"Sub-laboratory" Hypothyroidism and the Empirical use of Armour® Thyroid

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Abstract

Evidence is presented that many people have hypothyroidism undetected by conventional laboratory thyroid-function tests, and cases are reported to support the empirical use of Armour® thyroid. Clinical evaluation can identify individuals with "sub-laboratory" hypothyroidism who are likely to benefit from thyroid-replacement therapy. In a significant proportion of cases, treatment with thyroid hormone has resulted in marked improvement in chronic symptoms that had failed to respond to a wide array of conventional and "alternative" treatments. In some cases, treatment with desiccated thyroid has produced better clinical results than levothyroxine. Research supporting the existence of sub-laboratory hypothyroidism is reviewed, and the author's clinical approach to the diagnosis and treatment of this condition is described.
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Introduction

Hypothyroidism is a common disorder in which the amount of hormone secreted by the thyroid gland is inadequate to meet the body's needs. As the main function of thyroid hormone is to stimulate metabolism, hypothyroidism results in a slower rate of metabolism and its associated manifestations. The symptoms of hypothyroidism can vary considerably from person to person. Table 1 includes a comprehensive list of symptoms, while Table 2 lists signs of hypothyroidism seen on physical exam.

If not diagnosed and treated, hypothyroidism can in some cases become severely debilitating or even fatal. Appropriate hormone-replacement therapy, on the other hand, will ameliorate the clinical manifestations of the disease, allowing most affected individuals to have a normal or close-to-normal quality of life.

In cases of overt hypothyroidism, the serum concentrations of total and free thyroxine (T4) and triiodothyronine (T3) are below normal, and the concentration of thyroid-stimulating hormone (TSH) is increased. The magnitude of the increase in TSH level is roughly proportional to the severity of the hypothyroidism. TSH is released from the pituitary gland, which helps regulate the activity of the thyroid gland through a feedback mechanism. The pituitary secretes more TSH in response to a hypothyroid state, less TSH in the euthyroid state, and even less in the face of hyperthyroidism. The secretion of TSH from the pituitary gland is further regulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH), which helps control the set-point of the pituitary.

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Table 1. *Common Symptoms Associated with Hypothyroidism*

General
- Fatigue
- Weakness
- Constipation
- Weight gain
- Sluggishness
- Cold extremities, intolerance to cold
- Edema
- Muscle aches
- Headaches
- Decreased libido

Psychiatric
- Depression
- Poor mental concentration
- Memory loss

Miscellaneous
- Hoarseness
- Dry, rough skin
- Coarse, dry, or thinning hair

Medical texts and review articles are almost unanimous in recommending levothyroxine (T4) as the only appropriate treatment for hypothyroidism.[1,2] These sources acknowledge the human thyroid gland secretes both T4 and T3, in a ratio of approximately 9 to 1. Their reason for recommending only T4 is that peripheral (i.e., extrathyroidal) tissues are capable of converting T4, which is really a prohormone, into its biologically active form, T3. Thus, administration of T4 provides a constant reservoir from which the body can meet its needs for T3. Most authorities discourage the use of T3-containing preparations for thyroid-replacement therapy. They point out that T3 is rapidly absorbed and has a relatively short half-life, resulting in wide between-dose fluctuations in serum T3 levels that are not physiologic. Thus, it is argued, a person taking a T3-containing preparation might have a supraphysiological serum T3 concentration for several hours after each dose, followed by an excessive decline in T3 level. The fact that commercially available preparations (such as desiccated thyroid and synthetic T4/T3 combinations) contain 20-percent T3 (compared with 10 percent in human thyroid secretions) further exacerbates the problem, according to the prevailing point of view.

Another View of Hypothyroidism

The conventional approach to diagnosing and treating hypothyroidism has been of benefit to millions of patients. However, in the experience of this author and a number of other practitioners (perhaps between several hundred and a few thousand in the United States), reliance solely on this approach causes an unusually large number of patients to be misdiagnosed and deprived of effective treatment.

With regard to diagnosis, it appears many people have clinical hypothyroidism that is not detectable by standard laboratory tests. This syndrome of hypothyroidism with normal blood tests might reasonably be called "sub-laboratory hypothyroidism." In addition to the apparent lack of sensitivity of current diagnostic methods, the

In milder cases of hypothyroidism, serum levels of T4 and T3 are often normal (although typically in the low-normal range), while the TSH level is above normal. This pattern of laboratory values, which is frequently called "subclinical hypothyroidism," suggests the thyroid gland, while being stimulated to work harder, is only just keeping up with the body's needs. Most physicians recommend thyroid-replacement therapy for patients with grossly elevated TSH levels (suggesting more pronounced hypothyroidism); whereas, the risk/benefit ratio in treating patients with only slightly increased TSH values has been a topic of considerable debate. In the opinion of most authorities, a normal TSH level essentially rules out hypothyroidism.

conventional treatment for hypothyroidism (both the laboratory-documented and sub-laboratory types) can yield less-than-ideal results. This author has observed a significant number of hypothyroid patients treated with appropriate doses of levothyroxine fail to experience adequate symptom relief, and some patients do not improve at all. Many, although not all, of these levothyroxine nonresponders fare significantly better with Armour® thyroid (a brand of desiccated thyroid derived from porcine thyroid gland).

During 19 years of clinical practice, this author has recommended a therapeutic trial of thyroid hormone for approximately 1,500 patients who displayed signs and symptoms suggestive of hypothyroidism (often accompanied by a low basal axillary temperature; e.g., 97.4 degrees F or lower), but who had normal laboratory tests for thyroid function. The laboratory assessment usually consisted of measurements of TSH plus either free T4 or free-T4 index. In some cases, free- or total-T3 levels were also measured.

The empirical use of thyroid hormone was based initially on the work of Broda Barnes, MD, who pioneered and popularized the use of the basal body temperature test (which he considered a surrogate for the basal metabolic rate) as a tool for diagnosing hypothyroidism.[3]

With additional clinical experience, this author came to rely more on medical history and physical examination, and less on body temperature, for assessing thyroid function and monitoring treatment. In approximately 60 percent of patients so treated, one or more chronic symptoms improved to the extent that both doctor and patient considered the treatment worth continuing. Many patients reported dramatic relief of symptoms that had plagued them for years and interfered with their quality of life and ability to function – symptoms that frequently had failed to respond to a wide array of conventional and unconventional treatments. In the other patients the treatment was discontinued, either because it was not beneficial or because it caused side effects such as nervousness, insomnia, rapid pulse, or (rarely)

Table 2. *Signs of Hypothyroidism Noted on Physical Exam*

Myxedema – a non-pitting edema due to the deposition of mucin in the skin around the ankles, below the eyes, and elsewhere

Carotenodermia – an accumulation of beta-carotene in the skin because of impaired conversion of beta-carotene to vitamin A

Follicular hyperkeratosis – presumably due to vitamin A deficiency

Dry rough skin

Dry, coarse, thinning hair

Pallor

Observation of delayed return on the Achilles' tendon reflex (ATR) test

tightness in the chest. Side effects requiring discontinuation of treatment occurred in approximately 15 percent of patients who underwent a therapeutic trial of thyroid hormone.

Most patients were treated with Armour thyroid; some received levothyroxine (Synthroid®, Levoxyl®); and a few were treated with a combination of levothyroxine and T3 (Euthroid®). In addition, approximately 50 patients were seen over a 19-year period who had been diagnosed elsewhere with hypothyroidism and who had remained symptomatic despite appropriate replacement therapy with levothyroxine. When these patients were switched to Armour thyroid, marked improvement occurred, often within 24-48 hours. Occasionally, the opposite was observed: patients who failed to respond to Armour thyroid did well either with levothyroxine or levothyroxine-plus-T3.

