Against TSH-T4 Reference Range Thyroidology: The Case for Clinical Thyroidology

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Abstract

The current reliance upon the TSH to both detect hypothyroidism and direct its treatment is illogical and ineffective. Hypothalamic-pituitary function is modified by many known and unknown factors, and is known to deteriorate with age. Even if one could know that a person's hypothalamic-pituitary response is perfect, one cannot assume that the TSH response to once-daily oral thyroid replacement is identical to the response to continual thyroidal hormone production. The TSH level is only a measure of the hypothalamic-pituitary response to thyroid hormones. It is neither a test of free thyroid hormone levels nor of thyroid hormone effects throughout the body. It is useful for determining the cause of hypothyroidism; not for diagnosing or treating it. The most reliable serum tests of thyroid hormone sufficiency are free T4 and free T3, but their broad laboratory reference ranges are neither optimal nor treatment ranges, and there are marked individual variations. Ultimately, both the diagnosis and treatment of hypothyroidism must be clinical.

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

1. Introduction

The clinical practice of thyroidology has been gradually abandoned over the last 40 years. Most practicing physicians are now taught that a "normal" TSH test, and/or free T4 levels anywhere within the laboratory reference range indicate "euthyroidism". They will ignore gross symptoms and signs of hypothyroidism if the TSH is normal or slightly elevated. When they do decide to treat, they provide only enough levothyroxine, a prohomone, to normalize the TSH, in spite of the persistence of symptoms at that dose. They are taught that a low TSH on thyroid hormone replacement indicates hyperthyroidism and overtreatment, and will cause long-term health damage; in spite of "normal" free T4 and free T3 levels. This set of beliefs and practices has no basis in either human physiology or the literature. It is completely incompatible with that time-honored principle of medicine, "Treat the patient, not the numbers".

This TSH-T4 reference range thyroidology seems to have originated in articles published in 1972 and 1973 by Evered where he asserted that a "normal" TSH excluded mild hypothyroidism and was the therapeutic goal of T4 therapy.[2,3] However, considered logically, for this TSH-thyroidology to be true, each of these assumptions would have to be true:

1. HP function is always perfect, excepting rare persons with known anatomical disease of the hypothalamus or pituitary.
2. The response of the HP axis to circulating thyroid hormones is identical to that of all other tissues in the body.
3. The HP axis responds to once-daily oral T4 therapy exactly as it responds to continuous thyroid gland output.

All three are in fact, both improbable and proven to be false, as will be shown below. Evered's TSH-thyroidology was put to the test in a study that was published in 1986. Four experienced clinicians in an academic center adjusted the T4 doses of 148 hypothyroid patients based on clinical criteria only: signs and symptoms using the Wayne index. [4] They were blinded to the results of serum testing. For their clinically-euthyroid patients, the new TSH reference range (RR) was found to be <0.1-13.7mU/L (vs. the usual range of 0.35-5.0mU/L). The free T4 (FT4) treatment RR was significantly higher than the laboratory's RR (12-36 vs. 9-25pmol/l), and the free T3 (FT3) treatment RR was virtually identical to the RR (3.0-8.6 vs. 2.9-8.9pmol/l). The **TSH proved to be the least accurate** measure of replacement and the **FT3 the most accurate**, but even the FT3 was of no use to adjust any individual patient's dose. In some patients there were striking deviations from the usual reference ranges. The authors concluded that "biochemical tests of thyroid function are of little, if any, value clinically in patients receiving thyroxine replacement".

There has never been a comparable clinical study that has contradicted these findings. In fact the bulk of the evidence supports these conclusions. Clearly the physiology of thyroid absorption, metabolism, receptor-interaction and nuclear action are far too

complex to reduce all of thyroidology to serum TSH and FT4 results. The Fraser study also implies that the a "normal" TSH and FT4 due not rule out thyroid insufficiency in an untreated symptomatic patient. The diagnosis and treatment of hypothyroidism must be clinical, that is clear. The rest of this paper will demonstrate that the TSH-T4 reference range paradigm does not work, and why.

1. TSH/T4 Reference Range Thyroidology

Unfortunately, the very word "hypothyroidism" implies that insufficient thyroid effect is always due to an under-functioning thyroid gland, which tends to reinforce the belief that only a TSH test is needed to assess thyroid sufficiency. Secondary or tertiary hypothyroidism is known to exist, so doctors sometimes admonished to check the free T4 also "when in doubt". Thyroid hormone resistance, which can happen by various known and unknown mechanisms, is rarely considered.

The current reigning paradigm is best referred to as **TSH/T4 reference range thyroidology**. It is based upon the aforementioned assumptions, and supports the following interlocking, mutually-reinforcing doctrines that are also disconnected from clinical reality:

1. **Reference Range Endocrinology**: Laboratory reference ranges (**RR**s) that include two standard deviations from the mean for the tested population (95% of tested persons) define optimal hormone levels and can be used for both for diagnosis and for treatment.
2. **TSH Thyroidology**: A TSH result anywhere within the population RR (treated or untreated) indicates optimal thyroid levels and effects, for both untreated and treated persons (excepting rare "obvious" cases of hypothalamic-pituitary damage).
3. **Free T4 Thyroidology**: The body always converts just enough T4 to T3 for current needs in all tissues. Therefore the free T4 RR is both a diagnostic and treatment range, and replacement therapy requires only T4.

The result of these assumptions is the current **laboratory-based** nomenclature:

1. **Primary hypothyroidism:** Below-RR FT4 with above-RR TSH
2. **Secondary or Tertiary hypothyroidism:** Below-RR FT4 and below-RR TSH
3. **Subclinical hypothyroidism:** Within-RR FT4 and above-RR TSH
4. **Primary hyperthyroidism:** Above-RR FT4 with below-RR TSH
5. **Secondary or tertiary hyperthyroidism:** Above-RR FT4 with above-RR TSH
6. **Subclinical hyperthyroidism:** RR FT4 with below-RR TSH

In this scheme, "hypothyroidism" is defined as having a free T4 that is below the reference range. Two new "diagnoses" are created: "subclinical hypothyroidism" and "subclinical hyperthyroidism". These are misnomers as clinical criteria have no role in their definition. Notice that in neither is it specified whether the "normal" FT4 level is near the top or the bottom of the RR, which would have starkly different implications. **Strikingly, the FT3 level, the level of the active thyroid hormone, is not considered relevant to this scheme.** It is thus easy to understand why studies of the implications of

these "subclinical" classifications and their treatment are often contradictory and have created much confusion.

What is the result of these arbitrary assumptions and the resulting laboratory-based algorithm? Most physicians hold to the following practice "rules of thumb":

1. If the TSH and/or the FT4 are "normal", then hypothyroidism of any degree is excluded (regardless of signs and symptoms).
2. The sufficient treatment for primary thyroid insufficiency is once-daily T4-only supplementation that "normalizes" the TSH and FT4 (they are anywhere within the laboratory's RR).
3. The sufficient treatment for central hypothyroidism is a FT4 anywhere within the laboratory's RR.
4. A below-RR TSH on oral thyroid hormone supplementation indicates hyperthyroidism and has exactly the same pathological implications as a below-RR TSH caused by endogenous thyroidal overproduction (regardless of signs or symptoms or the FT4 and FT3 levels).

These practice rules have never been clinically validated, and have actually been contradicted by many studies. They represent a complete divorce of thyroidology and clinical reality. The TSH-T4 laboratory algorithm succeeds in diagnosing only some severe disorders of the thyroid gland and H-P axis, and in providing only partial alleviation of hypothyroidism in many cases. (See below.)

Interestingly, the faults of this algorithm are recognized by some experts and even in some organizational guidelines, but no serious attempt has been made to replace it. Some have advocated lowering the upper TSH RR to levels found in younger, more tightly screened populations. The American Association of Clinical Endocrinologists (AACE) recently lowered its recommended TSH upper limit to 3.0mIU/L.[5] The National Association of Clinical Biochemistry (NACB) and some authors have endorsed an upper limit of 2.5mIU/L.[6,7] This change is of little use as it continues the reliance up the TSH and ignores clinical criteria, FT4, and FT3 levels. It leads to overtreatment in persons with a vigorous TSH response (good FT4, FT3, and clinical state), and undertreatment of those with a weak TSH response.

The NACB guidelines also recognize that merely "normalizing" the TSH results in undertreatment of primary hypothyroidism. It advises that T4 therapy should reduce the TSH to below 2.0mIU/L and raise the **FT4 into the upper third of its reference range**. It states that the dose required for both primary and secondary hypothyroidism in middle-aged adults is usually around 1.6mcg/kg/day.[8] However, most physicians continue to merely "normalize" the TSH with much smaller T4 doses that leave the FT4 in the lower half of the RR. The AACE treatment guidelines call for only "normalizing" the TSH, and while suggesting that FT4 may be checked, offer no guidance on what FT4 level should be achieved during therapy.[9] **Physicians thus have no guidance for what to do when they have "normalized" the TSH but the patient is still symptomatic.** In practice, they simply declare the patient "euthyroid" and remaining symptoms to be due to fibromyalgia, depression, or chronic fatigue. They offer the patient psychotropic medications.

Interestingly, the AACE guidelines mention the **possibility of central hypothyroidism**, but offer **no guidance whatsoever for its diagnosis or treatment.** It is assumed that all central hypothyroidism arises from obvious pituitary damage. However, it is probable, and is the author's experience, that a significant portion of the population has some degree of partial central hypothyroidism that is due to dysfunction of the H-P axis rather than anatomical disease. If so, then relying on the TSH must result in a large amount of underdiagnosis and undertreatment.

As it stands, **patients with clinical evidence of hypothyroidism** but a "normal" TSH, and "normal" FT4, either with or without thyroid replacement, are considered to be "**euthyroid**". Not surprisingly, since the TSH-T4 RR paradigm began to be adopted in the 1970s, there has been an explosion in the number of people diagnosed with fibromyalgia, depression, and chronic fatigue. While their causes are certainly multifactorial, each shares many symptoms in common with thyroid insufficiency and should be considered as due to thyroid insufficiency until proven otherwise. Since the symptoms and signs of hypothyroidism are protean, the hypothyroid patient may receive other diagnoses as well.[10]

The TSH/T4-RR paradigm is the source of the continuing confusion surrounding the diagnosis of "subclinical hypothyroidism" and its treatment, the implications of TSH suppression with T4 therapy, and the studies of T3/T4 therapy. **The paradigm produces both over-diagnosis and under-diagnosis**, and produces inadequate replacement therapy in many cases. It fails to diagnose both partial central thyroid insufficiency and thyroid hormone resistance.

The TSH-T4-RR paradigm is supported by many specious arguments and rationalizations. The TSH is often touted as the best test of thyroid sufficiency due to its "sensitivity". This statement relies upon an ambiguity. The latest generation of the TSH test is indeed "sensitive" to very low TSH levels that could not be measured by earlier tests. The TSH level is "sensitive" in another sense because it responds in a logarithmically-amplified degree to minor changes in serum FT4 and FT3. **Neither of these facts implies, however, that the H-P axis is "right"**—that the TSH level is an accurate measure of whole-body thyroid sufficiency in either the untreated or treated state. As will be show, the evidence indicates otherwise.

The evidence and arguments against the above assumptions and conclusions will be presented. A clinical approach to the diagnosis and treatment of thyroid insufficiency will be described. This paper will deal with the thyroidal system in isolation, but the restoration of euthyroidism often requires attention to nutrient deficiencies and partial cortisol insufficiency. In what follows, the author will defend the following theses;

1. The diagnosis and treatment of hypothyroidism must be based upon **clinical criteria** primarily and the **FT4 and FT3** levels secondarily.
2. The TSH is useful only in **differentiating between** primary and central hypothyroidism in the untreated state. It cannot be used to diagnose thyroid sufficiency or excess, or to adjust therapy.

3. The Nature of the Laboratory Reference Range

Hormones are the most powerful molecules in the human body, affecting hundreds of known and unknown processes in the human body. It is essential that an individual have

optimal hormone levels for both current and long-term health and vitality. Yet the practice of endocrinology in general, and not just thyroidology, is today based upon the assumption that the laboratory RRs define optimal levels for both health and quality of life, and therefore can be used for diagnosis and monitoring of treatment. The use of the word **"normal"** instead of **"within the laboratory's reference range"** to describe a result is as inappropriate as it is common, and perpetuates the misunderstanding and misuse of RRs.

The daily reality is that if the doctor does not see a high or low value on a laboratory report, he/she declares the patient has sufficient hormone levels and cannot have a hormone-related problem. The physician falsely assumes that experts have carefully reviewed all relevant clinical and biochemical data and decided that the hormone RR should like within these limits. This is a false assumption, and it not the fault of the clinician. Laboratory RRs are carelessly constructed, and contain a mixture of raw statistical population ranges and adjudicated decision ranges. **The RRs for some substances are decision ranges that have been imposed on the laboratory by expert opinion.** Usually a panel of physicians have reviewed clinical and biochemical studies and made a determination regarding the optimal ranges. Examples of such ranges are those for serum glucose, LDL cholesterol, and more recently vitamin D. Unfortunately, the RRs on a laboratory report are not clearly labeled as either population or decision ranges. Because some RRs are adjudicated ranges, physicians believe that all RRs on laboratory reports are adjudicated decision ranges, defining what is optimal for the human species. This is simply not the case. Specifically, **hormone ranges are almost always reported with broad, statistical population ranges.**

A population RR includes two standard deviations from the mean for the tested population. It thus includes 95% of tested persons. Can such a broad measure of the population possibly define the range of hormone levels that are optimal for human beings? Look at the thyroid hormone RRs. One notices immediately that the **RRs for FT4 and FT3 are extremely broad**—the upper limits are 2 to 3 or more times the lower limits. It is highly improbable, indeed it is not possible that a person will have no physiological changes when his FT4 and FT3 levels are doubled or tripled, or reduced to 1/2 or 1/3rd of the previous levels, yet remain within the "normal" range. The statistical nature of the range is most obvious when, for some hormones, the calculated 2 S.D. lower limit of the RR is zero; no detectable hormone is "normal" (e.g. salivary cortisol and female free testosterone). Where the lower limit is not zero, this method still defines only the lowest 2.5% of that population as "deficient".

