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SCREENING FOR THYROID DISEASE IN THE COMMUNITY

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Thyroid disorders are known to be common in most countries, but it is difficult to determine their real frequency in any particular community. Different systems of health care, a lack of universally agreed upon and precise definitions of hyperthyroidism, hypothyroidism, and even goiter, together with variations in the techniques used to determine thyroid function compound the difficulties. In addition, hospital referrals are highly selective and the patients' conditions are usually well advanced at the time of clinical diagnosis. If the natural history of thyroid disease is to be determined, it will be necessary to detect the earliest abnormalities by examining a representative cross section of the community. Early detection may lead to measures that will prevent further progression of the disease. Whether community screening programs are justified in terms of public health is ultimately a socioeconomic decision, although benefit to the individual is usually the immediate concern of the physician.

Many important studies of the frequency of goiter in various communities led to the introduction of prophylactic iodine in some countries. However, relatively little is known of the frequency of autoimmune thyroid disease, a term that may be used loosely to embrace the whole spectrum of thyroid dysfunction, ranging from Graves' disease to myxedema, and including asymptomatic autoimmune thyroiditis. To determine the prevalence of autoimmune thyroid disorders in a noniodine-deficient community in northeast England, 2,779 persons were studied who represented a cross section of the adult population in the mixed urban and rural area of Whickham.[1] The findings of the Whickham survey may, of course, be peculiar to that area; however, the age and sex distribution of the community and of the sample obtained closely resemble that of Great Britain as a whole. Other studies in white communities as far apart as Finland,[2] New Zealand,[3] and the United States,[4] nevertheless suggest the frequency of certain thyroid disorders may be very similar in such populations. The prevalence of hyperthyroidism, hypothyroidism, asymptomatic autoimmune thyroiditis, and goiter found in the Whickham survey are reviewed below with data from other community studies, as well as the implications of these findings.

Prevalence and Incidence of Hyperthyroidism

The prevalence of previously undiagnosed cases of hyperthyroidism in the Whickham survey was five per 1,000 women studied.[1] All subjects had clear clinical features of hyperthyroidism; the diagnosis was confirmed by high total thyroxine (T4) concentrations (>2 SD above the mean) and correspondingly elevated free T4 indices (FTI). Fourteen per 1,000 women had been previously treated for hyperthyroidism, and the original diagnoses were confirmed by checking their hospital records for clinical details and confirmatory laboratory tests. Thus, the overall prevalence of established hyperthyroidism was 19 per 1,000 women. If possible cases whose original diagnoses could not be checked from hospital records are included, the prevalence is 27 per 1,000 women. The prevalence in women was tenfold greater than in men. Mean age at diagnosis was 48 years (range, 25 to 70 years). It was estimated that the annual incidence of hyperthyroidism in this community was likely to be two or three cases per 1,000 women. These figures are considerably higher than previous estimates that were based on analyses of hospital records.[5,6] The frequency of newly diagnosed cases, however, is similar to the 0.31% found in a recent health screening program in the United States where the FTI was used as a screening test.[4]

Unfortunately, there is no test of thyroid function that predicts the development of hyperthyroidism, although hyperthyroidism may be detected biochemically before it is apparent clinically. Since total triiodothyronine (T3) and T4 are subject to altered binding to T4-binding globulin (TBG), particularly during oral contraceptive therapy, neither is an ideal screening test. The number of false-positive high values will be considerable, especially in women of reproductive years. The FTI largely corrects for altered protein binding. However, although it is more suitable for screening purposes, this procedure involves two different tests and therefore adds to cost. Direct measurement of free T4, which is now more readily available, avoids most of the problems of protein-binding tests, but measurement of free T3 might be the most suitable test as elevation of T3 level is probably the earliest detectable biochemical disturbance in hyperthyroidism. Whichever measurement is used, the distribution of test results in the general population has to be determined[7] and a somewhat arbitrary decision must be made to define the upper limit of normal, or the cut-off point beyond which a person will be recalled for further tests. Even a cut-off point of 1% off the top of the normal distribution will involve a number of unnecessary tests for a condition with a prevalence of five per 1,000 women. This illustrates the problem of defining the cost/benefit ratio of any screening program. At present, screening for hyperthyroidism per se probably is not justified, but it is important that the relatively frequent occurrence of the condition be recognized in order to facilitate diagnosis in women of all ages.

