of normal vs. abnormal laboratory values. Yet, even in the face of multiple signs and symptoms suggesting hypothyroidism, should T3 and T4 levels fall within normal limits, the physician is ready to move on. One example is subclinical hypothyroidism (ScH), a thyroid hormone condition where the T3 and T4 levels are normal, but the TSH is elevated. Treatment may be offered, but typically will be directed at symptom relief, perhaps not directed at correcting the underlying problem. This is all understandable, given **1)** the controversies found in the literature, **2)** the fact that negative responses can occur attending thyroid hormonal replacement in ScH, and **3)** concern regarding complications due to over-supplementation. Therefore, ScH often goes untreated and uncorrected. Yet this is a thyroid hormonal imbalance associated with signs and symptoms, and has the power to compromise patient well-being.

There is another form of hypothyroidism perhaps more subtle than ScH, a form of hypothyroidism almost universally unrecognized and untreated. Ironically, this form of hypothyroidism automatically occurs from the conventional treatment of hypothyroidism. Yet this form of hypothyroidism can easily be identified and treated. **One goal of this presentation is to clearly define this form of hypothyroidism and to redefine hypothyroidism itself, not in terms of normal vs. abnormal T3 and T4 levels, but in terms of thyroid hormone levels at the tissue and**

cellular level that are not appropriate for a particular individual. As we redefine hypothyroidism, we will entertain an alternative approach to the treatment of this disease.

> *Although the patient may by euthyroid, as defined by circulating thyroid hormone levels (particularly TSH), symptoms may arise from uneven effect of T4 replacement on various tissues and organs or even regions within the brain.* (Joffe, 2008)

Lessons from subclinical hypothyroidism

> *The symptoms of sub-clinical hyper- and hypothyroidism show that **minor changes** in thyroid hormone levels can have **important consequences** for the quality of life, cognition, cholesterol metabolism, heart rate, bone mineral density, and atherosclerosis.* ***~Peeters et al., 2003, emphasis added***
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> *The condition may be clearly associated with somatic symptoms, depression, memory and cognitive impairment, subtle neuromuscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of total and LDL cholesterol, and an increased risk of atherosclerosis.*
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> *Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable.* ***~McDermott and Ridgway, 2001, emphasis added***
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> *Interestingly, treatment of patients with subclinical hypothyroidism with T4 alone frequently lowers T3 levels, despite normalizing TSH and T4 levels. This is almost certainly because the up–regulation of deiodinase levels in the thyroid that occurs in thyroid failure results in increased intrathyroidal T4 to T3 conversion and this effect is lost after exogenous T4.* ***~Saravanan and Dayan, 2004, emphasis added***

In the clinical approach to ScH, two camps clearly exist. One camp favors hormonal replacement and is best represented by Biondi and Cooper or McDermott and Ridgway. Perhaps leading the challenge against hormonal replacement in ScH are Chu and Crapo. All three research teams present persuasive arguments for or against hormonal replacement in this form of hypothyroidism. However, the negative impact ScH has on patient well-being is not in serious dispute. Certainly, the treatment of "s*omatic symptoms, depression, memory and*

cognitive impairment, subtle neuromuscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of total and LDL cholesterol, and an increased risk of atherosclerosis" seems warranted (McDermott and Ridgway, 2001). And clearly the symptoms of ScH are the symptoms of hypothyroidism. **ScH *is* hypothyroidism,** pure and simple, yet it is hypothyroidism that exists when T3 and T4 levels are normal.

Surprisingly, a normalization of the TSH in ScH may create another hormonal imbalance. *"Interestingly, treatment of patients with subclinical hypothyroidism with **T4 alone frequently lowers T3 levels, despite normalizing TSH and T4 levels**."* (Saravanan and Dayan, 2004, emphasis added) So the question remains, but not just with regard to ScH, "What is the best approach to take to correct the symptoms of hypothyroidism?" The answer lies in an understanding of the role played by the deiodinases in the regulation of thyroid hormone balance at the tissue and cellular level.

> *Because serum TSH responds with **logarithmically amplified variation** to minor changes in serum T4 and T3, abnormal serum TSH may indicate that serum T4 and T3 are not normal for that individual.* (Andersen et al., 2002, emphasis added)

> *An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with few exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes). We, indeed, believe that **subclinical hypothyroidism** represents mild thyroid failure and is a **clinically important disorder that has adverse clinical consequences and that should be treated in most, if not all, cases**.* (McDermott and Ridgway, 2001, emphasis added)

The deiodinases

> *The actions of the thyroid hormones (TH) differ from tissue to tissue depending upon a number of variables. In addition to varying expression levels of TH receptors, differing patterns of TH metabolism provide a critical mechanism whereby TH action can be individualized in cells depending on the needs of the organism.* ***~St. Germain et al., 2009, emphasis added***

> *The interplay of activating (D1 and D2) and inactivating (D3) pathways of thyroid hormones is responsible for the differential regulation of intracellular T3 levels in selected tissues.* ***~Santini et al., 2001***

> *Once inside the cell, T4 can be activated via conversion to T3 by the D2 pathway, such that the cytoplasmic pool includes both T3 from the plasma and T3 generated by D2.*

Alternately, D3 acts at the plasma membrane to decrease local T3 concentrations. Thus, the deiodinases are critical determinates for the cytoplasmic T3 pool and therefore modulate nuclear T3 concentration and TR [thyroid receptor] saturation. ***~Bianco and Kim, 2006***

Degradation of the D2 protein is accelerated when it is exposed to its own substrates T4 and rT3. ***~Peeters et al., 2006***

The D1 deiodinase enzyme, although important to the subject of hypothyroidism, will make only a brief appearance in this discussion. Here, the focus is on the regulatory dynamic that occurs at the cellular level between the D2 and the D3 deiodinase enzymes. *"Whereas the D2 and D3 appear to have well defined functions, the role of D1 is difficult to define and to a considerable extent remains an enigma."* (St. Germain et al., 2009) Its importance as a T4 to T3 converting enzyme has been clearly "downregulated" in importance with the discovery that the **primary site of T4 to T3 conversion occurs in the skeletal muscles** (Salvatore et al., 1996; Maia et al., 2005; Bianco and Kim, 2006; Olivares et al., 2007). And not just the skeletal muscles, it now appears that cardiac D2 (Salvatore et al., 1996) and bone D2 (Gouveia et al., 2005) also make a substantial contribution to plasma T3 concentrations.