Defining only the bottom 2.5% of the population as "low" is not consistent with the facts. It is clear that a much larger portion of the population has some degree of thyroid insufficiency. One study of individuals without a history of thyroid disease found high-TSH "subclinical hypothyroidism" in 19.7% of the population.[11] In a recent study of blood donors with no history of thyroid disease, ultrasounds of the thyroid glands were abnormal in 25%, and 47.9% did not meet all criteria for normal thyroid morphology and function.[12] Clearly, one cannot arbitrarily declare 95% of the population to be "disease-free" when there is such a high prevalence of glandular abnormalities. Such studies reveal only the tip of the iceberg. There are other kinds and degrees of thyroid hormone insufficiency.

How are the RRs for hormones actually constructed? Each laboratory determines its own RR, partly based on the RR recommended by the kit's manufacture, partly based on literature, and partly based upon the laboratory's own accumulated physician-ordered data. The range created by any survey will only be as valid and useful as was the care taken to screen for optimally-healthy individuals. In reality, little screening is done and laboratories introduce many biases in the selection of the population to be tested.[13] In determining the FT3 and FT4 RRs, **some laboratories include results from patients in their physician-ordered database who had "normal" TSH values**. This is not defensible and illustrates the interlocking, mutually-reinforcing nature of the TSH/T4-RR paradigm.

Laboratories using similar kits have FT4 RRs that extend from 1.5-1.8ng/dL at the top all the way down to 0.6ng/dL and even as low as 0.28ng/dL at the bottom, a severely hypothyroid range.[14] The author found the highest FT4 lower limit (1.01ng/dL) in a large military hospital where the RR is determined by studying 120 healthy soldiers each year.[15] In a study of healthy blood donors, the 95% reference range for FT4 for those with normal thyroid ultrasounds was **0.99-1.58 ng/dL**[16]. These studies of minimally-screened adults report much higher lower limits than found in most laboratories, and studies of optimally-healthy young adults would yield even higher lower limits. Given the available evidence, the lower limit of the FT4 range for labs that have upper limits of 1.7 to 2ng/dL should be 1.0ng/dL. The use of this RR would immediately redefine many millions of undiagnosed Americans as hypothyroid. However, this would still just be a population range and not a diagnostic range.

However, RRs, no matter how carefully constructed, can never tell the whole story of a patient's hormonal status. Even if a carefully screened, optimally healthy, young population were used to create a hormone RR, it is still the case that the hormone's effects vary on a continuum from low to high. There are no cut-offs in Nature. **Levels near the bottom of the RR will produce lower effects than levels near the top of the RR.** Studies have shown that there are benefits associated with FT4 and FT3 levels that are higher within the RRs. (See below.). There is also marked individual variability. Studies of thyroid function tests have shown that population RRs are insensitive when compared to subject-based RRs.[17] An individual's personal RR over time for serum T3 and T4 are about half the width of the population-based RRs. A significant variation from that individual's RR, while still within the population RR, may produce a state of thyroid insufficiency or excess for that person.[18] Also, persons can have within-RR test results and yet suffer from organ-specific thyroid insufficiency or excess due to many factors including differing rates of T4 to T3 conversion in different tissues, receptor/effector polymorphisms, cofactor deficiencies, toxins, etc.[19]

Another problem is that laboratory RRs for thyroid hormones include adults of all ages. However, the upper limit of the population RR for FT3 for children up to age 15 is 20% higher than for adults over age 25.[20] The FT3, TSH, and total T4 decline steadily with age in most persons,[21,22] skewing those RRs towards lower values. Aging persons have increased incidences of both primary and secondary thyroid insufficiency. Clinical investigation is required to determine if these age-related hormone losses are adaptive or deleterious, but it is most reasonable to conclude that all age-related hormone losses are deleterious until prove otherwise.

As a minimal reform, e**very laboratory report should clearly label adjudicated ranges as "decision ranges" and non-adjudicated ranges as "population reference ranges".** Median values should be included also.[23] Additionally, laboratories should make it clear that the **ranges for untreated persons cannot be used to guide treatment**. It would be helpful for laboratories to report treatment ranges for patients on both T4 monotherapy and natural dessicated thyroid. It is well-known that patients on T4 therapy require higher FT4 levels to achieve normal TSH values than seen in euthyroid control subjects.[24] For T4 monotherapy, the treatment ranges for TSH, FT4 and FT3 found in the Fraser study should be included in laboratory reports, until/unless additional research indicates that they should be otherwise. However, even the most carefully constructed ranges can only be considered as guides since individual factors such as hormone resistance or sensitivity may require deviations from these ranges.

4. On the Fallibility of the Hypothalamic-Pituitary System

As medical scientists, we must consider the various kinds of evidence hormonal sufficiency and rank them in order of causation and clinical relevance:

1. **First Rank: Indicators of end-organ response**—judged by symptoms, signs, and physiological testing. The patient's symptoms are the most sensitive, but least specific measure of thyroid hormone effect. Multiple symptoms of hypothyroidism in a given person are less likely to be due to another cause and therefore are more specific for the diagnosis. Objective signs and tests of thyroid sufficiency include cold intolerance, hair loss, need for excessive sleep, dry coarse scalp hair, myxedema, weight gain, dry skin, low heart rate, slow relaxation of reflexes, lower basal metabolic rate, lower body temperature, elevated cholesterol levels, etc.
2. **Second Rank: Serum levels of thyroid hormones**—free T4 and free T3. These are more concordant with end-organ effects than total T4 and T3 because the latter are affected by thyroxine-binding globulin levels. There are, however, many ways in which a relative resistance to thyroid hormones can arise (receptor-effector dysfunction, altered deiodinase activities, nutritional deficiencies, high reverse T3 levels, genetic polymorphisms, toxins, etc.). Thus First Rank indicators are most important.
3. **Third Rank: Thyroid stimulating hormone—TSH.** The TSH is an indicator of hypothalamic and pituitary function as influenced by thyroid hormones. It must always be interpreted in the light of the First and Second Rank indicators. First and Second Rank make the diagnosis of thyroid insufficiency or excess. The TSH is useful only to determine the cause—thyroid gland failure or hypothalamic-pituitary dysfunction.

The reliance on the TSH for diagnosis and treatment effectively precludes diagnosing and properly treating partial secondary or tertiary hypothyroidism. While the existence of severe low-TSH, low-FT4 central hypothyroidism is acknowledged by the current nomenclature, all lesser degrees or other types of central hypothyroidism are ignored. H-P dysfunction cannot be ruled out in any patient, and should be assumed when a mid-range TSH is seen in a patient with symptoms and a relatively low FT4 and/or FT3. H-P dysfunction is in fact universal with aging. There is an 80% decline in the hypothalamic-

pituitary response to low thyroid levels between ages of 20 and 80.[25] A within-RR TSH does not exclude H-P hypoactivity or peripheral thyroid hormone resistance, both of which may be far more common than realized.[26] In central hypothyoidism, the **TSH is below-RR in only a third of proven known cases of central hypothyroidism.** One known cause for this is that with hypothalamic dysfunction (TRH insufficiency) an altered TSH is secreted that that is biologically hypoactive.[27]

The TSH at best tells us the response of only one organ to the circulating thyroid hormones—the hypothalamic-pituitary system (H-P). All organs and tissues are not alike and do not respond the same to circulating thyroid hormones. We know of three different deiodinase enzymes,[28] four different thyroid hormone receptors,[29,30] and at least ten different active transport systems with variable tissue distribution. [31,32,33] The TSH level reflects the deiodinase, receptor, and transport systems in the H-P axis only. Single nucleotide polymorphisms can affect every receptor, transporter, and deiodinase enzyme causing aberrations in thyroid hormone action in various tissues. In addition, the H-P axis is a highly complex system and receives many inputs, with dense connections to various parts of the brain. A number of gene mutations and other molecular disorders have been associated with central hypothyroidism.[34,35]

In fact, it is likely that H-P function is just as often flawed as is any other function in the body. Due the immense complexity of influences on the H-P system—neurological, hormonal, toxic, etc.—it is even more likely to be impaired. This belief in the immaculate TSH explains why "hypothyroidism" has become practically synonymous with "primary hypothyroidism" as that's the only type of hypothyroidism in which the TSH (when elevated) is usually diagnostic. In fact, in the majority of patients with known central hypothyroidism due to documented pituitary disease, the serum TSH is within the RR. It is below-RR in only 8% and is elevated in 8%. 28% of patients with known central hypothyroidism have FT4 levels that are low within the RR, not below the RR, and these patient's symptoms are similar to those with FT4s below the RR.[36] **Reliance on the TSH and its RR amounts to a denial of the existence of any partial functional disorders of the hypothalamic-pituitary (H-P)** system, of any partial thyroid hormone resistance, of any inter-individual variability in thyroid hormone requirements, and of any difference in H-P response to oral replacement vs. endogenous production.

In no other hormonal system do we assume that the serum level of the pituitary stimulating hormone is a perfect indicator of the adequacy of the serum levels and effects of the concerned hormone. Why is the H-P-thyroidal axis treated differently? It works by the same logic and physiology. In all other cases, if we suspect a hormonal disorder based on clinical criteria, we first measure the levels of the concerned hormone, whether it be testosterone, estradiol, IGF-1, cortisol, or DHEAS. If the active hormone level is low, we try to determine the cause—whether it is primary (glandular), or central (hypothalamic-pituitary), or both. Inadequate or excessive H-P activity is often the cause of the hormonal disorders. **Inadequate LH production with aging** is the cause of most male hypogonadism, which is why we do not rely on the LH level alone to diagnose testosterone sufficiency in males. Neither due we rely on an ACTH level to judge cortisol sufficiency. We also do not use the LH or ACTH levels to adjust hormone replacement. We use serum levels of the active hormone, the clinical response, and other tests of hormone sufficiency or excess. Why should we approach disorders of the H-P-thyroidal axis any differently?

When it comes to replacement therapy, is it rational to assume that the H-P system, evolved to control thyroid gland activity, will be affected by once-daily oral thyroid hormone supplementation in exactly the same way? In fact there is evidence that is affected quite differently. (See Below) In the Fraser study previously mentioned, the TSH was the least accurate test for predicting clinical euthyroidism in T4-treated patients, the free T3 was the most accurate.[37] Attempts to normalize the TSH in some patients can lead to clinical thyrotoxicosis,[38] while most remain hypothyroid when the TSH is merely "normalized".(See below) Indeed, it is irrational to assume that any symptomatic patient has perfect hypothalamic-pituitary function, or that the H-P axis responds to oral therapy exactly as it responds to thyroid gland output. Therefore it is illogical to rely upon the TSH either for diagnosis or to guide therapy.

Many studies support the hypothesis that the best serum tests of thyroid hormone excess or deficiency are the free thyroid hormone levels. For instance, FT4, not TSH, was found to be the variable that discriminated best between control subjects and 3 groups of hypothyroid patients.[39] In fact, in the majority of patients with known central hypothyroidism due to documented pituitary disease, the serum TSH is within the RR. It is below-RR in only 8% and is elevated in 8%. 28% of patients with known central hypothyroidism have FT4 levels that are low within the RR, not below the RR, and these patient's symptoms are similar to those with FT4s below the RR.[40] Studies have shown that one cannot rely upon finding a below-RR TSH to diagnose central hypothyroidism, nor on finding a below-RR FT4. 28% of patients with documented central hypothyroidism have FT4 levels that are low within the RR, not below the RR, and these patient's symptoms are similar to those with FT4s below the RR.[41] Therefore the diagnosis of central hypothyroidism must be clinical. A clinician should diagnose partial central hypothyroidism in any patient with signs and symptoms, a relatively low FT4 within the RR, and a "normal" TSH. As it is, nearly all such patients are currently undiagnosed.

In 800 untreated, clinically hypothyroid patients seen in a private practice, the test that correlated best with symptoms was the 24-hour urine FT3, not the TSH.[42] In another study, the FT4, not the TSH, correlated best with hypothyroid symptomatology.[43] In patients with hypothyroidism and TSH levels >20 mIU/L, FT4 and T3 levels correlated very well with measures of tissue thyroid effects, whereas TSH levels showed no correlation.[44] These results are as one should expect given that FT4 represents the largest pool of bioavailable thyroid hormone in the body, and given that FT3 is the active thyroid hormone, derived both from thyroid gland production and from T4-to-T3 conversion in various tissues in the body.

