HYPOTHYROIDISM IN THE ELDERLY

Department of Internal Medicine

Grand Rounds

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I. Alterations in Thyroid Physiology with Age

II. Increased Prevalence of Hypothyroidism in the Elderly

III. Causes of Hypothyroidism in the Elderly

IV. Natural History of Hypothyroidism

V. Significance of Subclinical Hypothyroidism

VI. Problems in the Clinical and Laboratory Diagnosis of Hypothyroidism in the Elderly

VII. Treatment of Hypothyroidism in the Elderly and Its Potential Adverse Effects

These rounds review the evidence that hypothyroidism, though not part of the aging process, is common in the elderly, has multiple causes, is insidious in its onset, is of potential importance even when subclinical, may be difficult to diagnose, and should be treated cautiously. The subject has been considered in several reviews (1-5).

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I. Alterations in Thyroid Physiology with Age

The basal metabolic rate (BMR), an early measure of thyroid status, was observed to decrease with age. Subsequently, the decrease in BMR with age was shown to be due to a decrease in lean body mass (6). The thyroid radioactive iodine uptake (RAIU) and the absolute thyroid iodine uptake (or the 24-h RAIU X plasma stable iodine concentration) both decrease progressively in subjects from age 50 to age 90 (7, 8). In agreement with this decline in absolute thyroid iodine uptake in the elderly, the daily production rates of T_4 and T_3 are reduced by about 25% and 33%, respectively (9). The changes in T_3 production are primarily due to a diminished availability of T_4 in peripheral tissues (9), but there is also a decrease in T_4 disposal rate (10). The decreased T_3 production with age is not due to the well recognized low T_3 syndrome associated with illness (reviewed in 11) since reverse T_3 (rT_3) levels do not increase (9). There is, however, an overall age-related reduction in the sequential monodeiodination of T_3 and rT_3 to the diiodothyronines (12).

The resin T_3 uptake, a marker of serum thyroid hormone binding, and the measured serum thyroid binding globulin (TBG) concentration do not change significantly with age (8, 13). Almost all studies have found that the serum T_4 levels do not change with age (8, 9, 13). In contrast serum T_3 levels do decrease in healthy subjects with advanced age (9, 13). However, this change is within the range considered normal for younger individuals.

The studies of basal serum TSH concentrations in elderly subjects have reported variable changes compared with young adults. These differences may reflect variable inclusion of subjects with subtle thyroid disease. In studies with careful screening to include only healthy individuals, there appears to be a small but significant increase in basal TSH with age (13, 14), and it is more consistently observed in women (14). The response of serum TSH to an injection of thyrotropin releasing hormone (TRH) is maintained in elderly women but diminished in older men (14, 15). Elderly men have been noted to have smaller circadian variations in TSH levels (16).

The sensitivity of the pituitary to changes in thyroid hormone concentrations has been assessed by the TSH response to TRH following a small decrease in serum thyroid hormones induced by iodide administration (17). Whereas young subjects uniformly demonstrate an augmented TSH response to TRH with such treatment, only half of the elderly subjects showed similar changes in TSH response (17). These authors suggested that a normal plasma TSH level may not always be a reliable index of the euthyroid state in aged patients.

In summary (Table I), the alterations in thyroid physiology with age are primarily a decreased degradation of thyroid hormones with maintenance of normal serum thyroid hormone concentrations. The reduced production of thyroid hormones with age should not be regarded as hypothyroidism.

Table I. Alterations in Thyroid Physiology in the Elderly

BMR	Normal
RAIU	Decreased
T_4 and T_3 Production	Decreased
T_4 and T_3 Concentration	Normal
T_4 and T_3 Degradation	Decreased
TSH Concentrations	Normal to Increased
TSH Response to TRH	Decreased in Men
TSH Sensitivity to Thyroid Hormones	Decreased

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II. Increased Prevalence of Hypothyroidism in the Elderly

Since hypothyroidism is uncommonly secondary (i.e., due to abnormalities of the hypothalamic-pituitary system), only primary hypothyroidism (i.e., due to abnormalities of the thyroid) will be considered in these rounds. By definition, primary hypothyroidism should be associated with activation of the hypothalamic-pituitary system in an attempt to restore thyroid hormone levels to normal. Although the subtle degrees of mild hypothyroidism will be considered below, for the purposes of this section, an elevation of the basal serum TSH will be considered a minimal marker of primary hypothyroidism while recognizing that rare conditions such as TSH-producing tumors may elevate TSH levels in the absence of primary hypothyroidism.

Studies of the frequency of hypothyroidism have variable sensitivity for its detection depending upon whether only serum thyroid hormones are measured or whether TSH levels are also assessed. Since the range of serum thyroxine concentrations among the normal population is broad and encompasses more than a 2.5-fold range from the lower to the upper limit (e.g., 4.5-12.5 µg/dl), a given individual might have a 50% fall in his or her usual level of serum thyroxine and still be within the "normal range." Thus studies reporting only overt clinical hypothyroidism as assessed by the usual symptoms and physical findings accompanied by a decreased free thyroxine index will detect fewer hypothyroid individuals than those in which all subjects have serum TSH determinations.

Even studies in which TSH is used for screening may have limited value for determining prevalence of hypothyroidism in the population if only hospitalized subjects are included (18-21). These studies of primarily older patients have reported a combined prevalence of overt and mild hypothyroidism ranging from 4.4-12.1%. Interestingly, in the studies of inpatients with hypothyroidism men were affected as often as women (18, 20, 21).

There are three reports of relatively unselected healthy populations in which all individuals were screened by serum TSH levels (Table II) (22-24). One is from an English community, and two are from this country. The first study is not limited to only individuals over age 60 as are the second and third but includes a representative sampling of adults age 18 and older. In each of these three series only significant TSH elevations were considered such that the mean T_4 levels in the groups with elevated TSH were less than those with normal TSH values. The proportion of those with elevated TSH levels who had overt hypothyroidism is not clearly stated in all series. In the first series (22), 5% of the women with elevated TSH are said to have had overt clinical hypothyroidism. In addition 1.9% of all the women in the survey were noted to have had previously diagnosed hypothyroidism. The second study excluded those subjects with known hypothyroidism (23), but noted that 3.2% of the sample gave a history of hypothyroidism on replacement thyroxine. A subsequent recent report (25) of the Framingham original cohort considers prevalence of thyroid hormone usage in this older population and concludes that if individuals with previously recognized confirmed hypothyroidism are added to those with unsuspected TSH elevation (series 3, Table II) the total prevalence of thyroid failure over age 60 increases to 8.5% in this population (11.7% of women and 3.5% of men).

Table II. Prevalence of Significantly Increased Levels of Serum TSH in Three Population Studies

Series	Group (Ref. No.)	Women	Men	Total
1	English Community (22)	7.5	2.8	5.0%
2	Boston Senior Citizens (23)	7.1	2.7	5.9
3	Framingham Cohort (24)	5.9	2.4	4.4

Additional subjects in series 2 and 3 of Table II were identified as having mild elevations in TSH levels (i.e., not greater than twice the upper limit of normal or >10 μU/ml, the criteria used in Table II). The percentage of individuals with these slight elevations in TSH were 14.4 and 5.9 in these two series respectively. The significance of the slight TSH elevations is not known.