Table 3. *Conditions Associated with Hypothyroidism*

Cardiovascular
- Hypertension
- Angina pectoris
- Atherosclerosis
- Hypercholesterolemia
- Hyperhomocysteinemia

Gynecological/Endocrine
- Menstrual irregularities (amenorrhea, oligomenorrhea, menorrhagia)
- Infertility
- Premenstrual syndrome
- Fibrocystic breast disease
- Polycystic ovary syndrome
- Reactive hypoglycemia

Dermatological
- Psoriasis
- Urticaria

Ear, nose, and throat
- Vasomotor rhinitis
- Allergic rhinitis

The Broad-Ranging Potential of Thyroid Hormone

Many disorders may respond to thyroid hormone (Table 3). Several conditions associated with hypothyroidism are discussed in detail below, some illustrated with cases from this author's practice. These disorders were selected for discussion because either the association with hypothyroidism is not generally appreciated or because there are data indicating the TSH level is sometimes normal in hypothyroid patients with those particular ailments. In cases in which TSH was normal, the diagnosis was established by means of a TRH-stimulation test. This test involves the intravenous injection of the hypothalamic hormone TRH, followed by serial measurements of the serum TSH concentration. An abnormally large increase in TSH level following injection of TRH indicates hypothyroidism. Although the TRH-stimulation test is considered more sensitive than a TSH measurement for identifying hypothyroidism, it is rarely used in clinical practice because it is expensive, time consuming, and invasive, and the mainstream medical community believes measuring TSH is sufficient.

Case 1.

A 57-year-old woman presented with a lifelong history of depression. Her parents had been killed in the Holocaust and she had lived in orphanages during her early years. During 38 years in the United States she had worked with at least eight physicians, psychologists, and counselors. Although she had gradually learned to deal with issues related to post-traumatic stress syndrome, her depression had not improved over the years. She also experienced hot and cold sensations, which had occurred repeatedly for many years. Physical examination was unremarkable and the free-T4 index was 7.2 mcg/dL (normal range, 5-12 mcg/dL). Her basal axillary temperature was consistently below 96.4 degrees F.

She was advised to take 30 mg Armour thyroid daily for 10 days and then increase to 60 mg daily. Clear improvement was evident within two weeks, and at her three-month follow-up visit she reported a "remarkable improvement" in depression and energy. The hot and cold sensations also disappeared. She was seen at least annually for the next 10 years, during which time the improvement was maintained with a dose of 60 mg Armour thyroid daily, with an increase to 90 mg daily during the winter.

Depression

Depression is a common manifestation of hypothyroidism, often ameliorated after correction of hypothyroidism (Case 1). In a study of 250 consecutive patients referred to a psychiatric hospital for evaluation of depression, anergia, or both, 20 (8%) were found to have some degree of hypothyroidism.[4] Of those, half had a normal TSH level, and their hypothyroidism would not have been detected without the TRH-stimulation test. The results of this study demonstrate sub-laboratory hypothyroidism is present in some patients with depression. As there is no reason to assume the TRH-stimulation test identifies all cases of hypothyroidism, the prevalence of sub-laboratory hypothyroidism among patients with depression may actually be higher than the four percent suggested by this study. In the experience of this author, the prevalence is closer to 50 percent, which may be explained in part by selection bias (many patients come to the clinic specifically seeking a trial of thyroid hormone).

Chronic Fatigue

Fine-needle aspiration of the thyroid gland was performed on 219 patients complaining of chronic fatigue of more than one year's duration.[5] Eighty-seven patients (40%) were found to have definite histological evidence of chronic lymphocytic (Hashimoto's) thyroiditis. In those patients TSH levels were widely scattered (range, < 0.9 to > 15 mU/L); one-third had a TSH level of less than 3.0 mU/L and 58.6 percent had a level of less than 5.0 mU/L. The clinical response to levothyroxine therapy was "equally favorable" (details not provided) among patients with lymphocytic thyroiditis, irrespective of the initial TSH level. Thyroid autoantibodies (peroxidase, thyroglobulin, or both) were present in only half of those with definite histological evidence of lymphocytic thyroiditis.[6] These results indicate chronic lymphocytic thyroiditis is common among patients with chronic fatigue, that measuring thyroid autoantibodies in the blood may fail to detect thyroiditis in half of these individuals, and that treatment with thyroid hormone can relieve fatigue in patients with chronic lymphocytic thyroiditis, whether or not the TSH level is elevated.

Reactive Hypoglycemia/ Dysinsulinism

Barnes reported that the common, though controversial, disorder of blood-glucose regulation referred to as "reactive hypoglycemia," "hypoglycemia," or "dysinsulinism" often improves after empirical treatment with desiccated thyroid.[7] Case 2 is an extreme example of the many patients seen by this author in whom treatment with thyroid hormone improved the symptoms of reactive hypoglycemia.

Case 2.

A 23-year-old woman presented with the chief complaint of fainting when she did not eat every 2-3 hours. She sought medical treatment after being stopped by a policeman for speeding, while racing to the nearest store to purchase food. She collapsed while waiting for the ticket to be issued, and had to pay not only for speeding, but also for the ambulance and hospital evaluation. The review of systems was positive for intolerance to the cold. Physical examination revealed a delayed return on the Achilles' tendon reflex (ATR) test and mild dryness and coarseness of the skin. Thyroid-function tests were normal. Based on her history, a presumptive diagnosis of reactive hypoglycemia was made. The patient was treated with 30 mg Armour thyroid daily and within two weeks she was able to fast for up to eight hours without experiencing any significant problems.

Although thyroid hormone has not been systematically studied as a treatment for hypoglycemia, circumstantial evidence suggests it is involved in glucose homeostasis. In a study of healthy volunteers made hypoglycemic by administration of insulin, the mean serum concentration

of T3 increased significantly within 45 minutes after the insulin injection.[8] Other research has shown thyroid hormone stimulates the synthesis of glucose through the process of gluconeogenesis.[9,10] Taken together, these findings suggest that thyroid hormone plays a role in the metabolic adaptation to hypoglycemia.

Ear, Nose, and Throat Disorders

Forman observed in 1934 that vasomotor rhinitis and, to a lesser extent, allergic rhinitis are often associated with clinical evidence of hypothyroidism, and that treatment with thyroid hormone relieves the symptoms in some cases.[11] He commented that the nasal mucosa of patients with vasomotor rhinitis frequently has a myxedematous appearance. In 1956, Hollender reported on 126 patients seen in his otolaryngology practice who had a low basal metabolic rate and were treated with levothyroxine. The response rates were as follows: vasomotor rhinitis (68%), postnasal discharge (68%), hearing loss and/or tinnitus (69%), lymphoid hyperplasia of the pharynx (51%), and headache (57%).[12] Others have also reported treatment with thyroid hormone can ameliorate various otolaryngological problems;[13,14] however, some investigators have failed to observe any benefit from this treatment.[15] Withers reported in 1974 that treatment with thyroid hormone frequently enhances the response to allergy-desensitization therapy.[16]

Menstrual Disorders and Infertility

Conventional texts mention infertility, menorrhagia, and oligomenorrhea as common disorders associated with hypothyroidism. There is evidence these problems also may occur in association with sub-laboratory hypothyroidism (Case 3). In a study of 150 women with longstanding (> 2 years) infertility due to anovulation or luteal insufficiency, 13.3 percent were found to have hypothyroidism.[17] In most of the cases of hypothyroidism, standard tests of thyroid function were normal, and the TRH-stimulation test was needed to establish the diagnosis. After treatment with levothyroxine (50 mcg daily), luteal function improved and two of

the 20 women became pregnant. This author knows of several women with longstanding infertility and normal thyroid-function tests who have become pregnant after treatment with desiccated thyroid.

