Clinical Endocrinology (1995) 43, 55–68

The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey

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(Received 12 January 1995; returned for revision 16 February 1995; finally revised 17 March 1995; accepted 29 March 1995)

Summary

BACKGROUND AND OBJECTIVE The original Whickham Survey documented the prevalence of thyroid disorders in a randomly selected sample of 2779 adults which matched the population of Great Britain in age, sex and social class. The aim of the twenty-year follow-up survey was to determine the incidence and natural history of thyroid disease in this cohort.

DESIGN, PATIENTS AND MEASUREMENTS Subjects were traced at follow-up via the Electoral Register, General Practice registers, Gateshead Family Health Services Authority register and Office of Population Censuses and Surveys. Eight hundred and twenty-five subjects (30% of the sample) had died and, in addition to death certificates, two-thirds had information from either hospital/General Practitioner notes or post-mortem reports to document morbidity prior to death. Of the 1877 known survivors, 96% participated in the follow-up study and 91% were tested for clinical, biochemical and immunological evidence of thyroid dysfunction.

RESULTS Outcomes in terms of morbidity and mortality were determined for over 97% of the original sample. The mean incidence (with 95% confidence intervals) of spontaneous hypothyroidism in women was 3·5/1000 survivors/year (2·8–4·5) rising to 4·1/1000 survivors/year (3·3–5·0) for all causes of hypothyroidism and in men was 0·6/1000 survivors/year (0·3–1·2). The mean incidence of hyperthyroidism in women was 0·8/1000 survivors/year (0·5–1·4) and was negligible in men. Similar incidence rates were calculated for the deceased subjects. An estimate of the probability of the development of hypothyroidism and hyperthyroidism at a particular time, i.e. the hazard rate, showed an increase with age in hypothyroidism but no age relation in hyperthyroidism.

The frequency of goitre decreased with age with 10% of women and 2% of men having a goitre at follow-up, as compared to 23% and 5% in the same subjects respectively at the first survey. The presence of a goitre at either survey was not associated with any clinical or biochemical evidence of thyroid dysfunction. In women, an association was found between the development of a goitre and thyroid-antibody status at follow-up, but not initially.

The risk of having developed hypothyroidism at follow-up was examined with respect to risk factors identified at first survey. The odds ratios (with 95% confidence intervals) of developing hypothyroidism with (a) raised serum TSH alone were 8 (3–20) for women and 44 (19–104) for men; (b) positive anti-thyroid antibodies alone were 8 (5–15) for women and 25 (10–63) for men; (c) both raised serum TSH and positive anti-thyroid antibodies were 38 (22–65) for women and 173 (81–370) for men. A logit model indicated that increasing values of serum TSH above 2mU/l at first survey increased the probability of developing hypothyroidism which was further increased in the presence of anti-thyroid antibodies. Neither a positive family history of any form of thyroid disease nor parity of women at first survey was associated with increased risk of developing hypothyroidism. Fasting cholesterol and triglyceride levels at first survey when corrected for age showed no association with the development of hypothyroidism in women.

CONCLUSIONS This historical cohort study has provided incidence data for thyroid disease over a twenty-year period for a representative cross-sectional sample of the population, and has allowed the determination of the importance of prognostic risk factors for thyroid disease identified twenty years earlier.

Relatively few data exist on the incidence of thyroid disease in the community. Although cross-sectional studies provide

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data on prevalence, longitudinal studies are necessary to determine incidence rates, aetiological risk factors, and the natural history of the disease process (Tunbridge & Caldwell, 1991).

The original Whickham Survey, conducted between 1972 and 1974 in a mixed urban and rural area close to Newcastle upon Tyne, enrolled a randomly selected sample of 2779 adults which closely resembled the British population structure in age, sex and social class. Documented information included a questionnaire concerning details of thyroid disorders and clinical findings including thyroid size. Detailed thyroid function tests, autoantibody screen including anti-thyroid microsomal and anti-thyroglobulin antibodies, and fasting lipid profile were performed (Tunbridge *et al.*, 1977a,b).

This study was unique in providing data on the prevalence of thyroid disorders in a representative cross-section of the community.

The initial aim of the twenty-year follow-up survey was to determine the incidence and natural history of thyroid disorders in the community by establishing the outcomes in terms of thyroid disease of the total original survey population.

Experimental design and methods

Population

Two thousand seven hundred and seventy-nine subjects (82·4% of the available sample) were included in the original study. They were a systematic sample of the adult population drawn from the Electoral Register with the first name chosen at random and every sixth name selected thereafter. Subjects were traced at follow-up via the Electoral Register, General Practice Registers of the Whickham and Dunston Practices, Gateshead Family Health Service Authority (FHSA) Register and finally the National Health Service Central Register division of the Office of Population Censuses and Surveys (OPCS).

Sources of information

Subjects were approached in joint consultation with their general practitioners (GP) and invited to attend local study clinics at Dunston Health Centre or Dunston Hill Hospital in Gateshead after an overnight fast. Home visits were offered to subjects who resided in Durham and Northumberland. Those subjects who had moved away from the Northern Region, and who were not visiting the North-East, were first asked to answer a short postal questionnaire; subsequently more detailed information was obtained by telephone. Blood samples taken by their GP were forwarded by post to the central laboratory at Newcastle General Hospital after centrifugation locally to prevent deterioration in transit.

