Thyroid Disease in the Oldest Old
The Exception to the Rule

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The young man knows the rules, but the old man knows the exceptions.[1]

Oliver Wendell Holmes

ALMOST 4 DECADES AGO, BASTENIE AND COLleagues[2] used the term *subclinical hypothyroidism* to describe, for the first time, a group of clinically euthyroid individuals with circulating antithyroid antibodies, low normal plasma protein–bound iodine levels, and, using a mouse bioassay, elevated serum thyrotropin levels. Evered and colleagues[3] subsequently described a similar group of asymptomatic individuals in whom "conventional tests of thyroid function showed nothing abnormal . . . but they were all found to have a raised serum thyrotropin concentration." They also used subclinical hypothyroidism to describe this constellation of clinical and laboratory data. Since then, hundreds of articles have been published on this topic, but physicians are no closer to understanding whether this mild, usually asymptomatic form of hypothyroidism presents a clinical risk, requiring screening for detection and thyroid hormone treatment, or whether screening and therapy are unnecessary and possibly even counterproductive.[4]

Subclinical hypothyroidism is most often detected in older women (age >60 years), in whom the prevalence may be as high as 20%.[5] The majority of affected individuals have circulating antithyroid antibodies,[2] establishing the autoimmune etiology of subclinical hypothyroidism. Most patients have only slightly elevated serum thyrotropin levels (usually between 5 and 10 mIU/L), emphasizing the minimal nature of the biochemical abnormality.[5,6] Given the demographics of subclinical hypothyroidism, it is not surprising that symptoms consistent with mild hypothyroidism, including cold intolerance, dry skin, constipation, and depressed mood, are frequently seen in older patients with subclinical hypothyroidism.[5,7] However, whether these and other nonspecific symptoms are more prevalent or more severe than they are in an age-matched healthy control population remains to be established.

Starting with Bastenie et al,[8] some investigators have observed an association between subclinical hypothyroidism and atherosclerotic cardiovascular disease,[9,10] whereas others have been unable to establish an unambiguous link.[11,12] If an association does exist, it has been postulated to be mediated by dyslipidemia, long known to be present in overt hypothyroidism, or via nontraditional risk factors such as C-reactive protein, homocysteine, and lipoprotein(a).[13] However, the link between subclinical hypothyroidism and these putative risk factors is rather tenuous. For example, while some epidemiological studies have demonstrated a higher frequency of cardiovascular disease in individuals with subclinical hypothyroidism, they do not necessarily show altered serum lipid levels in affected individuals.[9] Furthermore, only a handful of controlled trials of thyroxine therapy have demonstrated improvement in serum lipid levels[14] or other putative risk factors[15] in patients with minimal serum thyrotropin elevations (ie, 5-10 mIU/L), with the majority of studies showing no effect.[16,17] More recent small trials of thyroxine therapy in subclinical hypothyroidism have shown improvements in other surrogate end points, including increased endothelium-dependent vasodilatation[18] and a decrease in carotid intimal thickness,[19] lending support to the hypothesis that subclinical hypothyroidism may be associated with atherosclerosis.

Just as an unequivocal relationship between subclinical hypothyroidism and prevalent cardiovascular disease or cardiovascular risk factors has been difficult to document in cross-sectional studies, until recently no study had shown an increase in overall or cardiovascular mortality in individuals with subclinical hypothyroidism followed up longitudinally. In fact, 2 long-term follow-up studies showed that patients with thyrotropin levels higher than 5 mIU/L had 10- and 20-year survival times comparable with euthyroid controls.[20,21] In a study published more recently, an increase in all-cause mortality was seen in men with subclinical hypothyroidism who were followed up for 12 years.[10] These data are difficult to interpret because the increase in all-cause mortality was observed only in years 3 through 6 of follow-up and was no longer present after 10 years, the causes of death were not available to the investigators, and the effect was limited to men.