In another study of three women with menstrual disorders (hypermenorrhea, polymenorrhea, and oligomenorrhea, respectively) the problem resolved in each case after treatment with thyroid hormone.[18] Each woman had a normal free-T4 index and TSH level, although TSH levels were near the upper limit of normal. In each case, a TRH-stimulation test was needed to demonstrate hypothyroidism.

Premenstrual Syndrome (PMS)

Of 54 women with PMS who were evaluated in one study, 94 percent had laboratory evidence of hypothyroidism, compared with none of 12 women without PMS.[19] Of those with hypothyroidism, 31 percent could be diagnosed by standard laboratory tests; whereas, in 69 percent an abnormal TRH-stimulation test was the only laboratory evidence of hypothyroidism. Administration of levothyroxine to 34 women with PMS resulted in complete relief of symptoms in all cases.

Fibrocystic Breast Disease

Nineteen women (ages 21-44) with mastalgia associated with fibrocystic breast disease were treated with 100 mcg levothyroxine daily for at least two months, and then as needed for cyclical recurrences of pain.[20] Nine patients (47%) experienced complete relief of pain and 73 percent obtained either complete or partial pain relief. In 11 of 19 women a softening of the breast nodules was observed. Only one woman had laboratory evidence of hypothyroidism prior to being treated; the others had normal levels of T4, T3, and TSH. Improvements in fibrocystic breast disease were reported in another series of 286 patients with "clinical or subclinical hypothyroidism" after treatment with desiccated thyroid.[21]

Case 3.

A 39-year-old woman presented with depression, hair loss, constipation, irritable bowel syndrome (manifesting as intestinal spasms), short-term memory loss, acne vulgaris, and irregular menstrual periods. Most of these symptoms had begun nine years previously, after the birth of her only child. At that time, her physician diagnosed her with hypothyroidism, and her symptoms were relieved by 120 mg Armour thyroid daily. Approximately 18 months before her first visit to this author's clinic, the patient changed physicians, was switched to levothyroxine, and promptly experienced a recurrence of symptoms. Despite this, her doctor reduced the levothyroxine dose progressively until her suppressed TSH level returned to the normal range. These dosage reductions, to a final level of 0.125 mg daily, resulted in a worsening of most of her symptoms, although she did experience a lessening of anxiety. Physical examination at the time of her first visit revealed a delayed ATR return bilaterally and a subtle myxedematous appearance around the ankles.

She was switched from levothyroxine to 90 mg Armour thyroid daily and rapidly experienced significant improvement in her symptoms, including normalization of her menstrual irregularities, with no exacerbation of anxiety. At her follow-up visit seven weeks later, the ATR return was almost normal and the ankle myxedema was reduced. She continued on 90 mg Armour thyroid daily and remained symptom-free for the next three years, after which she was lost to follow-up.

Polycystic Ovary Syndrome (PCOS)

Of 12 girls (ages 9-16) with severe and longstanding hypothyroidism, nine were diagnosed by pelvic ultrasound with PCOS. The cysts resolved rapidly after treatment with thyroid hormone.[22] In another study of hypothyroid patients with PCOS, administration of thyroid hormone was associated with normalization of ovulation.[23] These observations raise the possibility that sublaboratory hypothyroidism is a contributing factor in some cases of PCOS.

Dermatological Conditions

Barnes administered desiccated thyroid empirically to 214 patients with various skin conditions associated with a low basal body temperature.[24] One hundred ninety-eight patients (92.5%) showed marked improvement, 12 (5.6%) showed some improvement, and four (1.9%) did not improve. Conditions successfully treated included acne (n=88), boils (n=20), dry skin (n=14), eczema (n=57), ichthyosis (n=21), psoriasis (n=11), and ulcers (n=3). In those responding to therapy, treatment had to be continued for years, since symptoms recurred within a few months when treatment was discontinued.

Pelkowitz treated 200 patients with psoriasis using large doses of levothyroxine and an unspecified amount of "essential phospholipids."[25] The initial dose was 100 mcg daily, increased progressively to a maximum daily dose of 400-500 mcg. Propranolol was used as needed to control increases in blood pressure and heart rate resulting from supraphysiological doses of thyroid hormone. Typically, a marked improvement was seen after 5-6 weeks on the maximum dose of levothyroxine, although some patients responded to lower daily doses, such as 100-300 mcg. Patients with stable psoriasis and large plaques responded more slowly. After a few months of control, the dose of levothyroxine was reduced to a maintenance dose. Psoriatic arthritis also improved markedly with this treatment, even in patients whose arthritis had been refractory to other treatments. High-dose levothyroxine would not be considered a first-line treatment for psoriasis, because of its potential to cause adverse side effects and

the availability of other effective treatments. This author, however, has observed an improvement in psoriasis in several apparently hypothyroid patients during treatment with physiological doses of desiccated thyroid.

Thyroid hormone has also been found to be of value for individuals with chronic urticaria who have laboratory evidence of thyroid autoimmunity. In one study, 10 euthyroid patients with refractory urticaria were treated with levothyroxine.[26] The initial dose was 25-100 mcg daily, depending on the patient's age and medical condition; dosage was increased if a satisfactory response was not obtained. Of seven patients with elevated anti-thyroglobulin and/or anti-microsomal antibodies at baseline, all seven had a complete elimination of hives or marked improvement within four weeks. Two patients required an increase in the levothyroxine dose before a complete resolution was seen. In two others, already on levothyroxine therapy for hypothyroidism, an increase in the dose resulted in a resolution of the urticaria. The highest dose used was 250 mcg daily. The three patients without elevated anti-thyroid antibodies did not improve. Five patients had a recurrence after treatment was stopped, but the symptoms resolved again when treatment was restarted.

Asthma

Twelve "clinically euthyroid" patients (ages 20-38) with chronic asthma of more than five years' duration were treated with 40 mcg T3 daily for 60 days.[27] Seven patients reported obvious subjective improvement, three had no change, and two felt worse. The mean FEV_1 increased by 17.6 percent (p < 0.0025) and the maximal ventilatory volume increased by 13 percent (p < 0.025). The improvement in pulmonary function correlated well with subjective improvement and a reduction in use of bronchodilators. The marked improvement in asthma seen in Case 4 is supported by the findings of this study.

Other reports, however, suggest treatment with thyroid hormone can worsen asthma.[28] Because of these conflicting reports, lung function should be monitored in patients with asthma in whom treatment with thyroid hormone is initiated.

In asthmatics particular attention should also be given to the type of thyroid hormone preparation used. Commonly used levothyroxine products (e.g., Synthroid, Levothroid®, Levoxyl), contain artificial colorings (coal tar dyes) that have the potential to trigger asthma attacks.[29,30] Such coloring agents are present in all dosages of each of these products, with the exception of the 50-mcg dose of each.

Hypertension

Hypertension is relatively common among patients with laboratory evidence of hypothyroidism, occurring in 14.8 percent of patients in one study, compared with 5.5 percent of euthyroid controls.[31] In that study, adequate thyroid hormone-replacement therapy for an average of 15 months significantly reduced blood pressure; whereas, blood pressure did not improve in patients who received inadequate replacement therapy. Barnes observed that, among patients with hypertension who had some clinical evidence of hypothyroidism, treatment with desiccated thyroid alone normalized blood pressure in 80 percent of cases.[32] Menof reported a similar response rate in a group of 44 patients with essential hypertension treated with desiccated thyroid.[33] Dernellis et al administered levothyroxine to 30 patients with hypertension and laboratory evidence of hypothyroidism.[34] Fifteen of the 30 patients became normotensive, while the others showed only a small decrease in blood pressure. Failure to exhibit an adequate blood pressure response was associated with increased aortic stiffness, a concomitant of hypothyroidism. Because the increase in aortic stiffness was at least partially reversed during the treatment period, it is possible that some of the nonresponders would have had a greater reduction in blood pressure with a longer duration of treatment. Case 5 illustrates alleviation of borderline hypertension by treating for hypothyroidism.

