Diagnose and Treat Hypothyroidism in 2021, Part 1: New Endocrinology

By Alan B. McDaniel, MD (from the Townsend Letter)

This article reviews the functions of thyroid hormone and how to diagnose and treat its deficiency. Because the physiology of thyroid hormones is complex, featuring the processing of a pre-hormone to the active form—or its conversion to inactive and even inhibitory forms—good treatment of hypothyroidism is not as simple as many practitioners have been led to believe.

Important evidence is offered to help those who treat hypothyroidism achieve better success for their patients. Readers who in this article may recognize their own needs can show it to receptive providers. Four points are of paramount importance:

1. Thyroid hormone doses must be divided at least every 12 hours—even levothyroxine.

2. Therapeutic blood levels should be tested according to peak/trough fluctuations and mid-way between doses works best.

3. The ratio of totalT3 (tT3) to reverseT3 (RT3) is the best indicator of actual thyroid hormone function in the body.

4. Many patients will need to take T3 along with T4 for their best clinical results.

What Is Hypothyroidism?

Hypothyroidism is best defined as "the clinical consequences of inadequate thyroid hormone in the body."1 The lack of thyroid hormone is the world's most common endocrine disorder (unless you count menopause). It is estimated that about 5% of people in the US are hypothyroid2,3 which may be conservative.4 The disorder is four-times-more common among women than men and its prevalence significantly increases with age.5

Thyroid hormone metaphorically sets the thermostat for the metabolism – the process by which we make and use energy.6 The receptor for this most-important effect of thyroid hormone is located within the cell nucleus. When active thyroid hormone (T3) binds to this receptor, the resulting protein-complex is a transcription factor—it activates the "reading" of the cell's genetic code.

Sections of DNA that encode thyroid hormone-sensitive programs are marked by "thyroid response elements," to which the thyroid transcription factor joins. Here, the transcription factor "unzips" the DNA to make messenger RNA.7 This activates all genetic programs that up-regulate the activity of cells and their metabolism. Conversely, the DNA programs that reduce cellular activity are inhibited.8 Low thyroid is truly a serious condition.

The symptoms of thyroid insufficiency come from low metabolism and depressed cellular activity. The British National Health Service lists many of them (but not all): Tiredness; being sensitive to cold; weight gain; depression; slow thoughts and movement; memory problems; constipation; muscle aches, cramps, and weakness; dry and scaly skin; brittle hair and nails; loss of libido; irregular or heavy periods, and carpal tunnel syndrome (pain, numbness and tingling in the hand and fingers).9 Late symptoms can include low-pitched, hoarse voice; puffy face; loss of eyebrows; slow pulse; hearing loss, and anemia. Other useful and longer lists are available.10

Physiology 101: The Production of Thyroid Hormones

It is easier to fix something when you know how it works. So, before getting into the causes of thyroid insufficiency, let's review some basic facts—I promise that they are all relevant.

The production of thyroid hormones, their storage (a 100-day's supply11) within, and release from the thyroid gland into the bloodstream are regulated by the brain (hypothalamus) and the pituitary gland. Responding to the hypothalamus, the pituitary makes the appropriately named thyroid stimulating hormone (TSH or thyrotropin).12 TSH released from the pituitary travels in the blood to the thyroid gland. There, it connects to receptors on cell membrane surfaces to stimulate all thyroid cell functions, including their proliferation, growth, and maintenance (trophic function). Without TSH, the thyroid gland cannot make hormone, and it shrinks (atrophy = "no trophic").

Thyroid hormones are made from the amino acid L-tyrosine and iodine. These are assembled by enzymes, which require also selenium and iron (at least).13 Glutathione quenches their damaging oxidative by-products.14 Thyroid hormones don't dissolve well in water, so after their release from the thyroid gland, >99% are bound to and carried in the bloodstream by various proteins.15

Thyroid hormones exert some "non-genomic" effects at receptors on cell surfaces, ion pumps and more16; but the main event involves the entry of free (unbound) hormones into cells via transport proteins. After running a gauntlet of transformative enzymes,17 activated thyroid hormone enters the cell nucleus to unite with its nuclear receptor and exert its "genomic effect" on the DNA.

In the hypothalamus, circulating thyroid hormone regulates its own production by negative feedback. It blocks the DNA sequence coding thyrotropin-releasing hormone (TRH)—the little protein that stimulates the pituitary to make TSH. With less TSH, less thyroid hormone is made. Conversely, low thyroid hormone allows TRH to rise, so that more TSH and thyroid hormone may be made.18 Many clinicians consider a TSH value the most reliable indicator of low or high thyroid function—though it is not.

Pathology 101: Thyroid Gland Insufficiency

In the Victorian age, the function of the thyroid gland was not appreciated until Kocher had honed his surgical skills sufficiently to remove huge goiters …and discovered that this made patients even worse, causing "acquired Cretinism."19 For the next hundred years, clinicians remained focused on the gland itself as the cause of hypothyroidism. In the 21st century, we also examine the processing and intrinsic effects of the four variations of thyroid hormone: T4, T3, RT3 and T2.20

Hypothyroidism is a common problem. Every practitioner who is so inclined will have opportunities to treat it. Evidence for this is seen in the lists of most-prescribed drugs in the US: Thyroid hormone has been among the top four for decades, recently along with opioids, statin drugs, and ACE-inhibitors.21-23

Causes of Hypothyroidism

The most common cause of hypothyroidism in the "West" is autoimmune (formerly "lymphocytic") thyroiditis (AIT).24 The body's immune system attacks and destroys its own thyroid gland as though it were rejecting a mismatched transplanted organ. Indeed, this is the most common autoimmune disorder in the US: NHANES III found 13% of people have circulating anti-thyroid antibodies.25 At the end of life, autopsy reveals lymphocytic thyroiditis is found in up to 50% of women and 20% of men.26

Surgical and radio-iodine131 post-ablative hypothyroidism are the next most frequent in the US, from treatment for Graves', cancer, or goiter.27 Congenital hypothyroidism is a newborn-nursery diagnosis, found once in about 3,500 live births.28

Iodine deficiency—when severe—is the world's leading cause of preventable hypothyroidism.29 Deficiency of selenium and the presence of adverse chemicals (perchlorates, thiocyanates) worsen the problem. Milder iodine deficiency causes an enlarged thyroid gland (goiter) without frank

hypothyroidism (as Kocher discovered).30 In fact, in mild iodine deficiency, plasma T3 can be increased.31

Clinicians can expect to see other causes. High iodine causes pseudo-hypothyroidism.32 The gland becomes TSH-resistant to protect itself from high iodine-exposure.33 Lithium at doses used to treat type-I bipolar disorder cause toxic hypothyroidism in up to 20% of users by its effects on iodine-uptake into the gland and its "organification." However, lithium in these amounts more often produces a marked multinodular goiter.34,35 (Lithium supplementation up to 10 mg daily seems safe.36)

Diagnosis of Hypothyroidism

Before starting to treat hypothyroidism, one must make a correct diagnosis. Mindful that the problem is common, we identify patients who are at-risk by their symptoms and physical examination.

Symptoms

Endocrine symptoms are notoriously non-specific—so that authoritative guidelines actually discourage the use of questionnaires.37 However, we have been told that "patients who report multiple thyroid symptoms warrant thyroid testing."2 Therefore I use a questionnaire, the severity of each symptom being graded from 0 to 4 by the patient (free on request).38 It also provides a "baseline" inventory, against which the patients' progress (or lack thereof) later can be compared.

Be cautious about interpreting symptoms: Many symptoms of hypothyroid function are also symptoms of high thyroid function. We will later examine some of the physiological reasons for this. Patients with either high or low thyroid hormone levels can complain of the following:

- Fatigue
- Heart palpitations
- "Brain fog"
- Irritable bowel
- Hair loss
- Muscle weakness
- Urticaria
- "Joint stiffness"
- Insomnia
- Anxiety, irritability
- Menstrual irregularities… and more.

It should also be remembered that some patients can be symptom-free…or wholly unaware of them. A patient with a palpably "bad" thyroid gland whose labs repeatedly showed TSH over 50 with low freeT4 denied any symptom. She finally agreed to try my treatment. On her return six weeks later, she was embarrassed to admit her co-workers were commenting on how bright and alert she had become and had been asking her what she was doing differently.

Before closing this section, remember that failing spontaneous remission, the end-stage of Graves' disease (high thyroid) is low-thyroid function. Ask your people about a remote history of Graves' symptoms, including a huge appetite without weight gain; being underweight; having felt hot or tremulous etc.39 This history may influence treatment outcome.

Physical Examination

The physical exam is important; yet, after I've palpated their thyroid gland, many patients ask me what I had done, saying that nobody had ever examined them there. I am also dismayed by the prevalence of internet images showing practitioners supposedly examining the thyroid gland but nowhere near it—even on sites dedicated to the thyroid gland! Look at a diagram of thyroid anatomy: One of the best (unexpectedly) is on Pinterest.40

Operating many times on and around the thyroid gland has made me confident of finding it in the neck. I and others41 examine patients face-to-face with the neck in a neutral position, not hyper-extended—this relaxes the strap muscles covering the gland. Place one thumb on the patient's "Adam's apple" (for purists: the laryngeal prominence of the thyroid cartilage). Place the other thumb on the cricoid cartilage (about 2 cm lower) …these landmarks are easily found; no worries.

Noting the distance between your thumbs, drop the upper thumb from the Adam's apple to an equal distance below your cricoid thumb and nestle it in. It now rests on the trachea, below the thyroid isthmus—that's the spot! Now, put your cricoid thumb next to it, one on either side of the trachea and glide them up together. Before you get to the cricoid, you'll feel a "blip" as the thyroid gland slides under your questing thumbs. When you have identified the isthmus, circle about with your thumbs and palpate the lobes of the thyroid "bow tie."

What should we do when the larynx is ptotic and the gland is hidden behind the medial heads of the clavicles…or when it is buried deeply within an unusually stout neck? Keep your thumbs just below the cricoid and ask the patient to swallow. The thyroid gland is fixed to the laryngo-tracheal apparatus. With a swallow, the gland rises out of the depths and is palpable in its passage.

It is fine with me if your fingertips are more discerning than your thumbs: Alton Ochsner taught Tulane medical students to examine the thyroid gland from behind the patient. The excellent University of Washington web site is correct—this is a valid method, if you are examining the right spot.41

What should we expect to find? A healthy thyroid gland should be nearly as velvety as a lipoma. On examination, the inner voice says: "There it was, I think." A pediatric endocrinologist in my highest esteem has said we cannot feel a child's normal thyroid gland at all. Adult or child, when the gland is distinctly palpable, it is—to some extent—abnormal. If you can say "The thyroid is right here," it is probably unhealthy—and a biopsy usually shows fibrosis.42

As a rookie surgeon, I once thought hypothyroid people would have goiters. That's wrong; do NOT expect a big goiter—glands with lymphocytic thyroiditis are often smaller than normal.43 The worst glands can feel like a piece of over-cooked liver—firm but usually not enlarged. Following palpation, the skin over the thyroid can flush redly for many minutes afterwards, a sign I associate with autoimmune thyroiditis.

Sometimes we can feel nodules, single or multiple, which take us beyond the scope of today's subject. Please know how to work them up. An authoritative guideline is free to download.44

Occasionally, a diseased gland feels perfectly normal on exam. This makes other, "secondary" signs of hypothyroidism more valuable. Is your patient overly-dressed for the ambient temperature? A wool sweater in July is a clue! Check for cold hands and fingers; flaky, raggedy fingernails; a slow pulse or a sluggish biceps brachii reflex. Thinning hair is a common complaint, which is usually "relative" but often noticed by their hairdresser. Less commonly, the lateral one-third of eyebrows can be disappearing; or there may be puffy eyes and signs of "myxedema" (the 19th century name for hypothyroidism before the thyroid gland was understood).

Most Graves' patients (many of whom are subclinical and not diagnosed)45,46 end up hypothyroid. Is your patient oddly slender? Observe their eyes but remember: Inferior scleral show can be "normal" and the diagnosis of proptosis is made properly with an exophthalmometer.47,48

Laboratory Examination

Our history and physical examination having identified patients who may have thyroid trouble, we trust the laboratory for confirmation. Quoth the Expert: "In the majority of patients, thyroid disease symptoms are subtle… so only biochemical testing or cytopathologic evaluation can detect the disorder."49

We are very fortunate to have an excellent variety of tests from which to select—more options than most providers understand how to use! The information they offer affords us a medical version of "measure twice and cut once" and helps to avoid therapeutic surprises. I prefer to order thorough testing, not a "bare-bones" work-up, although minimalism is officially encouraged.50

Physicians are concerned about the cost of laboratory tests. Lab bills to insurance look expensive but insurance pays a small fraction. Uninsured patients can get tests affordably from direct-to-consumer labs online. These results give accurate diagnosis (priceless) and prepare us to anticipate complications as we initiate treatment, and prevent disappointments—ultimately a great savings.