For those subjects who did not respond positively to the initial letter from their GP, one further personal approach was made by a member of the survey team. A home visit or limited questionnaire was completed for those still unwilling to attend the study clinic. If this final approach yielded no information, GP and hospital notes were scrutinized where possible to identify morbidity and assess comparabilities of non-responders and participants. GP records of subjects who were untraced or who had emigrated were examined, if available, for information on their health status at their last contact with their GP.

Death certificates of subjects who had died were requested and causes of death classified by OPCS according to the 9th revision of the International Classification of Diseases (ICD) codes (World Health Organization, 1977). Information was sought from GP records, hospital records and post-mortem reports to identify other morbidity as well as the factors recorded on the death certificate as contributing to death.

Methods of enquiry

Subjects completed a verbal questionnaire administered by a member of the survey team. The structure and content of the questionnaire were similar to those used in the first survey (Tunbridge *et al.*, 1977a) and in addition, a history of relevant events during the intervening years was sought. Information documented included: personal details, personal and family history of goitre, hyperthyroidism or hypothyroidism with details of any treatment, symptoms and signs consistent with hyperthyroidism or hypothyroidism and current medication. A proforma was designed for use as a limited or telephone questionnaire for those subjects unable to attend the study clinics and who could not be visited at home. A separate proforma was designed to document morbidity prior to date of last contact or death in relevant subjects.

Thyroid size was graded according to palpability and visibility (WHO classification (Querido *et al.*, 1974)) as follows: A, not visible and not palpable; B, not visible, palpable but of normal size and consistency (both corresponding to WHO Stage O-A, i.e. no goitre); C, not visible, but palpable and enlarged (WHO Stage O-B); D, visible with neck extended and palpably enlarged (WHO Stage 1); E, visible goitre with neck in normal position (WHO Stage 2 and above). Subjects were classified as having a goitre at follow-up if the thyroid was thought

clinically to be palpable and abnormal (Grade C or WHO Stage O-B as above). Prior to the survey, the seven field-workers were trained in the administration of the questionnaire and examination techniques so that standardization could be achieved. The effect of observer variation with regard to detection of goitre was analysed over the period of the survey. At the completion of the field work, a cross-tabulation between observers and grading of goitre size was used to calculate a significant overall χ^2 of 118 with 24 d.f.. When each observer's contribution to the total χ^2 was examined, it was noted that one observer classified thyroid Grade A less often and Grade B more often than would be expected by chance; however, Grades A and B are considered to be clinically normal. Another observer, who examined 9% of the total subjects, classified thyroid Grade B less often and goitre (Grades C–E) more often. The age and sex distribution of subjects examined varied considerably between observers so some degree of deviation would be expected. In addition, if there was any doubt in classification of goitre size at the time of examination, the thyroid was palpated independently by another member of the survey team and the grading agreed.

Laboratory tests

Anti-thyroid microsomal and anti-thyroglobulin antibodies were measured by particle agglutination (Serodia-AMC and Serodia-ATG diagnostic kits, Fujirebio Inc., Tokyo, Japan) and were scored as positive if either was present at titres $\geqslant$ 1:100. (At the first survey, anti-thyroglobulin antibodies were measured by a tanned red cell technique and scored as positive if present at a titre $\geqslant$ 1:20. Anti-thyroid cytoplasmic antibodies were detected by immunofluorescence technique and scored as positive if present in serum diluted 1:10. Anti-microsomal antibodies were also measured by microhaemagglutination technique and were present at a titre $\geqslant$ 1:100 in 80% of sera giving positive results by immunofluorescence techniques. Subjects were classified as anti-microsomal antibody weakly positive (antibody titre 1:100–1:200), moderately positive (1:400–1:800) and strongly positive (> 1:800)).

Serum TSH and free thyroxine (FT4) were measured by an enzyme-linked assay system (ELISA) (ES300 analyser, Boehringer Mannheim, Lewes, England). The interassay coefficient of variation (CV) for serum TSH was 9% at 0·6, 4% at 4·3 and 5% at 26·2mU/l and for FT4 was 5% at 3·6, 3% at 13·4 and 2% at 55·3 pmol/l. Subjects with serum TSH concentrations < 0·5 mU/l and/or FT4 concentrations > 26 pmol/l on initial testing had total triiodothyronine (TT3) (ELISA assay on ES300 analyser, Boehringer Mannheim, Lewes, England; CV of 2% at 1·84 and 2% at 3·99 nmol/l) and a third generation TSH assay (confidence lower limit of detection of the assay of 0·01 mU/l) measured on the same specimen (Kodak Amerlite Third Generation TSH assay, Amersham, England; CV of 10% at 0·08 and 6% at 4·00 mU/l). Urinary iodine excretion, using the Sandell–Kolthofft colorimetric method (Dunn *et al.*, 1993) (CV of 6%) in single specimens, was measured in a randomly selected subsample of 102 surviving subjects over a 4-week period.

The field-work began in March 1992 and all the data were collected by 1 August 1993.