These findings suggest a more limited role of D1 in contributing to plasma T3 concentrations than previously thought. Furthermore, *"Although the large mass of D1 present in the liver does clearly allow for T4 to T3 conversion, this deiodinase seems much better positioned to clear from the circulation rT3 and other inactive, sulfated, and lesser iodothyronines, compounds generally not degraded efficiently by the D2 or the D3."* (St. Germain et al., 2009) It is the actions of D2 and D3 that determine the relative concentrations of T3 and T4 at the tissue, cell, and intracellular level. **It is here, at the intracellular level and not at the plasma level, where hypothyroidism does or does not truly exist.**

With respect to D3, positionally, D3 resides in the plasma membrane (PM) of a variety of cells, and projects in varying degrees into the extracellular fluid compartment to perform its metabolic role in dealing with thyroid hormone excess (Baqui et al., 2003). If D3 activity is upregulated in response to T4 excess in the immediate cellular environment, an increase in the conversion of T4 to rT3 will occur. Likewise, if D3 is upregulated in response to T3 excess, it will act to eliminate this excess by converting T3 into T2. **An excess of one iodothyronine, T3 or T4, will reduce the concentration of the other, as both are substrates for the actions of this enzyme.** The degree of D3 expression regulates the concentration of TH available for active transport into the cell—both T3 and T4—and influences the rate of cellular uptake by influencing the degree of transporter saturation. Both D3 expression and transporter activity are regulated according to individual cellular needs. D3 is located more extensively throughout the body than previously thought; perhaps in every tissue type but not in every cell (Bianco et al., 2002). The myocyte (Wassen et al., 2002), the skeletal and smooth muscle cell (Salvatore et al., 1996; Mizuma et al., 2001), both neuron and the astrocyte (Bernal, 2002), even osteoblast and osteoclast (Williams et al., 2008) are recent additions to the list of cells expressing D3 in various degrees, depending on the circumstances.

In contrast, D2 resides within the cell in the endoplasmic reticulum, where it plays a primary role in the conversion of T4 to T3 in close, strategic proximity to the nucleus of the cell (Bianco Lab, recent website posting). Degradation of this enzyme occurs during the performance of this task and, like D3, subsequently regenerates to again perform the

task of T4-to-T3 conversion (Bianco and Larsen, 2005).

Another role played by D2 is the conversion of rT3 to T2, an event that on a molecule by molecule basis will prevent the conversion of T4 to T3 within the cell, in a dynamic that may be called *competitive inhibition*. Later, we will discuss this dynamic, one that finely regulates D2 activity and controls the T3 concentration within the cell. *". . . D2 activity is under negative control of its substrates T4 and rT3 . . .."* (Visser, 2008a)

Understanding the modulating activities of both D2 and D3 gives us a view into the dynamic that occurs at the tissue and cell level with respect to the metabolism of thyroid hormone. **Intimate with this dynamic is the beneficial, regulatory role played by rT3.**

In order to regulate T3 concentrations within the cell, rT3, produced at the level of the PM in response to T4 excess, becomes readily available for cellular uptake. And when *intentionally* transported (invited) within the cell, the presence of rT3 therein will, in effect, give D2 something else to do. This is clearly a **diversionary tactic**, a purposeful and useful event. **Simply put, following rT3 uptake within the cell, with the attention subsequently turned to converting rT3 to T2, the conversion of T4 to T3, by D2, will be avoided and T3 excess will be limited within the cell.** In this way, D2 is *"dynamically"* regulated (Trentin, 2006) to serve the immediate, post-translational regulatory needs of the cell. rT3 should be called *"receptor inactive"* (Visser, 2008a). But it should also be called *"regulatory active"* (Kohrle, 1996). Additionally, rT3 should be called a *"competitive inhibitor"* (Salvatore et al., 1996; O'Barr, 2006). And, rT3 should be called a *"metabolite"* (Kuiper et al., 2005). Clearly, rT3 should <u>not</u> be called *"inactive"* (Gogila and De Lange, 2003; Hulbert, 2000). The use of the term *"inactive hormone"* is so unfortunate; it gives the impression that it has nothing to do and leads one away from an appreciation of its *valuable* role in the dynamic that occurs at the cellular level. **D2 is *"dynamically regulated"* by rT3.** And by influencing the rate of T4-to-T3 conversion by D2, **rT3 regulates the final concentration of T3 within the cell. <u>rT3 is transported into the cell for this very purpose</u>!** The rT3-to-T2 conversion performed by D2, to "compete" with T4-to-T3 conversion (by D2), is also useful to further meet the thyroid hormone needs of the cell. The formation of T2 that follows will be available to meet the needs of the mitochondria (Gogila, 2005). Like rT3, T2 should not be called *"inactive,"* even though it is popular to do so (Gogila and De Lange, 2003).