Case 4.

A 34-year-old female presented with a history of fatigue, low energy, and sensitivity to cold throughout most of her life. Other symptoms included waves of nausea, with no relation to meals or time of day, difficulty with mental concentration, a general tendency to edema, waking up nightly at 2-4 a.m., with difficulty falling asleep again, and recurrent palpitations. When she did not eat every 2-3 hours she would develop a feeling of agitation, followed by severe fatigue. She had developed asthma during childhood, which began to increase in severity in her late teens, and which required frequent use of inhaled glucocorticoids and bronchodilators. She suffered from ocular allergies and perennial allergic rhinitis with seasonal exacerbations, and had been treated with various oral, intranasal, and ophthalmic antihistamines and glucocorticoids. She had an eight-year history of irregular menstrual periods, with cycles occurring approximately every 40-50 days. Numerous medications, nutritional supplements, and herbs had been presecribed for her various symptoms, but the results had been for the most part unsatisfactory.

Two weeks prior to her first visit she had undergone extensive testing by an endocrinologist, who had concluded that her endocrine system was normal. At that time her TSH level was 2.34 mU/L (normal, 0.3-5.50 mU/L), and the calculated free T4 was 2.24 units (normal, 1.53-3.85 units).

On physical examination her ATR return was delayed and her ankles and lower legs had an appearance of subtle myxedema. Her basal axillary temperature had been taken on six occasions prior to her first visit and ranged from 95.8-97.2 degrees F, with three of the six readings below 97.0 degrees F.

On the basis of her symptoms, physical findings, and sub-normal body temperature, a provisional diagnosis of hypothyroidism was made. She was advised to take 15 mg Armour thyroid daily, increasing to 30 mg daily after five days, with a further increase to be considered, depending on her response and tolerance to the treatment. During the first two weeks, she experienced dramatic improvement in all symptoms except cold extremities. Two months after the start of treatment, there was a recurrence of nausea and a decrease in energy level. The dose of Armour thyroid was increased to 60 mg daily and those symptoms again resolved. One month later, a further increase in dosage to 90 mg daily was necessary in order to control her fatigue and nausea.

Of note, the patient's asthma and rhinitis improved rapidly after the start of treatment, to the extent she rarely needed medication for either condition. At her most recent follow-up, ten months after the start of treatment, she rated the degree of improvement in her various symptoms as follows (0% indicates no improvement, 100% indicates complete relief): fatigue and low energy (90%), nausea (90%), difficulty concentrating (95%), irregular menses (99%), asthma (85%), ocular allergies (80%; only seasonal exacerbations remained), palpitations (99%), edema (45%), and waking at night (70%). Her need to eat every 2-3 hours had been extended to every 3-4 hours; however, there was no improvement in her sensitivity to the cold. No adverse side effects occurred and pulse rate and blood pressure did not change.

Case 5.

A 41-year-old woman had a history of borderline hypertension, hypercholesterolemia, a tendency to depression and fatigue, dry skin, diffuse hair loss on the head, and diffuse edema. Thyroid-function tests were normal. On physical examination, carotenodermia was noted on the feet and hands, follicular hyperkeratosis was present on the arms, and the ATR return was moderately delayed. Because she had a history of extreme sensitivity to various medications, she was started on 7.5 mg (one-eighth grain) Armour thyroid daily, equivalent to approximately four percent of the daily secretion from a normal thyroid gland. On that dose she experienced a rapid and marked improvement in mood, energy level, exercise tolerance, sluggishness, edema, and hair loss; dry skin was moderately improved. Blood pressure became normal within several days and remained normal thereafter. The dose was increased to 15 mg daily after 20 days, resulting in a sensation of excessive heat for two weeks, which then resolved. As there was no additional improvement at the higher dose, the original dose of 7.5 mg daily was resumed and she was doing well 14 months later, at the time of this writing. Her serum cholesterol level was 270 mg/dL prior to starting thyroid hormone; after 12 months of treatment, with no change in diet, the cholesterol level was 223 mg/dL.

Cardiovascular Disease

Longstanding hypothyroidism is associated with an increased risk of cardiovascular disease, presumably due in part to the hypercholesterolemia that often accompanies hypothyroidism. An elevated plasma concentration of homocysteine, which is an independent risk factor for cardiovascular disease, also occurs frequently in people with hypothyroidism. In one study, treatment of hypothyroid patients with levothyroxine reduced the mean plasma homocysteine concentration by 38 percent;[35] in another study, thyroid-replacement therapy reduced the median plasma homocysteine level by 44 percent.[36] As mentioned previously, hypothyroidism is associated with hypertension (another cardiac risk factor), and the correction of hypothyroidism often reduces elevated blood pressure.

While the relationship between subclinical or subtle hypothyroidism and cardiovascular disease has been debated extensively, recent evidence supports the concept that mild hypothyroidism increases the risk of heart disease. In a population-based, cross-sectional study of 1,149 women (mean age 69) participating in the Rotterdam Study, subclinical hypothyroidism (defined as a TSH level greater than 4.0 mU/L, with a normal serum free-T4 concentration) was associated with an increased age-adjusted risk of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1-2.6]) and myocardial infarction (odds ratio, 2.3 [95% CI, 1.3-4.0]).[37] Further adjustment for body mass index, cholesterol level, blood pressure, and smoking status did not affect the results.

Anecdotal evidence suggests that the cardiovascular benefits of thyroid hormone also extend to those with sub-laboratory hypothyroidism. In a study of 1,569 patients treated empirically with desiccated thyroid and followed for a total of 8,824 patient-years, Barnes observed only four new cases of coronary heart disease, although 72 new cases would have been expected in a similar group of patients, according to data from the Framingham Study.[38]

Angina pectoris can result from hypothyroidism and sometimes responds to thyroid hormone,[39] as in Case 6. However, treatment with thyroid hormone may also exacerbate pre-existing angina, or trigger its appearance in patients with established coronary heart disease (CHD).[40] Furthermore, the use of excessive doses of thyroid hormone can trigger atrial fibrillation in susceptible individuals, particularly in the elderly. For

Case 6.

A 57-year-old woman complained of fatigue, nonexertional chest pain, and palpitations, beginning nine years previously. At that time another physician treated her with 0.1 mg levothyroxine daily (it was not clear whether thyroid-function tests were performed), which resulted in an improvement in her symptoms. Seven years later (two years prior to her first visit with this author), she was taken off levothyroxine, which resulted in a return of her previous symptoms. She underwent a stress thallium test, which revealed coronary artery disease with 80-90 percent probability, and her chest pain was diagnosed as angina pectoris. Treatment with a calcium-channel blocker (diltiazem) reduced the frequency of anginal episodes. The addition of coenzyme Q_{10} and L-carnitine three months prior to her first visit resulted in some additional improvement, but her symptoms persisted. Past medical history was significant for a partial thyroidectomy at age 14. Recent thyroid-function tests were normal.

Based on her history, a therapeutic trial was begun with 15 mg Armour thyroid daily, increasing to 30 mg daily after two weeks. The patient was advised to reduce the dose or to discontinue treatment if the angina became worse. Instead, there was a rapid improvement in symptoms and at her follow-up visit two months later she reported her angina, fatigue, and palpitations had disappeared. Although it was not possible to rule out a delayed response to coenzyme Q_{10} and L-carnitine as the reason for her improvement, the patient was convinced the benefit was attributable primarily to the desiccated thyroid. She did experience a recurrence of angina when she tried to discontinue diltiazem; therefore, she was maintained on diltiazem plus 30 mg Armour thyroid daily and continued to do well the next two years, after which she was lost to follow-up.