Data analysis

Data were stored on the mainframe computer at the University of Newcastle and verification procedures were carried out to ensure that there had been accurate transcription. The data from the original study were stored in a SPSS (Statistical Package for Social Sciences) system file which was compatible with programs written for the current study. Data were analysed using SPSS-X . All data were covered by the Data Protection Act.

Ethics

Ethical approval was granted by the Ethical Committees of Newcastle, Gateshead and Northumberland Health Authorities. In addition, approval was obtained from the Gateshead Local Medical Committee. There was close liaison between the general practitioners and the study doctors, followed by written consent from each subject. Information sheets given to the subjects stated that the interview and investigations were confidential, and that the results would be communicated in writing to the General Practitioner.

Results

Outcomes of total survey population

Table 1 summarizes the outcomes in terms of location at follow-up for the total original survey population of 2779 subjects. Almost 30% of the sample were still living at the same address and 80% of the survivors still resided within the district of Gateshead. Almost 30% of the sample had died and less than 3% were untraced.

Survivors. The overall median age of the survivors was 58 years (range 38–93 years). Of the survivors, 826 (44%) were men (median age when seen was 58 years) and 1051 (56%) were women (median age 59 years). Subjects currently residing in the North-East at follow-up were significantly

Table 1 Location of original Whickham Survey population at twenty-year follow-up ($n = 2779$)

Location	n	(%)
Living at same address	821	29·5
Living elsewhere in Gateshead	696	25·1
Living elsewhere in North-East England	231	8·3
Living elsewhere in Great Britain	127	4·5
Emigrated	22	0·8
No trace/no reply from GP	57	2·1
Dead	825	29·7
Total	2779	100

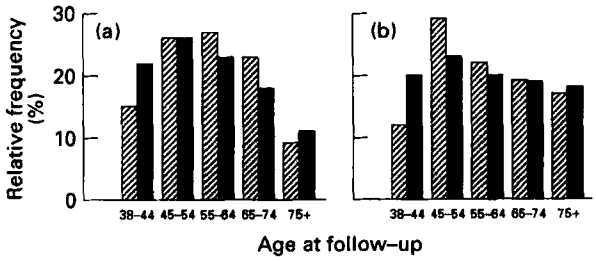

Fig. 1 The relative frequency of the population aged 38 and over at the twenty-year follow-up of ▨, the Whickham Survey compared to ■, the population of Great Britain (1991 Census). a, Men; b, women.

older (median age 59 years) than those living elsewhere in Great Britain (median age 53 years) (Mann–Whitney $P < 0·001$). The median duration of follow-up since the original survey was 19 years (range 18–21 years).

The sources of information gathered on the 1877 known survivors are shown in Table 2. In total, 96% agreed to provide information and for a further 3·6% information regarding morbidity was obtained from either GP or hospital records. At their GP's request 12 subjects were not approached owing to their ill health. For all 12 information was obtained from medical notes or from discussions with the GP. Two subjects who had emigrated were traced and gave information but were unable to provide a blood sample. The total number of blood samples obtained was 1704 including 73 by post. This represents 91·5% of those subjects alive and contactable within the UK (total number 1863).

In the follow-up survey, 63% agreed to participate in response to the first invitation and 16% in response to the second. A further 18% of the sample were recruited following a contact visit or telephone call. This total includes 187 subjects who initially declined to participate, but after a personal approach 142 (76%) agreed to supply further information.

Table 2 Sources of information in known survivors at twenty-year follow-up of the Whickham Survey ($n = 1877$)

Source	n	(%)
Attended study clinic	1470	78·4
Home visits	154	8·2
Telephone questionnaire	151	8·1
Postal questionnaire only	26	1·3
GP/hospital notes seen	67	3·6
No information	9	0·4
Total	1877	100

The age and sex distributions of the total known survivors were compared with those of the population of Great Britain aged $\geqslant 38$ years from the 1991 Census figures (OPCS, 1993) (Figs 1a and b). The sample at follow-up had fewer men and women aged less than 45 years but otherwise resembled the corresponding proportions of men and women in other age groups.

The total number of subjects for whom the outcome was not known at follow-up was 77 and comprised 20 subjects who had emigrated, five subjects who were registered with a GP in the UK, but whose GP did not respond to our request for their current address, and 52 subjects who were untraced.

Deceased. The overall median age at death of the 825 subjects was 72 years (range 22–99 years). Of these subjects, 421 (51%) were men (median age at death 71 years) and 404 (49%) were women (median age at death 76 years). The median duration from date seen in original survey to death was 10 years (range 1–20 years). A copy of the death certificate was obtained for all but one subject. GP or hospital notes were scrutinized for 448 (54%) and post-mortem reports were obtained for 176 (21%) of the deceased subjects. A total of 530 subjects (64%) had information from either notes or post-mortem reports to document morbidity other than that stated on death certificates. There was no significant difference in age at death between the group of subjects with notes or post-mortem records and the group of subjects for whom information was available only from death certificates (Mann–Whitney $P = 0·51$). Similar information was available for both sexes. By applying national mortality statistics to the age and sex distribution of the original Whickham Survey sample each year the expected mortality over 20 years was determined for this cohort and the standardized mortality ratio calculated was 99% for all cause mortality.