> ***That rT3 may function as an inhibitor of T3, offers an interesting new regulatory pathway in the thyroid hormone signaling cascade.*** (Tien et al., 2007, emphasis added)

> *The different thyroid hormones (T4, T3, **<u>and rT3</u>**) are transported via different transporters, except in the pituitary, where <u>they share the same transporter</u>.* (Hennemann, 2007, emphasis added)

> ***. . . rT3[,] often regarded as solely an 'inactivated' thyroid hormone, is sometimes more potent than T3. It has also been shown that 2,5-<u>T2 is an active thyroid hormone</u> with respect to the calorigenic action of the thyroid hormone.*** (Hulbert, 2000, emphasis added)

Regulation at the cellular level

Deiodinases play an essential role in the local control of brain T3, through mechanisms that operate under a variety of situations to keep T3 concentrations under a narrow range. ***~Bernal, 2002***

The deiodinases also modulate the thyroid status of individual tissues in response to iodine deficiency, hypothyroidism, or hyperthyroidism. Cells lacking the capacity to adjust the rate of activation or inactivation are most affected, as their thyroid status will be determined by plasma free T3 concentration. On the other hand, in cells expressing D2 and/or D3, the changes in the activity of these enzymes will mitigate the fluctuations in plasma T4 and T3, constituting a potent mechanism for thyroid hormone homeostasis. ***~****Bianco et al., 2002, emphasis added*

Remarkably, D3 expression causes cell hypothyroidism as a result of the inactivating effect on thyroid hormone . . .. ***~Bianco Lab, recent website posting, emphasis added***

Astrocyte D2 is a very short-lived enzyme, dynamically regulated by both T4 and 3,3',5'-triiodothyronine (rT3), but not T3. ***~Trentin, 2006, emphasis added***

. . . ***rT3 is a competitive inhibitor of D2****, which would result in an effective diminution of active cerebral T3 levels in AD [Alzheimer's Disease]. Thus localized hypothyroidism may be responsible for increasing APP gene expression and Aß plaque deposition in AD.* ***~O'Barr et al., 2006, emphasis added***

DII activity is controlled by thyroid hormones at two levels. T4 and rT3 suppresses DII activity mainly at the post-translational level through acceleration of the degradation rate of DII protein. ***~Mizuma et al., 2001, emphasis added***

The rT3 level tends to follow the T4 level: low in hypothyroidism and high in hyperthyroidism. ***~MayoClinic Laboratories, recent website posting, emphasis added***

Thus, measurement of rT3 concentration in serum reflects both tissue supply and metabolism of T4 and identifies conditions that favor this particular pathway of T4 degradation. ***~Franklyn and Shephard, 2000***

While numerous regulatory events occur at the cellular level, one event in particular stands out and can be quite impressive! The event is the profound upregulation in D3 expression. Elevated D3 activity from certain tumors or from a variety of tissues in response to injury can be extreme, leading to profound systemic hypothyroidism (Bianco and Kim, 2006). The

over-expression of D3 in response to an ischemic insult, as would occur during an acute MI, can cause systemic hypothyroidism to occur in a matter of hours (Kahaly and Dillmann, 2005). Extreme D3 expression defines the thyroid hormone abnormalities that are found in non-thyroidal illness (NTI). However, the role played by subtle D3 expression normally regulates, moment by moment, the concentrations of thyroid hormone available for transport into the cell.

Keep in mind, what follows is all occurring, not in the plasma compartment, but in a "slow-equilibrating" cellular environment. *Always* in response to TH excess, rT3 concentrations will be increased at the cellular level, **even in the event of T3 excess**! This is because D3 activity is indiscriminate in its degradation of either iodothyronine. For example, in response to T4 replacement therapy, D3 activity is increased in various degrees to regulate T4 availability to tissue and to cell. **This increase in D3 activity will, however, assure that a certain degree of T3 will also be lost, not just in the immediate cellular environment but also in the plasma compartment.** But it is not just hormonal replacement that can lead to T4 excess; T4 excess can also occur all on its own, perhaps for reasons that are not entirely clear (Fliers, 2002).

D3 activity normally creates rT3 during the day-by-day, moment-by-moment regulation of regional T4 levels. The cell regulates D3 expression, subtly or forcefully, to protect itself or to protect neighboring cells from TH excess. When T4 is in excess, rT3 production will increase. And, if significant, can be reflected by an increase in plasma rT3 levels (and a lowering of T3 levels). *"Thus, measurement of rT3 concentration in serum reflects both tissue supply and metabolism of T4 and identifies conditions that favor this particular pathway of T4 degradation."* (Franklyn and Shephard, 2000, emphasis added) In this respect, and in the absence of NTI or other confounders, **rT3 elevation signals T4 excess**. In fact, rT3 measurement was once used to diagnose hyperthyroidism and to determine if a replacement dose of thyroid hormone was excessive, adequate, or inadequate. However, another test became the "Gold Standard" and rT3 determination fell to the wayside. The TSH was believed to accurately reflect the metabolism of TH at the cellular level. However, it only reflects whether the pituitary, in concert with the hypothalamus, recognizes the thyroid hormone concentration as normal vs. abnormal. **The true indicator of the peripheral metabolism of thyroid hormone is not the TSH; it is the T3/rT3 ratio.** *"The T3/rT3 ratio is considered to be a sensitive indicator of the peripheral metabolism of thyroid hormone, being positively influenced by D1 and D2 and negatively by D3."* (Peeters et al., 2006)

"Interestingly, treatment of patients with subclinical hypothyroidism with T4 alone frequently lowers T3 levels, despite normalizing TSH and T4 levels." (Saravanan and Dayan, 2004) And the reason why T4 alone lowers T3 levels is because of an upregulation in D3 activity. This effort to modulate the uptake of T4 into the cell will reduce local concentrations of T3 in the immediate cellular environment, and this will reduce T3 availability for cellular uptake. T4 excess will create a degree of hypothyroidism at the tissue and cell level.