Not only is the vigor of the TSH response in question in any symptomatic patient, but we know that there is a universal a partial central hypothyroidism of aging. The TSH response to a given low FT4 level declines steadily after the age of 20, and is reduced by 75% at age 80.[45] In older persons, the TSH response to TRH is blunted.[46] In an elderly population, 2.5% were found to have a low FT4 index with an inappropriately normal TSH. No other hypothalamic-pituitary abnormalities were found. [47] Nearly 2% of persons over age 60 not on thyroid hormone had a TSH <0.1mIU/L, yet only 12% of that number developed hyperthyroidism over 4 years.[48]

Inadequate H-P response to circulating thyroid hormones may be a frequent cause of mild-to-moderate thyroid hormone insufficiency, in fact, it may be a more common cause

of moderate hypothyroidism than primary glandular dysfunction. This has been the experience of the author. In general, partial secondary thyroid insufficiency should be diagnosed in any symptomatic person with a TSH that is inappropriately "normal" or low within the RR. The diagnosis is supported if the FT4 or FT3 or both are below the mid-point of their respective laboratory RRs, and especially when FT4 and/or FT3 levels are both in the lower third of the RRs. Reports from many physicians and patients support the proposition that there are large numbers of people with multiple signs and symptoms of thyroid insufficiency, taking or not taking thyroid hormones, whose TSH is within the RR, yet who benefit from additional sufficient thyroid supplementation.[49]

5. The Benefits of Higher T3 and T4 Levels Within the Reference Ranges

It is evident that not all TSH, FT4 and FT3 values within the RRs are "normal" in the sense of being optimal. The extensive literature concerning subclinical hypothyroidism, its risks and treatment will not be covered here. Such studies have yielded contradictory findings precisely because the diagnoses were based upon TSH levels, not on the actual FT4 and FT3 levels. To extract meaningful data, all such studies need to be reinterpreted. Consider the evidence regarding free hormone levels and risk factors for coronary artery disease—the most common cause of death among adults. Lowering the TSH to less than 2.0mIU/L with sufficient T4 supplementation is associated with lower cholesterol, homocysteine, and CRP levels than simply "normalizing" the TSH.[50] In a study of elderly hypothyroid patients with coronary artery disease, it was found that a daily dose of 100mcg T4 or less allowed progression of coronary atherosclerosis in six of six patients, while doses of 150mcg or higher stopped progression in five of six patients.[51] In persons referred for coronary angiography, those with FT3 values in the lower third of the RR had nearly twice the incidence of severe atherosclerosis as those with FT3 values in the upper third of the RR.[52] Considering the role that clot formation plays in myocardial infarction and stroke, it is significant that lower FT4 levels within the RR are associated with hypercoagulability.[53] Lower FT4 values within the RR in untreated patients have been correlated with four of the five components of the metabolic syndrome independent of insulin resistance, and were correlated with insulin resistance also.[54] This implies a role for thyroid hormone optimization in persons with this disorder who have "normal" thyroid function tests (TFTs). Body mass index and weight gain are associated with lower FT4 values within the RR.[55] In euthyroid persons, lower FT3 but not FT4 levels were an independent predictor metabolic rate and of weight gain.[56] In elderly men, higher total T4 levels within the RR were associated with better cognitive function.[57] In older women, lower T4 levels within the RR were associated with a greater risk of cognitive decline over a 3-year period.[58]

It also appears that optimal thyroid hormone levels, not just within-RR levels, are necessary for optimal mental health. Lower thyroid hormone levels or higher TSH levels within the RR have been associated with depression or a worse prognosis for remission of depression.[59,60,61,62] Patients with major depression and TSH and T4 levels within their RRs who had failed therapy with SSRIs received significant benefit from 50mcg of T3 daily, a physiological dose. Nearly half had significant improvement, and 1/3rd experienced remission.[63] T3 added to sertraline increased response and remission rates in major depression by 20%.[64] T3 given to four desipramine non-responders with RR-TFTs converted all four into responders.[65] T3 given to depressed persons who failed to respond

to SSRIs and had TSH and TRH-stimulation tests within their RRs resulted in significant improvements in mood in 42% and in full remission in 25%.[66] T3 added to a variety of antidepressant regimens increase the likelihood of a positive response by a factor of 4.5.[67] Depressed patients who responded to thyroid supplementation had pre-treatment total T4 levels in the lower third of the RR.[68] In T4-treated hypothyroid patients, differences in FT4 and TSH within the reference range were significant determinants of psychological well-being.[69] Some will claim that patients who feel better on TSH-suppressive doses of T4 or T3 are experiencing an thyrotoxic euphoria. However, there is abundant evidence from the literature on endogenous clinical and subclinical hyperthyroidism indicated that people do not feel better when they are even mildly hyperthyroid.

In a recent open-intervention study, thyroxine was given to patients with symptoms of hypothyroidism but within-RR TFTs. The dose was adjusted for each patient to achieve clinical, not laboratory, euthyroidism. The study produced significant improvements in mood and energy in 80% of patients. The average thyroxine dose was 125mcg/d,[70] higher than the subreplacement TSH-normalizing doses given to many patients. Some studies of thyroid supplementation in symptomatic patients with within-RR TFTs failed to produce improvement, however, the treatment was not individualized and involved low doses. For instance, a fixed dose of 100mcg T4 was given to "euthyroid" but symptomatic patients. The dose decreased the TSH to a lower point within the RR, increased the free T4 only slightly within the RR, and did not significantly raise the FT3.[71] In contrast, clinically-effective T4 therapy requires doses that raise the FT4 to upper third of the RR or even slightly above.[72,73] In patients with known central hypothyroidism, where TSH cannot be used as a treatment guide, it was found that both FT4 and FT3 levels must be monitored along with clinical indices of thyroid action.[74] In another study of T4 dosing in central hypothyroidism, it was recommended that a fixed 1.6mcg/kg dose be used, then adjusted to keep FT4 levels near the upper limit of the RR, and FT3 in the upper half of the RR.[75]

Ignoring the abundant objective evidence for the physiological and psychological benefits of having higher free hormone levels with the RRs, some have argued against giving thyroid supplementation to symptomatic persons with "low-normal" FT4 or FT3 and "normal" TSH levels claiming that those who experience subjective improvement must have "thyrotoxic euphoria". This *ad hoc* "diagnosis" is inconsistent with the evidence of physiological benefit given above, and with the abundant evidence that humans feel worse, not better when they have excessive thyroid hormone levels. Studies of endogenous hyperthyroidism, TSH-suppressive therapy, and fixed T3-for-T4 substitution show that even mildly excessive thyroid supplementation causes symptoms that reduce one's quality of life. When asymptomatic controls were given 100mcg of T4 they experienced thyrotoxic symptoms and their serum levels of T3 and T4 increased more within the RRs than those of symptomatic subjects.[76] The controls felt worse, not better. Likewise, a group of patients with "preclinical hyperthyroidism" (FT4 within the RR) displayed the same negative, undesirable symptoms as a group of hyperthyroid patients.[77] A level of thyroid hormone supplementation that makes an individual feel and function better and produces no signs or symptoms of excess should be considered beneficial and necessary until proven otherwise, regardless of the TSH level.

6. TSH-Normalizing T4 Monotherapy Often Does not Restore T3 levels or Euthyroidism

T4 is a prohormone, although it may have some direct actions of which we are not aware. T3 has a 10-to-20 fold greater affinity for the thyroid hormone nuclear receptor.[78,79] The liver and kidneys, and possibly other organs also are dependent upon serum T3 rather than T4-to-T3 conversion. So it is sensible to presume, until proven otherwise, that restoring euthyroidism requires maintaining optimal T3 levels both in the serum and within in all tissues. This goal is not routinely achieved with TSH-normalizing T4 therapy. The serum FT3 reflects the amount of T4-to-T3 conversion throughout the body and the exposure of all tissues to the active thyroid hormone via the serum. A clue to the ineffectiveness of T4 therapy is the fact that it in low doses, it usually lowers the FT3 level, and in high doses often fails to raise the serum FT3 to the midpoint of the 95% population RR. TSH-normalizing T4 therapy produces abnormally low T3/T4 ratios and typically does not restore serum T3 concentrations to those of controls.[80,81]

Part of the explanation for the poor results with TSH-normalizing therapy is that FT3 levels are often not raised. TSH-FT4 Reference Range thyroidology asserts, improbably, that the serum level of FT3, the active thyroid hormone, is irrelevant to diagnosis or treatment. So FT3 are not routinely measured before or during T4 therapy. This practice is contradicted by many studies which show that FT3 is the best measure of thyroid sufficiency in persons on T4 therapy.

On T4 therapy, T4 levels are significantly higher than controls while T3 levels are lower.[82] T4 therapy give to patients with central hypothyroidism restored FT4 levels to within the RR in 94%, but FT3 levels remained below the RR in 51%.[83] The effects of T4 and T3 therapy on various tissues were revealed in an elegant series of experiments performed on rats. The investigators determined both serum and tissue levels of T4 and T3 with continuous infusions of various combinations of the two hormones. A T3-only infusion failed to restore T3 levels in all tissues—illustrating the necessity of T4 and peripheral T4-to-T3 conversion.[84] A continuous T4-only infusion also failed to restore serum and tissue T3 levels to those of controls until T4 levels were raised into the supraphysiological range and TSH was suppressed.[85] The addition of T3 to a T4 infusion in the same ratio produced by the rat's thyroid gland (1:6) allowed a normalization of both serum and tissue levels of both hormones without suppressing the TSH.[86] The human thyroid produces T3 and T4 in a lower 1:14 ratio,[87] but otherwise these findings have been shown to apply to our species also.

If TSH-normalizing T4 therapy constituted adequate treatment, then a majority of studies would demonstrate that it produces biochemical and clinical indices identical to those of healthy controls. In fact, studies of adequacy of TSH "normalizing" T4 therapy show that patients continue to have many signs and symptoms of hypothyroidism. A large study revealed that patients on thyroxine with "normal" TSH values (0.1-6.0 mU/L) displayed significant impairment in psychological well being compared to controls of similar age and sex.[88] In another study, hypothyroid patients on T4 had decrements in health status, psychological function, working memory, and motor learning compared to euthyroid controls.[89] Patients on "adequate" thyroxine therapy (TSH between 0.11 to 4.0mU/L) showed poor performance on various domains of neurocognitive functioning, and levels of well-being were significantly lower than

those of the general population. Neither serum TSH nor thyroid antibodies were determinants of neurocognitive functioning and well-being.[90]

Treatment of hypothyroid and "subclinical hypothyroid" patients with an avg. of 103±27.5mcg/day of T4 lowered the TSH to 1.9±1.5mU/L but produced lower T3 values, higher hypothyroid index scores, and higher BMIs than in the euthyroid controls.[91] Patients with treated primary hypothyroidism were found to have an increased risk of cardiovascular morbidity.[92] Patients who receive TSH-normalizing T4 therapy after thyroid ablation gain weight (avg. 4kg), whereas those who receive TSH-suppressive therapy do not.[93] Patients on long-term TSH-normalizing T4 therapy were found to have 21% greater fat mass and lower T3 levels than controls.[94] Patients on TSH-normalizing doses of T4 or T4 plus T3 had much worse scores than euthyroid controls on various measures of mentation and mood.[95]

Patients with untreated primary hypothyroidism were much less symptomatic if their FT3 was within the RR rather than below the range.[96] In patients with subclinical hypothyroidism, a subreplacement T4 dose of 85mcg (range 50-125) lowered the TSH from 12.8 to 3.1mU/L, raised the FT4 from low-RR to just above mid-RR, and further lowered the total T3, which before therapy was already below the mid-point of the RR.[97] Post thyroidectomy, the restoration of normal T3 and TSH levels required doses of T4 that produced significantly higher FT4 levels than prior to surgery.[98] In a study of TSH-suppressive T4 therapy (avg. TSH 0.03mU/L), the FT4 was 66% higher but the total T3 levels were identical to those of healthy controls whose average TSH was 1.36mU/L. These patients had no symptoms of hyperthyroidism despite the sub-RR TSH.[99] A group of patients treated with T4 and a group of untreated hypothyroid patients had identical 24-hour urine FT3 levels.[100] Patients with subclinical hypothyroidism had elevated lipid levels compared with controls. The difference was not eliminated until the patients were treated with enough T4 to reduce the TSH to below the RR.[101]

Untreated patients with subclinical hypothyroidism had TSH levels of 3.5–10mU/L and FT4 and FT3 levels slightly lower than healthy controls. Even relatively "aggressive" T4 therapy that lowered the TSH to 1.5mU/L (avg. dose 100mcg/day) did not produce a higher FT3 level than in the placebo group of similar patients.[102] Given that there was no improvement in the treatment group compared to placebo, the authors concluded that there is no cognitive impairment in subclinical hypothyroidism. An alternative conclusion is that TSH-normalizing T4 therapy does not provide sufficient thyroid replacement to produce physiological euthyroidism, and that the failure to raise the T3 level may be significant marker of under-replacement.

Increasing the dose of T4 given to hypothyroid patients on TSH-normalizing T4 therapy suppressed their TSH levels from mid-RR to low-RR but had no effect at all on patient's symptoms and did not cause any symptoms of overdosage. T3 levels were not reported. The authors concluded that merely normalizing the TSH to any point within the RR is sufficient.[103] An alternative conclusion is that TSH-normalizing T4 therapy is equally ineffective at any TSH level within the RR. Indeed, a careful study of T4 dosing and TSH responses to TRH found that patients felt better when their TSH was suppressed below the RR, their FT4 and FT3 were in the upper half of their RRs, and their T4 dose was 50mcg greater than that required to normalize their TSH response to TRH.[104]

The inability of TSH-normalizing T4 therapy to raise FT3 levels or produce laboratory or clinical euthyroidism has led some investigators to recommend adjusting T4 therapy

based upon the T3 level.[105,106] From the data in the studies quoted above, one can conclude that the dose of T4 needed to raise the FT3 of patients with hypothyroidism or subclinical hypothyroidism to at or above those of controls is generally greater than 100mcg/d and generally requires suppression of the TSH to below its RR (to <0.5mU/L). Since merely normalizing the TSH with T4 constitutes insufficient treatment in many if not most patients, we must reinterpret every study, review paper, textbook, and clinical practice that was based upon the assumption that TSH-normalizing T4 therapy produces euthyroidism.