Table 3 Assessment of thyroid function in survivors ($n = 1704$)

TSH at follow-up in survivors (mU/l)	Number	On T4 treatment	THY AB+	FT4 (pmol/l)
⩾10·0	31	4	27	23↓
>5·2, <10·0	60	11	41	8↓
0·50–5·2	1540	32	224	69↓ 13↑
⩾0·05 <0·50	61	22	18	8↑
<0·05	12	4	3	6↑

TSH normal range 0·5–5·2 mU/l; FT4 normal range 12–26 pmol/l; positive anti-thyroid antibodies (THY AB+): anti-microsomal antibody and/or anti-thyroglobulin antibody titre ⩾1:100.

Assessment of thyroid function in survivors

Table 3 demonstrates the results of assessing thyroid function in surviving subjects.

There was a clearly raised serum TSH concentration above 10mU/l in 31 subjects of whom 27 (87%) had positive anti-thyroid antibodies. Four of these subjects were already taking thyroxine at the time of follow-up. In 23 subjects the FT4 concentration was below normal and they were unequivocally hypothyroid. In addition, four subjects had FT4 concentrations at the lower end of the normal range, had symptoms of hypothyroidism and were begun on thyroxine replacement by their family doctors as a result of the study.

In 60 subjects there was a more borderline raised serum TSH (>5·2–<10 mU/l) and 41 (68%) had positive anti-thyroid antibodies. Eleven of these were already on thyroxine. Two subjects who had serum TSH concentrations above 9mU/l, low FT4 concentrations and symptoms of hypothyroidism were also begun on thyroxine replacement.

In 61 subjects there was a reduced but measurable serum TSH (⩾0.05–<0·5 mU/l) of whom 22 were on thyroxine. Of the 18 subjects (30%) who had positive anti-thyroid antibodies, 14 had been previously diagnosed as hypothyroid and were taking thyroxine. One woman had a markedly elevated FT4 and TT3 and was newly diagnosed as hyperthyroid. When the sera from these subjects were tested using the third generation TSH assay (TSH_3), 20 subjects had serum TSH_3 within the normal range (0·17–2·89 mU/l), 29 had reduced but measurable serum TSH_3 (⩾0·01–<0·17 mU/l), and 12 (including one newly diagnosed as hyperthyroid) had a suppressed serum TSH_3 below the detection limit of the assay (<0.01 mU/l).

In 12 subjects there was a reduced serum TSH below the detection limit of the second generation assay (<0·05 mU/l). Four new cases of hyperthyroidism were identified: three women had markedly elevated FT4 and TT3, one had raised TT3 only, and two had positive anti-thyroid antibodies. Four subjects were on thyroxine, one having positive anti-thyroid antibodies. The remaining four subjects had normal FT4 and TT3 concentrations and no anti-thyroid antibodies. When tested using the third generation TSH assay, one subject had serum TSH_3 within the normal range (0·17–2·89 mU/l), two had reduced but detectable serum TSH_3 levels (⩾0·01–<0·17 mU/l) including one newly diagnosed as hyperthyroid, and nine, including three newly diagnosed as hyperthyroid, had a suppressed serum TSH_3 below the detection limit of the assay (<0.01 mU/l).

Thirteen subjects had raised FT4 (>26 pmol/l) with normal serum TSH levels (0·5–5·2 mU/l) but all had TT3 and third generation serum TSH levels within the normal range.

Figure 2 shows the distribution of serum TSH concentrations in male and female survivors measured at follow-up. The left-hand distribution for each sex shows the 2·5, 5, 50, 95 and 97·5 centiles for the total sample excluding those already on thyroxine therapy and on the right a similar distribution for a 'thyroid negative' group. This group had no personal or family history of thyroid disease, no clinical evidence of goitre, and no anti-thyroid antibodies at follow-up. The 2·5, 5, and 50 centiles are similar for both sexes in both groups. In men the 95 centile in the total group approximates to the 97·5 centile of the 'thyroid negative' group (4·15 *vs* 4·29 mU/l), whereas in women the 95 centile of the total group is greater than the 97·5 centile of the 'thyroid negative' group (5·97 *vs* 4·54 mU/l). A serum TSH concentration greater than 10 mU/l is clearly above the 97·5 centile of the total group in both sexes.

The median urinary iodine excretion for the random sample of 101 subjects (excluding one subject on amiodarone therapy) was 102μg/g creatinine (range 44-990). This result did not suggest iodine deficiency in the population.

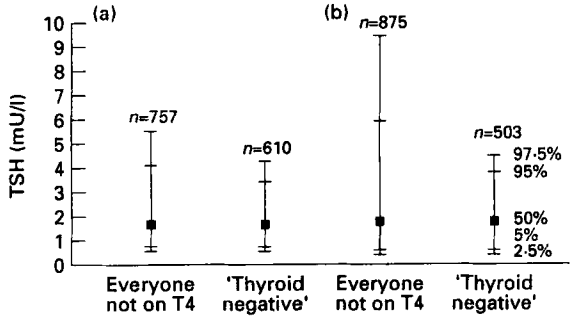

Fig. 2 TSH in survivors. a, Men; b, women.