Before You Test

Even the best laboratory tests are vulnerable. "Pre-analytical errors" are largely avoidable.51 Ask patients to stop biotin supplements 48 hours before the tests: Doses of 5 mg/ day can interfere with most immunoassays and may produce wholly misleading results.52 We should enquire about other potentially interfering agents: Steroids, OCP and HRT; amiodarone; "hormone-free glandulars" (which legally can contain T3); large lithium doses and iodine supplements greater than 1.1mg/ day.53 Remember that patients may be unaware of taking even large doses of iodine – or may, for their own reasons, withhold information about taking thyroid hormone.

"Analytical errors" occur, producing misleading assays. Immunoassays are vulnerable not only to biotin but to "heterophile" antibodies—immunoglobulins produced by the patient's immune system that cross-react with the assay components.54,55 When needed, liquid chromatography/tandem mass spectroscopy is a better method.56 Blood spot assays are for screening newborns…I don't trust them for this work.

Perhaps the most important issue is post-analytical error, which could be paraphrased: The ordering Doc doesn't know what the results mean.57 Even the most basic test, TSH should not be taken simply at face-value.

Thyroid Stimulating Hormone

An accurate TSH assay shows how much of that hormone was recently released from the pituitary gland (its half-life is six hours). When the thyroid gland is diseased, TSH becomes abnormal before freeT4 does; therefore, it is considered the "gold-standard" diagnostic test of hypothyroidism.49 However, a thyroid-stimulating hormone assay doesn't prove normal or abnormal thyroid hormone function.

Researchers state TSH is "neither normatively fixed nor a precise marker of euthyroidism."58 At best, it reflects the freeT4 concentration that acts on the hypothalamus and influences the pituitary.49

There are other issues with the TSH test. Clinical laboratories do not use a truly scientific "normal range" of TSH values.59 Analysis by the statistical method shows the median TSH value is 1.5 μIU/L

and the reference interval (-2SD to +2SD) should be 0.40 to 2.90.49 However, the upper limit of "normal" has been extended to bring the reference-interval into line with expectations based on treatment results. In the last twenty years, the upper limit has been reduced from "10" to "4.5" in most national labs…but statistically, TSH = 3.0 is a high value.

TSH results can be misleading in other ways: Major issues include heterophile antibody interference and importantly, the abnormal amplitude of pulsatile TSH-secretion when the gland is damaged ("spikiness"). This was demonstrated in the laboratory60,61 and can be observed in mildly hypothyroid patients.62 Other complex issues have been raised that are beyond our present scope.63,64

The error of depending on TSH alone was demonstrated in a medical malpractice case: A woman was declared hyperthyroid because her TSH was low and her gland was ablated with radioiodine-131. She did badly on replacement therapy, so she was referred to an "Ivory Tower" endocrinologist. He also relied on TSH to regulate her T4 dose with similarly poor results. A few years—and a few doctors—later, an Emergency Department CT scan identified the adenoma crushing her pituitary and impairing her ability to make TSH.

Physiology 102: Thyroid Hormones

Most authorities state tests for thyroid hormones are unnecessary, unless the TSH value lies between 5 and 10 (when low fT4 distinguishes "true" from subclinical hypothyroidism) …but I disagree. The TSH assay gives incomplete information and is prone to unreliable values. For these and other reasons, I also test thyroid hormones: freeT4, freeT3, totalT3 and reverse T3 (RT3). Reviewing more physiology will help readers to understand why. Let's get to know the players.

The "fully-loaded" thyroid hormone carries four iodine atoms. It is called 3,5,3',5'-tetraiodothyronine (T4) and it is the most abundant (90%) of the three main hormone-products released by the thyroid gland.65-67 The other two have three iodine atoms, lacking one on the outer (T3) or inner rings (reverseT3). Like the teeth on a key, the positions of the iodine atoms determine the functions of these variants.

We've seen that after release from the thyroid gland, the great majority of thyroid hormones are carried on proteins.68 This permits their passage in the aqueous (watery) bloodstream,69 and protects them from spilling out through the urine and from being broken down in the liver. Importantly, it also maintains a large, inactive but ready-reserve of hormone.

Modern assays are so sensitive they can accurately report the tiny amounts of free T4 and T3 (down to 2 pg/mL—that's 10-12 of a gram!). Most practitioners, knowing that only free hormones can enter cells,70 order "free" hormone tests, not "total." Besides, "total" measures are significantly distorted by anything altering the liver's production of these binding proteins, including oral contraceptives, pregnancy or women's hormone replacement therapy; liver or kidney disease; insulin resistance, and severe illness.

T4 is a pre-hormone and T3 is active.

Most importantly, as you provide and monitor patient care, remember: T4 is a pre-hormone with little genomic effect. The 19th-and-20th-century focus on the thyroid gland only—its ability to produce T4—is no longer adequate. We must know how the pre-hormone is being "processed."

To activate T4, cytoplasmic deiodinase enzymes within the cells of many tissues71 remove one iodine atom from the outer, "prime" ring, making T317 (See Figure 1). Why does the gland release a pre-hormone instead of making all active T3? For the same reason Campbell's puts soup in cans instead of steaming hot bowls: It is safer to transport; it has a long shelf-life; and you should be able to open it anytime you want.

From: Wikipedia. https://en.wikipedia.org/wiki/Reverse_triiodothyronine
As stated, T3 "sets the thermostat of the metabolism." Its genomic effect stimulates every DNA program that increases cell metabolism and activity—and impedes the DNA programs that slow them.

Conversely, removing one iodine atom from the inner ring of T4 makes reverseT3 (RT3), which everyone agrees has absolutely no stimulatory effect and cannot be retro-converted to T3 (Figure 1). Increased RT3 has long been noted to indicate an adaptive down-regulation of thyroid hormone effect during stress (injury, illness, starvation, or psychological distress).72-74

Remember this paragraph: Thus, the deiodination of T4 to either T3 or RT3 determines thyroid hormone function at the cellular level.71 This "processing" of T4 is tightly controlled75,76 and it is the primary means of regulating the biological activity of thyroid hormone.20 The best indicator of this is the ratio of T3 to RT3, both in clinical use and in research.77,78 Blood tests of these hormones are reliable too, accurately reflecting their values in tissue samples.79

Calculate the Ratio of T3 to RT3

Even using the best assay (LC/MS-MS), there is too little free reverseT3 in the blood to be measured; thus, "totalRT3" is reported. Because the amounts of binding proteins are so variable, the critical T3:RT3 ratio must be calculated comparing RT3 to totalT3—apples-to-apples, total-to-total. Efforts to compare freeT3 to RT3 are ultimately doomed to fail—as I learned years ago, when a congenitally athyreotic patient became pregnant.

The relative amounts of T4 and T3 within their "normal" ranges and the totalT3/totalRT3 ratio show how the body is processing its hormones. The value of analyzing these multiple parameters has been supported.80 Patient 2will show their clinical significance (Table 1): If T4 is a "can of Campbell's soup," does the body have a can-opener?

Table 1: Patient 2 taking all-T4 compared to T4+T3:

Treatment	TSH	freeT4	freeT3	totalT3	RT3	tT3/RT3
Divided Q12h		(0.82-1.77)				(10-14)
T4 56+56mcg	0.663	1.66	2.9	87	**36.1H**	**2.4**(L)
T4 25+25mcg T3 12.5+10mcg	0.711	**0.80** L	4.1	151	13.3	11.4

Examine the values for all five tests I've recommended in the same critical way a basketball coach watches his five players on the court: Is each one where he should be and doing his job? Are all five coordinated and running the same play—or is someone out of synch and hurting the team?

Pathology 102: Define the Cause of Hypothyroidism to Treat It Skillfully

It is important to diagnose the cause of your patient's thyroid problem—and as my Med-Mal anecdote suggests, skipping this step can be harmful. We should test for autoantibodies; here's why:

We know that autoimmune thyroiditis (AIT) is the most common cause of hypothyroidism in the US. There are two main forms of AIT: Hashimoto's disease, which we all understand to cause

hypothyroidism and Graves' disease—the most common cause of *hyper*thyroidism. Both can cause hypothyroidism, but they can respond very differently to our treatment efforts.

Hashimoto's is a T-cell mediated, destructive process.81 Its hallmark autoantibodies react with the thyroid peroxidase enzyme that constructs thyroid hormone (TPO-Ab) and with thyroglobulin, the protein in which thyroid hormone is manufactured and stored (Tg-Ab).13 These antibodies are probably cytotoxic, though that has been debated.82

Graves' disease involves both stimulating and destructive events: B-lymphocytes release antibodies that bind to thyroid cells' TSH-receptors (TSH-R) and, by molecular mimicry, make the cells respond exactly as they do to TSH.4 Most Graves' patients *also* make the destructive autoantibodies typical of Hashimoto's disease.83

Always remember that any hypothyroid patient could have end-stage, "burned-out" Graves' disease.24 This can affect your therapy: As long as a Graves' patient has a shred of functioning thyroid tissue, the TSH-receptor-stimulating antibodies (TRs-Ab or TSI, *formerly* LATS) can drive that residual thyroid to produce hormones unpredictably. We'll discuss this and other types of "autonomous function" presently.

Test Thyroid Autoantibodies

When a patient's thyroid gland is palpably abnormal, I test for both TPO-Ab and Tg-Ab. Yes, the medical literature now supports the value of testing Tg-Ab.84 Various other anti-thyroid antibodies exist for which no commercial tests are available.85
If the history and examination raise a question of prior Graves' or give a hint of autonomous function, order either TSI (a biological assay) or the faster, less-expensive immunoassay for TR-Ab (which does *not* differentiate between stimulating and blocking antibody).86 This complements your comparison of TSH and thyroid hormone levels and helps to predict autonomous function or unreliable TSH values. Identifying or anticipating such problems can improve treatment outcomes.

Disappointingly, not every case of AIT can be proven by these antibody tests. Probably because Hashimoto's is primarily a T-cell mediated disease, autopsy series have found up to 10% of glands with histological AIT are antibody-negative.87 Ultrasound can help,88 and I've learned to trust palpation.

Tests for Less-Common Causes of Hypothyroidism

Most post-ablative hypothyroid patients report their status; sometimes a surgical scar is the tip-off. Nutritional issues can be more challenging. As above, low iodine can cause goiters but less often hypothyroidism. In the US, we are more likely to see pseudo-hypothyroidism due to iodine toxicity,32, 89 often from people following ill-considered internet suggestions.

For iodine, test overnight-fasting blood or get a first-voided morning urine specimen—it is routinely used by the WHO, which considers 100 mcg of iodine/ L "replete."90 Others prefer a 24-hour urine collection. I will not use the "iodine-loading test,"91 which I believe is bogus – and *not* wholly safe.92

Pharmacological doses of lithium can cause hypothyroidism in up to 20% of chronic users.34, 35 More often, lithium in the amounts used to treat type-I bipolar disorder will produce a marked multinodular goiter. If you test, know that "therapeutic" blood values are actually thyroid-toxic, with cumulative effects.93

Basal Temperatures

It is tempting to measure basal axillary temperatures on waking in the morning. I believe low axillary temperatures imply low metabolic rate and may support laboratory testing,94,95 but they do not prove low thyroid function. I have tried and will testify: Basal temperatures cannot be used to safely guide doses of thyroid hormone replacement.

Therapeutics 101: Treat Hypothyroidism…Successfully.

It is unlikely that any practitioner in the US will need to treat iodine-deficient hypothyroidism. To the many clinicians who give supplementary iodine, a caution: The iodine-depleted thyroid gland enlarges and up-regulates all of its mechanisms for taking up iodine and incorporating it into thyroid hormone. Therefore, *hyper*thyroidism can occur if iodine is rapidly or excessively replaced; it is not uncommon and is sometimes severe.96-97

The amount of iodine supplementation should be moderate.98 NHANES-III found elevated urinary iodine (>401 mcg/L) is associated with higher risk of all-cause mortality, whereas low iodine was not.99 Some patients arrive for consultation with first-voided urine iodine values in the thousands of micrograms per liter.

Thyroid Hormone Replacement

It is important to ask if your patient has a preference for any particular form of thyroid treatment. For the sake of an orderly presentation, let's begin with a patient who prefers "orthodox" replacement with levothyroxine (T4).100 Levothyroxine is synthetic but biologically identical. Proponents have touted the fact that T4 is a pre-hormone as evidence of its safety: They state that only the required amount of T3 will be made.101 Critics ask if it *can* be…but that's for later.

Current guidelines encourage us to treat patients whose TSH value is >10 μIU.100 Those patients with TSH between 5 and 10 may have "subclinical hypothyroidism,"102 so treatment is recommended only if TSH is *consistently* elevated *and* freeT4 is low, regardless of their symptoms. Semantically, perhaps sub-*laboratory* is a more correct term. We'll re-visit this, at which time the truth of this statement will be validated: "(Our) needs include the development of superior biomarkers of euthyroidism to supplement thyrotropin (TSH) measurements."100

Pre-Treatment Considerations

Before starting treatment with levothyroxine (T4), always assess the patient's overall health, the nature of the thyroid disease, and the adequacy of other endocrine systems. For example, patients with no gland whatsoever—whether congenitally absent or ablated by operation or iodine 131*–are often said to be the *most* difficult: They have no endogenous production to "back them-up"100 when they miss a dose *or* if our treatment efforts go off-target.