7. Physician-Monitored TSH-Suppressive T4 Therapy is not Harmful

It is generally believed, without collaborating evidence, that a low TSH level with T4 monotherapy always has the same physiological implications as a low TSH due to endogenous production (subclinical hyperthyroidism). Scientific papers often refer to a low TSH but normal FT4 on T4 therapy as "subclinical hyperthyroidism". **Therefore physicians avoid any TSH suppression with T4** because they fear that they will cause all the complications of hyperthyroidism: bone loss, cardiac abnormalities, atrial fibrillation, and muscle wasting. However, the TSH cannot be relied upon as discussed previously. Also many studies show that endogenous and exogenous TSH suppression are not equivalent; either physiologically or biochemically.

Fortunately, there is an extensive literature describing the clinical and laboratory findings with high dose TSH-suppressive T4 therapy given to patients who have had thyroid cancer. These studies consistently show **no abnormalities and no long-term negative consequences if T4 doses are titrated to avoid any clinical signs or symptoms of hyperthyroidism**. The benign effects of TSH-suppressive T4 therapy lie in stark contrast to the thyrotoxicosis of persons with similarly low TSH values caused by endogenous subclinical hyperthyroidism. One study of endogenous "subclinical hyperthyroidism" found that the patients had both symptoms and signs of thyroid excess even thought their TSH was suppressed to only 0.15mIU/L. Their FT3 and FT4 were "normal" but both were in the upper thirds of their RRs, a combination not seen with TSH-normalizing T4 therapy.[107] In overt hyperthyroidism, FT3 levels are above the RR.[30] Calorimetry studies of energy expenditure in patients receiving TSH-suppressive therapy after thyroidectomy showed no increase in metabolism compared with the pre-surgical state.[108] Studies have failed to show any increase in mortality or fractures in patients on T4 with either RR-TSH or suppressed TSH levels.[109]

Perhaps the main reason given for avoiding any TSH-suppression is the fear of producing atrial fibrillation (AF). Increasing levels of thyroid hormones, even with the RRs, produce increased automaticity and trigger activity in the pulmonary vein myocytes which are known to initiate paroxysmal AF.[110] In a large study of elderly persons, those found to have AF had average FT4 levels that were near the middle of the bottom of the reasonable RR and only slightly higher than in those persons who did not have AF (avg. 1.14 vs. 1.10ng/dl). It is true that any increase in T4 levels, even from low levels, was found to increase the risk of AF. In untreated patients, the risk of AF rose from 3% at the bottom of the FT4 RR to 7% at the top of the RR.[111] Thus the decision to increase a patient's thyroid levels and effects with supplementation always entails a risk of producing AF in susceptible persons. In deciding to begin thyroid supplementation in any patient, the clinician must weigh known benefits of higher thyroid hormone levels to

health and quality of life for the great majority vs. the known increased risk of AF with higher hormone levels in the small minority. It is reassuring to know that AF induced by higher thyroid hormone levels generally resolves with a reduction in FT4 levels except in older patients with significant underlying heart disease.[112]

TSH-suppressive therapy is also feared because it is known that excessive T4 levels lower the systolic time intervals[113] and can produce a hyperkinetic heart with increased heart rate, excessive cardiac contractility, impaired diastolic relaxation, and thickening of the heart muscle. These changes produce increased cardiac work, which can be disadvantageous if cardiac blood flow is severely compromised. They also cause a symptomatic reduction in exercise tolerance. In one study, a downward adjustment of TSH-suppressive T4 therapy so that the TSH was between 0.01 and 0.1mIU/L produced a normalization of all echocardiographic and ergometabolic signs of thyroid hormone excess.[114] Another study looked at athyreotic patients whose TSH levels were suppressed to <0.01 to 0.06 mIU/L with thyroxine doses of 2.8mcg/kg/day (196mcg for a 70kg person). The patients had no cardiac symptoms, and cardio-vascular studies were similar to controls except for a mild increase in the left ventricular mass index—which was still within the normal range and which the authors considered to be of no clinical significance. The authors concluded that in the absence of symptoms of thyrotoxicosis, patients treated with TSH-suppressive doses of T4 may be followed clinically without specific cardiac laboratory studies. The explanation for the lack of thyrotoxic effect was again found in the FT3 level. The FT4 was above the upper limit of the RR, but the FT3 was identical to that of the healthy controls.[115]

Most physicians believe that T4 therapy will cause osteoporosis if the TSH is reduced below the reference range. To understand this risk, one must consider the effect of thyroid hormone on bone. Thyroid hormone increases metabolic rate in all tissues throughout the body. It therefore also increases the rate of bone turnover. If the person is in a net bone-catabolic state, then increased bone turnover will speed the rate of bone loss. **Most women enter a bone-catabolic state at around age 30,**[116] probably due to declining estrogen, progesterone, testosterone, and growth hormone levels. In such a bone-catabolic state, hypothyroidism is actually beneficial since bone density is better preserved. Osteoclastic activity is reduced in hypothyroidism causing increased cortical bone thickness.[117] The treatment of women with "subclinical hypothyroidism" with just 85mcg of T4 caused activation of bone turnover compared to similar untreated patients, producing an extra 1.3% decrease in lumbar bone mineral density within 24 weeks.[118] Hypothyroid female patients given T4 lost bone within the first month, while still hypothyroid, and continued to lose bone over the following 6 months.[119] Obviously, preventing bone loss by refusing to treat thyroid insufficiency is neither ethically nor medically justifiable. The correct response to bone loss in women is not to keep their thyroid hormone levels low but to restore their vitamin D and sex steroid levels.

The mechanism of thyroid hormone effect on bone turnover is sufficient to explain the disparate results of studies done on bone density in persons on TSH-suppressive thyroid replacement. If they are in a bone-catabolic state, they will lose more bone on TSH-suppressive doses—even if these doses merely restore higher youthful T3 levels in the tissues. If they are in an bone-anabolic state, they may gain bone mass. For instance, a mean thyroxine dose of 130mcg/day was found to have no effect on bone density in elderly men, [120] who generally have sufficient testosterone and estradiol to prevent bone

loss. TSH-suppressive T4 therapy (avg. dose 127.5mcg/d) given to adolescent females, presumably in a bone-anabolic state, actually produced a slight increase in bone mineral density in several sites compared to controls.[121] A review of 21 studies of TSH-suppressive therapy and bone density found that only postmenopausal women were at risk for reduced bone density.[122] This is as expected as postmenopausal women are the group with the highest prevalence of bone catabolism.

Other studies have shown a loss of bone density with TSH-suppressive therapy only in postmenopausal women who are not on hormone replacement therapy.[123] The Rancho Bernardo study found excess bone loss only in postmenopausal women on thyroxine doses greater than 1.6mcg/kg/day who were not taking estrogen.[124] Interestingly, not all studies of postmenopausal women without estrogen supplementation show increased bone loss. A study of 200 women on suppressive T4 therapy, with TSH values between 0.27 and 0.005mIU/L, found no increased loss of bone density for either the premenopausal or postmenopausal women compared with a cohort of women with untreated goiter.[125] In another study, no significant increase in bone loss was found with suppressive therapy in pre- or post-menopausal women compared with controls.[126] The best explanation for these negative findings in postmenopausal women is that given above: T4 therapy that suppresses the TSH does not necessarily induce a state of hyperthyroidism.

Muscle wasting is a problem seen only in endogenous hyperthyroidism where *both* FT3 and FT4 levels are 2 or more times the upper limit of their RRs and the TSH is always completely suppressed (<0.002 mIU/L). In one study of hyperthyroidism, anti-thyroid therapy that raised the TSH to an average of just 0.01mIU/L and lowered the FT3 and FT4 to high within the RRs completely eliminated muscle breakdown.[127] It is clear that muscle-wasting is not a relevant concern with physician-monitored thyroid replacement therapy. As with bone loss, muscle loss with excess thyroid hormone levels is probably also a matter of excessive metabolic rate, with increased breakdown of muscle for gluconeogenesis.

8. Why TSH-Normalizing T4 Therapy is Ineffective

The hypothalamic-pituitary (HP) feedback control system evolved to react to thyroid hormones being produced continuously by the thyroid gland, not to unphysiological once-daily oral T4 therapy. The bulk of the evidence indicates that the HP system is excessively suppressed by once-daily T4 therapy. The following phenomena are sufficient to explain the ineffectiveness of oral T4 therapy that is titrated to merely normalize the TSH:

1. H-P function may be insufficient in any given patient. Aging is accompanied by a universal reduction in H-P sensitivity to low FT4 levels, and middle-aged adults are the most frequent recipients of thyroid replacement.
2. Compared to continuous thyroidal T4 and T3 production, the temporary peak levels produced by once-daily oral therapy cause an excessive suppression of H-P responsiveness that can last more than 24 hours.
3. Higher levels or activity of the deiodinase D2 in the HP system convert T4 to T3 more efficiently there than in other tissues, producing excessive suppression of TSH secretion by peak T4 levels during T4-only oral therapy.

4. The lower TSH on T4 therapy reduces T3 production by the thyroid gland.
5. The lower TSH on T4 therapy reduces T4 to T3 conversion throughout the body.
6. The relatively high FT4 level required to compensate for #3 and #4 directly suppresses D2 deiodinase activity in the periphery, inhibiting T4-to-T3 conversion within various tissues.

Let us consider these points in depth. Endogenous T4 and T3 production are essentially constant over 24hrs, whereas oral dosing delivers the entire day's hormone into the circulation within a couple hours. With once-daily T4 therapy, studies have shown that peak FT4 levels are 13% to 36% higher, and peak FT3 levels are 8% higher at 3hrs than at the 24hr. trough. [128],[129],[130] These peaks produce peaks in HP T3 levels due to T4-to-T3 conversion (see below). TSH levels decline by 48% at 5 hrs post dose. Does such a T3 spike in the pituitary produce an excessive and prolonged suppression of TSH production compared to endogenous production? In rats, rapid T3 infusions suppressed the TSH levels for 7 hours, whereas rapid T4 infusions suppressed the TSH for over 22 hours.[131] During once-daily oral T3 therapy in humans, T3 levels varied between peaks of 350ng/dL 2 hrs. post dose and 100ng/dL after 24 hrs. (RR: 70-150ng/dL), yet the TSH did not vary significantly over the same 24 hr. period. Likewise, no variation was seen in the TSH with once-daily oral T4.[132] These data for human oral dosing indicate that the TSH is sensitive to peak levels and is overly suppressed for the following 24 hours or more.

Why would the TSH remained suppressed long after a temporary spike in thyroid hormone levels? First, this may be an evolutionary adaptation. Humans, like other omnivores and carnivores, have always ingested thyroid hormone, often in massive doses, by eating the thyroid glands, livers, and kidneys of other animals. It is reasonable to expect that the HP system and thyroid metabolism would have adapted to cope with this occasional excess thyroid hormone ingestion in order to avoid hyperthyroidism and its increased caloric requirements.[133]

A second cause of excessive TSH suppression on T4 therapy is the fact that the HP axis is more sensitive to circulating T4 than to T3. This was illustrated in a study of T4 and T3 monotherapies in patients with severe primary hypothyroidism. Once daily therapy with 200mcg T4 produced average 24hr. T4 levels around 9mcg/dL, well within the RR (5-11mcg/dL); yet lowered the basal TSH of patients from 45 to 4.3mU/L. On the contrary, a 50mcg daily dose of T3 (with a similar clinical effect) produced average 24hr. T3 levels of 186ng/dL, well above the upper RR limit of 150ng/dL, yet this supraphysiological T3 level only lowered the TSH from 77mU/L to only 11.8 mU/L.[134] Another study similarly found that T3 monotherapy normalizes many important measures of thyroid sufficiency at lower doses than are needed to normalize the TSH.[135] T4 has the dominant effect on TSH secretion because the pituitary and brain rapidly convert T4 to T3, whereas the rest of the body is more dependent on T3 levels.[136] The best explanation of this effect is the higher amounts or activity of the deiodinase D2 in the central nervous system and pituitary gland compared to other tissues. So the HP system converts T4 to T3 more efficiently than most other tissues in the body. This higher conversion rate causes oral T4 therapy to suppress the TSH more efficiently than it restores euthyroidism in other tissues. If the opposite were true, if D2 activity in the pituitary were low relative to other tissues, then normalization of TSH production would only be achieved when circulating

T3 levels had returned to control levels or higher,[137] and we have seen that this is not the case. In hypothyroid patients serum levels of T3, T4 and FT4 did not change after a single ingestion of 50mcg T4, while the TSH level dropped by 25 to 50%.[138] The heart appears to be another site of very active T4-to-T3 conversion as systolic time intervals are associated with T4 and TSH levels but not T3 levels.[139] Highly active T4-to-T3 conversion in the pituitary helps to explain why oral T4 therapy suppresses TSH output but fails to raise the serum FT3 levels or restore whole-body euthyroidism..