Case 7.

A 34-year-old male complained of a two-year history of greatly diminished libido and intolerance to cold. Physical examination and thyroid-function tests were normal, but basal axillary temperatures averaged 95.8 degrees F (two degrees below normal). A therapeutic trial was instituted of 30 mg Armour thyroid daily, increasing to 60 mg daily after 10 days. Both symptoms improved moderately on the lower dose and markedly within several days after increasing the dose. These improvements persisted with continued treatment.

these reasons, administration of thyroid hormone to people with CHD should be undertaken with extreme caution, starting with low doses. In some cases, full correction of hypothyroidism is not possible, as the diseased cardiovascular system is not able to tolerate the increased metabolic demand created by the administration of thyroid hormone.

On the other hand, Wren administered desiccated thyroid for five years to 132 patients with symptomatic atherosclerosis, of whom the great majority had no laboratory evidence of hypothyroidism.[41] The initial dose was 15-30 mg daily, which was increased gradually over a six-month period, based on clinical judgment and individual tolerance. In the majority of cases, the final daily dose was 120 or 180 mg. Of 41 patients who had angina at the start of the study, 29 (71%) reported benefit, such as increased exercise tolerance and decreased frequency and severity of attacks. No patient reported increased angina as a result of thyroid therapy, and the mortality rate was lower than the expected rate for a similar population, according to actuarial tables.

Resistance from the Medical Mainstream

The reaction of the conventional medical community to the empirical use of thyroid hormone has ranged from skepticism to derision and outright hostility. One editorial described this approach as "bizarre" and talked about practitioners who "dish out" (rather than prescribe) thyroid hormone.[42] A letter printed in a major medical journal referred to the "notorious work of Barnes."[43] Others cite the "indiscriminate" use of thyroid hormone by some practitioners, often in excessive doses, to treat obesity or as a general tonic for tiredness. Several physicians have been accused by state medical boards of practicing substandard medicine, merely because they diagnosed hypothyroidism on clinical grounds or prescribed desiccated thyroid instead of levothyroxine.

The emotional negativity that surrounds this controversy is reminiscent of academic medicine's resistance to the concept that supplementation with vitamins and minerals might have health benefits. Goodwin and Tangum noted in an editorial in *Archives of Internal Medicine* that the medical mainstream has a history of uncritically accepting reports of micronutrient toxicity, using an angry and scornful tone in discussions of micronutrient supplementation, and ignoring evidence of possible efficacy.[44] The debate surrounding micronutrient supplementation and that regarding the empirical use of thyroid hormone share two characteristics that, according to Goodwin and Tangum, tend to raise the ire of the medical establishment: (1) the ideas originated primarily from outside of the academic medical community, and (2) proponents often bypassed conventional medical channels and took their ideas directly to the public. Whatever the reason, it appears that conventional medicine has not made a serious attempt to evaluate the evidence regarding the empirical use of thyroid hormone, and that its wholesale dismissal of the concept represents, at least in part, a biased attitude.

A typical response to the anecdotal evidence is, "Of course, tired people are going to feel better if you crank up their metabolism with thyroid hormone; but, that doesn't mean they are hypothyroid." That argument overlooks two important points. First, tired people who are not clinically hypothyroid often feel worse, not better, when they take thyroid hormone. Second, a very specific set of symptoms, not just fatigue or depression, usually improves when clinical hypothyroidism is treated.

The firmness with which most physicians assert that a normal TSH level proves euthyroidism is surprising, considering such a notion is based largely on circular reasoning. Ever since the discovery in 1892 that an extract of animal thyroid tissue could cure myxedema, hypothyroidism has been defined as a clinical syndrome that responds to treatment with thyroid hormone. While various laboratory tests have been developed that correlate with thyroid status, hypothyroidism remains a clinical syndrome, and no clear reason has emerged to redefine it in terms of its laboratory correlates.

That laboratory testing provides a less-than-perfect picture is suggested by the number of different thyroid-function tests that have been abandoned over the years after being hailed initially as the new diagnostic "gold standard." One of the earliest such tests, the basal metabolic rate, was potentially one of the best, since it measured the effect of thyroid hormone in the body. This test, however, was subject to error, because metabolic rate is influenced by the emotional state of the person being tested. Later came the protein-bound iodine test, then the serum T4 and free-T4 index, and most recently the TSH.

There is no question that TSH levels go up when thyroid hormone levels go down, and vice versa. There is also no question that extremely high and extremely low TSH values correlate well with hypothyroidism and hyperthyroidism, respectively. However, there is no *a priori* reason to assume a TSH value within or just outside the normal range always (or even usually) gives an exact indication of thyroid hormone status. Computer-software-like precision is probably more the exception than the rule in biological systems, particularly in systems that are subjected to the disruptive influences of emotional stress, environmental pollution, chronic illness, suboptimal nutrition, genetic polymorphisms, and autoantibodies.

It has been reported, for example, that in a series of 45 hypothyroid patients given thyroid-replacement therapy the TSH level remained persistently elevated in 44 percent of cases, even though the patients became clinically euthyroid, with normal serum T3 levels and normal or elevated T4 levels. Increasing the dose of levothyroxine to an amount that normalized the TSH level caused some of these patients to become clinically and biochemically hyperthyroid.[45] Since, as this study shows, TSH levels are sometimes "inappropriately" elevated, one might expect to find other instances in which the TSH level is "inappropriately" normal, as in cases of sub-laboratory hypothyroidism.

Potential Explanations for the Disconnect between Clinic and Laboratory

The coexistence of clinical hypothyroidism and normal laboratory values may be explainable in some cases by tissue resistance to thyroid hormone (TRTH). A syndrome of TRTH is known to occur, although it is believed to be rare (only 250 cases had been reported as of 1992).[46] TRTH is frequently characterized by an elevated free thyroid hormone concentration in a clinically euthyroid person, and is typically associated with a genetic mutation of one of the two thyroid hormone beta-receptors.[47] Almost every family with TRTH that has been studied has been found to have a different mutation. That observation suggests there may be other, as yet undiscovered and possibly more prevalent, mutations that result in subtle thyroid-receptor dysfunction. Mild TRTH could manifest as clinical hypothyroidism with low-normal, normal, or even high-normal serum concentrations of T4 and T3.

Hypothyroidism could also result from a defect in the conversion of T4 to its biologically active metabolite T3, a phenomenon reported sporadically in the medical literature.[48,49] A mild defect in this metabolic pathway might reduce serum T3 to a level that, while still within the population range of normal, is below normal for a particular individual.[50] The conversion of T4 to T3 depends on the action of deiodinase, an enzyme

that catalyzes the removal of one iodine atom from T4. Two such enzymes, deiodinases I and II, occur in humans. Common variants of the genes for each of these enzymes have been identified,[51,52] and some of these genes might code for the production of a functionally defective enzyme. One variant of the deiodinase II gene (Thr92Ala) occurs with an allele frequency of approximately 35 percent. Its presence is associated with insulin resistance,[51] which could be a consequence of reduced availability of T3 to the peripheral tissues.[53,54] A common variant of the beta-3-adrenergic-receptor gene (Trp64Arg), which plays a role in the transcription of deiodinase II, has also been identified and is associated with abdominal obesity, insulin resistance,[55] and a tendency to a lower metabolic rate.[56]

Whether the pituitary would recognize, and respond effectively to, small but clinically important changes in thyroid hormone status could depend on many factors. In cases of TRTH, the pituitary would presumably respond appropriately if the abnormal receptors in peripheral tissues were also present in the pituitary. Thyroid hormone receptors in the brain differ, however, from those in the periphery. While the receptors in the brain contain a beta-1 and a beta-2 subunit, the peripheral receptors contain only the beta-1 subunit.[57] Consequently, some mutations of the thyroid hormone receptor might be experienced differently in the periphery than in the pituitary, resulting in a distortion of the feedback mechanism. Genetic variations in the activity of deiodinase I or II might also be experienced differently in these respective tissues. In rats, for example, 50 percent of the T3 in the pituitary gland is derived from the deiodination of T4 within the gland itself; whereas, in other tissues only 20 percent of the T3 is derived from intracellular deiodination of T4.[58] In addition, deiodinase I does not appear to be present in pituitary tissues, so genetic variations in its activity would likely affect peripheral tissues differently than the pituitary. Another possible scenario that could disrupt the feedback mechanism is the inhibition of peripheral thyroid hormone receptors by various environmental toxins, metabolites, or byproducts of intestinal flora. Although these substances would cause manifestations of hy-

pothyroidism in the periphery, they might be incapable of crossing the blood-brain barrier. Consequently, the pituitary receptors would be preserved, and the pituitary would erroneously sense that the thyroid status in the periphery is normal.