Prevalence and Incidence of Overt Hypothyroidism

The prevalence of previously undiagnosed cases of overt hypothyroidism in the Whickham survey was three per 1,000 women. All subjects had clinical features consistent with the diagnoses, low T4 and FTI values and raised thyroid-stimulating hormone (TSH) levels, and good responses to T4 replacement. A further 11 per 1,000 women had been previously diagnosed and treated for hypothyroidism; perusal of their original records confirmed the clinical features and appropriately low thyroid hormone levels. The overall prevalence of established hypothyroidism thus was 14 per 1,000 women. This figure rises to 19 per 1,000 women if possible unproven cases are included. The mean age at diagnosis was 57 years (range, 30 to 76 years). The prevalence of hypothyroidism was at least tenfold more common in women than in men. These figures pertain to spontaneous hypothyroidism and are increased by one third if iatrogenic hypothyroidism following surgery and radioiodine treatment for thyrotoxicosis are included.

Comparable figures have been found in community surveys in Finland[2] and the United States[4] for the detection of new cases of spontaneous hypothyroidism, two per 1,000 and five per 1,000, respectively. A similar overall prevalence of 0.6% for established hypothyroidism has been reported from New Zealand.[3] Follow-up studies of the Whickham patients for a period of four years confirmed the original estimate of an annual incidence of one to two new cases of hypothyroidism per 1,000 women in the community.[8] The condition may be diagnosed more frequently in selected groups, particularly elderly women admitted to hospital for whatever reason, and always must be considered in anyone who has had previous destructive therapy to the thyroid or irradiation to the neck.

False low total T4, FTI, and even free T4 values may be found in patients with severe acute or chronic nonthyroid illness.[9,10] This limitation must be kept in mind, particularly if these tests are used in hospital screening programs. In patients with primary hypothyroidism TSH is almost invariably increased thus, serum TSH provides a more specific test for its detection. The rise in TSH level following an intravenous bolus of thyrotropin-releasing hormone (TRH) is proportional to basal TSH; in primary hypothyroidism the response is exaggerated. The TRH test may be useful to clarify borderline elevated basal TSH values but is seldom necessary. For screening purposes the basal TSH test is sufficient.

Basal TSH values in the general population do not follow a normal distribution curve. The limit of detection of most routine TSH assays is at best 0.5 mU/L and more often 1 mU/L. Ten percent of persons screened will have TSH values below this limit. There is no significant variation of TSH levels with age in men, but there is a marked rise with age in women over 45 years. This rise in TSH levels with age in women is due almost entirely to the strong association between TSH and thyroid antibodies, and is virtually abolished if women with thyroid antibodies are excluded from the distribution (Figure 1). Median TSH values are approximately 2 mU/L; 97.5% of TSH values are below 6 mU/L in both sexes in the absence of thyroid disease. Thyroid-stimulating hormone level is inversely related to T4 level: the higher the basal TSH value, the greater the likelihood of finding additional evidence of hypothyroidism. Thyroid-stimulating hormone values greater than 6 mU/L are associated with significant reduction in T4 levels, although serum T3 levels are usually normal, reflecting a compensatory preferential secretion of T3 in the hypothyroid state. Thus, T3 measurement is of no value in screening for hypothyroidism.

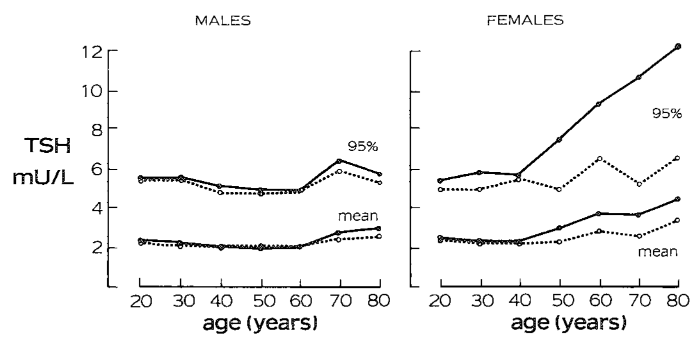

Figure 1
Mean and 95% TSH values by age and sex in the whole sample of the Whickham population (solid lines), and in the subsample that excluded any form of thyroid disease (broken lines).

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The Significance of Subclinical Hypothyroidism

The finding of raised TSH levels with low normal T4, but normal T3 levels, in persons with no clinical evidence of thyroid deficiency has been termed subclinical hypothyroidism.[11] Most cases of spontaneous myxedema are believed to be the end result of the destructive process of autoimmune thyroiditis. In the natural history of this process, thyroid antibodies develop while individuals remain asymptomatic. Only subsequently is there a gradual deterioration of thyroid function. The earliest biochemical marker of impending thyroid failure is an increase in serum TSH. A proportion of individuals with rising serum TSH levels will progress from this subclinical state to develop overt hypothyroidism. Others may remain clinically euthyroid for years.