The adrenal glands are essential to our metabolism; if thyroid sets the thermostat of the metabolism, the adrenal is the furnace. The entire spectrum of adrenal dysfunction, from Addison's to the lightly regarded "adrenal fatigue" should be addressed.103 Decreased adrenal mass is associated with long-term hypothyroidism, following experimental abnormalities of all three components of the hypothalamic-pituitary-adrenal axis.104 Correcting the thyroid deficiency can create increased demands for adrenal steroids.105 Thus, adrenal issues should be addressed before or concurrently with thyroid hormone replacement—*not* deferred to afterwards.

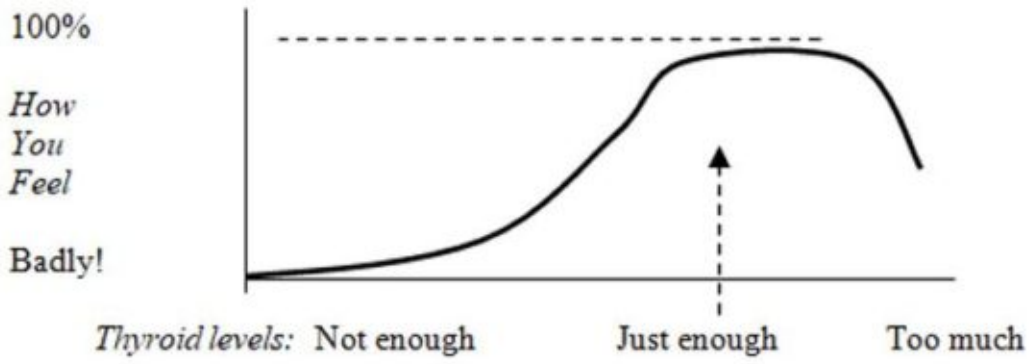
Steroid sex hormones also can be important: Postmenopausal women have complained that thyroid treatment provokes symptoms of estrogen deficiency. These included vasomotor flashes, mood swings and insomnia – none of which correlated to peak-and-trough fluctuations of thyroid hormone. This may be mediated by crosstalk at receptors in the nuclei106-108 or perhaps simply by increasing the hepatic metabolism of estradiol.

Give Informed-Consent Talk Before Starting Treatment

The goal of treatment is to restore normal thyroid hormone effect at the cellular level, resolving the symptoms and signs of hypothyroidism. The coincidental restoration of desirable blood levels is both a goal and our guide, for we use the laboratory to monitor therapy.100 In certain cases, slightly more thyroid hormone replacement is given to suppress TSH, as after thyroid cancer treatment109 or to shrink a goiter.110

Risks should be discussed. Treatment can harm patients if we give too much hormone, or too little—or if a patient disregards our instructions and self-medicates according to whim. In IC-talk, emphasize that provider and patient are jointly responsible and both must cooperate. As above, age and other health issues influence risk. Otherwise, harm is possible only if the patient is allergic to some "inert" component of the tablet or if he chokes on a pill. Fertility can be increased, menstrual cycles may resume, and rarely, allergies might get stronger as this unwanted portion of the immune system is strengthened.

Figure 2: Thyroid hormone dose-response curve



Explain the therapeutic dose-response curve: Too little treatment does nothing; just the right amount achieves all that T4 can—and too much makes things worse. Make sure the patient hears these words: "If you feel worse with treatment, we may have increased the dose too quickly, *or* the dose is incorrect, either in the amount or its timing111,112 *or* there is an unsuspected problem."

Trusting our history, physical and lab findings, we expect treatment to do good things. Importantly though, every new thyroid prescription begins a treatment-trial. If it does not help, the reason must be determined.

Start T4 Treatment: Dose and Timing

Despite optimistic declarations in the medical literature that starting with a "full dose" of T4 is safe in all but the elderly or infirm,100 I *never* do that. Whether treating with T4, "natural" thyroid or T3, *all* my patients receive gradually increasing doses. This is a good idea with T4 and *imperative* when treating with T3. I prescribe levothyroxine 25 mcg tablets, which can be divided to give the smallest accurate increment.

Typical T4-doses vary from 50-200 mcg/d daily.113 What daily dose will a particular patient probably need? It is wise to anticipate a safe maximum before writing the prescription. Lean body mass is proven to be the best initial indicator of the ultimate levothyroxine dosage.114 Age and gender differences mainly reflect different proportions of lean mass vs. total body weight.

Guidelines state the usual maximum daily-T4 is **0.73 mcg per pound** of body weight (1.6 mcg/kg) when TSH is markedly elevated.100 With experience and attention to situational clues and lab values, you will learn to modify the dose for frail or overweight people (hunters call such adjustments "Kentucky windage"). For safety, always bring patients back for follow-up *before* increasing their dose to reach the estimated "maximum."

My patients start taking 25 mcg T4-daily. Although remaining vigilant, I expect no problem, particularly as all have begun taking nutritional support for their adrenals and *other* steroid-forming tissues. I give written directions for the patient to increase the dose by 25 mcg weekly—as *tolerated*—and put it in writing on a fill-in MS Word form (free upon request).38 Figure 3 shows typical instructions for a person who may need as much as 125 mcg T4 daily:

Figure 3: Levothyroxine dose instructions to achieve 100mcg/day

Rx: Levothyroxine 25mcg (GF: Synthroid®); biologically-identical T4

Week	Dose	AM	PM	Tablets	Special Instructions
#1	T4	12.5 mcg +	12.5 mcg	(½ + ½)	Cut your caffeine dose in half
#2	T4	25 mcg +	25 mcg	(1 + 1)	Cut the caffeine in half again
#3	T4	37.5 mcg +	37.5 mcg	(1½ + 1½)	– and again
#4	T4	50 mcg +	50 mcg	(2 + 2)	Here, please be stimulant-free

Let me challenge you: If our goal is to restore normal hormone levels, why do we give thyroid treatment once daily? This is *so not* physiological! The healthy gland releases steady amounts of hormones throughout the day. Thus, circulating thyroid hormones remain quite stable all day.115 Yes, TSH varies a bit, rising from about 1.5 in the day to 2.2 at night—that's +/- 0.35 …no big deal.116 Healthy bodies do best with blood levels close to the "normal physiology."

Once-daily levothyroxine doses were suggested as a marketing strategy in the 1950s. Using tests that weren't available back then, we find this creates abnormal blood levels: A big peak of T4 occurs around three hours after the pill is swallowed,117 then the level drops steadily until the next dose. Because levothyroxine was approved long before good assays were available, no proper pharmacokinetic studies were, or ever have been published.

In their place, data for other drugs can represent the likely levothyroxine kinetics. Graphic representations of blood levels for topirimate118 and methadone119 in once- and twice-daily doses are available online. They clearly show that divided doses maintain therapeutic blood levels and avoid the supra- and sub-therapeutic values seen with once-daily doses.
If a patient asks, "What is the best way to take thyroid?" I may tell him the ideal would be to take a tiny tablet every minute; that impossible schedule would best-mimic normal physiology. Yes, most people can tolerate once daily-doses – but dividing it every 12 hours often works better. Osler, acclaimed as the greatest physician of the last century, prescribed desiccated "natural" thyroid every *eight* hours.120

Similarly, when someone asks me, "What is the best time to take thyroid?" I usually answer, "three hours before you wake up." People get out of bed a lot more easily with peak blood levels of thyroid than at trough. Although some practitioners endorse once-daily T4 doses at bedtime,121 taking divided thyroid doses, on waking and about 12 hours later, seems better for most patients. *Caution*: Avoid taking take the PM dose less than four hours before bedtime, as peak levels make it harder to fall asleep.

I am an agnostic regarding the stickers that pharmacies place on prescription bottles, advising that T4 should not be taken with food (especially soy) or supplements (particularly calcium and iron).122 The studies proved malabsorption is *statistically* significant,123 but experience shows it is

rarely clinically significant in adults—except in this way: Patients' efforts to follow this instruction commonly disrupt their doses.

So, my patients take thyroid every 12 hours, regardless of meals—though I ask them to avoid a bolus of soy.124,125 The patient should always have a few doses with them. My wife has a little pillbox in her purse; men can put a small pill-cylinder on their keychain. Also, reminders are helpful: Set an alarm on the cell phone to ring when the PM dose is due (that's the one most likely to be missed).

Dose Escalation: The Initial Phase of Treatment

While lean body mass predicts the maximum dose, the patient's symptomatic response to treatment helps to define the "optimal." From any dose adjustment, there are only three possible outcomes: The patient feels better, the same or worse. It takes up to a week before this can be determined with any certainty; each step results in many changes and protein-bound hormones are slow to reach their new equilibrium.

At the end of each week, the patient assesses her response to the current dose and decides upon the next step. Caution her that if any dose increase feels worse, she should reduce it: Drop back just one step and contact me (*I'm emphatic about this!*). If it seems unlikely that her dose would be too high, take a careful history for the use of stimulants and seek clues to any other, unexpected problem. If none can be found, ask her to continue the new, lower dose and after two weeks, check blood levels.

When Your Patient Unexpectedly Feels Worse

The most common reason people feel "worse" during the dose-escalation phase is simply over-stimulation from caffeine. I know this from my personal experience. People with hypothyroidism need something to give them energy and caffeine is the most available legal solution – I had a two pot-daily coffee habit.
As thyroid hormone levels rise towards normal, the high caffeine intake begins to produce the jitters and naturally, the thyroid replacement is blamed. Be pro-active: Their former "best-friend" caffeine must be tapered-off during build-up and temporarily discontinued (Figure 3) – even decaf products, which still have too much. The prohibition can be relaxed after the safe, effective thyroid dose is established.

Thyroid replacement can also reveal symptoms of low blood sugar and estrogen deficiency. However, it is unusual to get any such call using levothyroxine. People rarely feel worse during T4-escalation.

Schedule your first follow-up visit at the end of the planned build-up time—four weeks in the illustration given in Figure 3. By design, she will be taking *less* than the estimated "maximum." Her clinical response will then guide the next steps.

The First Follow-Up Visit

Inventory symptoms: If your patient feels 100% well, maintain the current dose and check blood levels to ensure safety and efficiency. This can be done after two weeks on a stable dose. Some writers prefer to wait four weeks or more.126
When symptoms persist – with no evidence of over-replacement—I recommend cautious increments of just 12.5 mcg T4/week until reaching the estimated maximum dose. Laboratory tests are then needed. When symptoms are resolved, the lab should validate the dose. If symptoms persist, your blood tests should show you the problem.

Daniel Boone was once asked if he had ever gotten lost. He replied no, but he had once been bewildered for three days. If you are ever "bewildered" about how to proceed, it is always appropriate to check blood levels on an equilibrated dose – the way a modern Boone checks her location by GPS.

Pathology 201: The First Laboratory Follow-Up

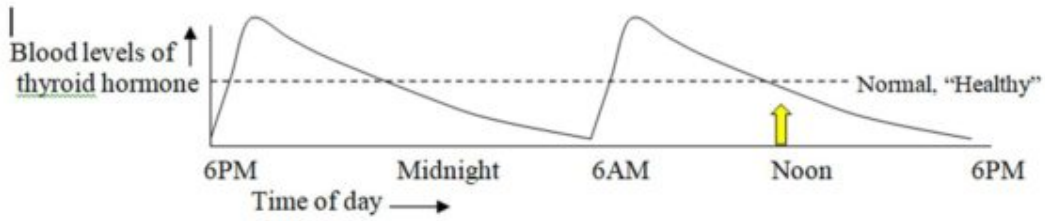
Let's re-visit "pre-analytical error": When a patient regularly takes levothyroxine, at what time should her blood be drawn? Graphs of peak and trough therapeutic values indicate random tests are imprecise. Accuracy requires specimens to be drawn in relation to doses…but when? It was written that *free* hormone values can vary by 30% following a dose (*in an article I can't find, alas!*). The best pharmacokinetic data I can find state thyroid hormones peak "some 3 or 4 hours" after a dose.127

Internists usually test at trough, just before the AM dose. This most sensitively detects insufficient treatment. However, excessive dosing can be missed – for example, among 25,862 health fair-attendees, 40% of all people taking thyroid hormone had out-of-range TSH values – 90% of which were low, suggesting over-treatment.2

Followers of the Belgian endocrinologist Thierry Hertoghe128 draw blood specimens three hours after the thyroid dose (at peak), which best reveals high levels. As the converse of the internists' method, it may be expected to miss *under*-treated patients—and it will (see Patients 4 and 5, following).

Given such uncertainty, I prefer to test my patients' blood levels exactly mid-way between evenly spaced doses, which are divided as evenly as possible. This tactic gives me an average: Half of the day, therapeutic levels are higher, and they're lower the other half (Figure 4). Admittedly, therapeutic values may be high when tested at peak or low if tested at trough – even with Q 12 hour divided doses.

Figure 4: Test thyroid hormones mid-way between evenly timed doses.