Even if the pituitary accurately sensed hypothyroidism in the peripheral tissues, its capacity to mount a TSH response might vary from person to person. In the extreme, the failure of the pituitary to manufacture and release adequate amounts of TSH results in the syndrome known as secondary hypothyroidism. While secondary hypothyroidism is uncommon, it is likely that milder gradations of pituitary weakness occur more frequently. If they do occur, they would presumably manifest as clinical hypothyroidism with a normal TSH level.

The extent to which any of these suggested malfunctions in the feedback mechanism actually occur is unknown. All are plausible, however, and each could explain how a person might be both clinically hypothyroid and biochemically euthyroid.

The recent recommendation by the American Association of Clinical Endocrinologists[59] that the upper limit of normal for TSH be changed from 5.0 to 3.04 mU/L should, if nothing else, raise further questions about the validity of the TSH test. If this proposed change in the reference range is accepted into the mainstream, then more than four times as many people as before will be classified as hypothyroid (20.0% versus 4.64% of the population),[60] indicating the current TSH test may be missing more than 75 percent of cases of hypothyroidism. After having been promoted for years as a nearly perfect test for thyroid function, the acknowledgment that the TSH test may be misdiagnosing so many patients is not encouraging. To be sure, lowering the upper limit of normal would increase the sensitivity of the test. On the other hand, it would likely decrease its specificity, too, resulting in some euthyroid patients incorrectly being classified as hypothyroid. Furthermore, doctors who relied solely on the new TSH reference range would continue to overlook many cases of hypothyroidism. In this author's experience, as many as half of clinically hypothyroid patients have a TSH level below 3.04 mU/L.

Why the Preference for Armour Thyroid?

The reason Armour thyroid is the preferred preparation for thyroid-replacement therapy is simple: as Barnes pointed out it sometimes achieves better results for a wider range of symptoms than levothyroxine. Most patients who try both preparations find them to be equally effective. Of those who can tell a difference between the two, probably five or more patients prefer Armour thyroid for every one that prefers levothyroxine. In many cases, the therapeutic advantage of Armour thyroid is pronounced.

For example, one woman rated her energy level a 2 on a scale of 10 while taking levothyroxine. Within a few days after switching to an equivalent dose of Armour thyroid her energy level improved to 9 and remained at that level thereafter. As is the case with many other patients, this woman had taken Armour thyroid in the distant past. When her doctor retired, she was informed by her new physician that desiccated thyroid is obsolete, and she was switched to levothyroxine. Although this change was followed by an obvious deterioration in her health, she was unable to find a doctor who would switch her back. After having resigned herself to a lesser state of health, she was pleasantly surprised when the issue of Armour thyroid was raised during a visit to the author's clinic.

Levothyroxine consists solely of T4, whereas desiccated thyroid contains approximately 80 percent T4 and 20 percent T3, as well as other iodinated compounds (diiodotyrosine and monoiodotyrosine). Each compound present in desiccated thyroid is secreted by the human thyroid gland, although the concentration of T3 in porcine thyroid tissue (from which Armour thyroid is derived) is approximately twice that of human thyroid secretions. While peripheral tissues are capable of converting T4 to T3, the use of T4-only preparations might alter the normal ratio of T4 to T3 in these tissues, especially in people who have variants in one of the deiodinase genes or in the beta-3-adrenergic-receptor gene.

In a study of thyroidectomized rats treated with levothyroxine alone, no single dose was able to restore normal concentrations of TSH, T4, and T3 in plasma and normalize T4 and T3 levels in all 10 tissues and organs analyzed.[61] In most tissues, the dose of levothyroxine necessary to produce normal T3 levels resulted in supraphysiological T4 concentrations. Only the combined administration of levothyroxine and T3 (in proportions similar to those secreted by the normal rat thyroid) completely normalized all values in both plasma and tissues.[62]

It was observed in humans as early as 1958 that the combination of levothyroxine and T3 is more effective for some patients than levothyroxine alone.[63] In a more recent crossover study of 33 hypothyroid patients, substitution of 50 mcg of the usual dose of levothyroxine with an equivalent amount of T3 (12.5 mcg) significantly improved measures of mood and cognitive function, compared to treatment with levothyroxine alone.[64] While three other studies have failed to demonstrate any advantage of the levothyroxine/ T3 combination over levothyroxine alone,[65-67] the results of those studies do not negate the possibility that combination therapy is preferable for a subset of the hypothyroid population. Some patients in these negative studies (those with weak deiodination mechanisms) may have felt better with combination therapy, while others (those with robust deiodination mechanisms) may have felt worse while receiving additional T3. That possibility is consistent with this author's observation that occasional patients feel worse on desiccated thyroid than on levothyroxine. If that is the case, then averaging the results of those who improved and those who became worse would lead to the erroneous conclusion that combination therapy is of no benefit. Measuring the ratio of free T4 to free T3 in serum might aid the clinician in choosing the best treatment for each particular patient; however, that approach has not been systematically investigated.

Diiodotyrosine: The Third Thyroid Hormone?

While the issue of levothyroxine-plus-T3 versus levothyroxine-alone is far from settled, there may be advantages to using desiccated thyroid unrelated to its T3 content. Barnes observed some patients treated with the combination of levothyroxine and T3 continued to experience residual symptoms, particularly dry skin and edema. Both symptoms disappeared in 1-2 months when the treatment was changed to Armour thyroid.[68] That observation suggests a third active substance is secreted by the thyroid gland. The most likely candidate is diiodotyrosine. Although little is known about the function of this compound in humans, the widely held assumption that it is metabolically inert may be incorrect. In a study of guinea pigs, oral administration of diiodotyrosine prevented alterations in thyroid and pituitary function induced by ovariectomy.[69] Administration of diiodotyrosine also accelerated the metamorphosis of tadpoles[70] and enhanced the growth of Tetrahymena (a protozoan).[71] It would be premature to conclude diiodotyrosine has no function in humans, merely because its function has not yet been elucidated. For many decades it was believed the adrenal hormone dehydroepiandrosterone (DHEA) had no function; now it is recognized as having a wide range of therapeutic applications.[72]

Objections to the Use of Armour Thyroid

The main objections voiced in textbooks and editorials[1,73] regarding the use of desiccated thyroid are: (1) its potency varies from batch to batch, and (2) the use of T3-containing preparations causes the serum T3 concentration to rise to supraphysiological levels. Regarding between-batch variability, there may have been some problems with quality control a half-century or more ago, and in a 1980 study a number of generic versions of desiccated thyroid were still found to be unreliable in their potency. The amounts of T4 and T3 in Armour thyroid, on the other hand, were found to be constant.[74] Moreover, two-year old tablets of Armour thyroid contained similar amounts of T4 and T3 as did fresh tablets.