The relationship of age to the prevalence of an increased serum TSH is shown in Table III from the survey of an English community (22).

Table III. Percent of Each Age Group with Elevated Serum TSH Concentrations in a Population Study

Age Group	18-24	25-34	35-44	45-54	55-64	65+
Women	4.0	5.7	4.1	9.6	10.0	10.7
Men	2.8	3.5	1.6	2.1	1.9	5.9

(from Ref. 22)

It thus appears that the frequency of an increased TSH approximately doubles in comparing older subjects to younger individuals. The increase in TSH in women with increased age could be accounted for almost entirely by the association of antithyroid antibodies (see below). The significance of the elevated TSH levels in series 2 and 3 of Table II is clear from the association with a diminished serum total T_4 or free T_4 index, present in 45 and 39%, respectively. However, viewed from a different perspective, these data indicate that less than half of mildly hypothyroid individuals would have been recognized by thyroid hormone measurements alone.

Even when hypothyroidism has been diagnosed previously, there is a high frequency of inadequate treatment in a randomly sampled older population (25). As mentioned above a recent report of thyroid hormone usage in the Framingham cohort found that 10% of women were taking thyroid hormone, 81% of them for appropriate reasons. Yet 37% of those who were definitely hypothyroid had a clearly elevated serum TSH (>10 μU/ml) despite thyroid therapy (25).

In summary, hypothyroidism is more common in the elderly, with an overall prevalence of overt (including previously recognized) and mild disease in about 6 to 10% of women and 2 to 3% of men.

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III. Causes of Hypothyroidism in the Elderly

Hypothyroidism in the elderly is most commonly due to autoimmune thyroiditis (1). However, hypothyroidism can also occur as a late consequence of treated Graves' disease, following head and neck surgery and/or radiation, and as a result of environmental factors or drugs either inducing thyroid abnormalities directly or worsening underlying autoimmune thyroiditis.

A. Hypothyroidism as a Late Consequence of Treated Graves' Disease

Hypothyroidism may occur following treatment of Graves' disease with any of the three available modes of therapy: radioactive iodine, subtotal thyroidectomy, or administration of thionamide drugs while awaiting remission. Since hyperthyroidism is common, occurring in about 2% of women (22), this represents a large number of potentially hypothyroid individuals.

Although some physicians routinely employ high doses of ^{131}I (such as 15 mCi) to treat Graves' disease trying to render patients hypothyroid immediately, many centers administer moderate doses (e.g. 8-10 mCi) with the hope that most patients will have control of thyrotoxicosis and without the goal of uniform early hypothyroidism. Although hypothyroidism in the first year is reduced with these more moderate regimens of ^{131}I, late hypothyroidism develops at a rate of 2-5% per year with an eventual cumulative incidence of hypothyroidism ranging from 30 to 70% at 10 to 15 years in various series (26-28). The serum TSH is a useful marker of which patients are prone to develop hypothyroidism after initially becoming euthyroid more than a year after ^{131}I treatment (28). In one study of clinically euthyroid individuals with normal serum thyroxine but elevated TSH 6 to 12 years after ^{131}I treatment, about 5% become overtly hypothyroid annually (29). In contrast, in a similar sized group (about 60 subjects) from the same pool but with normal TSH, no individual became hypothyroid during three years of subsequent observation.

The cumulative incidence of hypothyroidism following subtotal thyroidectomy is somewhat less than following ^{131}I treatment ranging from 25 to 50% at 10 to 15 years (26, 28). When the calculated delivered dose of ^{131}I is about 80 μCi/gram of thyroid tissue the incidence of late hypothyroidism is said to not be significantly different for radioiodine and surgical treatment modalities (29).

Three reports have now appeared in which the late occurrence of hypothyroidism in patients treated with antithyroid alone has been documented (30-32). Overt hypothyroidism developed in 6 to 20% of patients initially euthyroid following the course of thionamide drug therapy 4 to 25 years previously. This rate of late hypothyroidism is less than that seen with radioiodine or surgery and may indicate that these other modalities superimpose their toxic effects upon an underlying trend inherent in Graves' disease. The high prevalence of antithyroid antibodies in those subjects becoming hypothyroid late after withdrawal of thionamide drugs suggests that coexisting autoimmune thyroiditis is the likely explanation (31).

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B. Hypothyroidism Following Head and Neck Surgery and/or Radiotherapy

Mantle radiation for Hodgkin's disease is associated with a 45 to 66% of either mild or overt hypothyroidism when patients are evaluated four or more years later (33, 34). The majority of patients had mild disease, and adjuvant chemotherapy did not seem to affect the incidence or severity of hypothyroidism (33). In another study of 80 patients who had received radiation therapy for breast cancer on average 7 years earlier, 21% had mild or overt hypothyroidism (35). In one study of patients with squamous cell tumors in the head and neck, 30% of patients receiving radiotherapy alone developed hypothyroidism whereas 47% of patients with combined radiotherapy and surgery became hypothyroid (36). As with Hodgkin's disease, the addition of chemotherapy did not appear to increase the incidence or severity of thyroid dysfunction. Another study did not find an increased incidence of hypothyroidism following only radiation therapy, but did report an incidence of 40% when radiotherapy was combined with laryngectomy and partial thyroidectomy (37).

These reports suggest that all patients with upper trunk or head and neck radiation should be monitored for the development of hypothyroidism. Individuals being treated for squamous cell cancer of the head and neck with combined surgery and radiotherapy appear to be at particular risk.

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C. Autoimmune Thyroiditis

As indicated above the most common cause of hypothyroidism in the elderly is autoimmune thyroiditis. Antithyroid antibodies may serve as a marker for the presence of autoimmune thyroiditis, and thus both antithyroglobulin and antimicrosomal antibodies have been measured in older populations and related to the presence of hypothyroidism (22, 38-42). The prevalence of significant titers of antithyroglobulin and antimicrosomal thyroid antibodies increases with age (22, 38, 41). Antimicrosomal antibodies are felt to be more sensitive for the detection of autoimmune thyroiditis (see below) (42). These antibodies are present in only about 2-3% of men but are found in about 10% of women. The presence of antimicrosomal antibodies in women increased from about 4% in young women to 15 to 20% in women over age 45 (22, 38, 41). The prevalence of antithyroid antibodies appears to decline in the very elderly (23, 41).

In the population study of an English community the relative risk of a high TSH level in subjects with thyroid antibodies was 20-fold in men and 13-fold in women independent of age, and half of subjects positive for serum thyroid antibodies had elevated TSH (22). When elderly subjects with significantly elevated TSH concentrations were evaluated for the presence of antithyroid antibodies, antimicrosomal antibodies were present in 67%, and antithyroglobulin antibodies were present in only 29% (42). Thus one third of subjects with clearly elevated TSH would have been missed if only antithyroid antibodies were used for screening.