Incidence of hypothyroidism

Table 4 shows the calculation of the incidence rate per

Table 4 Incidence of hypothyroidism and hyperthyroidism during twenty-year follow-up of the Whickham Survey

	Hypothyroidism			Hyperthyroidism	
	Women (n = 1051)		Men (n = 826)	Women (n = 1051)	Men (n = 826)
	Spontaneous	Total	Total	Total	Total
Known from 1st survey	12	16	1	25	2
Diagnosed since 1st survey	48	59	3	14	1
Detected at follow-up	21	22	7	5	—
Prevalence in survivors (%)	7·7	9·3	1·3	3·9	0·2
Incidence/1000 survivors/year	3·5	4·1	0·6	0·8	—
(95% Confidence intervals)	(2·8–4·5)	(3·3–5·0)	(0·3–1·2)	(0·5–1·4)	—
Incidence/1000 deceased/year	2·5	3·6	0·8	1·2	—
Mean age at diagnosis (years)	59·9	59·2	57·5	48·3	35·0

thousand per year of hypothyroidism in surviving and deceased women and men. Where the number of observed cases was sufficiently large to permit calculation of a realistic confidence interval, the 95% confidence limits are shown (Vollset, 1993).

Women. When seen at follow-up, 16 women (12 cases of spontaneous hypothyroidism and 4 following treatment of hyperthyroidism) were known to have been diagnosed and treated for hypothyroidism at the first survey, 59 (48 spontaneous, 11 post-treatment) had been identified and treated since the first survey and 22 subjects were newly identified at follow-up (21 spontaneous, 1 post-treatment). The prevalence of spontaneous hypothyroidism in the surviving women was 7·7% (total hypothyroidism 9·3%). The incidence rate (i.e. number of new cases) of spontaneous hypothyroidism per 1000 female survivors over the twenty-year follow-up was 3·5/1000/year (95% confidence interval (CI) 2·8–4·5) rising to 4·1/1000/year (CI 3·3–5·0) if all cases including those following destructive treatment for hyperthyroidism are included. From the morbidity data documented on 64% of the deceased subjects, ten had been diagnosed and treated for hypothyroidism since the first survey (6 spontaneous, 3 post-treatment, and 1 due to hypopituitarism). The incidence rates calculated, with a mean follow-up of 10·1 years, were 2·5/1000/year for spontaneous hypothyroidism rising to 3·6/1000/year for all causes of primary hypothyroidism.

The mean age at diagnosis of spontaneous hypothyroidism was 59 years and of total hypothyroidism in all women was 60 years. The incidence of spontaneous hypothyroidism over the twenty years increased steadily from 1·4/1000/year in female survivors aged 18–24 years at first survey to 6·7/1000/year if aged 65–74 at first survey. Only 9% of cases of spontaneous hypothyroidism in female survivors were diagnosed when aged less than 45 years, and 51% were diagnosed between the ages 45 and 64 years. The hazard rate, that is, the estimate of the probability of a woman developing hypothyroidism at a particular time, increases with age to 14/1000/year in those subjects aged between 75 and 80 years (Fig. 3).

Men. One male survivor was known to have been diagnosed and treated for hypothyroidism at the first survey, three men had been identified and treated since the first survey, and seven were identified at follow-up. The aetiology was spontaneous hypothyroidism in all but one subject who was on lithium therapy. A further subject was on thyroxine therapy for hypopituitarism. The prevalence of primary hypothyroidism in the surviving men was therefore 1·3% and the incidence rate over the twenty-year follow-up period was 0·6/1000/year (CI 0·3–1·2). From the morbidity data documented on 64% of the deceased subjects, two had been

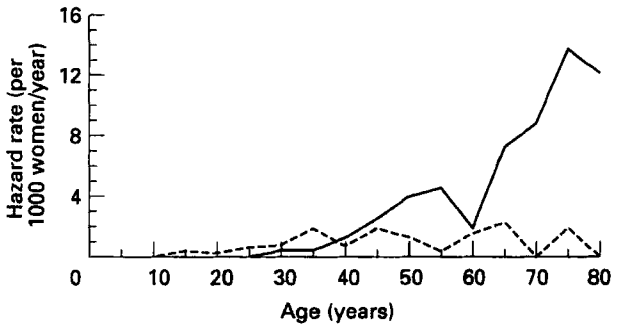

Fig. 3 The age-specific hazard rates for development of —, hypothyroidism, and ---, hyperthyroidism in women.

diagnosed and treated for hypothyroidism since the first survey (both spontaneous), and the incidence rate calculated, with a mean follow-up of 8·9 years, was 0·8/1000/year. The mean age at diagnosis of all men was 58 years.

Incidence of hyperthyroidism

Table 4 shows the calculation of the incidence rate per thousand per year of hyperthyroidism in surviving and deceased women and men.