Patient 1 provides a good example. Her endocrinologist tested her at "trough," 24 hours after her last AM dose of T4 125 mcg. Her values were TSH=**5.2** H; freeT4=0.8 and freeT3=2.9. The Doc increased the T4 dose by 25 mcg, but she felt no better and consulted me.

I suggested dividing her T4 to 75 mcg Q 12hrs., then testing in two weeks. But she was in a hurry: Late that afternoon, we checked her levels as close to mid-dose as possible – just before the lab closed. These values were typical of excessive levothyroxine treatment: TSH 0.488; freeT4=**1.96** H, freeT3=2.7 …and RT3=**39.6** H.
Testing at mid-dose is successful in my practice. I have no objection when other physicians adhere to a different strategy they like better, as long as they are consistent, minimize pre-analytical error before performing their tests, and are aware of relative drawbacks of their choice. However, I cannot endorse random testing.

Figure 5: Post-test dose and timing questionnaire and Excel record

At the time of the tests, you were taking:
- T4 (levothyroxine) _ + _ mcg
- T3 (liothyronine) _ + _ mcg

The blood was drawn:
- _ Hours after your AM thyroid dose
- That dose was taken _ hrs. after the PM dose

Ref Int.	9.2–24.1
tT3/tRT3 ratio	11 (10–14)
Blood Drawn	6/13:54 12
Taking:	T4 25+25
	T3 10+10

However, you prefer to test, keep good records to both facilitate your therapeutic choices and validate them. On receiving a lab report, I send the following form to my patient by e-mail (Figure 5). I ask her to copy it and paste it into an e-mail to me; then fill-in the blanks and return it for her records. I review many files from other physicians, and it is disappointing how little value reports offer without the dose and timing information.

Confirm Treatment Results with "All 5" Thyroid Hormones

The "ideal" therapeutic TSH-level is a matter of opinion. The 2014 American Thyroid Association (ATA) guidelines simply recommend "a value within the reference range" for adults (0.4-4.0 μIU/L) and no higher than 2.0 for children, lest their development lack support.100 Online, the ATA suggests 0.5 to 2.0 for all patients,129 which I and practitioners around me prefer. A Norwegian writer has suggested 0.5-1.5.130

If your goals include suppressing TSH, *first* be sure that the patient feels *well* on her levothyroxine. If not, taking more T4 will probably make her feel worse. Only after all other aspects of her therapy are satisfactory will I increase the replacement dose to suppress TSH.

In addition to TSH, it is important to check freeT4, freeT3, totalT3 and RT3. This is especially true when a patient's symptoms have not responded to treatment – yours or that of other physicians for whose failures you were consulted. If you are not yet inspired by the metaphor of the basketball coach, keep reading….

Subsequently, it is wise to follow your patient with an office visit and mid-dose labs at around three months and again at some six months after proving the "optimal dose." Then, schedule annual check-ups. As reviewed just below, thyroid function can be unstable, and adherence may be undisciplined. In the first year, it is prudent to metaphorically keep a finger on the pulse.

Therapeutics 102: Problems with Levothyroxine Treatment

Levothyroxine treatment should be sufficient – so we've been taught for 60 years. However, there are a number of potential problems. Among them is our dependency on the patient's (diseased) gland to keep producing.

It is not unusual to find patients taking T4 have undesirable TSH values,2,131,132 whether due to patient non-adherence, prescriber technique, or progressive disease. However, unless the T4 dose suppresses the patient's TSH, her gland will still contribute to the total amount of circulating thyroid hormone. With ongoing thyroiditis (e.g. Hashimoto's), the progressive failure of the patient's residual function is predictable—and she will need increasingly large replacement doses. For this reason, lab values must be followed at least annually and *any* time the patient seems to take a down-turn.

Pharmacies participate too: My patients have received incorrect prescriptions on occasion. Once dispensed, the pills can be damaged: A patient left her 90 days-supply of T4 on the dashboard in July, where the heat inactivated them and sparked great perplexity. Other, undiagnosed conditions also can prevent a good response.133

Autonomous function is unfortunately common, especially among "difficult" patients. You will hear from them during the escalation phase, earlier than you would expect. Because of this autonomy—whether undiagnosed Graves, "toxic" multinodular goiter, functioning adenoma, or even Hashitoxicosis—your calculated replacement dose will give them more than they can tolerate. Tests of "all-5" hormones should reveal this.

Spuriously elevated TSH can be deceiving. If you've correctly calculated the replacement dose, this patient won't be hyperthyroid at her first follow-up: As she increased the T4 dose, her (normal) hypothalamic-pituitary-thyroid (HP-T) axis will have reduced its production to maintain normal thyroid hormone levels. If she takes too much T4, though, she will feel worse and "5 tests" show the mismatch between the bogus TSH value and high thyroid hormone levels.

Up to 16% of patients report poor results using T4, despite normal test values for TSH and freeT4.134,135,136,137 That is one of every six people! The voices of this unfortunate minority have become increasingly angry.138,139

Lately, they have been given proper academic attention: Multiple centers sent a survey to their hypothyroid patients asking them to grade their satisfaction with thyroid replacement treatment on a scale of 1-10. They received 2,146 responses: Satisfaction with levothyroxine treatment was "5." Combined T4 and T3 treatment (as given) was better ("6") and best of all was "natural" thyroid, scored "7."134

Correct the Failure of T4 Treatment

Patient 2 was a 31-year-old woman on her arrival for consultation. She had been hypothyroid for 14 years due to Hashimoto's disease. She was unhappy with her results on once-daily levothyroxine 112 mcg Q AM: In the previous two years, she had three confirmed 1st-trimester miscarriages (ICD-10: N96) and a fourth had been likely.

Despite normal TSH and freeT4 on treatment, she had many symptoms suggesting low thyroid, including fatigue, feeling cold, cold hands and feet, tired on waking, gas and bloating, constipation, reduced libido, and dry skin. Adrenal issues were suggested by symptoms such as orthostatic lightheadedness and craving salt. She had 28-day cycles; no PMS; menstrual flow lasted three days with clots and pain for one day. Her diet had long been gluten-free (Dad has celiac). Her BMI was 19.6.
She began taking neonatal bovine "adrenal glandular" and divided her T4 dose to 56 mcg q 12h. After two weeks, she had blood drawn six hours after her AM dose; it showed: TSH= 0.663; fT4= 1.66, fT3= 2.9; tT3= 87, RT3= **36.1** H. Ratio tT3/ RT3= **2.4** (L)

We agreed to replace some of her T4 with T3. I used the common semi-equivalency that 25 mcg T4 ≈ 5 mcg T3 (5 to 1), though a few studies have used 3:1.140 Figure 6 shows her instructions38 for the four weeks of transition.

Figure 6: Plan to transition from T4 monotherapy to combined T4 plus T3.

	Dose: AM		PM	Tablets:
Now on: T4 (Synthroid) 56 mcg + 56 mcg				(112: ½ + ½)
Week	Go to:			
#1	T4 50 mcg	+	50 mcg	(2 + 2)
	T3 2.5 mcg	+	2.5 mcg	(½ + ½)
#2	T4 37.5 mcg	+	37.5 mcg	(1 ½ + 1 ½)
	T3 5 mcg	+	5 mcg	(1 + 1)
#3	T4 25 mcg	+	25 mcg	(1 + 1)
	T3 7.5 mcg	+	7.5 mcg	(1 ½ + 1 ½)
#4	T4 25 mcg	+	12.5 mcg	(1 + ½)
	T3 10 mcg	+	10 mcg	(2 + 2)

After two weeks on T4 25+12.5 mcg and T3 10+10 mcg, she felt much better. Blood was drawn 6 hrs. after her AM dose: TSH= 0.463; fT4= **0.59** L, fT3= 4.2; tT3= 152, RT3= 10.3 and tT3/RT3 ratio= 14.8 (*a more complete discussion of the ratio will follow*).

We had to increase T4 – which was lower than anticipated because she was again pregnant! Binding proteins are greatly increased with pregnancy, and like most women, she now needed a larger dose: T4 37.5+37.5 and T3 10+10. She delivered a healthy boy at term and after six weeks, she required less T4.

A year later, during her second pregnancy, she once again needed the same greater thyroid dose. She delivered her second healthy baby and in the postpartum, again reduced her T4 dose. Years later, her latest test results at mid-dose, taking T4 25+25 mcg and T3 12.5+ 10 mcg (divided Q 12 hours) were: TSH= 0.711; fT4= **0.80** "L" (0.82-1.77), fT3=4.1; tT3=151, RT3=13.3 and tT3/RT3 ratio= 11.4 ("10-14").

Physiology 201: Why Does T4 "Fail" So Many People?

Patient 2 raises important issues. Although the pre-hormone levothyroxine restored TSH and freeT4 to their normal ranges, the initial set of "5-labs" proved that her body could not efficiently activate T4 to T3; she made RT3 instead. The *first* therapeutic move was to divide her dose. Let's examine the reasons for this:
The healthy hypothalamic-pituitary-thyroid (HP-T) axis continually "trickles" hormones into the bloodstream. In contrast, once-daily thyroid hormone floods the body with a bolus of T4 sufficient to last 24 hours. This rush of T4 signals "*hyperthyroidism!*" during the hepatic "first pass" and with supra-physiological free T4 blood levels peaking in three hours.117

Excessive T4 redirects deiodinase enzymes from producing T3 to instead make RT3141—and deactivate T3 to T2 (Figure 2). An elevated T4/TSH ratio exerts the same effect.80 This has been reported in Graves' disease,142,143 for which it is considered adaptive and protective. When T4 is taken for hypothyroidism, it is neither.

Some patients treated with levothyroxine have frankly low values of T3,100 which can correlate with symptoms.144 In such cases, increasing the T4 dose can ultimately produce T3 levels somewhere in the "normal" range (there was no mention of symptom improvement).145 However, higher than normal RT3 levels consistently accompany once-daily oral levothyroxine, in both humans146,147,148,149 and beasts.150,151 I find no report to the contrary.

Like most patients whose activation of T4 is somehow dysfunctional, Patient 2 had hypothyroid symptoms and signs (miscarriages); normal TSH; normal T4 levels but a low ratio of tT3/ RT3. Unfortunately, even though taking divided T4 doses, Patient 2 continued to have both symptoms and excessive RT3 relative to T3.

Dysfunctional Deiodination and Low tT3/ RT3 Ratio

Prescribing T4 without testing the patient's ability to activate it might be compared to charitably sending cans of food to starving Third-World children without ensuring they have a can-opener. The thyroid "can-opener" is a 5'-deiodinase enzyme (there are two isoforms).

While 80% of the T3 we humans need daily is derived from T4,152 not everyone is able to efficiently perform this conversion. For some, the enzyme responsible for making 50-70% of our T3 (type-2 deiodinase, 2-DI)153 is faulty. A 2009 report showed that 16% of Britons carry loss-of-function mutations of the gene (DIO2) encoding this enzyme.136 The "mutated" patients responded significantly better to combined-therapy with T4 and T3 than to T4-alone. Patient 2 has Northwestern European ancestry.

Patient 2 also has hypothyroidism due to Hashimoto's disease (AIT). Research has strongly associated AIT with the excessive production of RT3 ($p<0.00002$).147 Many other factors can direct deiodination of T4 away from T3 to RT3, including drugs (*particularly* epinephrine,154 steroids,155,156 beta-blockers,157,158 and amiodarone159); iron-deficiency160; inflammatory cytokines161,162; bacterial endotoxin163,164; mold mycotoxins165; elements of metabolic syndrome166; and even some tumors.167,168

The effects of stress are also important: The acute stress response to severe illness reduces both TSH-release and peripheral T3 production. Thus, the metabolism slows to a low energy-consuming, conservative state.72,73,74 This can be adaptive in cases of serious injury, illness and starvation.169 However, it becomes maladaptive when inappropriately prolonged170,171,172 and is called "euthyroid sick syndrome" (ESS) or "non-thyroidal illness" (NTI).161,173,174

Emotional stress can also initiate this response, to the detriment of the patient. ReverseT3 can rise rapidly as patients enter a surgical suite175 or simply experience pre-operative anxiety.176,177 This has also been reported among medical students taking examinations.178

But the Problem Is Not "Low" T3

The alert reader may now ask: How can I say Patient 2 had dysfunctional deiodination? Her freeT3 and totalT3 values were normal all along! This question perplexes scientists studying ESS/ NTI.161,173 At first, it was called "low T3-syndrome"—until it became evident that indeed, *low* T3 was *not* the hallmark of the problem.

Harvard researchers wrote that altered deiodination may cause physiological hypothyroidism—"disruption of thyroid hormone signaling"—while T3 levels remain within the normal range.171 If not low T3, what test result identifies this physiological aberration—and what causes the severe ill-effects of ESS/NTI?