This excessive suppression of TSH output by short and long-term T4 therapy lowers T3 levels by two mechanisms: it reduces endogenous thyroidal T3 secretion and it suppresses peripheral T4-to-T3 conversion. The role of TSH in the latter case was the subject of two papers. The first documented that there are higher T3/T4 ratios in primary hypothyroidism (high TSH) compared to the lower T3/T4 ratios seen in central hypothyroidism (low TSH). In the patients studied, serum T3 values in primary hypothyroidism were double those in central hypothyroidism.[140] Since approximately 75% of T3 in the serum is produced peripherally from T4-to-T3 conversion[141], and the T4 levels were comparable in the primary and central hypothyroidism patients, this positive correlation between TSH and T3 strongly suggests causation. To further investigate this hypothesis, a study was performed on thyroidectomized dogs receiving T4 replacement. TSH-injections raised serum T3 levels to a peak at 12 hours and simultaneously lowered T4 levels.[142] **This was a direct demonstration that TSH stimulates T4-to-T3 conversion in a mammal.** Patients with suprasellar lesions have little or no TSH production. For their resulting hypothalamic obesity, supraphysiological T3 supplementation has been found to be superior to T4.[143] This effect is understandable if the absence of TSH reduces peripheral T4-to-T3 conversion to such an extent as to render T4 monotherapy less effective.

It also appears that higher FT4 levels with T4-only therapy directly suppress peripheral T4-to-T3 conversion, an effect that is independent of TSH. D2 in skeletal muscle is the source of ~72% of peripheral T3 production.[144] Post thyroidectomy, the restoration of normal T3 and TSH levels required doses of T4 that produced significantly higher FT4 levels than prior to surgery.[145] D2 is suppressed by higher FT4 levels and induced by lower levels, whereas D1 in the liver and kidneys is induced by higher and suppressed by lower FT4 levels.[146] This would explain why increases in already supraphysiological levels of T4 do not produce proportionate increases in FT3 levels.[147]

Another problem in using the TSH range as a therapeutic target is the possibility that the patient has some degree of HP dysfunction. The clinician frequently encounters symptomatic patients with TSH levels in the lower third of the RR accompanied by FT4 and/or FT3 levels that are also in the lower third of their ranges. This combination implies a subclinical secondary hypothyroidism. Any T4 or T3 therapy will easily suppress the TSH below its RR. Also, most people diagnosed with subclinical or overt hypothyroidism are middle-aged adults. It has been shown that the HP response to a given low T4 level declines markedly with age, beginning in the third decade of life.[148] By extension, the aging HP system is probably less responsive to “low-normal” levels also. Therefore we should expect that with increasing age, TSH secretion will be more easily suppressed with T4 therapy, potentially resulting in undertreatment if a “normal” TSH is the only guide to therapy.

In many patients with primary hypothyroidism or subclinical hypothyroidism, the TSH can be "normalized" (lowered to some point within the RR) with doses of only 25 to 50mcg T4, well below an average full replacement dose for a 70kg person of around 145mgc/day.[149] Such sub-replacement T4 doses run the risk of reducing endogenous T3 production and T4-to-T3 conversion by known mechanisms. There are no studies demonstrating the restoration of all parameters of euthyroidism with such low doses, indeed, there are no studies demonstrating the restoration of complete euthyroidism at any TSH-normalizing T4 dose.

With oral T4 therapy, the combination of the effects of peak T4 levels, increased D2 activity in the pituitary relative to other tissues, reduced TSH, reduced thyroidal T3 production, reduced peripheral T4-to-T3 conversion, and reduced HP function together are sufficient explanation for why T4 therapy that merely normalizes the TSH often does not restore whole-body euthyroidism.

5. The T4/T3 Combination Studies

Given the facts that T3 is the active hormone, that the thyroid gland secretes T3, and that T4 therapy often fails to restore and can even suppress T3 levels in the serum and in many tissues, one would expect that the addition of T3 to thyroid replacement therapy would be beneficial. Due to the fact that the peak levels occurring with once-daily oral T4 and T3 therapy cause disproportionate TSH reduction leading to reduced T3 production by the thyroid gland and the reduced peripheral T4-to-T3 conversion in various tissues, one would expect that the ideal T3/T4 replacement ratio should be higher than the 1:14 thyroid gland production ratio. Given the fact that oral T3 given alone does not suppress the TSH quite as vigorously as oral T4, one would expect that, at any given TSH level on therapy, a T3/T4 combination would produce a higher overall thyroid hormone effect compared with T4-only therapy.

We are fortunate to have several careful studies of T4/T3 combination therapy compared with T4-only therapy. These studies provide abundant detailed clinical data on the effects of substituting various amounts of T3 for T4. In all but one of the studies, the authors concluded that T3/T4 combination therapy offered no advantages, however one can come to a different conclusion upon reviewing the data. Statistical conclusions can be misleading. If one-half of the patients noticed marked improvements, and one-half felt worse, the author may conclude that there was no overall benefit. Indeed, one should expect such disparate reactions to arbitrary T3/T4 substitutions. There is a 3-fold range in the relative potency of T3 to T4 in different subjects treated with both hormones,([150]) so any fixed combination is going to have different effects in different persons. One would expect arbitrary substitutions to produce over-replacement in some persons and under-replacement in others. Indeed, as T3 and T4 are human hormones and not drugs, any fixed-dose scheme is of limited clinical relevance. Clinical dosing requires the fine adjustment of both the overall dose and of the T3/T4 to the patient's physiological and subjective responses.

From the data gained in the T3/T4 substitution studies, one can draw some conclusions.(See Appendix). Patients on TSH-normalizing doses of T4 frequently have much higher symptom scores than controls. Arbitrary substitutions of some amount of T3 for the T4 dose produce under- and over-replacement in a significant number of patients. The TSH level is reliably affected by T3 substitution—if the TSH rises with combination

therapy it generally indicates reduced overall thyroid hormone effect, likewise if it falls it generally indicates an increased thyroid hormone effect. TSH levels that are below the RR often yield optimal clinical effects with T3/T4 combination therapy just as with T4 therapy. Some patients, however, will not tolerate low or undetectable TSH levels on either kind of therapy (a portion of these persons may have some degree of cortisol insufficiency). At any given TSH level, and even when the TSH rises slightly, T3/T4 combination therapy produces a better subjective sense of well-being as indicated by the patients' preference for combination therapy. T3/T4 therapy also generally produces a greater improvement in scales at any given TSH level. Interestingly, the studies did not support the contentions that T3 therapy is dangerous or causes problems due to the shorter half-life of T3 and resultant fluctuations in free T3 levels. No deleterious effects were noted with T3 substitution—other than those related to general thyroid overdosage. The studies did support the hypothesis that the addition of T3 to T4 therapy can have benefits for many patients—and this leaves the possibility that combination therapy could benefit all patients with careful individualization of the doses of both hormones. Indeed the primary less of the T3/T4 substitution studies is that there is no substitute for individual adjustment of either T4 or T3/T4 combinations to achieve optimal clinical effects. Since the thyroid makes T3 and T4, and in the light of these studies, combination replacement should be considered superior to unphysiological T4-only therapy until proven otherwise.

6. Optimizing Thyroid Replacement Therapy

There is no substitute for careful clinical adjustment of thyroid hormone dosing. The Physician must gradually increase the dose of thyroid hormone until sufficient benefits are achieved, or until signs and symptoms of overdosing appear indicating a need to reduce the dose. The clinical signs of overdosing include elevated pulse, pressured speech, warm moist skin, papillary dilatation, upper eyelid retraction, scalp hair loss, frequent premature atrial or ventricular contractions. The symptoms of excessive dosing include increased fatigue, poor sleep quality, heat intolerance, excessive sweating, palpitations, irritability, fine tremor in the hands.

What should be the proportion of T4/T3 for oral thyroid replacement? Even though the human thyroid excretes a ratio of 14:1, we might expect that once-daily oral replacement would require a lower ratio (more T3 relative to T4) due to the reduction in TSH and therefore reduction in T4 to T3 conversion throughout the body. This fact explains the popularity and efficacy of natural dessicated thyroid products. They contain T4 and T3 in a 4:1 ration. 1 grain of NDT contains 9mcg of T3 and 39mcg of T4. The higher T3/T4 ratio assures sufficient availability of T3, the active thyroid hormone.

Also on T4 monotherapy, there is frequently and over-conversion of T4 to reverse T3 which produces and anti-thyroid effect. With NDT, this is much less likely as the amount of T4 supplied is lower. In the author's experience, RT3 levels decline when patients are given NDT. A few patients, however, will have persistent hypothyroid symptoms, sometimes with poor FT3/RT3 ratios even on NDT. In these cases, the NDT dose can be lowered and T3 prescribed in addition to the NDT. A small subset of patients appear to have some sort of thyroid resistance and do well only on T3 alone.

7. Conclusion

Oral T4 therapy differs in several significant ways from endogenous thyroid gland hormone production. The hypothalamic-pituitary axis does not respond to oral thyroid hormone replacement in the same way that it does to endogenous production. The TSH is overly suppressed by oral T4 therapy and tissue and serum levels of T3 are not restored. There is no evidence of harm with physician-monitored TSH-suppressive T4 therapy. Therefore T4 replacement therapy cannot be guided by the non-supplemented TSH reference range. The evidence presented here indicates that adequate thyroid hormone replacement with T4 therapy often requires some degree of TSH suppression. Therefore a new approach to the monitoring of thyroid replacement therapy is required; one based upon optimal serum levels of both FT4 and FT3, upon physiological parameters, and most importantly, upon the clinical response of the patient.

Appendix: Commentary on the T3/T4 Studies

Taylor 1970: [151] Thyroidectomized patients were treated with T4/T3 in ratios of 9:1, 4:1, and 3.3:1. Dosage was adjusted to achieve clinical euthyroidism. It was found that only the latter ratio was able to produce both optimal clinical effects and a normal protein-bound iodine level (a measure that generally indicated the amount of total T4 in the serum). The 9:1 and 4:1 ratios produced excessive P.B.I. levels. Many patients reported feeling much better on the T3/T4 combination. For most patients, the dose that made the patient "feel completely well" was 150mcg T4 and 45mcg T3 daily.
Commentary: This is the only study that adjusted both the doses and ratios of T4 and T3 to optimal clinical effect. The therapeutic dose arrived at included a much higher ratio of T3/T4 (1:3.3) than that produced by the human thyroid gland (estimated at 1:10 to 1:14). Using a 1:9 ratio, more like that of thyroidal production, clinical euthyroidism was not achieved without elevation of the PBI. The nature of oral thyroid replacement, including it's peak levels and over-suppression of TSH may cause a need for higher T3:T4 ratios than with normal thyroid gland production.

Smith 1970: [152] Patients were already on 200 to 300mcg/day of T4; doses much higher than given since the use of the TSH test. Each 100mcg of T4 was replaced with 80mcg T4 plus 20mcg T3. Patients previously on 200mcg T4 were given 160mcg T4 plus 40mcg T3. Patients on 300mcg T4 were given 240mcg T4 plus 60mcg T3. Given the average T3/T4 oral equivalence ratio of 3.3 to 1, the authors effectively substituted the equivalent of 146mcg of T4 for each 100mcg T4, a nearly 50% dose increase for each patient. Not surprisingly, the combination treatment produced **thyrotoxic** effects in many patients. Surprisingly, half of the subjects noted no preference for either treatment, and 1 in 5 preferred the combination.
Commentary: This was a case of grossly excessive "substitution" given to patients already taking high-doses of T4, yet the authors concluded "The shortcomings of combined therapy deduced from this study suggest that thyroxine has overall advantages for thyroid replacement therapy."

(In the preceding two studies, the T4 doses given, both as monotherapy and combined with the stated doses of T3, were higher than those generally required today to restore

clinical euthyroidism. One explanation is that the reformulation of Synthroid in 1982 increased its bioavailability from 48 to 81%.[153] So in the Taylor 1970 study, today's equivalent of the dose that produced the optimal subjective effect is 88mcg T3 and 45mg T3—a 1:1 ratio.)

Cooke 1982:[154] An open-label T3 add-on study of depressed patients on T4 therapy. The patients were already on antidepressants and 100 to 500mcg T4 daily with high-RR to above-RR T4 levels and partially-suppressed TSH levels (0.1-0.2mU/L in most cases). 15 to 50mcg of T3 was added to the patient's usual T4 dose. There was a marked objective and subjective improvement in refractory depression in 7 of 9 patients.
Commentary: Adding T3 to the current T4 dose can improve mood. This finding is supported by numerous studies of T3 in depression.[155,156,157,158,159,160]

Bunevicius 1999:[161] Half of the subjects were on suppressive therapy for thyroid cancer with very low or undetectable TSH levels. The avg. TSH was 0.8mU/L and average T4 dose was 175mcg. 50mcg of the usual T4 dose was replaced by 12.5 mcg of T3, a 4:1 substitution (avg. dose was 125mcg T4 plus 12.5mcg T3, a 10:1 ratio). The average TSH decreased slightly from 0.8 to 0.5mU/L. The average FT4 levels dropped from a supraphysiological 2.3 to 1.8ng/dL (RR: 0.7-2.1ng/dL) and average total T3 (2 hrs. after dosing) increased from 87 to only 117 (RR: 75-175pg/ml). Fatigue and depression improved overall. At the end, 20 patients preferred the T3/T4 combination, 11 had no preference, and 2 preferred thyroxine alone. Some cognitive tests also improved.
Commentary: Serum levels of the thyroid hormones were normalized with substitution—became more similar to those of normal persons. The positive results of this study indicate that the need for T3 may be especially great when the patient is on TSH-suppressive T4 therapy and therefore has a greater reduction in the portion of T4-to-T3 conversion stimulated by TSH. Dosage was not adjusted to optimize clinical effect. T3 levels remained low within the RR even at near peak, and thus were probably much lower throughout most of the day.