There is some variability in the prevalence of antithyroid antibodies in different populations. This variation has been associated with iodine intake in that autoimmune (Hashimoto's) thyroiditis is uncommon in areas of iodine deficiency and endemic goiter. In an animal model for lymphocytic thyroiditis (the BB/W rat), excess iodine intake increases and low iodine intake decreases the incidence of thyroiditis (43). In a brief report of two populations of elderly women with variable iodine intake studied by the same group of investigators, the prevalence of high titer antithyroid antibodies was 25% in women residing in Worcester, MA, with a sufficient iodine intake compared with less than 1% in women residing in Reggio Emilia, Italy, with a low iodine intake (44). Mild or overt hypothyroidism was also 15 times more common in the Worcester group with the higher iodine intake.

In summary, markers of autoimmune thyroiditis increase with age, especially in women, but may be absent in the presence of hypothyroidism without another presumed etiology.

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D. Environmental Factors Affecting Autoimmune Thyroiditis

As mentioned above environmental iodine intake may exacerbate or induce autoimmune thyroiditis in genetically susceptible individuals. The mechanism of action of iodine in stimulating autoimmunity is uncertain. Effects of iodine on B lymphocytes, macrophages, and the immunogenicity of thyroglobulin have been reported (reviewed in 45). In addition iodine may alter the course of existing autoimmune thyroid disease. Patients are often exposed to pharmacologic doses of iodine in a wide variety of drugs including amiodarone (75 mg iodine per 200 mg tablet). Amiodarone is a potent inhibitor of the 5'-deiodinase enzyme in all tissues and lends to characteristic alterations in thyroid function tests (reviewed in 11). In areas of iodine deficiency amiodarone commonly is associated with iodine-induced hyperthyroidism (46). In this country, with sufficient iodine intake, amiodarone is more commonly associated with hypothyroidism. Hypothyroidism was noted in 22% of patients in Worcester, MA, treated with amiodarone (46). Hypothyroidism is more likely to be persistent after withdrawal of the amiodarone if antithyroid antibodies are present (47). Amiodarone-induced hypothyroidism may occur in the absence of antithyroid antibodies (49), and amiodarone has been shown to be associated with an increased percent of a monoclonal antibody-defined T cell subset in the absence of hypothyroidism (48). The increase in Ia-positive T cells and the percent reacting with monoclonal antibody 3G5 suggests that amiodarone may precipitate organ-specific autoimmunity in susceptible individuals (48). It is not known whether amiodarone itself or released iodine from the drug is responsible for these T-cell changes.

Lithium impairs thyroid hormone formation and release resulting in increased TSH and goiter formation (45). Most patients receiving lithium compensate for these effects and do not become hypothyroid. In one study 20% of women receiving lithium for more than two years developed hypothyroidism (49). Antithyroid antibodies were present in about two-thirds of those patients developing hypothyroidism while on lithium therapy. Although lithium does not appear to induce autoimmune thyroiditis, it has been reported to have effects on T-cell and macrophage function (reviewed in 45).

Recently interleukin-2 and lymphokine-activated killer cells given to patients with advanced neoplasms have been shown to be associated with the development of overt hypothyroidism in 7 of 34 patients in one study (50). Five of the 7 patients had borderline or elevated serum antimicrosomal antibody titers before and after treatment. The course of the index patient is shown in Fig. 1.

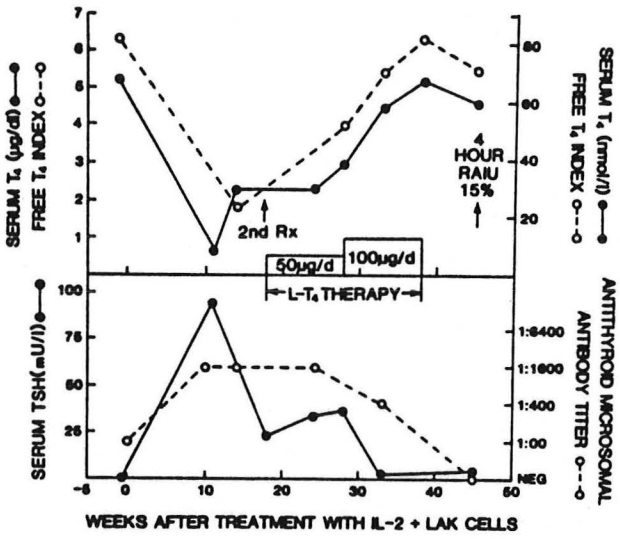

Figure 1. Thyroid Function and Thyroid Antibodies in the Index Patient, in Relation to Interleukin-2–LAK-Cell Therapy and Oral Thyroxine Administration (L–T_4, Sodium Levothyroxine, in Grams per Day).

TSH denotes thyrotropin, T_4 thyroxine, and RAIU radioiodine uptake over four hours.

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IV. Natural History of Hypothyroidism

As implied in the discussion above, hypothyroidism progresses from very mild thyroid failure to overt disease. This section of the rounds will consider studies detailing the progression of hypothyroidism as assessed by laboratory tests and what information is available on predicting the course of its progression.

Perhaps the optimal group in which to study the natural history of hypothyroidism from the standpoint of subtle laboratory abnormalities is the group of patients who have been treated with ^{131}I for thyrotoxicosis. The implications of an elevated basal TSH for the subsequent development of overt hypothyroidism have been mentioned above. In a detailed study of 128 patients treated 3-17 years previously with radioiodine for thyrotoxicosis, three categories of biochemical abnormality were used for grouping patients: decreased free T_4 index, elevated basal TSH with normal free T_4 index, abnormally enhanced response of TSH to TRH stimulation with normal basal TSH and free T_4 index (Table IV) (51).

Table IV. Degrees of Abnormal Thyroid Function Tests in Patients Previously Treated with Radioiodine for Hyperthyroidism

Category	n	Free T_4 Index	Total T_3 (ng/dl)
Decreased free T_4 index	34	2.8 ± 1.2*	63 ± 36*
Increased basal TSH	21	5.7 ± 0.8*	126 ± 38
Increased TSH after TRH	16	6.9 ± 0.8*	110 ± 41
Biochemically Normal	57	8.2 ± 1.7	122 ± 28
Controls	40	8.2 ± 1.5	115 ± 24

*Significantly different from the value immediately below, $p < 0.0025$ (from Ref. 51)

Although the mean free T_4 index was not below the normal range in the groups with exaggerated TSH response to TRH with either an increased or normal basal TSH, the mean corrected T_4 levels were lower than in those treated subjects with normal response after TRH or in control subjects. This decrease in mean T_4 levels in these groups suggests mild hypothyroidism.

Similar observations about mild levels of hypothyroidism have been made in subjects with autoimmune thyroiditis as evidenced by the presence of antithyroid antibodies (52, 53). All subjects were studied by a 200 μg TRH test in which peak TSH after TRH in controls was 18 μU/ml, and they could be grouped by severity of biochemical abnormality as those patients studied with prior radioiodine therapy (Table V) (53).