> *Importantly [,] the local thyroid status of D2-containing tissues may not be reflected in the plasma thyroid-stimulating hormone [TSH], T4, and T3 levels.* ***There is no simple way to measure local thyroid status in humans, but it is easy to imagine that derangements in these processes could have important pathophysiological consequences****.* (Koenig, 2003, emphasis added)

T4 excess creates hypothyroidism!

*5D **[D3]** appears to play a major role in T4 and T3 inactivation in organs and at times or conditions where **inappropriate presence of high amounts of the prohormone [T4]** or the . . . active hormone T3 might be deleterious for cell function.* ***~Kohrle, 1999, emphasis added***

*Since the molecular characterization of D1 in 1991, much progress has been made in the understanding of the molecular biology and physiology of these enzymes. One of the major achievements is the growing realization that **D3 plays a much more important role in the regulation of thyroid hormone bioactivity than previously assumed**.* ***~Kuiper et al., 2005, emphasis added***

Interestingly, both higher fT4 and rT3 levels were associated with brain atrophy. ***~de Jong et al., 2006***

In a population of independently living elderly men, higher FT4 and rT3 concentrations are associated with a lower physical function. ***~van den Beld et al., 2005***

Substitution of thyroid hormone with LT4 [T4] in patients with primary hypothyroidism, when titrated to normalize serum T4, results in a mean serum T3 level that is lower than normal. However, when T4 is administered in amounts to normalize T3, T4 parameters will rise to supranormal concentrations. ~Hennemann et al., 2004, emphasis added

*Finally, the dose of T4 needed to ensure a normal T3 concentration (and presumably, euthyroidism) is not the same in all tissues. It is evident that even if the **undesirable effects of excessive T4 concentrations were disregarded, peripheral conversion of T4 to T3 did not fully compensate for the absence of thyroidal secretion of T3**.* ***~Escobar-Morreale et al., 1996, emphasis added***

T4 excess is created in the treatment of hypothyroidism . . . *intentionally!* T4 excess is problematic. Two problems can be readily identified as a physiological response to T4 excess. One is a systematic lowering of T3 plasma concentrations, leading to a generalized reduction in systemic T3 availability (Escobar-Morreale et al., 1996; Hennemann et al., 2004). The other is more subtle and is clearly not measurable (Koenig, 2003). It is best described by Bianco et al. as follows: *"The deiodinases also modulate the thyroid status of individual tissues in response to iodine deficiency, hypothyroidism, or hyperthyroidism.* ***Cells lacking the capacity to adjust the rate of activation or inactivation are most affected, as their thyroid status will be determined by plasma free T3 concentration."*** (Bianco et al., 2002, emphasis added) This is clinically relevant. And this should be of clinical concern.

In the more subtle problem associated with T4 excess, the protective action of one cell negatively impacts the TH status of another cell. Elevated D3 action, in response to T4 excess, in effect, "picks off" a certain amount of regional T3 in the process, effectively reducing the concentration of T3 in the immediate cellular environment, thereby limiting its availability for cellular uptake. This is particularly significant because it is not simply D2-mediated T4-to-T3 conversion that accomplishes T3 adequacy at the cellular level; it is also the availability of T3 for cellular uptake that determines the T3 status of tissue and cell. T3 availability may be "everything" for a certain cell, one that relies heavily on T3 accessibility and uptake and not on internal T4 to T3 conversion by D2. ***". . . at normal serum T3 concentration, the contribution from serum T3 <u>alone</u> results in an approximate 50% TR [thyroid hormone receptor] occupancy in most tissues."*** (Gereben et al., 2008, emphasis added)

T4-only in the treatment of hypo-thyroidism, although seemingly well tolerated and overt symptoms favorably respond giving the appearance that all is well, calls for the regulatory efforts of D3 to become elevated <u>persistently</u> above normal. **In order to raise plasma T3 levels by T4 alone, the strategy clearly calls for T4 to be given in excess of what would be the normal thyroidal output of this hormone.** The elevation in rT3 levels that follow are related to a cellular effort to limit T4 excess and to restrict T4 uptake into the cell. In this regard, the actions of D3 are beneficial, yet T3 reduction will follow. ***"It is implicitly admitted that to attain euthyroidism in hypothyroid patients with T4 alone, it might be necessary to maintain circulating T4 concentrations in the upper limits of the normal range. Indeed, circulating T4 concentrations are higher in hypothyroid patients on T4 than in normal individuals with similar concentrations of plasma T3 and TSH. On the contrary, <u>plasma T3 concentrations in patients receiving T4 treatment with normal plasma T4 and TSH concentrations are only 80% of those in normal individuals</u>."*** (Escobar-Morreale et al., 1996, emphasis added) In support of Escobar-Morreale et al., we read: *"Substitution of thyroid hormone with LT4 [T4] in patients with primary hypothyroidism, when titrated to normalize serum T4, results in a mean serum T3 level that is lower than normal. However, **when T4 is administered in amounts to normalize T3, T4 parameters will rise to <u>supranormal</u> concentrations."*** (Hennemann et al., 2004, emphasis added) **It is not that the T3 and T4 levels are now within normal range; it is how this result is created that is of concern.** T4-only, given in a dose that normalizes plasma T3 concentrations, **forces D3 over-expression**, resulting in a degree of T3 deficiency at the cellular level. **It is actually impossible for this not to occur!**

It is hard to believe that the favored treatment for hypothyroidism would actually create hypothyroidism, but it does, and does so at the level that matters the most! T4 excess guarantees that there will be a form of hypothyroidism established and perpetuated at the tissue and cell. And no one, or so it seems, is identifying and addressing the form of hypothyroidism created by T4 excess. (Well, almost no one.) The TSH may validate the belief that hypothyroidism is corrected by this approach, yet signs and symptoms of hypothyroidism persist and indicate otherwise. Look closely! Be honest! T4-only is not as successful at it seems. ***"It is not possible!"*** Importantly, the degree of T4 inactivation required, hence the degree of T4 excess, can be reflected by the rT3 level.