Three studies are typically cited to support the contention that T3-containing preparations should not be used. Smith et al reported a levothyroxine-plus-T3 product caused adverse side effects in 46 percent of patients; whereas, side effects occurred in only 10 percent of those receiving levothyroxine alone.[75] In that study, however, the combination product and the levothyroxine product differed substantially in potency. For the combination treatment, each 100 mcg of levothyroxine was replaced by 80 mcg of levothyroxine plus 20 mcg of T3. Considering 20 mcg of T3 is equivalent to 80 mcg of levothyroxine, the total hormone dose in the combination product was 60-percent greater than that in the levothyroxine preparation. Therefore, the high incidence of adverse side effects may not have been due to the T3, but to the higher total dose of thyroid hormones.

In the second study, by Surks et al, the administration of T3-containing preparations to hypothyroid patients caused the plasma T3 concentration to become markedly elevated for several hours after ingestion of the medication.[76] In most cases, however, the amount of T3 administered (50-75 mcg) was considerably greater than that contained in a typical dose of desiccated thyroid (9 mcg T3 per 60 mg),[77] and/or the total dose of thyroid hormones given was excessive (180 mcg of levothyroxine plus 45 mcg of T3). By contrast, in a patient given 60 mg of desiccated thyroid, the plasma T3 concentration increased from a hypothyroid level to a euthyroid level. Of two hypothyroid patients treated with 120 mg per day of desiccated thyroid, one showed a relatively constant plasma concentration of T3. In the other patient, the T3 level increased by a maximum of 80 percent, to the bottom of the range seen in hyperthyroid patients, and returned to the baseline value within 24 hours. In that patient, the pre-dose plasma T3 concentration was near the top of the normal range, suggesting that this patient may have been receiving too high a dose of desiccated thyroid.

Finally, Jackson and Cobb reported that the serum T3 concentration (measured 2-5 hours after a dose) was above normal in most patients receiving desiccated thyroid.[2] They concluded there is little use for desiccated thyroid in clinical medicine. Most of the patients (87.5%) in that study, however, were taking a relatively large dose of desiccated thyroid (120-180 mg daily). Moreover, 57.5 percent of the patients were not being treated for hypothyroidism, but rather to suppress the thyroid gland. Nearly half of the patients continued to have an elevated serum T3 concentration after they were switched to levothyroxine, even though the equivalent dose was reduced in 62.5 percent of patients. Thus, the elevated serum T3 concentrations found in this study can be explained in large part by the high doses used and by the selection of patients, the majority of whom were not hypothyroid. What this study does suggest is that desiccated thyroid should not be used for thyroid-suppression therapy.

Although the oral administration of T3 causes a transient increase in serum T3 concentrations, that fact does not appear to be of significance for hypothyroid patients receiving usual replacement doses of Armour thyroid. In this author's experience, reports of post-dose symptoms of hyperthyroidism are extremely rare, even among patients taking larger doses of desiccated thyroid. An occasional patient reports feeling better when he or she takes Armour thyroid in two divided doses daily. The nature of that improvement, however, is usually an increase in effectiveness, rather than a reduction in side effects. For patients taking relatively large amounts of desiccated thyroid (such as 120 mg daily or more), splitting the daily dose would obviate any potential concern about transient elevations of T3 levels. In practice, however, splitting the daily dose is rarely necessary.

A Clinical Approach to Sub-laboratory Hypothyroidism
Diagnosis

The decision to initiate a trial of thyroid hormone in a patient with normal laboratory tests is based on the clinical history, physical examination, and basal body temperature. Many symptoms of hypothyroidism are nonspecific and overlap considerably with those of reactive hypoglycemia, food allergy, hypoadrenalism, Candida-related

complex, iron deficiency, depression, and anxiety. In the typical patient complaining of fatigue or depression, the presence of additional symptoms such as cold extremities, dry skin, hair loss, decreased mental concentration, poor memory, constipation, or menstrual irregularities increases the index of suspicion for hypothyroidism. Many patients do not volunteer these symptoms; indeed, some are not even aware they have them. For this reason, patients should be carefully questioned about the various symptoms associated with hypothyroidism. One patient, for example, denied having fatigue, dry skin, and constipation. Further questioning revealed that she slept 10 hours per night to avoid suffering from fatigue, put skin cream on her legs every day to control dryness, and consumed bran and other high-fiber foods to prevent constipation.

Additional questioning might help distinguish hypothyroidism from other conditions. Fatigue caused by hypothyroidism is often, although not always, most pronounced in the morning. Fatigue or poor concentration caused by food allergy is frequently relieved by fasting and may become worse after meals. Fatigue caused by hypoadrenalism may be accompanied by hypotension, hypoglycemia, and poor tolerance to stress and exercise. The combination of fatigue, hair loss, emotional lability, poor mental concentration, and cold extremities may be caused by iron deficiency. Patients experiencing those symptoms should be asked about menstrual blood loss, use of non-steroidal anti-inflammatory drugs (which can cause gastrointestinal bleeding), dietary iron intake, and consumption of foods and beverages that inhibit iron absorption (such as coffee, tea, and soy); blood tests for iron status should also be considered. A family history of hypothyroidism increases the likelihood that a patient is hypothyroid.

On physical examination, hypothyroid patients often have a general appearance of pallor, with dry, coarse skin, particularly on the lower legs. A small amount of non-pitting edema is frequently present around the ankles or below the eyes. Follicular hyperkeratosis may be observed, particularly on the posterior aspect of the upper arms or the lateral portion of the thighs. A slight orange tinge to the skin (carotenodermia), especially on the palms of the hands and soles of the feet, may be apparent. If carotenodermia is not associated with excessive intake of carrots, other orange or yellow vegetables, or beta-carotene supplements, then hypothyroidism should be considered. In this author's experience, a delayed ATR return is the most reliable physical sign of hypothyroidism, and other investigators have made the same observation.[78] While a slow ATR return is strongly suggestive of hypothyroidism, a normal reflex does not necessarily rule it out. A delayed ATR return on one side but not the other may indicate a radiculopathy, rather than hypothyroidism. An absent ATR provides no information about thyroid status.

Patients with suspected hypothyroidism are usually asked to take their basal axillary temperature, which provides a crude estimate of basal metabolic rate. The test is performed by placing a thermometer deep in the axilla for 10 minutes, immediately upon awakening in the morning, before getting out of bed. Women should begin taking their temperature on the second day of menstruation, which is the time of the cycle that the temperature is the lowest. Typically the temperature is taken for five consecutive days and the results averaged. If the temperature is consistently below 97.0 degrees F, then taking it for three days is sufficient. The underarm temperature is preferred because taking it orally has a greater potential for error (due to chronic sinusitis or "mouth breathing"). Barnes recommended a trial of thyroid hormone if the average axillary temperature is below 97.8 degrees F. This author uses a lower cut-off point (97.4 degrees F) and views body temperature as only one data point in the context of the entire clinical picture. For example, some patients are prescribed thyroid hormone on the basis of symptoms and a delayed ATR return, even though their temperature is normal. In other cases the use of thyroid hormone is not considered appropriate, even though body temperature is below normal.