Table V. Parameters of Thyroid Function in Patients with Autoimmune Thyroiditis

Group	n	T_4 (μg/dl)	T_3 (ng/dl)	Basal TSH (μU/ml)	Peak TSH after TRH (μU/ml)
Overt hypothyroid	8	0.8 ± 0.1[a]	45 ± 4	79.6 ± 5[a]	313 ± 24.7[a]
Mild hypothyroid	10	6.1 ± 0.4[b]	160 ± 15	9.9 ± 1.2[c]	39.6 ± 3.0[c]
Biochemically hypothyroid	29	6.9 ± 0.4[b]	145 ± 9	2.8 ± 0.3	27.0 ± 1.7[d]
Biochemically normal	21	8.8 ± 0.5	161 ± 8	2.8 ± 0.3	7.6 ± 0.4
Controls	27	8.1 ± 0.3	155 ± 6	2.5 ± 0.2	7.2 ± 0.3

(from Ref. 53), mean ± SEM

[a] $P<0.001$ vs other group of thyroiditis patients and controls
[b] $P<0.01$ vs biochemically normal thyroiditis and controls
[c] $P<0.001$ vs biochemically hypothyroid and biochemically normal and controls
[d] $P<0.001$ vs mild hypothyroid and biochemically normal and controls

It is interesting to note that serum T_3 levels are not decreased in the groups in Tables IV and V except in the overt hypothyroid category. In Table V, in which mean TSH levels baseline and after TRH are given, it seems clear that in some patients subtle degrees of hypothyroidism only have an abnormality detectable when studied following TRH injection. Reactions of the pituitary thyrotrophe to progressive hypothyroidism appears to include changes in both synthesis and storage of TSH and in active secretion. The earliest phase seems to be increased TSH storage without sustained secretion.

Since the frequency of antithyroid antibodies in older women is greater than the frequency of elevations of serum TSH, a number of studies have attempted to evaluate the utility of antithyroid antibodies as markers for the prognosis of individuals with autoimmune thyroiditis developing eventual hypothyroidism. [Recall that a third of older subjects with clearly elevated TSH levels do not have positive antithyroid antibodies even though autoimmune thyroiditis is presumably the cause of their mild hypothyroidism (see above).] When subjects with positive antithyroid antibodies and elevated basal TSH are followed for the

development of overt hypothyroidism, 5 to 7% of such subjects per year become frankly hypothyroid (54-57). One study has attempted to use the antimicrosomal antibody titer in elderly subjects with elevated TSH to determine which subjects are likely to develop overt hypothyroidism (58). Twenty-six subjects with elevated basal TSH were followed for 4 years without treatment. Overt hypothyroidism developed in one-third. All subjects with initial basal TSH above 20 μU/ml and 80% of those with antimicrosomal antibody titer 1:1600 or greater (regardless of initial TSH level) became overtly hypothyroid. Those with antibody titers lower than 1:1600 and lesser TSH elevations did not develop overt thyroid failure during the 4 years (58). The mean T_4 levels and TSH levels of the 26 subjects for 4 years divided into two groups according to the antimicrosomal antibody titer are shown in Figs. 2 and 3.

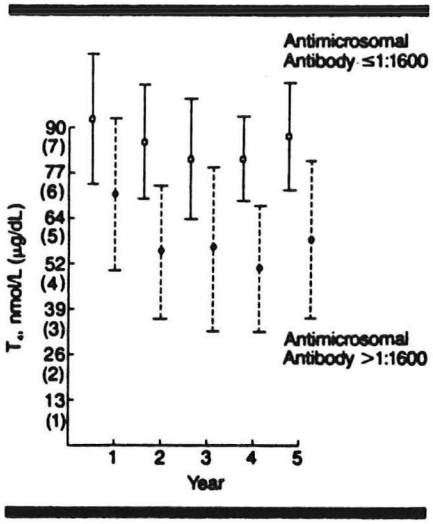

Fig 2. Mean thyroxine (T_4) levels for four years in 26 elderly subjects with initial thyrotropin (thyroid-stimulating hormone) levels greater than 4.0 mU/L (μU/mL). Subjects have been divided by initial level of antimicrosomal antibody titer. Mean ± SD are also shown.

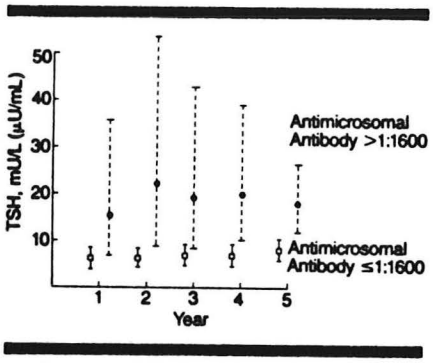

Fig 3. Geometric mean thyrotropin (thyroid-stimulating hormone [TSH]) levels over four years in 26 elderly subjects with initial TSH levels greater than 4.0 mU/L (μU/mL). Subjects have been divided by initial level of antimicrosomal antibody titer. Mean ± SD were computed from log-transformed values and then transformed back to original scale.

The authors suggest that prophylactic treatment of those subjects with initially high TSH (>20 μU/ml) or high titer antimicrosomal antibody is warranted.

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V. Significance of Subclinical Hypothyroidism

The term "subclinical hypothyroidism" seems to be the preferred term to describe individuals with no clinical features of hypothyroidism, normal T_4 and T_3 levels, but enhanced TSH response to TRH and usually, but not invariably, a slightly raised basal TSH level (59). As is clear to the careful observer, this description involves an overlap of two categories in Tables IV and V in regard to the laboratory test classification. Specifically, some of the patients termed "mild hypothyroid" who had elevated basal TSH in Table V would be added to those labelled "biochemically hypothyroid" who only had an enhanced TSH response to TRH to comprise this category. The reason for this is that many patients with grossly elevated basal TSH (e.g. >20 μU/ml) may have symptoms and/or some clinical features of hypothyroidism even though the serum T_4 (and free T_4 index) have not decreased below the "normal range" (see above). These latter individuals would be considered to have mild hypothyroidism on combined clinical and laboratory evaluation. Since few would doubt the significance of mild hypothyroidism and presumably no one would doubt the significance of overt hypothyroidism in which the T_4 and usually the T_3 are decreased with obvious clinical features, the issue of importance for these rounds is the biological significance of subclinical hypothyroidism. The fact that these subjects are at risk for the development of overt hypothyroidism has been considered above. However, one could argue that not all subjects with subclinical hypothyroidism will necessarily progress to clinical hypothyroidism; and, thus, if there is no biological significance to subclinical disease, such individuals should not be treated.

The epidemiological study of thyroid disease in an English community examined the association of subclinical hypothyroidism with lipid abnormalities and cardiovascular disease, and no association was found (60). A number of subsequent reports have approached the problem by identifying a population with subclinical hypothyroidism and then observing whether replacement therapy with thyroxine results in any change in the parameters studied (61-64).