Elevated RT3 is characteristic of ESS/NTI, and it predicts a bad clinical outcome.172,179,180 However, a far more accurate diagnosis of this problem is established by a low **tT3/RT3 ratio**, which has a ten times-greater prognostic significance than elevated RT3 alone.77 This ratio is our best indicator of thyroid hormone signaling; to some, it seems even a better marker of euthyroid status than TSH.78

Inhibitory Thyroid Hormones: The Actions of RT3

Many ideas are proposed to explain ESS/NTI. "Occam's razor" states the simplest of these is the most likely to be valid: ReverseT3 inhibits the effects of thyroid hormone. Lying buried in the medical literature is a surprising amount of evidence supporting this hypothesis.

The existence of an inhibitory thyroid hormone-metabolite was recently proven with the discovery that 3-iodothyronamine (3-T1AM) can rapidly and reversibly cause tissue-hypothyroidism.181,182 The validity of these observations is generally accepted. Reverse T3 is a parent molecule of 3-T1AM, but the accumulated evidence that RT3 also is thyroid-inhibitory has not been reviewed in a publication. Here's a brief summary.

Inhibitory effects of RT3 were reported in some of its earliest studies.183,184,185,186 Its hypometabolic effect comes partly from antagonizing the actions of T3.187 Perfused RT3 blocks the genomic effects of T3 at a number of hepatic thyroid-response (T3-stimulated) genes.188 Studies show T3 cannot displace RT3 that is bound to the nuclear thyroid-receptor—and vice-versa.189,190 Thus, RT3 and T3 have the same relationship with the thyroid-receptor as do antihistamine and histamine at the histamine-receptor.

Reverse T3 exerts various non-genomic effects independently of T3.191,192,193 Acting at critical regulatory effectors, RT3 deactivates both 5'-deoidinase enzymes that convert T4 to T3: Type-2194,195,196,197,198 and type-1.199,200,201 An active role for RT3 was indicated in a well-designed study by the administration of RT3 to volume-depleted dogs, which resulted in significantly elevated death rates.202

Intriguing evidence for the inhibitory role of RT3 comes from AIDS patients, whose infections almost uniquely lead to pathologically *low* values of RT3.203,204 Low-RT3 and *not* high T3 correlated with their hyper-metabolic state and weight loss—apparently because their metabolism is disinhibited by the lack of RT3.205 Conversely, greater RT3 has been associated with increased whole-body fat mass and decreased lean mass in healthy men.206

Pathology 202: Laboratory Tests for Dysfunctional Deiodination

Well, this is news to *nearly* everyone. How can we use the laboratory to validate complaints of patients who are dissatisfied with their response to levothyroxine—who may have, in effect, ambulatory ESS/NTI?207 If so, the problem may be corrected.

Measuring ReverseT3 alone is insufficient, either to diagnose ESS/ NTI208 or to monitor therapeutic response209; it is just the *denominator*. We rely upon the tT3/ RT3 ratio: It quantitates hormone effect at the thyroid receptor, comparing the binary and competitively antagonistic products of T4 deiodination. The ratio also minimizes some common concerns about thyroid testing, including observed non-Gaussian distribution206 and vagaries of binding proteins (as long as we compare the *total* values of both!).

As an indicator of thyroid function, the tT3/RT3 ratio is as significant to the body as the annual profit/loss statement is to your practice. Think of T4 as representing billing, a necessary potential; consider T3 your collections, essential cash—and RT3 represents your operating costs. You *live* off the surplus!

Neither totalT3 nor RT3 is part of "standard thyroid panels"; they must be ordered separately. The tT3/ RT3 ratio is calculated with the values expressed in the same units. On request, LabCorp USA reports both tests (in ng/dL) and provides the ratio with a single order code: 002193. Your Rep can activate it for use in your online portal. The ICD-10 code for dysfunctional deiodination is E07.81. If you prefer to use Quest or any other lab, just contact them and *ask*.

"Normal" tT3/ tRT3 Ratio

What value is desirable? First, thyroid hormones are released from the thyroid gland in a 10:1 ratio: 90% T4, 9% T3 and 0.9% RT3.65,66,67 Thus, the "baseline" ratio of T3/RT3 is 10. A lower value implies deactivation. But what is "good?"
Three studies measured and reported tT3/ RT3 in their healthy control groups: The average values ranged from 11.03 to 12.5 with narrow variation (+/- 0.5). 210,211,212 In contrast, groups of unhealthy people with metabolic syndrome *and* their age, BMI and TSH matched-controls had tT3/ RT3 of 8.8 and 7.3, respectively.213 Following treatment results, I find my patients feel well in the 10 to 14 range and I believe it can or should be a bit higher in adolescents. In comparison, Patient 2 had a ratio of only 2.4 while taking only T4—that is *unusually* poor.

Therapeutics 201: Options for Patients Who Fail to Benefit from T4

For years, my efforts to remove or remediate the above-listed causes of dysfunctional deiodination without using T3 were unsuccessful. Importantly, a 2012 review reported that *most* comparison trials indicate replacement with both T4 and T3 is superior to T4-only.214 Now, responsible voices of endocrine experts have stated that combined T4 and T3 therapy can improve results for at least some hypothyroid patients.215,216,217 The long-term safety of combined treatment has been demonstrated.218

The simplest and most generally acceptable method of adding T3 is demonstrated by Patient 2. Let's examine a few issues before moving to our next treatment option.

Replace Some T4 with T3: What Happens?

First, please understand that when TSH has been restored to "normal," adding T3 while maintaining the same T4—even divided Q 12H—will fail. T4 must be reduced as T3 is added. This is why:

Continuing the same T4 that had "normalized" TSH as you add T3 will predictably suppress TSH. Abundant T4 and suppressed TSH can be expected to maintain so much RT3 production that even *robust* T3 cannot restore a good tT3/ RT3 ratio…that's "no joy."

Adding T3 to the treatment increases blood T3 values. Reducing the T4 dose decreases RT3 levels, because **95% of circulating RT3 comes from T4**-deiodination.65 After replacing *some* T4 with T3, your patient has more T3 and less RT3, which improves and ultimately, can restore normal tT3/ RT3.219

How Much T4 Should We Replace?

Physiology informs us: People need *some* T4. It is the precursor of T3 and of RT3. In addition, T4 (like RT3) has many non-genomic functions.220 Results of an ill-planned trial disregarding this fact validate the statement: People taking T3 with immeasurably low T4 do badly.221

The variable determining the amount of T4 we need to prescribe is the patient's *own* thyroid hormone production, which is 90% T4. If her gland is surgically absent or otherwise ablated, T4 replacement is essential – in my experience, at least 75 mcg daily. When hypothyroidism is mild, a person might need little added T4; she'll make some of her own if your T3 dose doesn't suppress TSH.

Patient 2 is a typical case: She arrived with normal TSH and robustly normal freeT4. It was safe to use the 5 mcg T4=1mcg T3 replacement. It was wise to make small steps as tolerated. **I recommend reducing the T4 dose to no less than 70% of the total thyroid replacement** until blood test results prove that ratio should be altered.

The "70% T4/ T3 30%" suggestion may surprise some readers. The healthy human thyroid produces only 10% T3. The *PDR* informs us that "natural" thyroid (desiccated thyroid extract, porcine USP—

currently in medical literature "DTE") is only 20% T3. In fact, some endocrinologists advise giving no more than 5% T3 in combined T4 and T3 treatment.222 Compared to healthy human thyroid or DTE thyroid, why give patients so much T3?

These people have dysfunctional deiodination; they need more T3 than "normal." Also, they are taking hormones orally and about 20% will *not* be absorbed.223 Furthermore, some of the oral T3 is destroyed in the hepatic "first pass," for all of which we accommodate by following clinical indicators and blood values (discussed below). Reviewers have recommended individualized treatment for each patient,214 and I certainly agree. Patient 2 is quite well now, currently taking 70% T4 and 30% T3.

Repeat for emphasis: For optimal T3 treatment results, WE MUST DIVIDE T3 DOSES. T3 has a short half-life.224 In healthy people, a single T3 dose peaks at 2½ hours and reaches its nadir at 12 hours.225,226 Our more-sensitive patients often prefer taking doses every 8 hours, as advocated by Osler in 1901.120 Interestingly, I find that after switching from Q 12 hours to Q 8 hours, patients may require slightly less T3 daily.

Problems During T3 Escalation Are More Noticeable

The instructions given to Patient 2 (Figure 6) demonstrate a cautious T3 dose escalation, as though the patient were being given her initial thyroid replacement. Predictably, the problems associated with restoring thyroid function are more frequently and emphatically reported by patients taking *active* hormone. Some of these were discussed above, including issues of adrenal support, estrogen replacement, and interacting caffeine and stimulants.

Unlike Patient 2, some patients who fail T4 treatment would rather *not* become pregnant. Therefore, warning of increased fertility is an important part of informed consent-talk before adding T3. Everything seems to work better with good thyroid replacement, including every aspect of reproduction. Women can discover they were not menopausal, just amenorrheic due to poor thyroid function.
With correctly prescribed T3 treatment, two issues in particular can be remarkable. First, the potency and short half-life of T3 makes missed doses more consequential; people can feel the *lack* of it!

Patients also complain more often of anxiety, jitters, and tremulousness. Against expectation, it rarely occurs from too much T3—their thyroid blood tests are usually fine. Before ordering labs, ask when the symptoms occur: If neither at peak nor trough—and the adrenals are supported—then reactive hypoglycemia is the probable cause, via the adrenergic counter-regulatory response. When excessive RT3 slows the metabolism, the glycemic and insulinemic responses are blunted. T3 "frees" the glucose to swing up and down, so it gets blamed; but the *real* problem is a sugary/starchy diet. I recommend a Mediterranean, Paleo, or ketogenic diet for most of my patients.

Other problems will be encountered: Even the best verbal and written instructions may be forgotten or ignored. Patients may not consider the dose-response curve when building T3. If too much makes one feel tired again, he can choose to take more—and upon feeling worse, *still* more!

People may build their T3 dose to greater than optimal—or ignore your directions and take more than you had recommended. Mildly high T3 may feel stimulating for a few people but it is risky; don't consent to it.

When patients get "too busy" to come back for follow-up, it implies they feel well but it bodes ill. The lack of follow-up is never desirable – especially when taking T3.
For these reasons, schedule a timely follow-up appointment for your patients, preferably before they leave your office with the Rx for T3. Hold them to keeping it! It is wise to prescribe no more tablets than will be sufficient to allow for a couple of goofs and one reschedule; limit their refills to ensure

safety. A test to validate the dose is needed before authorizing multiple Rx refills is sensible. A final caution: Low tT3/RT3 ratio is adaptive in some circumstances.227 A rare patient "needs" low tT3/RT3 and if so, T3-treatment can "dis-inhibit" protective adaptation. Two patients have been intolerant of even tiny doses of T3: One had received multiple courses of cancer chemotherapy; the other took four mitochondria-toxic psychoactive medications. I believe their elevated RT3 was adaptive, and my efforts were misdirected.

At the First Follow-Up Visit

When your patient arrives feeling wonderful, simply test her blood levels after she's been on the dose for at least two weeks. However, having conservatively brought her in before she reaches her calculated "maximum" replacement, you can *expect* to make small adjustments of 2.5 mcg T3 for 12.5 mcg T4—still replacing on a 5-to-1 basis. After her total dose has been moved to no less than 70% T4, not more than 30% T3, test her blood levels.

Blood tests are necessary to monitor therapy. The brief half-life of T3 makes its levels labile and testing mid-way between doses becomes even more important. I consult with patients who have been over-dosed because they were tested at trough and under-dosed because of being tested at three hours.

Ideal *therapeutic* values on combined T4 + T3 treatment are slightly *different* from normal reference intervals. When they feel best, their reports will *not* all be at the 50th centile! First, the patient is not healthy; she probably has deiodination problems (*hence* she needs T3). Secondly, her thyroid hormones are taken orally, not received intravenously; both hormones are altered during the hepatic first-pass. Also, doses every 12 hours, or even every 8 hours are not physiological. What blood levels "work" safely?

We've seen that patients seem to feel best with a tT3/RT3 ratio of 10 to 14. Since various local and national labs use different reference intervals for hormone assays, I will suggest relative values within those ranges, rather than numbers: The best freeT3 seems to be in the 75th to 90th centile while the "ideal" TSH, freeT4 and RT3 drop into the 1st quartile of "normal."

At your second follow-up, when you review the lab reports on 70% T4 and T3 30%, the results may show your patient's tT3/RT3 is still low. If so, make the adjustments you need to correct the ratio. Some people need less T4 and more T3. Others need either less T4 or a bit more T3. You will know after reviewing "all 5" tests to see which values are undesirable. Don't worry—this is a skill that comes easily with practice.

Now: Review standard treatment goals.100 The first criterion is to restore tissue euthyroidism with resolution of symptoms and signs. On combined treatment, taking 70% T4 and 30% T3, Patient 2 seems to have fulfilled this. The second was also achieved: We maintained normal TSH and the most important physiological marker of thyroid function, the tT3/RT3 was restored to normal.77, 78 Thirdly, there is no evidence of thyrotoxicosis, clinical or biochemical.