Walsh 2003:[162] Baseline TSH for the study participants was 1.4mU/L, and the baseline T4 dose was 136mcg/d on average. The investigators replaced 50mcg of the patient's T4 dose with only 10mcg T3 (5:1 substitution). However, the use of 15mcg T3, a 3.3:1 substitution, would have been necessary to sustain equivalent thyroid replacement for most persons. The average patient was on 86mcg T4 and 10mcg T3—likely a sub-replacement dose. Blood was drawn in the morning just prior to next dose. With combined treatment, the TSH rose from 1.5 to 3.1mU/L. FT4 levels dropped from 15.3 to just 11.4pmol/L (RR: 10-19pmol/L). The FT3 at trough did not change with substitution and remained relatively low at 3.5pmol/L (RR: 3.0-5.5pmol/L). There was no improvement in scales. There was deterioration in the scores on the general health questionnaire. 46 patients preferred T4 vs. 36 who preferred combination treatment. In the subgroup whose TSH did not change by more than 0.99mu/L, 16 preferred T4 only vs. 19 who preferred combination therapy. On combination therapy, SHBG was lower and cholesterol higher.

Commentary: 5:1 substitution of 50mcg of the patients' dose was **inadequate** to maintain TSH and total thyroid hormone sufficiency. Those whose TSH did not rise significantly tended to favor the combination treatment.

Sawka 2003:[163] Patients had depressive symptoms. Usual dose of T4 was given once daily plus a placebo twice daily, or half the usual dose of T4 plus T3, 12.5 mcg twice daily, for 15 weeks. The dose of T3 was adjusted by an independent investigator to maintain "normal" serum TSH concentrations. At baseline, the T4 group was receiving 120mcg T4 daily, and the study group was receiving 132mcg/day. The T4 group was more undertreated as indicated by a baseline TSH of 2.2mU/L compared with the study group baseline TSH of 1.75mU/L. The TSH was nearly the same in both groups after 15 weeks of treatment (1.7vs1.8mU/L), but had declined by 0.5mU/L in the T4 group and risen by 0.1mU/L in the treatment group. There were marked improvements in both groups, yet the improvements were generally greater in the T3/T4 group, especially in cognitive functioning, role-physical, and social functioning scales.
Commentary: The patients' baseline and end-study TSH levels were in the middle of the RR, indicating **under-replacement in both groups.** The T4 group received a different T4 preparation that lowered their TSH by 0.5mU/L and raised their free T4 levels by 1 pmol/L—explaining their improvements in the scales. The T3/T4 group had greater improvements across the board—in spite of the fact that their average TSH actually increased slightly. The study therefore demonstrated that T3/T4 produced greater improvements in scales without lowering the TSH compared to an increased dose of T4 that did lower the TSH. The authors ignored the differences in pre- and post-study TSH levels and the greater improvements in the study group, preferring only to report a lack of $p < 0.05$ statistical significance in comparing the improvements in both groups. Patients were not asked which treatment they preferred.

Clyde:[164] Patients responded to an advertisement for a thyroid treatment that might make them feel better—so they probably represented an under-replaced population. Baseline Hypothyroid Health-Related Quality-of-Life Score Questionnaire scores were ~42% higher (worse) than those of controls, implying the ineffectiveness of TSH-normalizing T4 therapy. The baseline TSH was 2.2mU/L in T4 group and 2.6mU/L in T3/T4 group. The patients were randomly assigned to receive their usual dose of T4, less 50mcg, once daily and a capsule containing 25 mcg of T4 twice daily (T4 group), or their usual dose of T4, less 50mcg, once daily and a capsule containing 7.5 mcg of T3 twice daily, for four months. This was an equipotent 3.3:1 substitution. The T4 dose was adjusted in both groups to keep the TSH between 0.5 and 3.5mU/L, but the final doses in both groups was not reported. TSH levels at the end of the study were slightly lower in both groups (~2.0mU/L). Both groups improved in most scales with no substantial overall differences between groups. The FT4 levels were 1.2ng/dL in the T4 group (below the midpoint of the RR) vs. 0.8ng/dL in the T3/T4 group (at the bottom of the usual RR of 0.8-1.8ng/dL). The total T3 level at one-hour post dose was 87ng/dL in the T4 group (near the bottom of the RR) vs.135ng/dL in the T3/T4 group (usual RR: 0.85-205ng/dL). Total cholesterol and LDL decreased in T3/T4 group but increased in the T4 group.
Commentary: This was a study of **TSH-normalizing therapy**. The study patients were under-replaced with TSH-normalizing T4 therapy to start with as demonstrated by FT4

levels below midpoint of RR and FT3 levels near bottom of the RR. Dosage was adjusted to maintain the TSH within the "normal range", not to optimize the clinical effect. The study found little difference between these two under-replaced groups. Both groups had thyroid hormone levels well below the optimal levels seen in young healthy adults. Those on T4/T3 had an FT4 near the bottom of the RR and a FT3 below the midpoint of the RR at one hour post dose—and probably much lower during much of the day. Patients were not asked which treatment they preferred.

Siegmund 2004:[165] A 3 month study involving 23 asymptomatic patients already on 100 to 175mcg T4. 5% of their T4 dose was substituted mcg for mcg with T3 (5 to 8mcg T4 replaced by 5 to 8mcg T3). The TSH in the T4 group declined from an average baseline of 1.72mU/L to 1.5mU/L, and to 0.5mU/L in the T3/T4 group. Free T4 was 22pmol/L at baseline--high normal (upper limit 25pmol/L). So this group was being given more optimal doses of T4 than most patients today. Trough FT4 and FT3 levels were not different in the control or combination group. On combination therapy, trough FT3 increased from 4.5 to 5 pmol/L (RR: 3.4-7.1pmol/L). FT3 area-under-curve from 0 to 8 hrs. increased by 6pmolxh/L, FT4 $AUC_{0\text{-}8hr}$ dropped by 17pmolxh/L. In 8/23 subjects whose TSH was completely suppressed (< 0.02 mU/l), mood was significantly impaired by the T4/T3 combination. Removing these patients from the Beck Depression Inventory scales revealed a large reduction from 7.8 to 4.07 for the combination group compared with 6.9 in the T4 control group. Even including this 1/3 of subjects who were overdosed by clinical criteria, the BDI and some other subjective and objective scales improved on the T3/T4 combination.
Commentary: A 1:1 substitution study, essentially a **T3 add-on study. Patients were already on relatively high-dose T4 with TSH < 2mU/L and free T4 near the upper limit of its RR.** The add-on T3 was equivalent to increasing their T4 dose by 16 to 26mcg daily. **This made at least 1/3rd of the subjects thyrotoxic**--skewing the overall results. The authors conclude that replacement therapy (not specified) has no benefit and can cause subclinical hyperthyroidism due to the fluctuations in T3 levels. The mild fluctuation in T3 levels documented was shown to correlate with the TSH suppression, but not with general CNS or cardiac thyrotoxicity. The authors ignored the fact that the overtreatment of a subset of patients by T3 add-on therapy produced the bulk of the undesirable results. One has to wonder how marked the improvements were in the other 15 patients who were not over-replaced. The appropriate conclusion to this study would have been, "Many patients on T4 therapy with TSH levels between 1.5 and 2mU/L will benefit from the addition of small amounts of T3. Some may become thyrotoxic requiring a reduction in either the T3 or the T4 dose."

Escobar-Morreale 2005:[166] A study of 28 women with primary hypothyroidism on a T4 dose of 100mcg. In the study group, this dose was replaced with 75mcg + 5mcg T3, a 1:5 substitution ratio and a marked under-substitution (average efficacy ratio being 1:3.3). In an 8-week add-on period, all patients received 87.5mcg+7.5mcg T3 (a 1:1.7 over-substitution). TSH levels were 1.95 on 100mcg T4, 2.65 on low-dose combination therapy, 1.09 on the add on combination therapy—only the latter giving an effective increase in thyroid hormone effect on the H-P axis. 12 of 28 patients preferred the low-ratio combination treatment in spite of the under-substitution and rise in TSH. 6

patients preferred the add-on over-substitution combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference. Thus 18 of 28 patients preferred T3/T4 combinations compared with 2 of 28 who preferred T4 only. The visual analog scale for depression for all treatment groups was much higher than that of controls, and showed improvement only in the add-on combination group
Commentary: Another **TSH-normalizing** study in which most patient were under-replaced. Fortunately, controls were also tested and revealed much better scores on the profile of mood states and visual analog mental scales scores. These marked differences should be considered to be due to the inadequacy of T4 and of the tested T3/T4 combinations until proven otherwise.

Appelhoff 2005:[167] Patients on levothyroxine had TSH levels low within the reference range. The T4 dose was reduced and T3 added to produce overall T4/T3 ratios of 10:1 or 5:1. For instance, they reduced a 100mcg dose to 75mcg and replaced that 25mcgs of T4 with either 7.5 or 15mcgs of T3. Assuming an oral T3/T4 efficacy ratio of 3.3/1, the first group received about the same amount of thyroid hormone, the second group received an increase. Median end point TSH values in the three groups were 0.64, 0.35, and 0.07 mU/L, respectively. Study medication was preferred to usual treatment by 29.2, 41.3, and 52.2% in the T4, 10:1 ratio, and 5:1 ratio groups, respectively**.** Objective testing revealed no differences except that Mean body weight change was +0.1, -0.5, and -1.7 kg, respectively. Patients preferred the replacement of some of their T4 with an effectively greater amount of T3. Those who preferred the addition of T3 had their TSH suppressed to 0.35 and 0.07 mU/L. They lost more weight. Typical subjective scales could not differentiate between the groups.
Commentary: These patients were already on a relatively high dose of T4 as their TSH was 0.64 on average, lower than most treated patients in the community, yet equipotent substitution (1mcg T3 for 3.3 mcg T4) produced subjective improvement, and superpotent substitution (3mcg T3 for 5mcg T4) produce greater reported improvement and weight loss. Notice also that no deleterious subjective effects were noted with suppression of the TSH to 0.07mU/ml.

Rodriguez 2005:[168] Substituted 10mcg T3 for 50mcg of T4; an **inadequate 1:5 substitution and an effective reduction in dose.** Avg. baseline T4 dose was 121 mcg and baseline TSH was 1.9mU/L. 12 vs. Symptoms worsened on average as TSH increased by 2.7mU/L in the substitution group. Even so, 7 preferred standard treatment, 8 had nor preference, and 12 preferred the substitution treatment.
Commentary: A 5:1 T4/T3 substitution increased both TSH values and symptom scores. Inadequate substitution led to a significant increase in the TSH. Some symptoms worsened. **In spite of this more patients preferred the T3/T4 combo** than preferred T4 only. This indicates that T3 has benefits that are not reflected in the TSH level.

Slawik 2007:[169] TSH not followed as patients had central hypothyroidism. Patients were on low-dose T4 therapy (receiving 1.1mcg/kg) T4 daily. They were randomized and crossed-over to receive 1.6mcg/kg T4 daily, or 1.44mcg/kg plus 0.16mcg/kg T3. The T4/T3 group received an excess of thyroid hormone effect over the body-weight T4 group (for an 80kg person, the BW-adjusted T4 dose was 128mcg, and the T4/T3

dose was 115mcg/13mcg. Given a T3/T4 potency of 3.3/1, the T3/T4 combo produced a T4-equivalent dose of 158mcg/d. The T4/T3 combination produced slightly above-RR FT3 levels—but at the 2hr peak post dose. The fixed higher BW-adapted T4 dose reduced hypothyroid symptoms, but further reductions in muscle CK and ankle reflex time occurred with the T3/T4 combination. There was no increase in any side effects (i.e. hyperthyroid symptoms) on the T4/T3 combination.
Comentary: A higher BW-adjusted T4 dose raised FT4 levels into the upper end of the RR or slightly above the RR and eliminated most hypothyroid symptoms and signs. The addition of T3 with a slightly lower amount of T4 brought more improvements without signs or symptoms of overdosing. Interestingly, T4 levels did not decline with the reduction in T4 dose in the T4/T3 group, indicating a reduction in T4 to T3 conversion when sufficient T3 is supplied.

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[1]Greenspan FS, Rapoport B. 1991 Tests of thyroid function. In: Greenspan FS, ed. Basic and clinical endocrinology, 3rd ed. London: Appleton & Lange, Prentice Hall International; 211.

[2]Evered D, Hall R. Hypothyroidism. Br Med J. 1972 Jan 29;1(5795):290-3.

[3]Evered D, Young ET, Ormston BJ, Menzies R, Smith PA, Hall R. Treatment of Hypothyroidism: A Reappraisal of Thyroxine Therapy. Br Medl J. 1973, 3, 131-134

[4]Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986 Sep 27;293(6550):808-10.

[5]AACE Thyroid Task Force. AACE medical guidelines for clinical practice of the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002;8:457-469.

[6]Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003 Feb;58(2):138-40.

[7]Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8.

[8]Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003 Feb;58(2):138-40.

[9]American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism http://www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf, 2006

[10]Schindel B [Unusual presenting symptoms of hypothyroidism] Harefuah. 1991 Jul;121(1-2):13-5.

[11]Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J. Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. Clin Endocrinol (Oxf). 2004 Aug;61(2):232-8.

[12]Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, Sabri O, Matthes G, Thiery J. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem. 2005 Aug;51(8):1480-6.