Treatment

In most cases, the initial daily dose of Armour thyroid is 30 mg (one-half grain) (equivalent to 50 mcg levothyroxine) in the morning. The patient is instructed to increase to 60 mg (1 grain) in the morning if, after 10 days on the lower dose, no marked improvement and no side effects have occurred. Further increases in the dose may be considered at six-week intervals. Patients with a history of sensitivity to medications, and those who are neurasthenic or have clinical evidence of hypoadrenalism, are often started on 15 mg (one-fourth grain) daily, increasing stepwise over a period of 4-6 weeks to a maximum of 60 mg daily, depending on response and tolerance. Patients are advised to watch for side effects, including anxiety, nervousness, insomnia, palpitations, rapid pulse, and pain or tightness in the chest. If any of these symptoms occur without some other obvious explanation (such as drinking too much coffee or experiencing a major stressful event), the dose should be reduced or the treatment stopped, and the practitioner should be contacted. Patients should be advised that side effects sometimes occur only on the day the treatment is started, or on the day the dose is increased. If adverse effects that appear on the first day are tolerable, then the patient may continue treatment to see if they diminish or disappear. If side effects do not decrease on the second day, or if they become more severe, then the dose should be reduced or the treatment stopped. It is not uncommon for side effects to appear gradually, so patients should be cautioned to remain vigilant.

A follow-up visit is scheduled approximately six weeks after the start of treatment. At that time changes in symptoms, pulse rate, blood pressure, appearance of the skin, and ATR return (if initially delayed) are assessed. If adequate symptom relief has been obtained with no adverse side effects, then the patient continues on the same dose and is reassessed at progressively increasing intervals (three months, six months, and annually thereafter). The dose should be reduced, however, if untoward physical findings such as tachycardia or a fine hand tremor are observed. A TSH level below the normal range, unless markedly suppressed, would not necessarily lead to a reduction in the dosage. If symptoms have not been relieved sufficiently, then an increase in the dose may be considered; however, this author tends not to increase the dose if a previously delayed ATR return has become normal, or if the pulse rate has increased by more than 10 beats per minute over the pretreatment rate. If there has been no clear benefit after 6-8 weeks on the maximum dose considered safe, then treatment is usually discontinued. Occasionally, however, patients take longer than two months to respond to treatment, so the treatment period may be extended, if desired. In some cases, an initially favorable response diminishes after a month or two of treatment. In most of these instances, an increase in the daily dose (typically by 30 mg) relieves the symptoms that have recurred, and further increases are usually unnecessary.

In the author's practice, the final daily dose of Armour thyroid has been 15 mg or less in approximately 10 percent of patients, 30 mg in 20-25 percent of patients, 60 mg in about 40 percent of patients, 90 mg in 15-20 percent of patients, and 120 mg or more in 10 percent of patients. Some patients appear to need a slightly higher dose during the winter than during the rest of the year.[79] The doses used by this author are somewhat lower than those used by Barnes and other proponents of the empirical use of thyroid hormone. This author uses a comprehensive approach to patient care that often includes a blood sugar-stabilizing diet, identification and avoidance of allergenic foods, treatment of *Candida albicans* when indicated, and supplementation with various nutritional supplements. It is possible that some of these treatments help "unblock" thyroid receptors, thereby allowing lower doses of thyroid hormone to be effective. These interventions are usually not begun at the same time as thyroid-replacement therapy, so as to avoid potential confusion about which treatment is working.

Most patients take the entire daily dose of desiccated thyroid in the morning. A few patients, however, find they feel better (either greater efficacy or prevention of side effects) if they take one-half or two-thirds of the daily dose in the morning and the remainder in the afternoon or

evening. Patients taking 120 mg or more daily are encouraged to consider splitting the dose, in order to avoid receiving a large amount of T3 at one time. Most patients taking larger doses, however, do not feel any different with once-a-day dosing than with split dosing.

In patients in whom severe hypothyroidism and hypoadrenalism coexist, the administration of thyroid hormone prior to correcting the adrenal insufficiency can trigger an "adrenal crisis." In a proposed milder version of this scenario, the inability of a clinically hypothyroid patient to tolerate even 15 mg desiccated thyroid daily suggests the possibility of subtle (sub-laboratory) hypoadrenalism. In such cases, thyroid hormone is discontinued and the patient is invited to try an extract of licorice root (for example, 6-10 drops of a 1:1 tincture twice daily). Licorice root (*Glycyrrhiza glabra*) delays the breakdown of adrenal hormones by the liver and was considered the treatment of choice for adrenal failure prior to the discovery of adrenal steroid hormones. In this author's experience, treatment with licorice root may either lead to a resolution of "hypothyroid" symptoms or (more commonly) allow for the resumption of low-dose thyroid hormone without the previous side effects. It should be noted that correcting hypothyroidism (when the treatment is tolerated) may ameliorate hypoadrenalism[80] and, conversely, correcting hypoadrenalism may ameliorate hypothyroidism.[81] Although the amount of licorice used is not likely to raise blood pressure or cause potassium depletion, patients taking licorice are advised to have their blood pressure monitored and to consume abundant amounts of potassium in their diet.

Discontinuing Therapy

Most patients with sub-laboratory hypothyroidism who have responded to treatment are urged to try weaning themselves from thyroid hormone after approximately 18 months of treatment. In one-half to two-thirds of patients, symptoms do not return when the treatment is stopped. In the other cases, symptoms recur as soon as the first day the dose is reduced to as long as several months after the treatment is stopped.

If symptoms do recur, then the treatment is resumed for at least another 18 months. Because it can take four weeks or more for the thyroid gland to compensate for the loss of exogenous hormone,[82] the weaning process is usually done over a four-week period: half the usual dose for two weeks, then one-fourth the usual dose for two weeks, then discontinue. In contrast to adrenal suppression that results from long-term glucocorticoid therapy, neither severe nor long-term suppression of thyroid-gland function occurs, even after treatment with thyroid hormone for many years.

Side Effects, Precautions, and Interactions

In addition to the common side effects described previously, treatment with thyroid hormone can trigger atrial fibrillation, particularly in the elderly and in people with heart disease. For this reason, an attempt should be made to use the lowest effective dose. Although treatment with thyroid hormone can increase the pulse rate, pre-existing tachycardia is not necessarily a contraindication to the use of thyroid hormone. In several patients with tachycardia (100-110 beats per minute) treatment with thyroid hormone was associated with a reduction in the pulse rate by 20-30 beats per minute. The need for thyroid hormone tends to decrease as people age; therefore, the dosage requirement should be re-evaluated periodically, particularly in the elderly. Thyroid hormone should not be discontinued during pregnancy since doing so may increase the risk of spontaneous abortion.[83] If anything, the requirement for thyroid hormone increases during pregnancy.[84]

While the use of excessive doses of thyroid hormone may promote the development of osteoporosis, treatment of hypothyroid patients with physiological doses of thyroid hormone does not appear to lead to accelerated osteoporosis or to an increased risk of fractures.[85] The effect of treating sub-laboratory hypothyroidism on bone density has not been investigated, however. Therefore, to be cautious, patients undergoing long-term treatment with thyroid hormone are strongly encouraged to supplement with

micronutrients that play a role in preserving bone density (e.g., calcium, magnesium, trace minerals, B vitamins, vitamin D, and vitamin K).[85]

Patients receiving DHEA will, on occasion, require a reduction in the dosage of thyroid hormone, possibly because of a potentiating effect of DHEA on the action of thyroid hormone, as has been reported in rats.[86] Patients receiving both hormones should, therefore, be monitored closely.

Conclusion

Hypothyroidism appears to be considerably more prevalent than is generally appreciated in the medical community. Reliance solely on the conventional diagnostic approach will overlook many people who could benefit from thyroid-replacement therapy. A careful history and physical examination, combined with the results of a basal body temperature test, can be used successfully to identify potential candidates for treatment. In some cases, desiccated thyroid produces better clinical results than levothyroxine. While thyroid hormone is generally well tolerated, it has the potential to cause significant side effects and should, therefore, be used with caution and respect. Properly administered, thyroid hormone can benefit millions of people for whom a diagnosis of hypothyroidism is currently not being considered.

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