> ". . . ***plasma T3 concentrations in patients receiving T4 treatment with normal plasma T4 and TSH concentrations are only <u>80%</u> of those in normal individuals."*** (Escobar-Morreale et al., 1996, emphasis added)

Relevancy of "The Rat Studies"

> *We have recently shown that it is not possible to restore euthyroidism completely in all tissues of thyroidectomized rats with T4 alone.*
>
> *Finally, the dose of T4 needed to ensure a normal T3 concentration (and presumably, euthyroidism) is not the same in all tissues. It is evident that even if the undesirable effects of excessive T4 concentrations were disregarded, peripheral conversion of T4 to T3 did not fully compensate for the absence of thyroidal secretion of T3.* ***~Escobar-Morreale et al., 1996, emphasis added***

The landmark studies conducted in the mid-1990s pose a challenge to the T4-only approach to the treatment of hypothyroidism. In these studies, conducted by Escobar-Morreale et al., 1996, rats were thyroidectomized and maintained on T4 alone in order to achieve normal T3 and T4 parameters. Tissue studies that followed revealed TH abnormalities in *"all tissues studied."* It was concluded that *"it is not possible"* to achieve euthyroidism at the tissue level with T4 alone. Perhaps more impressive was the fact that euthryoidism at the tissue level could be ***"assured"*** if T3 was given in combination with T4 in the ratio that a normal thyroid gland would ordinarily produce. However, the question remained: "Do these studies apply to man?" The deiodinases and the lessons of ScH say **"Yes!"** And the degree of nuclear receptor occupancy (approximately 50%) dependent on circulating levels of T3 certainly echoes this sentiment. (see Gereben et al., 2008)

The hypothyroidism observed in "the rat studies" occurred in the context of normal T3 and T4 levels! (Sound familiar? Recall the lessons of ScH.) Though normal thyroid hormone levels occurred in the rat studies, they were not normally created and obviously not normal for the individual (rat). T4 excess is required to achieve the appearance of euthyroidism in the absence of normal thyroid hormone production. **In hypothyroidism, treated with T4 alone, T4 excess is required to achieve normal T3 and T4 levels, period! And the deiodinases tell us why T4 excess subtly creates hypothyroidism at the cellular/tissue level.**

The rat studies demonstrate that T4 excess is harmful, period! Why? Because tissue hypothyroidism is harmful, period! But T4 excess does not only occur from T4 replacement therapy, it can occur all on its own, *"for reasons that are not entirely clear."* (Fliers, 2002). And the "euthyroid" individual, the one clearly exhibiting the signs and symptoms of hypothyroidism, will be left untreated. Tissue hypothyroidism will be allowed to continue. His or her T4 excess will not be identified and it will not be corrected. Disregard the human studies and clinical trials conducted with no consideration of the degree of T4 excess occurring in each of the study participants! These studies are intrinsically defective! Listen closely to "the rat studies!" It is not normal levels of T3 and T4, not even a TSH level that is pleasing that matters; what matters is a correct balance between T3 and T4 for the individual. ***This*** **is a cellular-level issue!** And this form of

hypothyroidism can easily exist, undetected under the radar of the TSH and other thyroid function tests. "The rat studies" will never go away! They will usher in a new era in our approach to identifying and correcting hypothyroidism. You will love this new era! I will introduce you to it.

> ***. . . despite normalization of TSH as a target of treatment, a substantial minority of hypothyroid subjects on T4 replacement complain of various symptoms of depression and malaise and, consequently, reduces quality of life. Clinical hypothyroidism may present with various psychiatric symptoms, including depression, and T4 replacement therapy producing normal TSH levels may not completely produce a euthyroid state in all organs and tissues."*** (Joffe et al., 2007, emphasis added)

A new approach to the treatment of hypothyroidism

> *Combined replacement therapy with T4 and T3 (in proportions similar to those secreted by normal rat thyroid)* ***completely restored*** *euthyroidism in thyroidectomized rats at much lower doses of T4 than those needed to normalize T3 in most tissues when T4 alone was used.* ***~Escobar-Morreale et al., 1996, emphasis added***

> *In all these studies T3 was used in the plain form that results in non-physiologic serum T3 peaks. In these studies it is suggested that substitution with T3 should preferably be performed with a preparation that slowly releases T3 to avoid these peaks. In the study reported here we show that treatment of hypothyroid subjects with a combination of T4 plus slow-release T3 leads to a* ***considerable improvement*** *of serum T4 and T3 values, the T4/T3 ratio and serum TSH as compared to treatment with T4 alone.* ***~Hennemann et al., 2004, emphasis added***

> ***The T3/rT3 ratio is considered to be a sensitive indicator of the peripheral metabolism of thyroid hormone, being positively influenced by D1 and D2 and negatively by D3.*** *This ratio is also relatively independent of thyroidal T4 production and of variations in serum binding proteins.* ***~Peeters et al., 2006, emphasis added***

In this new era, we will approach hypothyroidism a little differently. We will think differently. **We will draw a rT3 level, not because it may be elevated and that rT3 elevation could be a problem. We will draw a rT3 level because we anticipate that it may be elevated, and we suspect that T4 excess is a problem!** We will again recognize the fact that rT3 elevation signals T4 excess. We will acknowledge that T4 excess guarantees that a certain degree of hypothyroidism will occur at the cellular level and may contribute to the symptoms that persist. We will consult the TSH to get a sense of what the pituitary may be "thinking," but we will turn to the T3/rT3 ratio to determine the nature of the thyroid hormone status at the cellular level. **This strategy will change everything!** We will certainly give T4, but we will also become most successful giving T3 and T3/T4 in combination

and doing so in the most physiologic manner possible. And if circumstances require T4 alone, we will be careful to limit its excess as reasonably as possible. T4-only is not this "easy thing" that it appears to be on the surface (Roberts and Ladenson, 2004; Reddy, 2006).