[13]Henny J, Petitclerc C, Fuentes-Arderiu X, Petersen PH, Queraltó JM, Schiele F, Siest G. Need for revisiting the concept of reference values. Clin Chem Lab Med. 2000 Jul;38(7):589-95.

[14]Pocono Medical Center, Stroudsbug, Pennyslvania.

[15]Personal communication with laboratory director of Walter Reed Army Medical Center, 2009.

[16]Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, Sabri O, Matthes G, Thiery J. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem. 2005 Aug;51(8):1480-6.

[17]Nagayama I, Yamamoto K, Saito K, Kuzuya T, Saito T. Subject-based reference values in thyroid function tests. Endocr J. 1993 Oct;40(5):557-62.

[18]Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002 Mar;87(3):1068-72.

[19]Wawrzyn H, Hesch RD. [Autonomy of the thyroid gland: is there an "organ hyperthyroidism" of "euthyroid" patients?] Med Klin (Munich). 2000 Aug 15;95(8):421-8.

[20]Midgley JE, Gruner KR. Effects of age and health on the euthyroid RRs for serum free thyroxine and free triiodothyronine. Nuklearmedizin. 1985 Apr;24(2):57-65.

[21]Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002 Feb;87(2):489-99.

[22]Mariotti S, Barbesino G, Caturegli P, Bartalena L, Sansoni P, Fagnoni F, Monti D, Fagiolo U, Franceschi C, Pinchera A. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab. 1993 Nov;77(5):1130-4.

[23]Henny J, Petitclerc C, Fuentes-Arderiu X, Petersen PH, Queraltó JM, Schiele F, Siest G. Need for revisiting the concept of reference values. Clin Chem Lab Med. 2000 Jul;38(7):589-95.

[24]Iverson JF, Mariash CN. Optimal free thyroxine levels for thyroid hormone replacement in hypothyroidism. Endocr Pract. 2008 Jul-Aug;14(5):550-5.

[25]Carlé A, Laurberg P, Pedersen IB, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Knudsen N. Age Modifies the Pituitary TSH Response to Thyroid Failure. Thyroid. 2007 Feb;17(2):139-44.

[26]Tjorve E, Tjorve KM, Olsen JO, Senum R, Oftebro H. On commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues.Med Hypotheses. 2007 Mar 23; [Epub ahead of print]

[27]Faglia G, Bitensky L, Pinchera A, Ferrari C, Paracchi A, Beck-Peccoz P, Ambrosi B, Spada A. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. J Clin Endocrinol Metab. 1979 Jun;48(6):989-98.

[28]Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002 Feb;23(1):38-89.

[29]Lazar MA. Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr Rev. 1993 Apr;14(2):184-93.

[30]Alkemade A, Vuijst CL, Unmehopa UA, Bakker O, Vennström B, Wiersinga WM, Swaab DF, Fliers E. Thyroid hormone receptor expression in the human hypothalamus and anterior pituitary. J Clin Endocrinol Metab. 2005 Feb;90(2):904-12.

[31]Hennemann G, Docter R, Friesema EC, de Jong M, Krenning EP, Visser TJ. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev. 2001 Aug;22(4):451-76.

[32]Everts ME, de Jong M, Lim CF, Docter R, Krenning EP, Visser TJ, Hennemann G. Different regulation of thyroid hormone transport in liver and pituitary: its possible role in the maintenance of low T3 production during nonthyroidal illness and fasting in man. Thyroid. 1996 Aug;6(4):359-68.

[33]Dietrich JW, Brisseau K, Boehm BO. [Absorption, transport and bio-availability of iodothyronines] Dtsch Med Wochenschr. 2008 Aug;133(31-32):1644-8.

[34]Winter WE, Signorino MR. Review: molecular thyroidology. Ann Clin Lab Sci. 2001 Jul;31(3):221-44.

[35]Yamada M, Mori M. Mechanisms related to the pathophysiology and management of central hypothyroidism. Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):683-94.

[36]Alexopoulou O, Beguin C, De Nayer P, Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol. 2004 Jan;150(1):1-8.

[37]Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986 Sep 27;293(6550):808-10.

[38]Brajkovich IE, Mashiter K, Joplin GF, Cassar J. Serum T4, T3, and TSH levels in primary hypothyroidism during replacement therapy with thyroxine. Metabolism. 1983 Aug;32(8):745-7.

[39]Ferrari C, Paracchi A, Parisio E, Codecasa F, Mucci M, Boghen M, Gerevini G, Rampini P. Serum free thyroid hormones in different degrees of hypothyroidism and in euthyroid autoimmune thyroiditis. Acta Endocrinol (Copenh). 1987 Apr;114(4):559-64.

[40]Alexopoulou O, Beguin C, De Nayer P, Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol. 2004 Jan;150(1):1-8.

[41]Alexopoulou O, Beguin C, De Nayer P, Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol. 2004 Jan;150(1):1-8.

[42]Baisier WV, Hertoghe J, Eeckhaut W, Thyroid Insufficiency. Is TSH Measurement the Only Diagnostic Tool? J Nutr Environ Med Jun;10(2):105-113

[43]Ferrari C, Paracchi A, Parisio E, Codecasa F, Mucci M, Boghen M, Gerevini G, Rampini P. Serum free thyroid hormones in different degrees of hypothyroidism and in euthyroid autoimmune thyroiditis. Acta Endocrinol (Copenh). 1987 Apr;114(4):559-64.

[44]Meier C, Trittibach P, Guglielmetti M, Staub JJ, Müller B. Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. BMJ. 2003 Feb 8;326(7384):311-2.

[45]Carlé A, Laurberg P, Pedersen IB, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Knudsen N. Age Modifies the Pituitary TSH Response to Thyroid Failure. Thyroid. 2007 Feb;17(2):139-44.

[46]Sell MA, Schott M, Tharandt L, Cissewski K, Scherbaum WA, Willenberg HS. Functional central hypothyroidism in the elderly. Aging Clin Exp Res. 2008 Jun;20(3):207-10.

[47]Lewis GF; Alessi CA; Imperial JG; Refetoff S Low serum free thyroxine index in ambulating elderly is due to a resetting of the threshold of thyrotropin feedback suppression. J Clin Endocrinol Metab 1991 Oct;73(4):843-9.

[48]Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med.1991 Jan;151(1):165-8.

[49]Skinner GRB, Holmes D, Ahmad A, Davies JA, Benitez J, Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients J Nutr Environ Med 2000 Jun;10 (2):115-124

[50]Gursoy A, Ozduman Cin M, Kamel N, Gullu S. Which thyroid-stimulating hormone level should be sought in hypothyroid patients under L-thyroxine replacement therapy? Int J Clin Pract. 2006 Jun;60(6):655-9.

[51]Perk M, O'Neill BJ. The effect of thyroid hormone therapy on angiographic coronary artery disease progression. Can J Cardiol. 1997 Mar;13(3):273-6.

[52]Auer J, Berent R, Weber T, Lassnig E, Eber B. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol. 2003 Dec;26(12):569-73.

[53]Chadarevian R, Bruckert E, Ankri A, Beucler I, Giral P, Turpin G. Relationship between thyroid hormones and plasma D-dimer levels. Thromb Haemost. 1998 Jan;79(1):99-103.

[54]Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007 Feb;92(2):491-6. Epub 2006 Nov 7.

[55]Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab. 2005 Jul;90(7):4019-24.

[56]Ortega E, Pannacciulli N, Bogardus C, Krakoff J. Plasma concentrations of free triiodothyronine predict weight change in euthyroid persons. Am J Clin Nutr. 2007 Feb;85(2):440-5.

[57]Prinz PN; Scanlan JM; Vitaliano PP; Moe KE; Borson S; Toivola B; Merriam GR; Larsen LH; Reed HL Thyroid hormones: positive relationships with cognition in healthy, euthyroid older men. J Gerontol A Biol Sci Med Sci. 1999 Mar;54(3):M111-6.

[58]Volpato S; Guralnik JM; Fried LP; Remaley AT; Cappola AR; Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. Neurology 2002 Apr 9;58(7):1055-61.

[59]Hatterer JA, Kocsis JH, Stokes PE. Thyroid function in patients maintained on lithium. Psychiatry Res. 1988 Dec;26(3):249-57.

[60]Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ, Frank E. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. Am J Psychiatry. 2002 Jan;159(1):116-21.

[61]Kraus RP, Phoenix E, Edmonds MW, Nicholson IR, Chandarana PC, Tokmakejian S. Exaggerated TSH responses to TRH in depressed patients with "normal" baseline TSH. J Clin Psychiatry. 1997 Jun;58(6):266-70.

[62]Gitlin M, Altshuler LL, Frye MA, Suri R, Huynh EL, Fairbanks L, Bauer M, Korenman S. Peripheral thyroid hormones and response to selective serotonin reuptake inhibitors. J Psychiatry Neurosci. 2004 Sep;29(5):383-6.

[63]Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. J Affect Disord. 2006 Feb 14; [Epub ahead of print]

[64]Cooper-Kazaz R, Apter JT, Cohen R, Karagichev L, Muhammed-Moussa S, Grupper D, Drori T, Newman ME, Sackeim HA, Glaser B, Lerer B. Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry. 2007 Jun;64(6):679-88.

[65]Schwarcz G, Halaris A, Baxter L, Escobar J, Thompson M, Young M. Normal thyroid function in desipramine nonresponders converted to responders by the addition of L-triiodothyronine. Am J Psychiatry. 1984 Dec;141(12):1614-6.

[66]Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. J Affect Disord. 2006 Feb 14; [Epub ahead of print]

[67]Posternak M, Novak S, Stern R, Hennessey J, Joffe R, Prange A, Zimmerman M. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. Int J Neuropsychopharmacol. 2007 Mar 13:1-11

[68]Nakamura T, Nomura J. [Adjunctive thyroid hormone therapy and comparison between responders and non-responders] Nippon Rinsho. 1994 May;52(5):1291-6.

[69]Saravanan P; Visser TJ; Dayan CM. Psychological well-being correlates with free thyroxine but not free 3,5,3'-triiodothyronine levels in patients on thyroid hormone replacement. J Clin Endocrinol Metab. 2006 Sep;91(9):3389-93.

[70]Skinner GRB, Holmes D, Ahmad A, Davies JA, Benitez J, Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients J Nutr Environ Med 2000 Jun;10 (2):115-124

[71]Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJ, McMahon AD, McLaren EH. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. BMJ. 2001 Oct 20;323(7318):891-5.

[72]Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986 Sep 27;293(6550):808-10.

[73]Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003 Feb;58(2):138-40.

[74]Ferretti E, Persani L, Jaffrain-Rea ML, Giambona S, Tamburrano G, Beck-Peccoz P. Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism.J Clin Endocrinol Metab. 1999 Mar;84(3):924-9.

[75]Slawik M, Klawitter B, Meiser E, Schories M, Zwermann O, Borm K, Peper M, Lubrich B, Hug MJ, Nauck M, Olschewski M, Beuschlein F, Reincke M. Thyroid hormone replacement for central hypothyroidism: a randomized controlled trial comparing two doses of thyroxine (T4) with a combination of T4 and triiodothyronine. J Clin Endocrinol Metab. 2007 Nov;92(11):4115-22.

[76]Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJ, McMahon AD, McLaren EH. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the RR: randomised double blind placebo controlled crossover trial. BMJ. 2001 Oct 20;323(7318):891-5.

[77]Rockel M, Teuber J, Schmidt R, Kaumeier S, Hafner H, Usadel KH. [Correlation of "latent hyperthyroidism" with psychological and somatic changes] Klin Wochenschr. 1987 Mar 16;65(6):264-73.

[78]Oppenheimer JH, Schwartz HL, Mariash CN, Kinlaw WB, Wong NC, Freake HC 1987 Advances in our understanding of thyroid hormone action at the cellular level. Endocr Rev. 8:288-308.

[79]Morreale de Escobar G 1976 Conversion of T4 to T3 and its relation to hormonal activity. In: Reinwein D (ed) Regulation of Thyroid Function. vol 1, FK Schattaner Verlag, Stuttgart, pp.109-29.

[80]Woeber KA 2002 Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. J Endocrinol Invest 25:106-9.

[81]Mortoglou A, Candiloros H 2004 The serum triiodothyronine to thyroxine (T3/T4) ratio in various thyroid disorders and after Levothyroxine replacement therapy. Hormones 3:120-6.

[82]Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, Metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med. 1987 Mar 26;316(13):764-70.

[83]Alexopoulou O, Beguin C, De Nayer P, Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol. 2004 Jan;150(1):1-8.

[84]Escobar-Morreale HF, Obregon MJ, Calvo R, Escobar del Rey F, Morreale de Escobar G 1993 Continuous infusion of different doses of T4 or T3 in thyroidectomized rats: circulating and tissue levels of T4 and T3. 67th Annual Meeting of the American Thyroid Association, Tampa FL, p. T49 (Abstract)

[85]Escobar-Morreale HF, Obregon MJ, Escobar del Rey F, Morreale de Escobar G 1995 Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J Clin Invest 96:2828-38.

[86]Escobar-Morreale HF, del Ray FE, Obregon MJ, de Escobar GM 1996 Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology 137:2490-502.

[87]Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzuola F, Bianchi R. Thyroidal and peripheral production of 3,5,3'-triiodothyronine in humans by multicompartmental analysis. Am J Physiol. 1990 Apr;258(4 Pt 1):E715-26.

[88]Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM 2002 Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 57:577-85.

[89]Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS 2007 Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid 17:249-58.

[90]Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, Wiersinga WM. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005 Dec;153(6):747-53.

[91]Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab. 1997 Mar;82(3):771-6.