Women. Twenty-five of the female survivors were known to have been diagnosed and treated for hyperthyroidism when first surveyed, three of whom subsequently relapsed. Eleven others had been diagnosed as hyperthyroid and treated since the first survey. The aetiology of hyperthyroidism in the 11 new cases was confirmed from medical records as Graves' disease in 7, multinodular goitre in 3 and Hashimoto's thyroiditis in 1. Five women with hyperthyroidism were detected at follow-up. The aetiology based on clinical findings was Graves' disease in 3, a solitary nodule in 1 and unknown in 1 with T3 toxicosis. The prevalence of hyperthyroidism (previously treated and new cases) in the surviving women was 3·9% and the calculated incidence rate over twenty years was 0·8/1000/year (CI 0·5–1·4). In addition, two women had developed Graves' ophthalmopathy with no documented biochemical disturbance of thyroid function. In the records of the deceased women, three new cases of hyperthyroidism (2 multinodular goitre, 1 Graves' disease) were identified and a similar incidence rate of 1·2/1000/year was calculated.

The mean age at diagnosis of hyperthyroidism was 48 years. The incidence of hyperthyroidism in female survivors over the twenty years is 2·2/1000/year in women aged 18–24 years at first survey and less than 1·0/1000/year at all other ages. In contrast to hypothyroidism, 44% of those with hyperthyroidism were diagnosed when aged less than 45 years and 38% were diagnosed between 45 and 64 years. The hazard rate for the development of hyperthyroidism showed no rise with age and averaged 1/1000/year between the ages of 35 and 60 years (Fig. 3). No association was found between either past or current anti-thyroid antibody status and the development of hyperthyroidism.

Men. One male survivor had a recurrent episode of hyperthyroidism diagnosed and treated since the first survey. There were no new cases of hyperthyroidism in male survivors or documented in deceased men. The incidence over twenty years was therefore negligible.

Treatment of hyperthyroidism. Eighteen per cent of subjects received drug treatment only, 40% received treatment by surgery only, and 33% received radioiodine therapy only. Nine per cent received a combination of treatments.

Table 5 Classification of thyroid size in survivors at follow-up according to classification of thyroid size at first survey

Thyroid size at 1st survey (WHO stage)	Thyroid size at follow-up					
	Women			Men		
	A,B	C	D,E	A,B	C	D,E
A,B (O–A)	623	25	13	674	9	2
C (O–B)	100	10	6	29	0	0
D,E (1,2)	82	11	22	6	1	1

Natural history of goitre

Table 5 shows the outcome in terms of whether a goitre was palpable at either the first or follow-up survey for men and women. At the first survey the frequency of goitre (C, D and E) ranged between 13 and 20% amongst regular observers but one occasional observer recorded no goitres and another found 24% with goitre. The frequency of goitre at follow-up ranged between 5 and 7% amongst six of the seven observers but the one observer who examined 9% of subjects classified goitre in 18%. The mean frequency of goitre for all observers was 7%.

Women. Of the surviving women, 10% had a palpable goitre at follow-up as compared to 26% in the same women at first survey. Six hundred and twenty-three (70%) women had no goitre at either survey, 38 (4%) developed goitres, 49 (6%) had goitres at both surveys, whilst 182 (20%) had a goitre at the first survey but not at follow-up. Of the 38 women who developed a goitre, one had been diagnosed as hyperthyroid at the first survey and none was hypothyroid. Three had developed hyperthyroidism since the first survey including one identified at follow-up and five had developed hypothyroidism (4 spontaneous, 1 post-treatment) including one identified at follow-up. Twenty-five had small goitres (Grade C) and 13 had obvious goitres (Grades D and E).

In the 182 women who had lost their goitre since the first survey, 100 had been reported to have had small goitres (Grade C) and 82 had had obvious goitres (Grades D and E). Nine had been diagnosed and treated for hyperthyroidism and one for hypothyroidism at first survey. Four had been newly identified as hyperthyroid, of whom two were recurrences, and 12 were newly identified as

Table 6 Natural history of anti-thyroid antibodies in survivors

Age (Follow-up)	Number	THY AB+ (1st survey) (%)	THY AB+ (Follow-up) (%)	Anti-thyroid antibodies		
				Kept (%)	Developed (%)	Lost (%)
Women						
<45	124	8·1	24·2	7·3	16·9	0·8
⩾45 <55	276	8·3	22·5	6·9	15·6	1·5
⩾55 <65	221	10·0	29·4	8·6	20·8	1·4
⩾65 <75	184	15·8	27·7	12·0	15·8	3·8
⩾75 <85	117	14·5	29·9	11·1	18·8	3·4
⩾85	20	20·0	30·0	20·0	10·0	0·0
Total	942	11·2	26·4	9·1	17·3	2·0
Men						
<45	111	1·8	4·5	0·0	4·5	1·8
⩾45 <55	190	3·2	6·8	3·2	3·7	0·0
⩾55 <65	211	3·3	12·3	2·8	9·5	0·5
⩾65 <75	189	3·2	8·5	2·7	5·8	0·6
⩾75 <85	52	0·0	11·5	0·0	11·5	0·0
⩾85	9	0·0	11·1	0·0	11·1	0·0
Total	762	2·8	8·8	2·2	6·6	0·5

hypothyroid (8 spontaneous, 4 post-treatment) including one identified at follow-up.

Those who had kept or developed a goitre were significantly younger than those who had never had, or who had lost a goitre (54·3 ± 10·1 *vs* 59·9 years ± 12·9; $P = 0·0001$).