The first of two studies of this type from Boston detected consistent reductions in systolic time intervals as assessed by two different methods (Fig. 4) (61). The normalization of the serum TSH was associated with changes in at least one marker of systolic time interval even in those patients with minimal elevations of TSH. In no instance was the post-treatment systolic time interval below the normal range which might have suggested excessive T_4 therapy.

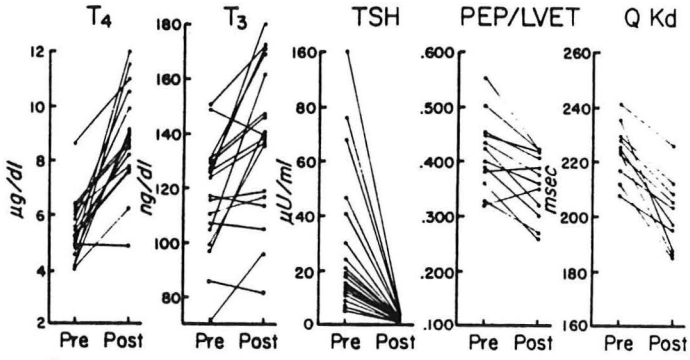

FIG. 4. The response of STI and serum T_4, T_3, TSH, and cholesterol levels to L-T_4 therapy. Pretreatment serum T_4 and T_3 levels were normal, and STI time intervals were either normal or slightly above the normal range. PEP/LVET and QK_d intervals as well as thyroid hormone levels were consistently changed by doses of L-T_4 which normalized serum TSH levels.

A subsequent placebo-controlled, double-blind trial reported by the same group used patients with even less severe elevations of TSH, mean level about 11 µU/ml in both groups (62). In addition to measuring cardiac parameters, a detailed symptom score was recorded and serum lipid profiles and BMR were measured following one year of thyroxine or placebo. Although serum lipid, BMR, and mean systolic time interval did not change in the treated group, the systolic time interval became normal in the 5 patients with the most abnormal baseline values, and symptoms improved in 8 of 14 treated patients compared with 3 of 12 placebo controls ($p < 0.05$) (Fig. 5) (62).

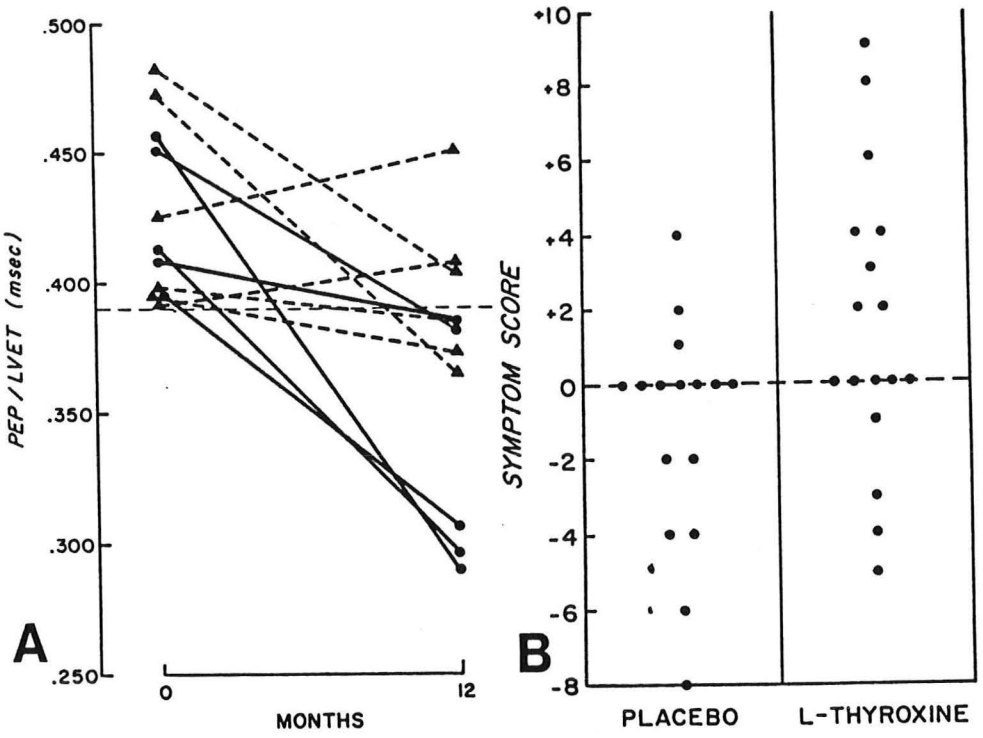

Figure 5. Changes in pre-ejection period/left ventricular ejection time ratio (*PEP/LVET*) in patients with an initial PEP/LVET ratio of 0.390 ms or more. Placebo treatment (▲— — —▲) resulted in no significant change (0.426 ± 0.03 [SE] ms before versus 0.397 ± 0.03 after therapy), whereas L-thyroxine treatment (●———●) was associated with a significant decrease in PEP/LVET ratio (0.425 ± 0.02 ms before versus 0.331 ± 0.03 after; $p < 0.01$). **B.** Symptom scores for individual patients treated with placebo or L-thyroxine. Scores for L-thyroxine-treated patients were significantly higher than those for placebo-treated patients ($p < 0.05$). (*See* Methods for details.)

Two studies from the same group in Edinburgh have evaluated left ventricular ejection fraction (LVEF) as assessed by radionuclide ventriculography (63, 64). Both reports are consistent in demonstrating an improvement in LVEF only with exercise. No change in mean sleeping heart rates, peripheral nerve conduction, or lipid profiles could be detected. In the second of these studies sodium nitroprusside was given for afterload reduction. At high level exercise LVEF increased from 61±10% to 68±10% following thyroxine replacement ($p < 0.025$) (64). No change was noted in relative cardiac output in response to exercise both before (Fig. 6A, upper panel) and after (Fig. 6B, upper panel) afterload reduction. After administration of sodium nitroprusside the mechanism of increase in cardiac output was different in the two groups. Both at rest and on exercise, stroke volume was reduced in the subclinical hypothyroid group (Fig. 6B, lower panel), similar increases in cardiac output being achieved by a relatively greater exercise-induced tachycardia. Sodium nitroprusside increased resting heart rate from 68±11 to 94±16 beats/min before and from 74±11 to 84±15 beats/min after thyroxine. At high level exercise, heart rate increased from 113±16 to 139±21 beats/min before and from 111±11 to 124±19 beats/min after thyroxine ($p < 0.05$ for both).