Patient 2's first and latest values are compared in Table 1. Her lab reports show that replacing T4 with T3 on a 5:1 equivalency maintained a stable TSH, confirming that for her, this substitution was satisfactory. As T3 was added to her regimen, blood T3 values predictably rose. With reduced T4, she produced less RT3: Her tT3/RT3 ratio was restored to normal. Her babies suggest this was efficacious.

Table 1: Patient 2 taking all-T4 compared to T4+T3:

Treatment	TSH	freeT4	freeT3	totalT3	RT3	tT3/RT3
Divided Q12h		(0.82-1.77)				(10-14)
T4 56+56mcg	0.663	1.66	2.9	87	**36.1**H	**2.4**(L)
T4 25+25mcg T3 12.5+10mcg	0.711	**0.80** L	4.1	151	13.3	11.4

The sharp-eyed observer will notice her latest freeT4 value is low. For several reasons, this does not worry me. First, the current reference intervals for freeT4 are skewed high. I say this from my experiences and consultations in 2009, when a national lab changed test platforms, raising the lower limit of their reference interval from 0.61 to the new 0.82. I followed many patients during this transition and the change was spurious.

Secondly, I observe that ***low* RT3 is the best marker for *physiologically* low-T4**. When freeT4 is maintained at or above 0.6 ng/dL, we predict the RT3 shall be 8 ng/dL or higher (I prefer "9"). Yes, I have erred in my learning curve and I've seen both freeT4 and RT3 go low; in that case, TSH rises and the patient feels just a bit "off"—but not badly, so long as her freeT3 is good. Once discovered, the problem can be corrected uneventfully.

Problems Particular to T3 Treatment

Patients need to cut the 5-mcg tablet in half. Recommend a good quality pill cutter with a cover; otherwise tablet halves will fly across the room. Until they develop skill at cutting pills, they may get a good half and the other as powder. Cut the pill when the dose is due; save the solid half for later and promptly take the powdered one. An alternative solution is to request compounded 2.5 mcg doses.

When prescribing compounded T3, *never* use the "SR delay-resin." I have much experience with people taking this and I am wholly convinced: The microcrystalline methylcellulose or whatever they use does *not delay* absorption; it BLOCKS it by 50%–consistently. I am enough of a lab geek to feel certain of this.

Finally, generic T3 (liothyronine) is legally allowed to contain RT3—and it may. The FDA apparently considers RT3 inert. That this can occur in batches of T4 was noted in 2005.228 The contamination of generic T3 with RT3 was first identified by Denver's Dr. Bob Menter, and it recurs periodically. Having no financial interest in any company, my experience shows the best generic is Sigma and the worst has changed its name repeatedly.

Therapeutics 202: Initiate Treatment for Hypothyroidism with "Natural" Thyroid

Desiccated thyroid extract, porcine USP (DTE or "natural thyroid") is a valid option for treating hypothyroidism. Its use – originally from sheep's glands – was first reported in 1892.229 DTE was still authoritatively endorsed as "highly satisfactory" in 1975224; and considering the recall statistics for "synthetic" T4 and T3 products, it has been relatively trouble-free. Despite criticisms and perhaps implausible attacks claiming natural thyroid carries a risk of prion-exposure,181 it is popular today and patients are more satisfied *taking* DTE than any other option.134
Most prescribers who treat with DTE do so because it contains T3.230 However, as I poll my patients for their choice of treatment, many have misconceptions about "natural vs. synthetic" that should be clarified.

***What is better, natural or synthetic*?** Many people answer that "natural" is best, citing people like Patient 2, who do badly on T4. They say levothyroxine is synthetic, unnatural and therefore no good. *Nope*, that is *not* the explanation. To clear up confusion: Whether a hormone is from a "natural" or "synthetic" source is immaterial (unless you are allergic to the natural source, as some people are to pork).

Two issues are *relevant*. First: Is the hormone biologically identical, so it can perfectly fit its receptor and perform exactly as a human hormone should? Women have taken conjugated equine estrogens (CEE) for decades; these are hormones concentrated from **pre**gnant **mar**es' ur**in**e (Premarin®) and wholly natural.231 They are *not* biologically identical: Some of the horse estrogens are so different from the human that they cannot be detected by laboratory tests. We cannot expect them to properly "fit" human estrogen receptors, either.

The second question is equally important: Is it the *active* hormone, or just a *pre*-hormone? Levothyroxine, on which Patient 2 had no joy, is biologically identical – the exact duplicate of human T4232—having been made-so (from what I *cannot* find) by chemical processing (i.e. "synthetic"). Being bio-identical, levothyroxine is 100% present and accounted-for on any lab test for T4. The problem with levothyroxine, as we've just seen, is not its mysterious origin or synthetic processing, but that it is a *pre*-hormone, not *active*.

The great merit of "natural thyroid" is that 20% of it is active T3. Proponents have claimed benefits also from the T2 it contains, but the quantity present is miniscule, so any effect is unlikely.233 We've just seen that Patient 2 needs to take 30% T3, not 20%; therefore, remember: DTE does give T3, but it may not give *quite enough* T3!

Which Patients Are Well-Suited for Treatment with DTE?

I believe anyone who asks for "natural" thyroid is an excellent candidate. There are reasons it would be an inappropriate choice, especially allergy to pork. It is, of course, decidedly not kosher or vegan; and I leave the final decision up to the patient and her rabbi, imam, or nutritionist—who *usually* endorse it.

The pre-treatment assessment of "all-5 hormones" importantly contributes to this decision. While most studies report hypothyroidism is associated with *increased* tT3/ RT3 as the scarce T4 is optimally utilized, some patients have *low* tT3/ RT3 even in their hypothyroid state.211 It is very unlikely that T4-only treatment would correct this imbalance, and recommending DTE is appropriate.

DTE Pre-Treatment Considerations and Informed-Consent Counseling

Prescribing DTE is similar to *properly* giving T4. Your informed consent talk will review the therapeutic goals for treatment; dose-response curve and the risks, complications and side-effects already discussed. Immune hypersensitivity to the natural product should be mentioned; it is more common than sensitivity to levothyroxine. Caution women about increased fertility: Accidents cause people!
Add this information too: Most other practitioners were trained to believe "natural" thyroid is unreliable and even dangerous. Your patient must know *in advance* that she may have to defend her use of it and refuse to let a well-intended provider replace it with "safe and reliable" levothyroxine.

Before treating hypothyroidism with desiccated thyroid extract, estimate the patient's likely maximum dose. If there is no concern about autonomous function, a healthy adult's "maximum" dose is about 1 mg DTE thyroid per pound of *lean* body weight per day (2.2 mg/ Kg). So, a fit, active woman of 120 lbs. may be able to take 120 mg DTE daily. *I think the use of DTE seems sufficiently archaic without quantitating it in "grains." If anybody* needs *to know, one grain is about 60 mg*.

As it is for levothyroxine, the optimal DTE dose seems most closely-related to lean body mass. If my patient was once a 120 lb. athlete but she is now exhausted and weighs 200 lbs., her maximum dose of DTE should *not* be 200 mg/day. Adipose won't require as much thyroid hormone as muscle …but she has built more muscle from carrying the extra weight! Here again, be conservative …and gain the experience to use "Kentucky windage."

We prescribe DTE because it has T3, but its half-life is brief – just six hours. Therefore, **it is *imperative* to *divide* the dose of DTE at least every 12 hours**, and sometimes, like Osler, every eight hours. Tell patients to set a reminder alarm on their cell phone and to carry a few doses at all times. It is a good rule to take DTE no less than four hours before bedtime, lest peak-levels of T3 keep them awake. Taken every eight hours, the bedtime dose causes no sleep disruption and usually improves its quality!

Begin Treatment with DTE: Dose and Timing

Adult patients start taking 15 mg DTE every twelve hours. These tablets are the smallest made and the dose can be adjusted to an excellent "fit." NEVER start a "full dose" of DTE; it is too risky. Hypothyroidism increases the population of nuclear thyroid-hormone receptors.234,235,236 This large cadre of "hungry" receptors is very sensitive to replacement T3—especially to overly exuberant initial doses or too-rapid escalation.

Gradually increase this dose once-weekly, as tolerated; patients must understand this concept before they take any thyroid preparation containing T3. As with T3, DTE pre-treatment counseling about caffeine use, symptoms of low estrogen, and reactive hypoglycemia from a poor diet is more important than for levothyroxine. Complaints are more frequent because DTE is more effective.

Dose Escalation

Give written instructions for patients to build their DTE dose once-weekly, as tolerated. Again, the dose-response curve (Figure 2) is a useful "visual-aid." Direct her escalation to *less* than the calculated "daily maximum" and follow-up promptly as a safety measure. For example, plan to give a 5' 5" tall young woman weighing 130 lbs. *no* more than 120 mg DTE /day before reviewing her progress. Conservative instructions are shown in Figure 7.

Figure 7: Typical DTE thyroid dose escalation for 130 lb. patient

Rx: "Natural" thyroid, USP 15mg (Armour®, Nature Throid®;

Week	Dose: AM		PM	Tablets:
#1	USP	15 mg +	15 mg	(1 + 1)
#2	USP	30 mg +	30 mg	(2 + 2)
#3	USP	45 mg +	45 mg	(3 + 3)
#4	USP	60 mg +	45 mg	(4 + 3)

Make an appointment for the end of the final week of escalation, to review her responses during the process and inventory the remaining symptoms. Remain alert for complaints and issues during escalation. Again, these are somewhat *more* troublesome with DTE than T4, due to the T3 content. Usually, all goes smoothly.

As always, dose escalation is conditional, depending on results of the last change: Better, same, or worse? People often feel "unsettled" for a few days after a dose change, so wait a week before deciding. Your patient should call if she unexpectedly feels worse.

Most patients on DTE feel incrementally better as the dose is increased. Think of a person climbing a ladder—each step noticeably takes him closer to the top. A few people simply feel no better until about five days after the *precisely* correct dose is reached; then suddenly all is great. I suspect this is when the tT3/ RT3 ratio finally "pops" into place. I think of them as "vending machine" people; if it takes 40 cents to get a pack of gum, nothing happens until you've put in the quarter, the dime *and* that *last* nickel.

The First Clinical Follow-Up on DTE

If your patient feels "100% well," which often happens, the path is certain: Check blood levels. Repeat the blood tests in a few months if all is still well and again after another six months. After that, annual follow-up labs are mandatory—sooner if symptoms change.

When symptoms indicate her therapeutic response is incomplete, ask more questions: Do the symptoms worsen shortly before the next dose is due? This suggests under-treatment. However, if she feels noticeably worse 2-3 hours after her dose, suspect an over-dose or allergy to pork…or caffeine interaction etc. Consider the adrenals, low estrogen, and a bad diet if not all is well.
If she seems still under-dosed, that's actually the plan, right? Build her dose by smaller steps: 15 mg increments weekly. For the hypothetical 130 lb. woman above, give first 60 mg Q 12h and the next week, maybe as much as 75 mg and 60 mg. I'd go no higher without the assurance of the laboratory that she needs more. Any time you feel "bewildered," use the laboratory for a navigational fix.

The first laboratory follow-up is performed the same as always: At pharmacological equilibrium, the blood sample is drawn mid-way between regularly timed doses. Test "all-5"; the "ideal" results will be the same as those of combined T4 and T3 treatment.

Problems with "Natural" Thyroid Treatment

Allergy to pork has been mentioned and uniquely, "natural" thyroid also contains elements of the thyroid glands from which it has been extracted. Rarely, DTE has significantly intensified thyroid inflammation in a patient with Hashimoto's, apparently from adding reactive-antigens to the already hyper-immune gland. This problem resolves once the dose is raised sufficiently to suppress TSH—but it gives everyone some concern initially. I add this to my IC-talk prior to treating with DTE, as a possible adverse event and relative-contraindication.

Unfortunately, TSH is often suppressed by the DTE dose that gives the best symptom-relief. My best explanation is that the patient's thyroid gland continues making too much T4 (converted to RT3) until it is suppressed by DTE's richer mix of T3. Simply put, more than 80% T4 is often too much.

As long as blood levels of the thyroid hormones are normal, low TSH is no physiological problem. Low TSH does not damage bones – high T4 does!237 Low TSH doesn't affect the heart; high T3 does.238 However, some practitioners incorrectly assume low TSH means that you've made the patient *hyper*thyroid. So, your TSH-suppressed patient must understand this to defend her treatment from "good intentions."

There have been shortages of "natural" thyroid. Since the "great Armour® famine of 2009," we've had recalls of NP Thyroid® and Nature-Throid®. Rest assured; it is simple to convert from DTE to bio-identical synthetic. The *PDR* tells us 60 mg of Armour® delivers 38 mcg T4 and 9 mcg T3: Just do the math. While many patients had to switch from DTE to T4 and T3 in 2009, not all switched back when the "natural" was again available.

Trouble-Shooting Other Providers' DTE-Patients

Expect to see other practitioners' patients doing badly on once-daily DTE. As you now know, dividing doses is necessary because the 20% T3 in DTE has a short half-life and the 80% T4 in a single bolus can and will be excessively converted to RT3. **Patient 3** was one of these.