Men. Of the surviving men, 2% had a palpable goitre at follow-up as compared to 5% in the same men at first survey. Six hundred and seventy-four men (93%) had no goitre at first survey or follow-up, 11 (2%) developed goitres, 2 (0·3%) had kept their goitres, whilst 35 (5%) had had a goitre previously but had not at follow-up. None of the 11 men who developed a goitre had been diagnosed as hyperthyroid or hypothyroid at first survey and none developed either condition over the twenty-year study period. Nine had small goitres (Grade C) and 2 had obvious goitres (Grades D and E). Of the 35 men who had lost their goitre, one had been diagnosed and treated for hyperthyroidism and one for hypothyroidism at the first survey. At follow-up one subject had had a recurrent episode of hyperthyroidism and none had had hypothyroidism.

In contrast to the women, the men who exhibited a goitre at follow-up were not significantly younger than those who never had, or who had lost a goitre (58·7 ± 11·5 *vs* 55·2 years ± 12·3; p = NS).

Goitre and TSH. There was no significant association in either men or women between the presence of goitre at follow-up and serum TSH concentration measured at first or follow-up survey.

Goitre and anti-thyroid antibody status. A significantly greater number of women with positive anti-thyroid antibodies at first survey exhibited a goitre at follow-up ($P = 0·02$) and a similar relation existed with respect to current anti-thyroid antibody status ($P = 0·0004$).

The women who had goitre at follow-up were divided into those who had kept a goitre and those who had developed a goitre since the first survey. In those who had kept a goitre a similar relation was seen with previous anti-thyroid antibody status ($P = 0·012$) and current anti-thyroid antibody status ($P = 0·012$). In those subjects who had developed goitre, there was no association with anti-thyroid antibody status at the first survey but there was an association with anti-thyroid antibody status at follow-up ($P = 0·005$).

In men there was no significant association between the presence of goitre at follow-up and anti-thyroid antibody status at either survey.

Natural history of anti-thyroid antibodies

Table 6 demonstrates the age distribution of women and men who had positive tests for anti-thyroid antibodies at

follow-up. In only one subject scored as anti-thyroid antibody positive was anti-thyroglobulin and not anti-microsomal antibody present.

Women. Of the female survivors 26% were anti-thyroid antibody positive at follow-up, 86 (9%) were anti-thyroid antibody positive at first and follow-up survey and 163 (17%) had developed anti-thyroid antibodies since the first survey. Of the 19 subjects (2%) who lost antibodies, six were known to be hypothyroid at the first survey and four had been diagnosed since the first survey. The remaining nine subjects had no history of thyroid disease: three had had weakly positive, five moderately positive and one strongly positive anti-microsomal antibodies at first survey. Table 6 demonstrates the age distribution of anti-thyroid antibodies in women and shows that the peak development of anti-thyroid antibodies occurred in the group aged 55–65 years at follow-up, i.e. 35–45 years at first survey.

Men. Of the male survivors, 9% were anti-thyroid antibody positive at follow-up, 17 (2%) were anti-thyroid antibody positive at first and follow-up survey, and 50 (7%) had developed anti-thyroid antibodies since the first survey. Of the four subjects (0·5%) who lost antibodies since the first survey none had a history of thyroid disease, one had had weakly positive, two moderately positive and one strongly positive anti-microsomal antibodies.

Risk factors for development of hypothyroidism

The risk in survivors of developing spontaneous hypothyroidism by the time of follow-up was examined with respect to the evidence of minor degrees of thyroid failure at the first survey. The odds ratio (with 95% confidence limits) of developing hypothyroidism in women with (a) raised serum TSH (> 6mU/l) alone was 8 (3–20); (b) positive anti-thyroid antibodies alone was 8 (5–15); (c) both raised serum TSH and anti-thyroid antibodies was 38 (22–65). Either risk factor alone or in combination is associated with a significantly increased risk of developing hypothyroidism. Table 7 demonstrates that the odds are greatly increased when both risk factors are present and that each has a similar effect.

In men, the odds ratio (with 95% confidence limits) of developing hypothyroidism with (a) raised serum TSH was 44 (19–104); (b) positive anti-thyroid antibodies was 25 (10–63); (c) both raised serum TSH and positive anti-thyroid antibodies was 173 (81–370). The smaller number of observed cases in men resulted in wide but highly significant confidence limits but also did not allow the calculation of the independent effects of these risk factors.

Table 7 Development of spontaneous hypothyroidism at follow-up in female survivors: odds ratios (with 95% confidence limits)

TSH raised, regardless of THY AB status	14 (9–24)
THY AB+ , regardless of TSH status	13 (8–19)
If THY AB– , effect of raised TSH alone	8 (3–20)
If THY AB+ , additional effect of raised TSH	5 (2–11)
If TSH normal, effect of THY AB+ alone	8 (5–15)
If TSH raised, additional effect of THY AB+	5 (1–15)
TSH raised and THY AB+, combined	38 (22–65)

In female survivors the annual risk of developing hypothyroidism was 4·3% per year if both raised serum TSH and anti-thyroid antibodies were present, 2·6% per year if raised serum TSH was present alone, and 2·1% per year if anti-thyroid antibodies were positive alone. At the time of follow-up, hypothyroidism had developed in 55% of the female survivors who initially had both raised serum TSH and positive anti-thyroid antibodies, 33% of those who had raised serum TSH alone, and 27% of those who had positive anti-thyroid antibodies alone.