[92]Flynn RW, Macdonald TM, Jung RT, Morris AD, Leese GP 1997 Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab 91:2159-64.

[93]Tigas S, Idiculla J, Beckett G, Toft A 2000 Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? Thyroid 10:1107-11.

[94]Langdahl BL, Loft AG, Eriksen EF, Mosekilde L, Charles P 1996 Bone mass, bone turnover and body composition in former hypothyroid patients receiving replacement therapy. Eur J Endocrinol 134:702-9.

[95]Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med. 2005 Mar 15;142(6):412-24.

[96]Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ 1997 Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 82:771-6 (See graph p.775).

[97]Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R, Muller B 2001 TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 86:4860-6. (Table 2)

[98]Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy.JAMA. 2008 Feb 20;299(7):769-77.

[99]Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, Nanna M, Ferrick K, Surks MI 1997 Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. J Clin Endocrinol Metab 82:2592-5. (Table 2)

[100]Baisier WV, Hertoghe J, Eeckhaut W 2000 Thyroid Insufficiency. Is TSH Measurement the Only Diagnostic Tool? J Nutr Environ Med 10:105-113

[101]Franklyn JA, Daykin J, Betteridge J, Hughes EA, Holder R, Jones SR, Sheppard MC 1993 Thyroxine replacement therapy and circulating lipid concentrations. Clin Endocrinol (Oxf) 38:453-9.

[102]Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG 2006 Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab 91:145-53.

[103]Walsh JP, Ward LC, Burke V, Bhagat CI, Shiels L, Henley D, Gillett MJ, Gilbert R, Tanner M, Stuckey BG 2006 Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. J Clin Endocrinol Metab 91:2624-30.

[104]Carr D, McLeod DT, Parry G, Thornes HM 1988 Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf) 28:325-33.

[105]Salmon D, Rendell M, Williams J, Smith C, Ross DA, Waud JM, Howard JE 1982 Chemical hyperthyroidism: serum triiodothyronine levels in clinically euthyroid individuals treated with levothyroxine. Arch Intern Med 142:571-3.

[106]Liewendahl K, Helenius T, Lamberg BA, Mahonen H, Wagar G 1987 Free thyroxine, free triiodothyronine, and thyrotropin concentrations in hypothyroid and thyroid carcinoma patients receiving thyroxine therapy. Acta Endocrinol (Copenh) 116:418-24.

[107]Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Sacca L, Filetti S, Lombardi G, Perticone F 2000 Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab 85:4701-5.

[108]Nozaki H, Funahashi H, Sato Y, Imai T, Oike E, Kato M, Takagi H. [Study of hormone replacement therapy following total thyroidectomy in thyroid cancer--with special reference to the analysis of thyroid hormone peripheral effects, using indirect calorimetry] Nippon Geka Gakkai Zasshi. 1991 Dec;92(12):1700-7.

[109]Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC. Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. Clin Endocrinol (Oxf). 1992 Dec;37(6):500-3.

[110]Chen YC; Chen SA; Chen YJ; Chang MS; Chan P; Lin CI Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. J Am Coll Cardiol 2002 Jan 16;39(2):366-72.

[111]Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, Sheppard MC, Franklyn JA. Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med. 2007 May 14;167(9):928-34.

[112]Woeber KA. Thyrotoxicosis and the heart. N Engl J Med. 1992 Jul 9;327(2):94-8.

[113]Jennings PE, O'Malley BP, Griffin KE, Northover B, Rosenthal FD 1984 Relevance of increased serum thyroxine concentrations associated with normal serum triiodothyronine values in hypothyroid patients receiving thyroxine: a case for "tissue thyrotoxicosis". Br Med J (Clin Res Ed) 289:1645-7.

[114]Mercuro G, Panzuto MG, Bina A, Leo M, Cabula R, Petrini L, Pigliaru F, Mariotti S 2000 Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. J Clin Endocrinol Metab 85:159-64.

[115]Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, Nanna M, Ferrick K, Surks MI 1997 Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. J Clin Endocrinol Metab 82:2592-5.

[116]Speroff L, Fritz M 2005 Clinical Gynecologic Endocrinology and Fertility, 7th Ed, Lippincott Williams & Wilkins, Philadelphia, p.653.

[117]Mosekilde L, Melsen F 1978 Morphometric and dynamic studies of bone changes in hypothyroidism. Acta Pathol Microbiol Scand [A] 86:56-62.

[118]Meier C, Beat M, Guglielmetti M, Christ-Crain M, Staub JJ, Kraenzlin M 2004 Restoration of euthyroidism accelerates bone turnover in patients with subclinical hypothyroidism: a randomized controlled trial. Osteoporos Int 15:209-16.

[119]Coindre JM, David JP, Rivière L, Goussot JF, Roger P, de Mascarel A, Meunier PJ 1986 Bone loss in hypothyroidism with hormone replacement. A histomorphometric study. Arch Intern Med 146:48-53.

[120]Schneider DL, Barrett-Connor EL, Morton DJ 1995 Thyroid hormone use and bone mineral density in elderly men. Arch Intern Med 155:2005-7.

[121]Poomthavorn P, Mahachoklertwattana P, Ongphiphadhanakul B, Preeyasombat C, Rajatanavin R 2005 Exogenous subclinical hyperthyroidism during adolescence: effect on peak bone mass. J Pediatr Endocrinol Metab 18:463-9.

[122]Heemstra KA, Hamdy NA, Romijn JA, Smit JW 2006 The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma. Thyroid 16:583-91.

[123]Ongphiphadhanakul B, Puavilai G, Rajatanavin R 1996 Effect of TSH-suppressive doses of levothyroxine on bone mineral density in Thai women. J Med Assoc Thai 79:563-7.

[124]Schneider DL, Barrett-Connor EL, Morton DJ 1994 Thyroid hormone use and bone mineral density in elderly women. Effects of estrogen. JAMA 271:1245-9.

[125]Appetecchia M 2005 Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine in a cohort women study. Horm Res 64:293-8.

[126]Lopez Alvarez MB, Hawkins F, Rigopoulou D, Martinez G, Jodar E, Estenoz J, Ortuno B, Arnaiz F 1999 [The risk factors and bone mineral density in women on long-term levothyroxine treatment] Med Clin (Barc) 112:85-9.

[127]Riis AL, Jorgensen JO, Gjedde S, Norrelund H, Jurik AG, Nair KS, Ivarsen P, Weeke J, Moller N 2005 Whole body and forearm substrate metabolism in hyperthyroidism: evidence of increased basal muscle protein breakdown. Am J Physiol Endocrinol Metab 288:E1067-73.

[128]Ain KB, Pucino F, Shiver TM, Banks SM 1993 Thyroid hormone levels affected by time of blood sampling in thyroxine-treated patients. Thyroid 3:81-5.

[129]Wennlund A 1986 Variation in serum levels of T3, T4, FT4 and TSH during thyroxine replacement therapy. Acta Endocrinol (Copenh) 113:47-9.

[130]Carpi A, Toni MG, De Gaudio C. Effect of a single oral dose of L-thyroxine (150 micrograms) on serum thyroid hormone and TSH concentrations in clinically euthyroid goitrous patients. Thyroidology. 1992 Aug;4(2):69-73.

[131]Larsen PR, Frumess RD 1977 Comparison of the biological effects of thyroxine and triiodothyronine in the rat. Endocrinology 100:980-8.

[132]Saberi M, Utiger RD 1974 Serum thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. J Clin Endocrinol Metab 39:923-7.

[133]Crockford S 2006 Rhythms of Life: Thyroid Hormone & the Origin of Species. Trafford, Victoria, BC, Canada, p. 70.

[134]Saberi M, Utiger RD 1974 Serum thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. J Clin Endocrinol Metab 39:923-7.

[135]Ridgway EC, Cooper DS, Walker H, Daniels GH, Chin WW, Myers G, Maloof F 1980 Therapy of primary hypothyroidism with L-triiodothyronine: discordant cardiac and pituitary responses. Clin Endocrinol (Oxf) 13:479-88.

[136]Larsen PR 1982 Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. N Engl J Med 306:23-32.

[137]Saravanan P, Dayan CM 2004 Understanding thyroid hormone action and the effects of thyroid hormone replacement--just the beginning and not the end. Hot Thyroidology (www.hotthyroidology.com), October, No.1.

[138]Wennlund A 1986 Variation in serum levels of T3, T4, FT4 and TSH during thyroxine replacement therapy. Acta Endocrinol (Copenh) 113:47-9.

[139]Ridgway EC, Cooper DS, Walker H, Rodbard D, Maloof F 1981 Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 53:1238-42.

[140]Kabadi UM 1993 Role of thyrotropin in triiodothyronine generation in hypothyroidism. Thyroidology 5:41-7.

[141]. Bianchi R, Mariani G, Molea N, Vitek F, Cazzuola F, Carpi A, Mazzuca N, Toni MG 1983 Peripheral metabolism of thyroid hormones in man. I. Direct measurement of the conversion

rate of thyroxine to 3,5,3'-triiodothyronine (T3) and determination of the peripheral and thyroidal production of T3. J Clin Endocrinol Metab 56:1152-63.

[142]Kabadi UM 2006 Role of thyrotropin in metabolism of thyroid hormones in nonthyroidal tissues. Metabolism 55:748-50.

[143]Fernandes JK, Klein MJ, Ater JL, Kuttesch JF, Vassilopoulou-Sellin R 2002 Triiodothyronine supplementation for hypothalamic obesity. Metabolism 51:1381-3

[144]Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest. 2005 Sep;115(9):2524-33.

[145]Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy.JAMA. 2008 Feb 20;299(7):769-77.

[146]Larsen PR, Davies TF, Schlumberger MJ, Hay ID 2003 Thryoid Physiology and Diagnostic Evaluation of Patients with Thyroid Disorders. In: Williams Textbook of Endocrinology, Tenth Edition, Elsevier, Philadelphia, p. 341-3.

[147]Liewendahl K, Helenius T, Lamberg BA, Mahonen H, Wagar G. Free thyroxine, free triiodothyronine, and thyrotropin concentrations in hypothyroid and thyroid carcinoma patients receiving thyroxine therapy. Acta Endocrinol (Copenh). 1987 Nov;116(3):418-24.

[148]Carlé A, Laurberg P, Pedersen IB, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Knudsen N 2007 Age Modifies the Pituitary TSH Response to Thyroid Failure. Thyroid 17:139-44. Table taken from Utiger RD ed. 2007 Clinical Thyroidology 19:32

[149]Maeda M, Kuzuya N, Masuyama Y, Imai Y, Ikeda H 1976 Changes in serum triiodothyronine, thyroxine, and thyrotropin during treatment with thyroxine in severe primary hypothyroidism. J Clin Endocrinol Metab 43:10-7.

[150]Sawin CT, Hershman JM, Chopra IJ. The comparative effect of T4 and T3 on the TSH response to TRH in young adult men. J Clin Endocrinol Metab. 1977 Feb;44(2):273-8.

[151]Taylor S, Kapur M, Adie R. Combined thyroxine and triiodothyronine for thyroid replacement therapy. Br Med J. 1970 May 2;2(5704):270-1.

[152]Smith RN, Taylor SA, Massey JC. Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. Br Med J. 1970 Oct 17;4(5728):145-8.

[153]Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med. 1987 Mar 26;316(13):764-70.

[154]Cooke RG, Joffe RT, Levitt AJ. T3 augmentation of antidepressant treatment in T4-replaced thyroid patients. J Clin Psychiatry. 1992 Jan;53(1):16-8.

[155]Rack SK, Makela EH. Hypothyroidism and depression: a therapeutic challenge. Ann Pharmacother.2000 Oct;34(10):1142-5.

[156]Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. J Affect Disord. 2006 Feb 14; [Epub ahead of print]

[157]Cooper-Kazaz R, Apter JT, Cohen R, Karagichev L, Muhammed-Moussa S, Grupper D, Drori T, Newman ME, Sackeim HA, Glaser B, Lerer B. Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry. 2007 Jun;64(6):679-88.

[158]Schwarcz G, Halaris A, Baxter L, Escobar J, Thompson M, Young M. Normal thyroid function in desipramine nonresponders converted to responders by the addition of L-triiodothyronine. Am J Psychiatry. 1984 Dec;141(12):1614-6.

[159]Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. J Affect Disord. 2006 Feb 14; [Epub ahead of print]

[160]Posternak M, Novak S, Stern R, Hennessey J, Joffe R, Prange A, Zimmerman M. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. Int J Neuropsychopharmacol. 2007 Mar 13:1-11

[161]Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med. 1999 Feb 11;340(6):424-9.

[162]Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab. 2003 Oct;88(10):4543-50.

[163]Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab. 2003 Oct;88(10):4551-5.

[164]Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA. 2003 Dec 10;290(22):2952-8.

[165]Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sanger E, Engel G, Hamm AO, Nauck M, Meng W. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol (Oxf). 2004 Jun;60(6):750-7.

[166]Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial

comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med. 2005 Mar 15;142(6):412-24.

[167]Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab. 2005 May;90(5):2666-74.

[168]Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF. Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract. 2005 Jul-Aug;11(4):223-33.

[169]Slawik M, Klawitter B, Meiser E, Schories M, Zwermann O, Borm K, Peper M, Lubrich B, Hug MJ, Nauck M, Olschewski M, Beuschlein F, Reincke M. Thyroid hormone replacement for central hypothyroidism: a randomized controlled trial comparing two doses of thyroxine (T4) with a combination of T4 and triiodothyronine. J Clin Endocrinol Metab. 2007 Nov;92(11):4115-22.