She arrived taking DTE 90 mg every morning. She was tested as close to mid-dose as possible, just before the lab closed at 5PM and her values were: TSH= 0.54; fT4= 0.77; RT3= 320 and tT3/ RT3= **4.3**. Her dose was divided Q 12H and because of her body size, increased to 60 mg AM and 45 mg PM. Her next blood tests were drawn six hours after the AM dose: TSH= 0.42; fT4= 1.28; RT3= 256 and tT3/RT3= **8.7** (*better but she needed less T4*).

Confusion can arise also from "pre-analytical" decisions to test at what might be called "the wrong time."

Patient 4 consulted me because she was unhappy taking DTE 60 mg every AM, which had been followed with tests drawn 3 to 4 hours after her dose. Because of high freeT3= **4.5** H at this time ("peak"), she was told this was her maximum allowable dose.

After discussion, Patient 4 divided her DTE to 30 mg Q 12h. Predictably, she reported her energy was "more consistent, but only moderate." She had *less* energy in the AM and early afternoon but *more* energy in the late afternoon and evening. When tests were drawn at mid-dose, 6 hrs. after her AM dose, her freeT3 was just 3.1 and tT3/RT3 was only **4.2** (L). No, she was *not* on her maximum dose; her story is continued below.

Patient 5 came from the same provider, with the same set-up: Once-daily DTE 90 mg was tested four hours after her dose and her high freeT3= **4.6**H implied she was maximally treated. On my recommendation, she was re-tested on 45 mg DTE Q 12h at six hours after the AM dose. Her freeT3 on the same daily dose was now only 2.8.
Other patients have simply *not* been *monitored* for therapeutic levels.

Patient 6 was treated with DTE by an open-minded doctor who adjusted doses solely according to her clinical response. As the dose was increased, she felt better in some ways but worse in others. When she came to see me, the 221 lb. young woman was taking 240 mg DTE daily. The doses were divided, 120 mg twice-daily, but she had to take the second dose only five hours after the first – otherwise, she couldn't fall asleep at night.

On my request, Patient 6 endured taking DTE 120 mg every 12 hours for long enough to be accurately tested at mid-dose. She was therapeutically *hyper*thyroid. She had an "acceptable" tT3/RT3 because *very* high T3 levels balanced her excessive RT3: TSH=**0.007**L; fT4=1.43, fT3=**7.0**H; tT3= **31.6**H, RT3= 30.7 and tT3/RT3= **10.3**. We are emphatically reminded that symptoms *alone* cannot be trusted to guide therapy.

Therapeutics 301: Use "Natural" Thyroid to Correct Failed T4-Treatment

When T4-only treatment fails, replacing some T4 with T3 can succeed and is now acceptable to most of our colleagues. It is also possible to replace T4 with DTE. Patients ask for this, and it is often very satisfactory. Several tactics can be successful.

First, one can use the rough equivalent 25 mcg T4 ≈ 15 mg DTE. The steps are simple: First, prescribe 25 mcg T4 tablets and 15mg DTE tablets to make dose adjustments easier. Next, divide your patient's daily T4 dose to Q 12 hours for a week, allowing her to get into equilibrium—and then start replacing T4 with DTE. Because T3 gives "more energy" than T4, start DTE first with the AM dose.

Caution: This formula makes 100 mcg T4 the equivalent of 60 mg DTE—which is rather a low dose and may not be sufficient. Using this semi-equivalency, patients often need to continue building their DTE dose after the T4 has been wholly replaced. True confessions: Patients have reported feeling great after replacing T4 with DTE; their tT3/ RT3 was about 11 and to my surprise, so was the TSH—it's that learning curve again!

Secondly, one can think of DTE in terms of its constituent T4 and T3, rather than as milligrams or grains. As above, each 60 mg ("1 grain") DTE thyroid contains 38 mcg T4 and 9mcg T3.239 When you examine your patient's "all-5" lab values on her unsuccessful T4 treatment, you'll see whether she needs only some added T3 or a reduced amount of T4 plus T3. Then, you are able to substitute-in the DTE with scientific finesse. But it *doesn't* always work, because DTE offers no less than 80% T4.

Therapeutics 302: Correct the Failure of DTE Thyroid Treatment

Over the years during which I logged hundreds of patients for whom T4-only treatment gave poor results, I also recorded many *scores* of patients who had suboptimal results from DTE thyroid. Here again, the "post-analytical analysis" of lab reports is *so* important! As with T4, incorrect dosing occurs—either too much or too little, as the patients above demonstrate—but by *far* the most frequent problem was dysfunctional deiodination of T4, indicated by low tT3/RT3.

The DTE content of 20% T3 and 80% T4 would *not* be a "rich" enough mixture for Patient 2, who needed 30% T3 and 70% T4—as validated by her outcomes, both laboratory and obstetrical. **Patient 7** also needs more than the 20/80 in DTE: This 68 year-old man felt better after replacing T4 with DTE but even so, his tests on "natural" 60 mg Q 12 hrs., taken six hours after his AM dose showed a low tT3/ RT3 ratio: TSH=**0.01**L; fT4=1.0, fT3=3.6; tT3=83, RT3=20 and tT3/RT3=**4.2**(L).

Coach, review "all 5-players" on Patient 7's report: Low TSH indicates his *total* dose is *plenty* and that all the thyroid hormones in his blood come from DTE treatment. Excessive T4 intake is indicated by two things: A. His freeT4 is higher than my "goal" *and* B. The tT3/ RT3 is *very* poor due to robust RT3. Hence, DTE gives him too much T4. He also may need more T3: His freeT3 could be higher and totalT3 clearly looks sub-par. We agreed to adjust his intake.
DTE failed: It gave Patient 7 too much T4.

During informed-consent talk, Patient 7 was given several options. The first is a commonly used method, to replace DTE 15 mg with T3 5 mcg (each is the smallest tablet of its kind). This inexact exchange is based upon their comparable effects on a *healthy* person's TSH-production. However, healthy people activate T4 normally and Patient 7 cannot.

The second option is to do the math: Upon calculating the amounts of T4 and T3 in DTE 15 mg, we find this exchange would undesirably increase T3 as it reduces his T4. Let me "show my work": We've seen that 60 mg DTE contains T4 38 mcg and T3 9 mcg;239 thus, we calculate 15 mg DTE contains 9.5 mcg T4 and 2.25 mcg T3.
To achieve our goal of reducing Patient 7's T4 dose, we should replace DTE 15 mg (9.5 mcg T4 and 2.25 mcg T3) with only 2.5 mcg T3 (½ tablet). I have come to rely on simple mathematics—and to regard DTE as a vehicle for delivering an 80% T4/20% T3 mixture.

An engineer, Patient 7 surprised me and chose a third option: He wanted to stop DTE altogether and to take T4 and T3 individually—so we did. The required substitution was simply calculated: From DTE 60 mg Q 12 hrs., Patient 7 *daily* received 76 mcg T4 and 18 mcg T3. We replaced it with levothyroxine (T4) 75 mcg and liothyronine (T3) 20 mcg daily (*divided* Q 12hrs.).

Because "the Coach" predicted Patient 7 was taking too much T4, his T3 dose was maintained at 10 mcg Q 12 hrs. while the T4 was sequentially reduced once a week: It dropped from 37.5 mcg Q 12…to 25 mcg Q 12…to only 12.5 mcg Q 12 hours. This T4 dose—now diminished by 50 mcg daily—felt

best to him. Admittedly, we dropped below my 70/30 "guideline": The proportion of T4 had fallen to only 56% T4, with 44% T3. He was tested.

"Mid-dose" blood tests (on T4 12.5 Q 12h and T3 10 Q 12h) verified that for him, "less is more": TSH=1.80; fT4=**0.68** L; fT3=3.7; tT3=115, RT3=9.1 and tT3/RT3=**12.6**. His TSH had become normal. As predicted, he needed about the same T3 he had gotten from DTE. Although I was tempted to increase his T4 a bit, this dose was maintained…and his subsequent fT4 values rose to 0.88 and 0.82, "normal."

DTE thyroid failed: Patient 4 needs less T4 and more T3.

Patient 4 had insufficient energy and undesirable mid-dose blood values on DTE 30 mg Q 12 hrs.: TSH=1.93; fT4=1.16, fT3=3.1; tT3=85, RT3=20.1 and tT3/RT3=**4.2** (L). She and I reviewed her options. We agreed she would take a little less T4 and increase her T3 by replacing DTE 15 mg (9.5 mcg T4 and 2.25 mcg T3) with 5 mcg T3 to reach DTE 15 mg Q 12 and T3 5 mcg Q 12: A 50:50 mix. This was done in two small steps (Figure 8).

Her new therapeutic values at mid-dose were better: TSH= 1.97; fT4= 0.87; fT3= 3.5; tT3=121, RT3=12.1 and tT3/RT3=10. She later divided her doses to take the same amounts divided every eight hours, and her tT3/ RT3 ratio rose to *12.5* (DTE 0+15+15 and T3 5+2.5+2.5). She has referred five people to my practice in the last year.

Figure 8: Patient 4 - Replace DTE ("natural") with T3 (liothyronine)

	Dose: AM		PM	Tablets:
Now on:	USP 30 mg	+	30 mg	(2 + 2)
Week	Change to:			
#1	USP 15 mg	+	30 mg	(1 + 2)
	T3 5 mcg	+	0	(1 + 0)
#2	USP 15 mg	+	15 mg	(1 + 2)
	T3 5 mcg	+	5 mcg	(1 + 1)
#3	This is a good time to report to me re: your status			

Patients may need only more T3. When the laboratory shows your patient has enough T4 and "the Coach" says they need T3, just add it—cautiously!

Therapeutics 401: Challenges in Hypothyroidism

Athyreotic patients have no thyroid gland. They are the least tolerant of once-daily levothyroxine, for they make no T3 and have no endogenous safety-net! On arrival to your office, they collectively are on the widest variety of unusual dosing strategies. Be of good cheer: You now have all the skills to delight them with the results of your work. Keep them on the same average daily T4 dose they arrived taking (add up their weekly dose and divide by 7) but divide it evenly every 12 hours. Then, after two weeks, test "all-5" at mid-dose and see what they need.
They will need T3, of course. Let your well-honed "Coach" tell you how to modify their T4 during the process of escalating T3. Every eight hour-dosing may ultimately be best. These will actually be easy and rewarding patients: Their thyroid gland is "gone" but that means its function is stable. Once they are "right," they'll probably be low maintenance.

Unfortunately, NOT all hypothyroid patients are stable. They can offer an uncomfortably "moving target." In these cases, residual thyroid function keeps changing, and the treating practitioner must stay alert and adaptable.
Progressive loss of thyroid function occurs and not uncommonly. When we treat hypothyroidism due to Hashimoto's disease and maintain TSH=2.0, it is likely the patient's thyroid gland is adding some hormones to the mix. If thyroiditis continues to destroy the gland, it can add less hormone and TSH will rise, indicating the patient needs a larger dose. Follow blood tests annually—and sooner if symptoms change.

Autonomous function mocks our efforts to calculate "maximum" doses. When any portion of the patient's *residual* thyroid function carries-on without appropriate HP-T feedback, it can make treatment difficult. The simplest of these is Hashitoxicosis, which can be present to some degree in up to 10% of cases.240 The destructive autoimmune process causes the uncontrolled release of hormones stored in the colloid, resulting in transient hyperthyroidism or unexpectedly high hormone levels.241 Because it usually resolves in two months, it should not interfere with treatment for hypothyroidism in advanced cases – unless there is an ongoing, "smoldering" process that is unmasked when TSH-suppression is a therapeutic goal.

Graves' disease and "switching" offers the most complex autonomous function we are likely to encounter. Graves' is caused by the production of TSH-receptor *stimulating* antibodies, which cause *hyper*thyroidism. It can also feature TSH-receptor blocking-antibodies, which produce *hypo*thyroidism ("atrophic Hashimoto's"). Finally, most Graves' cases also test positively for the (probably cytotoxic) anti-TPO and anti-Tg antibodies of Hashimoto's.242 The diseased thyroid can flip from hyper- to hypothyroidism at a whim – and may then become hyperthyroid again.243,244,245
Patient 8, a woman age 34, gained 40 lbs. in three months in 1996 and then quickly lost it again. Her endocrinologist correctly diagnosed Graves' disease (TSH**< 0.03** L, tT4= **14.8** H and 123I* uptake= **67%** H) and put her on methimazole; she promptly regained 30 lbs. and quit taking the drug.

Seven years later (March 2003), she consulted me for symptoms of hypothyroidism; tests showed her TSH was 2.04 and her tT3/ RT3= **4.0** (L). I next heard from her a year later, 3/2004, when unemployed and tested at a free clinic, her TSH= **51.5** H. She took replacement thyroid hormone for a while and again became lost to follow-up.

Three years later, in 12/2006, she was working, insured and had marked hyperthyroidism. Taking no thyroid treatment, her labs showed: TSH=**0.013** L; fT4=**2.29** H, fT3= **6.3** H; tT3= **268** H, RT3=**51.3** H. tT3/RT3= **5.2** (L). Validating the diagnosis of Graves, tests showed: TPO-Ab=**72** H, Tg-Ab=**161** H, TR-Ab= **36.6** H; 123I* Uptake= **48%** H.