Differences in the techniques of measuring thyroid antibodies make difficult a comparison of studies between populations. Whatever the techniques employed, however, all studies agree on the increased frequency of occurrence of both thyroglobulin and microsomal antibodies in women compared with occurrence in men, and that there is a marked increase with age in the prevalence of these antibodies in women. Microsomal antibodies in serum diluted 1:100 or more were found in 2.7% of men, in 10.3% of women of all ages, and in up to 13.7% of postmenopausal women in the Whickham study. The age and sex distribution is very similar to that of raised TSH values (Figure 2); nearly half the subjects with thyroid antibodies had TSH values greater than 6 mU/L. Conversely, 60% of subjects with TSH values greater than 6 mU/L, and 80% of those with TSH values greater than 10 mU/L, had thyroid antibodies. Three percent of the population of the Whickham survey (5% of women) had both thyroid antibodies and raised TSH values. A similar prevalence was found in a study in Finland.[2]

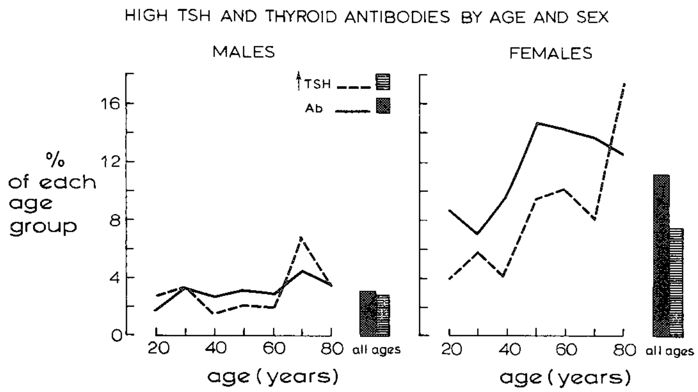

Figure 2
Age and sex distribution of thyroid antibodies (solid lines) and raised TSH values (broken lines) in the Whickham survey.[1]

In order to determine the rate of progression to overt hypothyroidism, subjects with thyroid antibodies and/or raised TSH values and age- and sex-matched controls without either abnormality were followed for four years.[8] During this time overt hypothyroidism developed in six of 30 women who initially had microsomal and thyroglobulin antibodies, and increased TSH (6 mU/L), an annual incidence of 5%. Three additional women became biochemically hypothyroid without concurrent clinical signs. Only one case of overt hypothyroidism developed in 67 women who initially had thyroid antibodies but normal TSH levels; no cases of overt hypothyroidism developed in women who had initial borderline TSH values (6 to 10 mU/L) in the absence of thyroid antibodies, or in the controls. The finding of thyroid antibodies alone, or of a borderline TSH value in the absence of any underlying evidence of autoimmune thyroiditis, thus was of no prognostic significance for the development of overt hypothyroidism over the four-year duration of this study. The finding of a raised TSH value in a woman with thyroid antibodies is of prognostic significance in that at least one in 20 women in this study developed overt hypothyroidism per year. In a selected group studied in Finland, the incidence of overt hypothyroidism has been shown to be as high as 10% per year in women with autoimmune thyroiditis and with initial TSH values greater than 19 mU/L.[12]

It also has been claimed that subclinical hypothyroidism may be an additional risk factor for the development of ischemic heart disease,[13,14] but the evidence is conflicting. A possible mechanism for such an association might be elevation of serum lipids leading to increased atherogenesis. Although fasting cholesterol and triglyceride levels often are raised in frank myxedema, no significant differences in the levels of these lipids could be found in subjects with or without thyroid antibodies or raised TSH levels in the Whickham population survey. There was, however, a weak association between raised TSH levels, but not thyroid antibodies, and minor ECG abnormalities in women, independent of age, obesity, and blood pressure[15]; however, this association disappeared during the four-year follow-up.[8] Minor ECG abnormalities often are transient and do not necessarily signify ischemic heart disease. Other studies on hospital patients nevertheless continue to show a higher prevalence of coronary heart disease in women with raised TSH values compared with age- and sex-matched controls,[16] and independent of cholesterol. The mechanism of such an association thus remains unexplained. In the author's view, the present evidence for the possible association between subclinical hypothyroidism and an increased risk for the development of ischemic heart disease is too slender to justify the attendant risk of widespread introduction of prophylactic T4 therapy for asymptomatic women who have either thyroid antibodies or raised TSH values. The case for prophylactic T4 therapy to prevent the morbidity of undiagnosed hypothyroidism is, to a certain extent, a separate matter.