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Because of its high prevalence in older persons and a possible association with cardiovascular disease, subclinical hypothyroidism has become a public health issue of some prominence. For example, the Institute of Medicine evaluated the advisability of covering thyrotropin screening among the Medicare population. After analyzing the available evidence and performing a cost-benefit analysis, the Institute of Medicine found the evidence for a benefit of screening to be lacking, and consequently determined that coverage for screening should not be provided as a Medicare benefit.[22] A similar conclusion against screening for mild hypothyroidism in the adult population was reached by a consensus development panel sponsored by the 3 major professional societies published earlier this year in *JAMA*.[23] The panel also recommended against routine treatment of subclinical hypothyroidism. The panel's recommendations were so contentious that the 3 sponsoring societies (the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society) have declined to endorse the statement.

The article by Gussekloo et al[24] in this issue of *JAMA* must be assessed against this background. The authors used a population-based, prospective study of all 85-year-olds living in Leiden, the Netherlands, who were invited to participate between 1997 and 1999 during the month of their 85th birthday. Of the individuals who were approached, 87% or 599 agreed to participate in the study. Their thyroid status was assessed at baseline, and individuals who were found to have overt thyroid disease (hyperthyroidism or hypothyroidism) were referred to their primary care physicians for possible treatment. Individuals with subclinical hypothyroidism (elevated serum thyrotropin, normal free thyroxine) and subclinical hyperthyroidism (subnormal serum thyrotropin, normal free thyroxine) were followed up without therapy. Through annual personal follow-up visits in the individuals' homes, the investigators assessed activities of daily living, cognitive performance, and depressive mood using a battery of validated rating scales. Survival was prospectively monitored.

At baseline, the prevalence of hypothyroidism in this elderly cohort was 12%, and somewhat surprisingly, subclinical and overt hypothyroidism occurred with equal frequency. Astonishingly, none of the patients who had been found to have overt thyroid disease was prescribed treatment by their physicians. Consequently, at the end of the 4-year follow-up period at age 89 years, the only patients who were taking thyroid medications were those few who had been taking it when the study began. This is important because prior cohort studies that have followed up individuals with subclinical hypothyroidism prospectively have not ascertained whether they had been given thyroid hormone replacement during the follow-up period.[20,21]

At the start of the follow-up period, individuals who had elevated serum thyrotropin levels at baseline had comparable activity, cognitive function, and depressive feelings compared with individuals with normal thyroid function. Thus, there was no evidence that overt or subclinical hypothyroidism affected elderly individuals' performance status or mood. After 3 years, none of the individuals with subclinical hypothyroidism had progressed to overt hypothyroidism. Furthermore, during the annual follow-up examination, those participants with increased serum thyrotropin levels actually had a similar or less rapid decline in specific disability measures compared with individuals with normal thyroid function. Most surprising, perhaps, was the observation that individuals with both overt and subclinical hypothyroidism had lower all-cause and cardiovascular mortality than clinically euthyroid individuals. Lower mortality rates were seen in both men and women, and this occurred even though serum cholesterol levels were higher in this group at baseline. In contrast, increasing serum levels of free thyroxine and low serum thyrotropin levels (ie, overt or subclinical hyperthyroidism) were associated with an increased risk of cardiovascular mortality.

These data seem to be at odds with the preconceived notions of the effects of hypothyroidism on functioning, cognitive ability, mood, and cardiovascular outcomes. Several intervention trials have suggested that subclinical hypothyroidism is associated with memory deficits in younger individuals[25-27] that are reversible to some extent with thyroid hormone therapy. On the other hand, cross-sectional studies of geriatric populations have not shown differences in cognitive function between euthyroid individuals and those with mild hypothyroidism.[28,29] Although one prospective study did show an increase in cognitive decline in individuals with below normal serum thyroxine levels.[30] Data on mood in younger individuals with subclinical hypothyroidism are similarly inconsistent, with some studies showing depressed mood[26,31] that improves with thyroxine,[26] while other studies have not documented any change after treatment.[27] In cross-sectional studies focusing on depression in geriatric populations, some found a possible relationship between depression and elevated serum thyrotropin levels,[32] while others did not.[29] And although one might have thought that the investigators in the present study would have found a higher cardiovascular mortality in patients with subclinical hypothyroidism, they did not, and this is at odds with the most recent prospective study,[10] but similar to the 2 other studies.[20,21]