Despite the high hormone levels, her symptoms mostly suggested hypothyroidism; perhaps from the very high and in this case *adaptive* levels of RT3. Thyroid ablation was indicated. Reviewing this case, it is easier to understand why so many US physicians promptly ablate Graves' hyperthyroidism with 131I*.246

During pregnancy, thyroid binding proteins are remarkably increased. For this reason, up to 80% of hypothyroid women who become pregnant will need larger replacement doses—increased by as much as 45%.247 American Thyroid Association (ATA) pregnancy-guidelines are available as a free download.248 They recommend testing as soon as the pregnancy is diagnosed and following blood levels every four weeks thereafter.

Prompt testing is needed because hypothyroidism is associated with first trimester miscarriage, as Patient 2 showed us. In fact, ATA publications even state there is a "clear association between thyroid antibodies and spontaneous pregnancy loss."248 Thus, their guidelines are exacting, to protect the child and safeguard its development: The upper limit of TSH should never exceed 4.0 (others say "2") and freeT4 must be kept above the 10th centile.

Do not feel dismayed when a pregnant patient's totalT3 and RT3 values zoom up: It is because of the greatly increased thyroid binding proteins! Fortunately, the binding constants of T3 and RT3 are very similar, and their ratio will continue to be valid for comparison. After delivery, the hormone doses can be reduced. The literature and experience agree that new mothers can reduce their doses about six weeks postpartum.

Gestational transient thyrotoxicosis is an unusual disorder that is not immune-mediated. Hyperthyroidism develops because the pregnancy hormone, human chorionic gonadotropin can too closely resemble TSH. It cross-reacts with the TSH-receptor and over-stimulates thyroid gland.249 Fortunately uncommon, it could make your patient's pregnancy even more challenging, depending on the amount of her residual thyroid function.

Oral contraceptive pills and ovarian hormone replacement also stimulate the liver to make greater amounts of thyroid binding-proteins. Thus, when hypothyroid women start these treatments, they too may need increased thyroid replacement and should be tested.250,251,252 Conversely, when these treatments are discontinued, their thyroid levels should again be checked.

Therapeutics 402 (Senior Honors): Subclinical Hypothyroidism

Subclinical hypothyroidism is a conundrum for experts. The diagnosis describes a mild case of hypothyroidism, in which patients *theoretically* have *no* symptoms (*this criterion is now generally disregarded*); have elevated TSH to less than 10 μIU/mL, and freeT4 within normal limits.37,253,254

Because no clear benefit has been proven in placebo-controlled T4 treatment-trials lasting up to 18 months, committees of experts consistently state these patients should *not* be treated,255 with the exceptions of women hoping to become pregnant and possibly of adults younger than 30.256 Some endorse giving T4 to markedly *symptomatic* "subclinical" patients—as a trial, which must be stopped if there is no clear benefit.253

Pediatricians "consider it reasonable to initiate treatment to avoid any potential risk of negative impact on growth and development."100 Doing so, they recommend therapeutic T4 levels in the mid to upper half of the reference range and the TSH "optimally between 0.5 and 2.0 μIU/L."

Subclinical hypothyroidism creates controversy because of this paradox: Many studies have shown that these "subclinical" patients without treatment will, in the long term, have worse rates of dysfunction and death compared to healthy controls.257,258,259,260 However, we've seen that many other studies can show no benefit from T4 treatment until TSH rises above 10 or freeT4 becomes sub-normal.37, 254, 259,261

So, even though people with mildly abnormal tests have significantly worse outcomes, T4-treatment should be given to only markedly ill patients, else it will not help. Another way to state this is that levothyroxine is so ineffective that it can help only severely deficient patients.

None of the authoritative reviews or a meta-analysis262 have examined or mentioned T3 treatment arms. In fact, the definition and treatment criteria for subclinical hypothyroidism do not account for T3, which we know correlates with symptoms,144—much less do they consider RT3.255

We are returning to an age of combined T4 and T3 treatment. We now can ask: Will adding T3 to T4—and achieving the "desirable" blood levels I have suggested above—succeed in delivering the benefit these "subclinical" patients fail to receive from T4? From my patients' results, I answer this question with an unqualified "yes – it can."

It has been 21 years since the first good evidence that T4 + T3 combination treatment can be superior to T4 alone was published.263 Let's hope we do not have to wait equally long for the proof

of what seems so likely to be the case, that subclinical hypothyroidism can respond *better* to T4 + T3.

Post-Graduate Seminar: **Resistance to thyroid hormone (RTH)**

We have just seen that subclinical hypothyroidism is a condition without any clinical symptom (so said) that is revealed only by the laboratory. For years, some physicians have believed the *converse* must exist. They see patients with many thyroid symptoms and signs, but the standard tests (TSH, freeT4) are negative: One could call it "Sub-laboratory hypothyroidism."

Some physicians offer thyroid hormone supplementation to these patients. When they are rewarded by clinical improvement, they continue the treatment – despite some risk to themselves.264 Thirty years ago, 12% of patients taking thyroid hormone were thought to do so "inappropriately," by prevailing guidelines.111 These patients usually took "natural" thyroid, not levothyroxine, for a variety of indications and most continued taking it.

What do these risk-tolerant physicians believe they are treating? In browsing the internet or standing by the coffee urn at medical meetings, one encounters the phrase "resistance to thyroid hormone." This does indeed occur. There are three hereditary types; the causes are different and presentations distinctive.

Dysfunctional Thyroid Hormone-Receptors

The first type of resistance to thyroid hormone (RTH) is caused by mutated genomic thyroid hormone-receptors,265 known as Refetoff syndrome. There are two major types of thyroid receptors, alpha and beta, each of which can be affected by loss-of-function mutations. The consequences can be mild to severe, depending on the degree of impairment.266

There are about 1,000 cases world-wide, many more beta than alpha. Mutations of THRB, the gene encoding thyroid hormone receptor-beta are more common and less severe. The clinical features include elevated levels of both TSH and thyroid hormones (since the receptor lacks sensitivity) and a goiter. Treatment with T4 can help symptomatic patients but should not be offered to all affected.267 Laboratory values will *not* return to "normal,"268 and *all* surgically removed goiters have recurred.267

Patients with a mutated THRA gene encoding thyroid hormone receptor-alpha were first identified in 2012.269 The effects of this mutated, dysfunctional receptor range from delayed puberty to more severe dysmorphic features.270 Their laboratory profile is unusual: "Standard" tests are normal but unusually, RT3 is low and consistently, the T4/T3 ratio is also sub-normal. While higher T3 concentrations can reverse receptor dysfunction *in-vitro*, T4 has been employed for clinical treatment and it may help—or not.266

Disorders of Thyroid Hormone Transporters

Lipophilic thyroid hormones enter cells via trans-membrane transporters.271 In this second type of RTH ("Visser syndrome"), defective MCT8 transporters cause severe neurodevelopmental disabilities, which are usually identified in infancy. These children also have high serum total and free T3 and low RT3 concentrations. T4 is reduced in most cases and TSH levels can be slightly elevated but rarely above 6 mU/L.267 Symptomatic problems with the other major transporter, OATP1C1 also have been described.272 Treatment efforts are largely unsuccessful for both types.

Dysfunctional Deiodinase Enzymes

This third type has two subsets also. This type of resistance to thyroid hormone is caused by dysfunctional deiodination of T4. Refetoff included **hereditary thyroid hormone metabolism defect** in his recent review of insensitivity to thyroid hormone.267

In the first subset, *nine families* (it's rare!) have an inherited defect of selenoprotein synthesis, resulting in *severely* dysfunctional deiodinase enzymes and clinical hypothyroidism. The children have growth delay, mental and neuromuscular defects. The only known adult (male) had fatigue, muscle weakness, severe Raynaud's, vertigo and hearing loss; skin UV-sensitivity and infertility.267 No patient had an enlarged thyroid.

Laboratory tests show low T3, high T4, high RT3 and normal or slightly elevated TSH. These lab values resemble acute ESS/NTI (note the authors), from which it is distinguished by elevated TSH and by a general medical evaluation.267 For the few patients treated, T3 was successful: It bypassed the hereditary defect, suppressed TSH as it does in normal people and improved the children's delayed linear growth.273,274

DIO2 Mutation: In contrast to the *severe* dysfunction caused by the above selenoprotein synthesis-defect, the mutated DIO2 carried by **16% of** tested **Britons** causes a mild problem.136 The mutant type 2-DI works well enough for normal childhood growth and development. Its dysfunction may not be detected, as long as the carrier's thyroid normally makes its modest contribution of T3. The defect is unmasked when a hypothyroid patient is treated with levothyroxine and deiodination of T4 must produce not 80% but 100% of the daily T3. When hypothyroid, they respond better to T3 + T4 treatment than to T4 alone.

Resistance to Thyroid Hormone, Part 2

Those physicians who treat patients with normal TSH and normal freeT4 based on clinical grounds… *could* they have valid reasons for doing so? Is there a situation in which a person could be physiologically hypothyroid despite having plenty of T4 and normal TSH? Well, *sure* – we've just reviewed a variety of cases and conditions.
Tabor's defines "hypothyroidism" as the clinical consequences of inadequate thyroid hormone in the body"1; perhaps "active-hormone" would be *more* precise. The deiodination of thyroid hormones is purposefully directed, and it is the primary means of regulating the biological activity of thyroid hormone.20 As cited above and repeatedly supported, altered deiodination causes symptomatic "disruption of thyroid hormone signaling," even when T3 levels remain within the normal range.171

This physiological hypothyroidism occurs in the tissues, at the *second* level of regulation, *not* at the HP-T axis. Its laboratory hallmark is a low tT3/RT3 ratio—neither high TSH nor low freeT4… not even low T3. Indeed, even with normal freeT4 and TSH, the developmental defects in hereditary thyroid hormone metabolism defect267 and the high death rate in ESS/NTI prove dysfunctional deiodination can be *very* serious.

Many causes of *acquired* dysfunction of deiodination are listed above, from emotional stress to metabolic syndrome, drugs, and toxins. If the resulting thyroid hormone derangement is clinically relevant, by what name can we call this condition? The term "**type 2-hypothyroidism**" has been proposed275: It seems appropriate, as adult-onset diabetes with lots of insulin that "doesn't work" is called type 2-diabetes.

If this were a valid clinical problem, our first indicators would be patients who fail treatment with T4-only, which indeed happens.134,135,136,137 If the problem occurred in people who were *not* hypothyroid, the concept could be lifted out of the Critical Care Unit and applied to ambulatory patients—and it has been.207,276
If dysfunctional deiodination causes clinical symptoms, as proponents of type-2 hypothyroidism assert, we should expect to see low tT3/RT3 demonstrated in studies of patients with otherwise unexplained symptoms—such as chronic fatigue. This also has been reported.276

More evidence may be found in studies of euthyroid Hashimoto's disease (AIT), which is strongly associated with excessive RT3 ($p<0.00002$)147—likely due to (intra-thyroidal) cytokines.277,278,279,280,281 Although AIT is often judged inconsequential except as a risk for future hypothyroidism, patients have increased miscarriages248 and symptoms with decreased quality-of-life that correlate with anti-TPO antibody level, *not* TSH.282 Conversely, chronically fatigued patients are significantly more likely to have AIT.283

If dysfunctional deiodination causes over-production of RT3 and low tT3/RT3, then we expect that T3-replacement, which as Refetoff says "bypasses the defect," should correct these patients' imbalance and restore a desirable ratio. This also has been demonstrated.219

If correcting the tT3/RT3 ratio relieves patients' symptoms, we should see reports claiming T3 treatment helps such symptomatic "euthyroid" people. These too we have, in a wide variety of settings. The publications range from animal research on demyelinating diseases284,285 to ADHD in hereditary RTH286; from depression287,288,289,290 and dementia-related behavior problems219 to heart failure.291,292 They also include toxin-induced euthyroid sick syndrome (NTI)293 and simply "low metabolism."294,295

The limitations of this review prevent taking the discussion of type 2-hypothyroidism beyond this point. The prescription of T3 for euthyroid patients is currently discouraged by authorities,37 despite its apparent success: After average follow-up of 6.9 years, 58% of "inappropriate users" of desiccated thyroid were still taking it.111 It is my experience that T3 treatment for "type-2 hypothyroidism" is highly rewarding for patients, though it can be risky for a physician whose state board of medicine begins an inquiry.

In closing, I'd like to remind you of the four most important points I have tried to prove in this review:

1. Thyroid hormone doses should be divided at least every 12 hours.
2. Therapeutic blood levels must be tested according to peak/trough fluctuations; preferably at mid-dose.
3. The ratio of tT3/ RT3 is the most accurate measure of the actual thyroid hormone function in the body.
4. Some people need to take T3 along with T4 for their best clinical results.

It is possible to achieve truly remarkable results with the simple suggestions I've offered. I would love working with the thyroid even if I did not personally have Hashimoto's. I hope you will find this work rewarding *without* being motivated by needing it yourself!

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