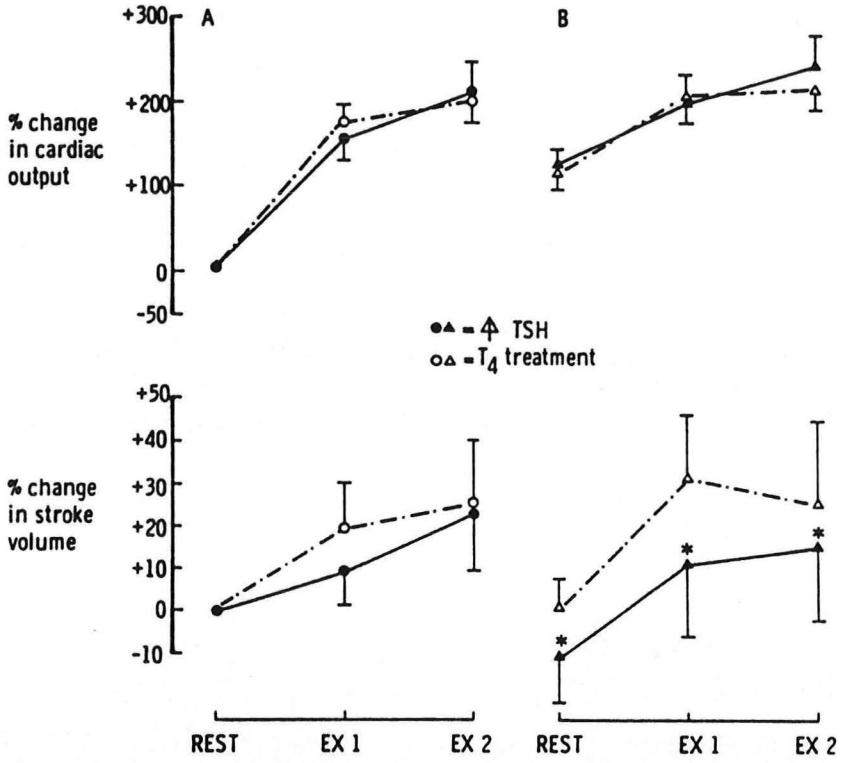

FIG. 6. Changes in cardiac output and stroke volume at rest and during exercise before (A, circles) and after (B, triangles) afterload reduction: comparison between subclinical hypothyroidism (↑ TSH) and thyroxine (T_4) treatment. *$p < 0.05$ compared with T_4 treatment. Normalised data for resting parameters at each level of thyroid function.

The authors conclude that a true reduction in myocardial contractile activity and compensating tachycardia are present in subclinical hypothyroidism.

Although it is recognized that overt hypothyroidism may be associated with dementia and organic psychoses, functional psychoses with paranoia, and

depression, there is confusion about the correlation of subclinical hypothyroidism with depression. Gold et al reported an 8% frequency of hypothyroidism among 250 consecutive patients referred to a psychiatric hospital for treatment of depression, half of which had the most subtle form of subclinical hypothyroidism, i.e., only detectable by TRH testing (65). If this were correct and the hypothyroidism was causative and not coincidental it would mean that all depressed individuals would require a TRH test. However, no control group was assessed in a similar manner, three of the 10 patients with only the abnormal TRH test had a history of lithium therapy, and the response to thyroxine treatment alone was not reported (or thyroxine even given) in all patients. Subsequently the same investigator reported a study of 100 similar depressed patients and claimed to find 15 with hypothyroidism, two-thirds of which were only identified by an abnormal TRH test (66). However, half of these ten were only included because of an arbitrary lowering of the upper limit of normal for the maximal TSH increment after 500 µg TRH from 35 to 29 µU/ml. In this same report an increased prevalence of antithyroid antimicrosoaml antibodies was also claimed with 60% of those with TSH abnormalities having titers of 1:10 or more. However, as discussed above such a frequency of antimicrosomal antibodies would be expected. The relationship of the subclinical hypothyroidism to the depression was not proven, and 10% of an unselected population might be seen with elevated TSH if they were predominately middle-aged or older women.

In studies by others the contribution of subclinical hypothyroidism to depression is also unconvincing (67-70). In a study of 47 depressed patients only 2 had enhanced TSH response to TRH above the normal range (67). Examining for a geriatric depression scale in nursing home patients, there was no greater depression score in a group with increased basal TSH than a control group (68). Some psychiatrists have claimed that the administration of triiodothyronine to depressed patients who fail to respond to antidepressants alone is beneficial. One report claims that the mean TSH response to TRH is higher in those who seem to benefit from the thyroid hormone addition to antidepressant than those who do not. However, most of the responders did not meet criteria for subclinical hypothyroidism, and the response to a few days or so of T_3 therapy added to antidepressants hardly proves that hypothyroidism caused the depression (69). Finally, one somewhat better study examined geriatric inpatients (both psychiatric and general medical) and found an overall prevalence of hypothyroidism of 3.8% in 147 psychiatric inpatients versus 1.9% of 104 nonpsychiatric patients (not significant) (70). Among the psychiatric patients, in a subgroup of 27 with neurotic depression, 4 had hypothyroidism or 14.8% vs. 2.3% of 88 with senile dementia ($p < 0.05$). However, the nature of the association of the two entities was not demonstrated.

In summary, the evidence for subclinical hypothyroidism being a common correlate of neurotic depression is weak, and no study adequately details a causal relationship.

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VI. Problems in the Clinical and Laboratory Diagnosis of Hypothyroidism in the Elderly

Hypothyroidism, not produced iatrogenically by radioiodine, has an insidious onset and progresses slowly over many years. Thus not all signs and symptoms are present at the time of examination, and the diagnosis may be difficult requiring a high index of suspicion. The difficulty of diagnosing hypothyroidism in the elderly is clear from two reports in which very restrictive criteria were used for the diagnosis (i.e., overt hypothyroidism with decreased thyroxine levels) (71, 72). In these reports of assessment of 3417 and 2000 geriatric patients, respectively, only 10 to 20% of patients with eventual clear laboratory diagnosis of hypothyroidism were recognized on clinical examination. A nonspecific clinical picture of hypothyroidism is

common in the elderly. All of the nonspecific clinical syndromes with which elderly subjects commonly present, i.e., failure to thrive, mental confusion, weight loss with poor appetite, falling episodes, incontinence, and depression, may be caused by hypothyroidism (73). Hypothyroidism often goes unrecognized until an advanced state because of a resemblance of the manifestations to aging itself. Both conditions are associated with dry skin, constipation, depression, increased atherosclerosis and hyperlipidemia. A partial list of some confusing presentations of hypothyroidism in the elderly is given in Table VI (73). Most common is diminishing mobility and deteriorating general health. Because of poor appetite weight loss is more common than weight gain. The falling episodes may be due to weakness or neurologic disease.

Table VI. Confusing Presentations of Hypothyroidism in the Elderly

Failure to thrive	Neurologic
Weight loss	Psychoses/"myxedema madness"
Falls	Dementia
Joint symptoms/weakness	Depression
Exudative effusions	Coma, seizures
Ileus	Deafness
Anemia	Ataxia
Hyponatremia	Carpal tunnel syndrome

(from Ref. 73)

The classical clinical features are described in detail in the usual texts. Two recent reports help define the role of hypothyroidism in cardiovascular findings (74, 75). The controversial issue of hypothyroid cardiomyopathy was shown to have echocardiographic documentation of reversibility (74), and diastolic hypertension was shown to be caused by hypothyroidism in 1.2% of a referred population (75).