Hypothyroidism is insidious in onset and the diagnosis of even frank myxedema is readily overlooked until it has been present for some time. No one doubts that it is proper to treat myxedema once the diagnosis has been confirmed by presence of low T4 and raised TSH levels. Replacement T4 therapy may need to be undertaken cautiously in anyone with angina or other evidence of ischemic heart disease for fear of exacerbating the latter. However, if the diagnosis of possible hypothyroidism is entertained in a patient who initially shows mild nonspecific symptoms, and who has a raised TSH level on the basis of autoimmune thyroiditis, but a normal T4 level, it may be reasonable to administer T4 in a sufficient dose to suppress the TSH level to normal. Such therapy may lead to improved well-being in women who had not previously recognized impaired mental or bodily functions. Although this could simply represent a placebo effect, it may be justified in preventing the subsequent development of overt hypothyroidism which, as pointed out above, would otherwise appear at the rate of about 5% per year. Nevertheless, many such individuals, if left untreated, do not go on to develop overt hypothyroidism; their TSH and T4 levels may remain unchanged for years. At the least, such individuals should be followed up to detect any further deterioration at an early stage.

If it is deemed appropriate to treat subclinical hypothyroidism in the individual, then it may be considered worthwhile to screen apparently normal healthy populations. However, the returns for the effort, or cost/benefit analysis, will be greater if screening is confined to higher risk groups, eg, postmenopausal women. The decision to undertake such programs finally will depend on local socioeconomic factors and health care systems. The above data on prevalence and incidence of overt hypothyroidism, and the prognostic importance of subclinical hypothyroidism, at least provide a basis on which such decisions can be made.

Prevalence of Goiter

Goiters that are palpable and visible are more common in younger women and decline in frequency with age, whereas thyroid nodules are found more frequently in older women. The much lower prevalence of goiter and nodules in men does not vary significantly with age (Figure 3). Relative iodine deficiency may contribute to the development of goiter in young women, particularly during puberty and pregnancy, but no significant difference in mean iodine excretion was detected between women with and without goiter in the Whickham survey. Multinodular goiters tend to be associated with thyroid antibodies, but the association between goiter and antibodies was very weak, and the age distribution of visible goiter contrasts markedly with that of thyroid antibodies (compare Figures 2 and 3). There was no significant difference between mean TSH values in women with and without goiter in the Whickham population. This implies that autoimmune thyroiditis only accounts for sporadic cases of goiter and that increased TSH is not a prominent factor in the development of goiter in the majority of patients. Such cases of goiter require further investigation but the causes may not be easily established in most patients. Longer follow-up studies are needed to ascertain the natural history of sporadic cases of goiter in noniodine-deficient areas.

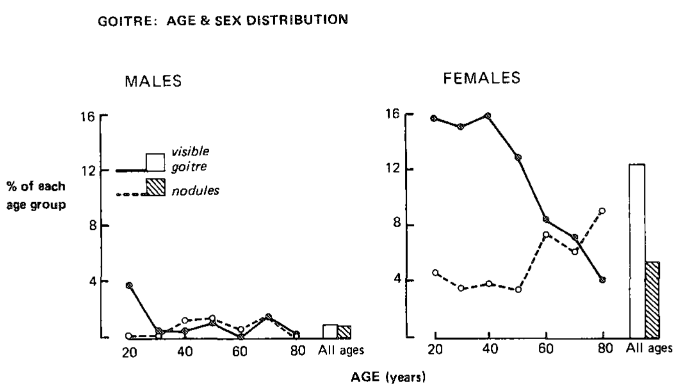

Figure 3
Age and sex distribution of visible goiter (solid lines) and thyroid nodules (broken lines) in the Whickham survey.[1]

Summary

Screening noniodine-deficient white communities as far apart as England, Finland, New Zealand, and the United States reveals a high prevalence of autoimmune thyroid disease. Women are affected between five and ten times more frequently than men. Hyperthyroidism affects up to 2% of all adult women; up to five new cases may be found per 1,000 women screened. Overt hypothyroidism affects a similar proportion of adult women with one third of the cases following thyroid surgery or radioiodine treatment. Previously undiagnosed hypothyroidism also may be found in up to five per 1,000 women screened. The incidence of overt hypothyroidism is between one and two per 1,000 women per year. Thyroid antibodies and raised TSH values are more common in older rather than in younger women and are not clearly associated with goiter, which is most common in younger women. Although most cases of nodular goiter may be due to autoimmune disease, the etiology of the sporadically occurring diffuse goiter remains undetermined. Thyroid antibodies alone, and borderline raised TSH values alone in the range of 6 to 10 mU/L, do not significantly enhance the rate of development of overt hypothyroidism over four years; but in women with raised TSH values and the presence of thyroid antibodies, subclinical hypothyroidism progresses to overt hypothyroidism at the rate of at least 5% per year. This may justify prophylactic T4 therapy in such individuals. Data from population studies provide a basis for determining the cost effectiveness of screening programs for the early detection of thyroid dysfunction in the adult population.

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