In this new era, our focus will be on the metabolic events that occur at the cellular level. Of course, our interest will be on achieving normal T3 and T4 levels, but we will approach things differently. **We will approach hypothyroidism with a strategy that will attempt to mimic the proportional release of T3 and T4 that should be occurring by the actions of a healthy thyroid gland.** The balance between T3 and T4 at the cellular level will be our overriding concern. What follows is how things will look in the new era of thyroid hormone replacement, in an approach that may be appropriately described as

The physiological approach to the treatment of hypothyroidism

In the physiological approach to the treatment of hypothyroidism, we will draw a *f*T3 level, along with a rT3 level, and calculate a T3/rT3 ratio in order to get a sense of the metabolic events that are occurring at the cellular level. We will compare the T3/rT3 ratio calculation to what one might consider to be an ideal T3/rT3 ratio. And **our therapeutic approach will be one that aims to limit T4 excess and mimic the proportional release of T3 and T4 typical of a normally functioning thyroid gland.** Importantly, when T4 excess is occurring, rT3 elevation will follow. And the degree of T4 excess in play is best determined by calculating the T3/rT3 ratio. The method of calculating the T3/rT3 ratio that I recommend is based on the popularity of drawing *f*T3 levels. This new approach to the treatment of hypothyroidism will appear generally as follows:

Calculating the T3/rT3 ratio: Using the *f*T3 level and the rT3 level, calculate a T3/rT3 ratio by dividing the rT3 level by the *f*T3 level. For example: A *f*T3 level of 3.0 pg/ml, and a rT3 level of 14.8 ng/dl, will give you a T3/rT3 ratio of 4.9. (14.8 divided by 3 = 4.9) If a rT3 level comes back in pg/ml instead of ng/dl, move the decimal point one number to the left. For example, 291 now becomes 29.1. (Be aware that there are other methods of calculating a T3/rT3 ratio.) Next . . .

Interpreting the T3/rT3 ratio: Assess the T3/rT3 ratio in terms of what might represent **"ideal"** *f*T3 and rT3 levels. A T3/rT3 ratio of 4.9, as per the above example, may seem ok, but perhaps a better T3/rT3 ratio might look like this: A *fT3* level of 3.2 and a rT3 level of 12.4, yielding a T3/rT3 ratio of 3.9. On the other hand, a *f*T3 level of 3.4 and a rT3 level of 14.4 would yield a ratio of 4.2. Should the *f*T3 level be 2.8 and the rT3 level is 24.2, a ratio would be 8.6. A much lower T3/rT3 ratio like 3.9, or even 4.2, might be more appropriate, particularly in the face of continuing signs and symptoms of thyroid hormone imbalance. Should the *f*T3 be on the low side and the rT3 level be on the high side, the T3/rT3 ratio is likely abnormal for the

individual. Physiologic therapy should normalize the fT3 level while lowering the T3/rT3 ratio.

The therapeutic approach: In this new approach to the treatment of hypothyroidism, hormonal supplementation will be given in an attempt to mimic the proportional release of T3 and T4 that would normally occur if the thyroid gland was in a healthy state. T4 and/or T3 will be prescribed. Under normal circumstances, a healthy thyroid gland produces about 80% T4 and about 20% T3 (Escobar-Morreale et al., 2005; Visser, 2008b), **and does not rely on T4 excess to force D2-containing cells to make up for a chronic deficit**. Little in the way of rT3 production generally occurs and plasma concentrations of this hormone remain low, even in the healthy elderly individual (Goichot et al., 1994; Kim and Ladenson, 2007). This gives rise to the use of rT3 elevation as a means of estimating the degree of T4 excess. And in context with the calculation of a T3/rT3 ratio, one can assess more clearly the relationship between T3 and T4 at the cellular level. But just like everything else, this is a tool and is not the last word. Confounders and exceptions will always exist, and individual issues should be taken into account. If T4 is prescribed to compensate for thyroid hormone insufficiency, after initial or established therapy, T4 should be limited and combined with supplemental T3 in context with a follow-up T3/rT3 ratio calculation. Typically, significant rT3 elevation will be evident with T4-only supplementation and reflects the degree of T4 excess in play. Recall, along with the rT3 elevation comes a certain degree of T3 reduction below ideal values. T4 given by itself does this intrinsically, perhaps reducing the T3 level by as much as 20% (Escobar-Morreale et al., 1996).

In order to favorably adjust the T3/rT3 ratio, that is, to favorably influence the T3/T4 balance at the cellular level, clearly the best choice is the use of slow-release T3. Although "immediate-release" T3 (Cytomel, liothronine) will effect a favorable change in the balance between T3 and T4, slow-release T3 is more physiologic because it is absorbed more slowly and thereby avoids transient peaks in T3 that require the cells to take prompt, defensive action. Importantly, in response to the "intermittent" T3 excess that occurs after each dose of "immediate release" T3, D3 activity will be elevated to protect the cells from T3 excess! **This alone can drive up the rT3 level!** Fortunately, the use of slow-release T3 is becoming more and more popular and can easily be formulated by a local or regional compounding pharmacist. But to be successful with T3 replacement, the issue of supplemental T4 excess must be addressed and it must be prevented. **The secret of achieving exceptional results with supplemental T3 is to limit T4 excess, as T4 excess will limit T3 availability and limit cellular uptake.** The use of the T3/rT3 ratio will serve as an indispensable guide.