In summary, it appears that neither subclinical hypothyroidism nor overt hypothyroidism is a cause of decline in performance, altered cognition or mood, or long-term survival in the oldest old. Gussekloo et al[24] cite data in animal studies showing that hypothyroidism is associated with a longer life span, possibly related to a lower metabolic rate. Whether this might also be the case in humans with subclinical hypothyroidism or overt hypothyroidism remains speculative. There is a large body of work comparing thyroid physiology in older and younger individuals,[33] which demonstrates decreased thyroid hormone action at the tis-

sue level, decreased thyroid hormone metabolism, and alterations in the hypothalamic-pituitary-thyroid axis in the elderly; whether these changes or others might be responsible for some of these observations is not known. The results from the study by Gussekloo et al should not be extrapolated to young or middle-aged individuals with hypothyroidism who may experience adverse health consequences if not treated.[9,10]

From a clinician's point of view, the data presented by Gussekloo et al[24] need to be replicated by other groups. If these results can be confirmed, they would strongly imply that thyroid hormone therapy could have adverse effects on mortality in the oldest old with subclinical hypothyroidism or overt hypothyroidism, particularly when the thyroid disease is diagnosed by screening. Without long-term, prospective randomized controlled trials of treatment for subclinical hypothyroidism, it is hard to recommend for or against treatment, and clinicians must rely on imperfect evidence from observational studies, such as the one by Gussekloo et al.[24] Currently, there is little debate among endocrinologists regarding thyroxine treatment of individuals with overt hypothyroidism or subclinical hypothyroidism with serum thyrotropin levels higher than 10 mIU/L.[23] This is based on the likelihood of reversible dyslipidemia[34] and its known link with adverse cardiovascular outcomes, as well as the relatively high likelihood of progression of subclinical hypothyroidism to overt hypothyroidism over a 10- to 20-year period.[35]

It may be that individuals with hypothyroidism who are older than 85 years are being protected from adverse outcomes by a lower metabolic rate or other factors, and that current clinical guidelines and recommendations should not apply to this select group. However, one study should not challenge clinical practice so radically that more than a century of successful treatment of hypothyroidism would be called into question. However, given the totality of evidence,[22,23] combined with data from the study by Gussekloo et al,[24] it is reasonable to recommend against screening for thyroid disease in asymptomatic elderly individuals. If an elderly individual is found by screening or case finding to have overt hypothyroidism, it would be reasonable to initiate thyroxine treatment, although the serum thyrotropin target might be 4 to 6 mIU/L, rather than the target of less than 3.0 mIU/L that has been recommended by some groups.[36] If subclinical hypothyroidism is identified in an individual aged 80 years or older, and the serum thyrotropin level is between 5 and 10 mIU/L, initiation of thyroxine therapy probably is not necessary. If the serum thyrotropin level were higher than 10 mIU/L, initiating thyroxine therapy would be appropriate as has been recommended,[23] but again, the target serum thyrotropin level would be relatively high (eg, 4 to 6 mIU/L).

The provocative data presented by Gussekloo et al[24] prompt a number of questions and speculations. First, a major clinical concern is whether treatment of subclinical hyperthyroidism would improve survival because both Gussekloo et al[24] and others[20] have shown increased mortality in affected individuals. Current recommendations support therapy in patients with serum thyrotropin levels of less than 0.1 mIU/L,[23] but no randomized controlled trials have been performed and they are sorely needed. Second, is there a survival advantage to having autoimmune thyroiditis, the likely cause of the thyroid disease in this cohort of older individuals? Third, if the data on a possible protective effect of hypothyroidism are correct, what is the mechanism? The answers to this more fundamental question must await additional research into the relationship between the aging process and thyroid hormone action at the cellular level.

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