The laboratory diagnosis of hypothyroidism would seem straightforward. Although some patients with the mildest form of subclinical hypothyroidism may only have an abnormality detected on TRH testing, since there are no studies identifying a biological significance to this subgroup specifically, I do not recommend routine TRH testing. These individuals have higher serum T_4 levels than those with elevated basal TSH (Tables IV and V) and presumably would be less likely to have any biological consequence of their abnormality. Moreover, they probably have a gradual progression over time to a state with elevated basal TSH before becoming symptomatically hypothyroid. Thus the laboratory assessment of possible hypothyroidism should include a routine thyroid panel, i.e., serum total T_4 and correction of the total T_4 by the resin T_3 uptake to obtain the free T_4 index plus a serum TSH level. One would look for a diminished corrected T_4 with an elevated TSH (assuming normal pituitary function) or a normal to low normal T_4 with an elevated TSH.

These criteria for the laboratory diagnosis of hypothyroidism work reasonable well in ambulatory subjects, but problems exist in hospitalized or recently sick individuals. The alterations of the total T_4 and free T_4 index

in the euthyroid sick patient were reviewed at these rounds previously (11). In brief, because of tissue catabolism and release of inhibitors of thyroid hormone binding to TBG, the free fraction of total T_4 can be increased and the free hormone concentration be normal when the total T_4 and free T_4 index are low. The absence of actual hypothyroidism can usually be confirmed in such patients by finding a normal serum TSH. However, it is now recognized that in the recovery phase of critical illness associated with severely decreased thyroxine levels, the TSH level may increase above the normal range, usually preceding slightly the rapid rise of T_4 levels (Fig. 7) (76). Follow-up TSH levels more than a month following recovery were normal in all subjects.

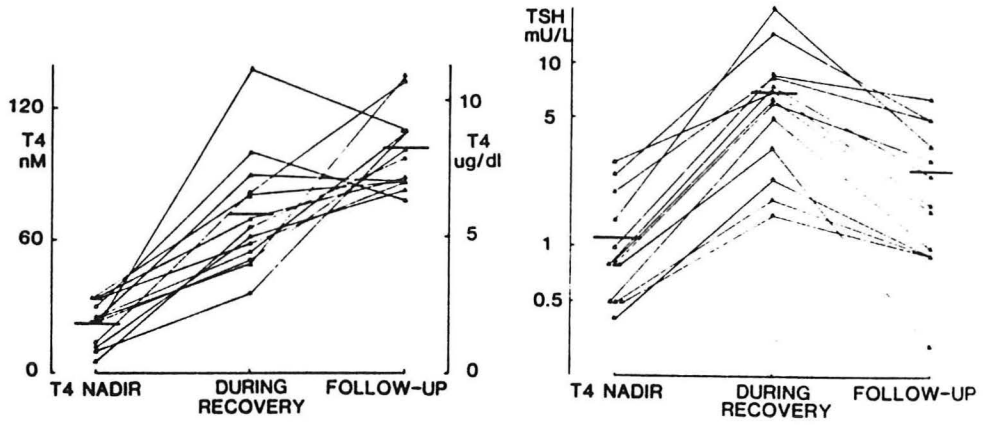

FIG. 7. Serum T_4 and TSH concentrations at the time of the T_4 nadir, during recovery at the time of maximum TSH, and at follow-up (4–20 weeks) in 13 episodes of recovery in 10 critically ill patients who had a rapid T_4 rise (Table 1). Mean values are shown by the *horizontal lines*.

In none of these subjects was the TSH during the recovery phase actually above 20 μU/ml, a value typical of overt primary hypothyroidism. However, in three unusual case reports described in another article, TSH levels greater than 20 μU/ml were felt to be associated with severe nonthyroidal illness (77).

One must also keep in mind medication effects in evaluating possible hypothyroidism in seriously ill patients. As previously reviewed (11), high dose glucocorticoids or dopamine infusions can lower TSH values to normal in patients with overt primary hypothyroidism. Thus, in such a setting, a normal serum TSH cannot be relied upon as reassurance of the absence of hypothyroidism in someone with a low T_4.

Patients with nonthyroidal illness, normal T_4 and elevated (>20 μU/ml) TSH levels have a higher prevalence of positive antimicrosomal antibody titers (>1:400) than do those with normal TSH values (40% versus 7%, respectively, $p < 0.001$), despite comparable free T_4 index levels, suggesting subclinical hypothyroidism (78). The elevated TSH remained elevated on recovery from nonthyroidal illness in the patients with antithyroid antibodies but returned to normal in those individuals who were antibody negative (78). The magnitude of the problem of elevated TSH in hospitalized patients being due to non-thyroidal illness is surprising. In the most comprehensive study of the newer TSH assay in hospitalized patients, only half of the unequivocally increased TSH levels (>20 μU/ml) proved to be due to thyroid disease (78).

In summary, a high index of suspicion and appropriate laboratory tests are necessary to diagnose hypothyroidism in the elderly. Care must be taken in

interpreting the T_4 and TSH in hospitalized sick patients. A normal T_4 and mildly elevated TSH in hospitalized patients warrants observation, particularly if the problem appears to be primarily nonthyroidal illness.

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VII. Treatment of Hypothyroidism in the Elderly and Its Potential Adverse Effects

A number of studies have reported that L-thyroxine replacement therapy of primary hypothyroidism requires a lower dosage in the elderly (79-83). Most of these studies concluded that elderly subjects require 20 to 30% lower L-thyroxine dosages than younger individuals. However, these studies all utilized older insensitive TSH radioimmunoassays and took place in the early 1980s during a transition period in the formulation of L-thyroxine tablets to tablets with a more uniform and greater potency. Thus the absolute dosage levels reported in these studies are probably incorrect with today's formulations and means of monitoring replacement. However, the conclusions of these papers concerning the lower dosages in the elderly should still be valid and are consistent with the known decrease in T_4 degradation rate with age (see above). The lean body mass has been suggested as a predictor of thyroxine requirement (81), and another group suggests that elderly patients with coexisting other medical illnesses and medications may require lower doses than older subjects without these confounding variables (83).

The change in L-thyroxine tablet formulation by one of the major manufacturers (Flint) in 1982 prompted a comprehensive study of tablet

formulation, absorption and mean adult replacement dosage (84). Most generic brands were shown to have acceptable L-thyroxine content by HPLC. The absorption of the reformulated tablet appeared to average 80% compared to prior studies in which only about 50% appeared to be bioavailable. The mean replacement dose in 19 adults (age not stated in the paper) was 112±19 µg per day (84). This contrasts with a value reported 13 years earlier of 169±66 µg/day based on the prior tablet formulation. This paper as well as a prior one (85) noted that with optimal replacement doses of L-thyroxine serum T_4 levels on average were increased compared with controls while serum T_3 levels were normal. This should not be taken as evidence that serum T_3 is appropriate to monitor in thyroid hormone replacement therapy since subclinical hyperthyroidism can be present during thyroxine treatment with serum T_3 levels still in the normal range (see below).