The "euthyroid" patient, one presenting with signs and symptoms of hypothyroidism in the face of normal T3 and T4 levels, and with a normal TSH level, can successfully be treated for evidence of hypothyroidism by the use of slow-release T3. A T3/rT3 ratio may reveal a significant degree of T3/T4 imbalance at the cellular level. By giving slow-release T3, one can, in effect, tell the pituitary to "back off" a little in its stimulation for thyroid hormone production. A lowering of T4 production will follow, along with a concurrent decrease in

thyroidal T3 production. But this reduction in T3 output will be adequately compensated for by supplemental T3. The overall goal is to reduce excess T4 availability at the cellular level (reflected by a lower rT3 level), along with achieve a higher T3 plasma concentration to meet individual needs.

For the individual with untreated ScH, a low rT3 level will indicate that T4 is too low to support the requirements of the cells. The lower T3 level typically found in ScH reflects both a decrease in thyroidal T3 production, but also a decrease in the extra-thyroidal contribution to T3 levels (from peripheral T4-to-T3 conversion) as from the skeletal muscles, for example. In the treatment of ScH, T4 alone can be given, a T3/T4 combination can be prescribed, and the T3/rT3 ratio can be used to evaluate the appropriateness of dosages and the need to make further adjustments. T4 excess accompanying conventional treatment of ScH may give rise to the unfavorable responses, often occurring in ScH patients supplemented with T4. **In the setting of ScH, giving T3 alone will not compensate for the lack of T4 production and will not raise the T4 level to meet the cellular requirements of this essential hormone.** Again, it appears that a T3/T4 combination is the most physiological approach to the treatment of ScH. In any case, the T3/rT3 ratio will be the best indicator and suggest the best course of action to take in this clinical situation.

For the hypothyroid patient, one taking T4-only replacement, the use of the T3/rT3 ratio becomes essential in an evaluation of the degree of T4 excess that is occurring at the cellular level. Remember, T3 insufficiency is also occurring at this level, as a result of thyroid failure in addition to the elevated D3 expression that is occurring in response to supplemental T4 excess. T4 excess is, unavoidably, the treatment strategy when T4 alone is prescribed for hypothyroidism. **Euthyroidism in the setting of hypothyroidism can *only* be achieved by successfully mimicking the proportional release of T3 and T4 that should be occurring in a normally healthy thyroid state.** Supporting the cells with supplemental T3 (preferably slow-release T3), and reducing T4 to a more physiologic level, is a better approach than giving T4 only and hoping for the best (and creating and perpetuating hypothyroidism at the tissue/cell level, guaranteed).

This physiologic approach to the treatment of hypothyroidism, outlined above, is really a commonsense approach. And it is not difficult to put into practice. T4 only, in the treatment of hypothyroidism, is not as physiologic as it would seem. Again, look closely! You will see that there is a lot of patient dissatisfaction related to the standard therapeutic approach to hypothyroidism. This practice, using T4 only, calls for T4 excess to compensate for low thyroidal output, **a practice that can only increase T3 levels if T4 is given in excess! Supplemental T3, skillfully used, can adjust the T3/rT3 ratio number from a higher number to a lower number and indicate that a state of relative T4 excess has been significantly reduced and the balance between T3 and T4 is more appropriate for the individual.** In this new era, T3 will **never** be intentionally given in excess! T3 does, however, need to be appropriately given along with measures that reduce T4 excess at the cellular level. Again, **limiting T4 excess is the secret of achieving exceptional results with the use of supplemental T3.**

The symptoms of sub-clinical hyper- and hypothyroidism show that minor changes in thyroid hormone levels can have important consequences for the quality of life, cognition, cholesterol metabolism, heart rate, bone mineral density, and atherosclerosis. (Peeters et al., 2003, emphasis added)

*However, thyroid hormone **[thyroxin] has a narrow toxic-to-therapeutic ratio;** and **despite the assumption** that treatment should be straightforward, researchers in several studies—undertaken in large populations and patients cared for in general and specialist practices—have noted that about a fifth of hypothyroid patients are receiving an inadequate thyroxin dose, and **a fifth are given an excessive amount of medication**.* (Roberts and Ladenson, 2004, emphasis added)

My experience with slow-release T3 . . .

At one point in time, the author was taking slow-release T3, prescribed for a chronic fatigue issue. At baseline, my TFTs were TSH 1.8, *f*T3 3.1, rT3 29.1, with a **T3/rT3 ratio of 9.38**—certainly nice euthyroid values except for an elevated rT3 level and elevated T3/rT3 ratio. After 1 month on Liothyronine SR 10mcg, taken AM and HS, my TFTs were as follows: TSH 1.44, *f*T3 3.6, rT3 15.2, with a **T3/rT3 ratio of 4.2**. While on slow-release T3, I experienced no side effects typically associated with T3 administration. The HS dose did not disturb my sleep. After 2-3 months on slow-release T3, my fatigue issues largely resolved, and my sense of well-being greatly improved. Then, in an attempt to further improve my thyroid status, the decision was made to increase my Liothyronine SR dose to 15 mcg, AM and HS. My follow-up labs were as follows: TSH 0.22, *f*T3 4.6, rT3 17.3, with a **T3/rT3 ratio of 3.8**. In view of a relatively low TSH and a relatively high T3 level, my dosage of Liothyronine SR was returned to the previous dosage. I was maintained on the Liothyronine SR dose of 10 mcg, AM and HS for a number of years—again with no indication of thyroid hormone excess. My experience with slow-release T3 was a very positive one. The use of slow-release T3, in my situation, limited my thyroidal output of T4, limited the need for the cells to correct for a certain degree of T4 excess—as indicated by a lower rT3 level and a lower T3/rT3 ratio number—and raised my T3 level to a higher level within the normal range. Interestingly, sometime after beginning supplemental iodine, I discontinued slow-release T3 and my thyroid hormone labs, along with the T3/rT3 ratio, normalized.

A recent paper may be relevant to my experience, outlined above. Ruiz-Núñez et al identified a low T3 syndrome associated with elevated rT3 levels in chronic fatigue syndrome patients, and suggest that T3 and iodine supplementation may be indicated in response (Ruiz-Núñez et al., 2018). They also recognize a low T3 syndrome *"experienced by a subgroup of hypothyroid patients receiving T4 monotherapy."*

Gold standard?

> *. . . Reliance on circulating TSH is supported by many years of experience, and most patients are satisfied with the results, but it implies assumptions that are not supported by direct evidence.*
>
> *First, although approximately 80% of the T3 circulating in the blood is originated by peripheral 5'-deiodination of the T4 secreted by the thyroid gland, as much as 20% is secreted directly by the gland, suggesting a physiological role for the latter fraction. When patients are given levothyroxine alone, it is assumed that the peripheral conversion of T4 to T3 provides the exact amount of T3 needed by each particular tissue or organ that is usually provided by the missing thyroid secretion.*
>
> ***But the scarce evidence available for man does not support this.*** *Hypothyroid patients on levothyroxine replacement therapy have* ***higher serum T4 levels when serum TSH and T3 concentrations*** *are similar to those of euthyroid controls. In as many as 25-32% of hypothyroid patients on levothyroxine therapy, serum T4 has reached the upper limit of normal range, or even exceeded it, to normalize serum TSH and its normal response to TSH-releasing hormone. These findings suggest that the levothyroxine doses needed to normalize serum TSH in hypothyroid patients are relatively* ***supraphysiological****, possibly to compensate for the absence of the fraction of circulating T3, secreted directly by the thyroid.*
>
> *Second, TSH is widely used to monitor levothyroxine replacement therapy, assuming implicitly that its level within normal range indicates euthyroidism in all tissues of hypothyroid patients.* ***Serum TSH levels, however, only reflect the feedback effect of thyroid hormones at the hypothalamus-pituitary level****. In patients on long term replacement with levothyroxine presenting with biochemical abnormalities suggestive of hyperthyroidism, free T4 was raised in 85% of them, whereas an undetectable serum TSH was present in only 67%. Moreover, athyreotic patients present a different end-organ responsiveness to suboptimal thyroid hormone concentrations. It is thus unlikely that a single end-point of thyroid hormone action, such as serum TSH, accurately reflects the thyroid hormone concentrations in all tissues and organs.* ***~Escobar-Morreale et al., 2005, emphasis added***
>
> *TSH is a poor measure for estimating the clinical and metabolic severity of primary overt thyroid failure.* ***~Meier et al., 2003***
>
> *Interestingly, treatment of patients with subclinical hypothyroidism with* ***T4 alone frequently lowers T3 levels****, despite normalizing TSH and T4 levels.* ***~Saravanan and Dayan, 2004, emphasis added***

Not much to comment on here except, for a "Gold Standard," this thing is in a lot of trouble! Even in the face of normal T3 and T4 levels, its elevation may persist. **And a large proportion of hypothyroidism patients on T4-only can also be classified as having ScH** (Biondi and Cooper,

2008). Little thought, it seems, is given to the need to balance a patient's T3 and T4 levels to achieve the right balance between T3 and T4 for the individual patient. And for the "euthyroid" individual, the one exhibiting signs and symptoms of hypothyroidism, nothing is typically offered except the pharmacological treatment of symptoms and assurances that a thyroid problem is corrected and does no longer exist. The TSH will say, "All is well!" when all is not well. Check a rT3 level and you may identify a considerable degree of T4 excess in play. And no matter how it occurs or why, T4 excess requires elevated D3 activity and will subsequently create a degree of hypothyroidism at the tissue and cell level. The balance between T3 and T4 will not be normal for the individual concerned. The patient may have improved *remarkably* on T4, but this person continues to have hypothyroidism at the tissue and cell level.

> *SHypo [Subclinical Hypothyroidism] is frequently observed in patients with overt hypothyroidism receiving inadequate replacement therapy due to poor compliance, drug interactions, or inadequate monitoring of therapy. In fact, between 17.6 and 30% of patients with overt thyroid failure were reported to have SHypo due to inadequate thyroid hormone supplementation.* (Biondi and Cooper, 2008, emphasis added)

Concluding remarks

There is evidence derived from mouse knock-out studies that question the relevance of D3 and D2 in thyroid hormone regulation. (see St. Germain et al., 2009 for review) The mice seem to be doing fine. I'm happy for them (but have not offered them a home). We, on the other hand, are not D3 and/or D2 knock-out mice. We have intact D3 and D2 enzymes, along with regulated transmembrane transporters along with an array of other auto-regulatory mechanisms, that carefully orchestrate and "fine-tune" the concentrations of the various iodothyronine hormones within tissues and at the level of the cell. In this context, the TSH will not identify the true state of thyroid hormone balance at the cellular level. But the T3/rT3 ratio will! It is a *"sensitive indicator"* of thyroid hormone metabolism at this level. It should be in everyday clinical use. This will happen in the new era that is already here.

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