The other major change in thyroid hormone replacement therapy in the last ten years in addition to tablet reformulation was alluded to above and is the development of the ultrasensitive immunoradiometric TSH assay (86). The prior RIA of TSH was useful for the diagnosis and management of primary hypothyroidism in a limited way. Since the RIA had no lower limit of normal with typical normal values stated as being <6 µU/ml, it was primarily helpful only if abnormally high, i.e., indicating inadequate thyroid hormone feedback at the pituitary. However, one could never be certain that a reported value of 1.0 µU/ml was actually a "normal" TSH or really an undetectable value. Thus the TRH test was necessary to confirm suppression of the pituitary in patients with equivocal hyperthyroidism. And the only way to be certain that a hypothyroid patient on L-thyroxine therapy was not receiving excess thyroid hormone was either to give just slightly more than the dose that allowed the TSH to rise or perform a TRH test. The immunoradiometric TSH has a lower limit of normal with a stated range of 0.4-4.5 µU/ml (varies slightly with specific assay). The usual lower limit of detection is 0.1 µU/ml, and patients with abnormally elevated levels of thyroid hormones for their set points (either from endogenous hyperthyroidism or thyroxine treatment) usually have undetectable TSH levels in this assay (i.e., <0.1 µU/ml). An undetectable ultrasensitive TSH is usually associated with an absent response of TSH to TRH injection. This is the routine TSH assay now used in local hospitals and commercial labs.

Thus the logical goal in wishing to restore the hypothyroid patient to normal is to administer a dose of thyroxine sufficient to lower the TSH into the normal range but not so high as to suppress the TSH to below the normal range. Studies to compare the sensitivity of the thyrotrophs to other tissues to thyroxine treatment evaluated the TSH level and a number of serum markers of peripheral tissue response to thyroid status in hypothyroid patients given graded doses of thyroxine (87). Abnormally elevated levels of glutathione S-transferase, sex hormone binding globulin, angiotensin-converting enzyme, alanine aminotransferase, and γ-glutamyl transferase indicative of hyperthyroidism were only found if the TSH level was undetectable (87).

In treating hypothyroidism one does not want to substitute one undesirable condition for another, i.e., subclinical hyperthyroidism for overt, mild or subclinical hypothyroidism (88). There is increasing evidence that this has occurred in the past when means of assessing the appropriate doses of thyroxine were less available. The evidence suggests that subclinical hypothyroidism may be present with a "normal" corrected serum T_4 and T_3 (reviewed in 88). Even

before the ultrasensitive TSH assay it was recognized that patients with a flat TRH test with normal T_3 had falls in their systolic time intervals on reducing their thyroxine dosages (89). Likewise administration of thyroxine slightly above replacement doses to normal subjects sufficient to induce a flat TRH test resulted in increases in mean nocturnal heart rates (90). In addition clinically euthyroid subjects on thyroxine therapy with generally undetectable TSH levels had erythrocyte oaubain binding capacity, a marker of sodium pump sites, lower than controls but not as low as untreated thyrotoxic subjects (91).

Perhaps the aspect of subclinical hyperthyroidism in thyroxine-treated patients receiving the most attention is the report of reduced bone density in women on long-term thyroxine therapy (92-95). The first report was a histomorphometric study from France (92). Serial iliac bone biopsies were done before and during treatment and reported to show a decreased trabecular bone volume and an increased cortical bone porosity with hyperremodelling similar to hyperthyroidism. These changes were said to be present during the first month of graded therapy even before serum thyroid hormone levels were normalized. Another study found reduced radial bone density in premenopausal women on L-thyroxine therapy for 5 or more years, most of whom had undetectable TSH (93). Those who had taken thyroxine for 10 or more years had a 9% reduction in bone density. A third study noted decreased femoral trochanter and femoral neck density but normal lumbar spine bone density in clinically euthyroid women receiving thyroxine for 5 or more years with the majority having a suppressed TSH. However, no study has reported an increased fracture rate in such women, and one similar study did not confirm a decreased bone mineral density in women on suppressive doses of L-thyroxine (95). In any case the current recommendation would be not to give such excessive doses of thyroxine to treat hypothyroidism. [The issue remains to be evaluated and relative risks weighed for patients with thyroid cancer in whom it is considered desirable to suppress the TSH level to the undetectable range.]

Other issues in the thyroxine therapy of hypothyroidism are the coexistence of atherosclerotic heart disease with angina and the compromise that may be necessary in management of the two conditions (96, and reviewed in 97) and the effect of drugs such as phenobarbital (11) and rifampin (98) which induce liver enzymes on increasing the required replacement dose.

In summary in regard to treatment of hypothyroidism in the elderly, lower doses of L-thyroxine are sufficient for replacement therapy in older individuals than younger subjects. My recommendation is that even in the absence of myxedema or recognized coronary artery disease the initial dose of L-thyroxine should be less than 100 µg, the usual starting dose in younger subjects. After initiating therapy with 50 or 75 µg per day, wait four to six weeks to asses the appearance of possible symptoms of coronary artery disease and to allow a steady state level of serum T_4 to be reached. [Recall that thyroxine has a 7 to 8 day half life.] At that point repeat the ultrasensitive TSH assay to see if it has decreased to within the normal range. If overt hypothyroidism was present with very high TSH levels (e.g. >60 µU/ml), even though the T_4 returns in the high normal range, it may require more than six weeks for hypertrophied thyrotropes to decrease their secretion of TSH. In this setting if the TSH is decreased but still not in the normal range and the patient's symptoms of hypothyroidism are resolving, delay increasing the thyroxine dose. When making increases in thyroxine dosage, only increase by 25 µg per day. If the ultrasensitive TSH

becomes undetectable, decrease the thyroxine dosage slightly. It is possible to effect changes in dosage of less than 25 µg by varying the dosage on alternate days.

Patients with coronary artery disease with angina or with clinical myxedema should be started on 12.5 or 25 µg L-thyroxine daily. Some patients with angina and difficulty in tolerating even low doses of L-thyroxine might be candidates for coronary artery bypass surgery before being rendered completely euthyroid (reviewed in 97). For special considerations of management of myxedema coma see the standard texts.

My personal recommendation in regard to the management of subclinical hypothyroidism is that such patients should be treated. The reason for this recommendation is that some patients may have improvement in cardiac parameters or only recognize in retrospect a relief of nonspecific symptoms. In addition, since the ultrasensitive TSH is now available for monitoring thyroxine therapy, it should be possible to avoid potential adverse effects of overzealous thyroxine replacement. Finally there is an unconfirmed report that thyroxine therapy in patients with autoimmune thyroiditis and elevated TSH may induce a fall in antithyroid antibodies presumably ameliorating the destructive process in the thyroid (99).

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