The logit probability (log odds) of hypothyroidism in female survivors was plotted against log serum TSH as measured at first survey for the 912 women who had their serum TSH measured at first and follow-up survey. The data were smoothed for the purpose of graphical representation but the model was fitted to the actual raw data (Fig. 4). The

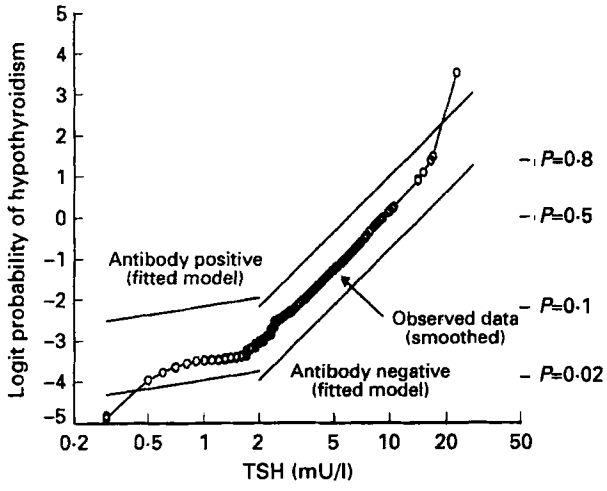

Fig. 4 Logit probability (log odds) for development within twenty years of hypothyroidism with increasing values of TSH as measured at first survey in 912 female survivors. $\log\{P/(1-P)\}$ $= b_0 + b_1 \ln \text{TSH} + 0{\cdot}27$ age ($+1{\cdot}79$ if antibody + ve). $b_0 = -5{\cdot}02$, $b_1 = 0{\cdot}30$ if TSH < 2 mU/l; $b_0 = -6{\cdot}38$, $b_1 = 1{\cdot}97$ if TSH ≥ 2 mU/l.

right hand vertical axis shows the equivalent probability of becoming hypothyroid in twenty years. The graph clearly indicates that a rise in serum TSH above 2 mU/l is associated with an increased probability of development of hypothyroidism. This probability is further increased if the subject was anti-thyroid antibody positive and decreased if anti-thyroid antibody negative. The relation indicated in this figure is independent of age. For example, a twofold increase in serum TSH from 2·5 to 5·0 mU/l (anti-thyroid antibody negative) would increase the probability from 0.01 to 0·04 (i.e. from 1 to 4%), a rise from 4·0 to 8·0 mU/l (anti-thyroid antibody positive) would increase the probability from 0·14 to 0·38, and a rise from 6·0 to 12 mU/l (anti-thyroid antibody negative) would increase the probability from 0·06 to 0·19. The coefficients of the fitted model are shown in the legend of Fig. 4. In practice, this would indicate that the probability of developing hypothyroidism twenty years later in a 50-year-old woman with a serum TSH of 6·0 mU/l and positive anti-thyroid antibodies is 0·57 (57%).

The development of spontaneous hypothyroidism in the 92 female survivors who were anti-thyroid antibody positive measured by the microhaemagglutination technique but not hypothyroid at first survey correlated with the strength of titre of anti-microsomal antibodies. In total 38% of the female survivors who were initially anti-microsomal antibody positive by microhaemagglutination had developed hypothyroidism twenty years later: 4% if negative, 23% if weakly positive (odds ratio (OR) 8 (3–19)), 33% if moderately positive (OR 13 (7–24)), and 53% if strongly positive (OR 29 (17–49)).

A positive family history of thyroid disease, the presence of goitre at either first or follow-up survey, or increased parity in women were not associated with increased odds of developing hypothyroidism. Fasting cholesterol and triglyceride level at first survey, when corrected for age, did not show an association with the future development of hypothyroidism in women.

Discussion

The problems encountered by epidemiological studies of thyroid disorders are those of definition, e.g. overt hypothyroidism and subclinical hypothyroidism, selection criteria of the population studied and the influence of age, sex, environmental factors and the different techniques used for the measurement of thyroid function. Most cross-sectional studies have concentrated on middle-aged women and elderly people in the community (Kågedal *et al.*, 1981; Nyström *et al.*, 1981; Falkenberg *et al.*, 1983; Okamura *et al.*, 1989; Parle *et al.*, 1991), hospital clinics (Baldwin & Rowett, 1978; dos Remedios *et al.*, 1980), and hospital in-patients (Kaplan *et al.*, 1982; Gow *et al.*, 1986; Small *et al.*, 1990; DeGroot & Mayor, 1992). The original Whickham Survey documented the prevalence of thyroid disorders in a cross-section of the adult population in the community (Tunbridge *et al.*, 1977a). The standardized mortality ratio for this cohort compared with national mortality rates for all cause mortality was 99%. The Whickham Survey cohort has been shown to be representative of the British population in terms of age and sex distribution (Fig. 1) and mortality over twenty years.

Despite the obvious limitations in methodology, that is, no regular follow-up at intervals during the twenty years and the use of medical records, information concerning outcomes was established in over 97% of the sample thus confirming a very stable community. Detailed data on morbidity, essential as thyroid disease is rarely mentioned on death certificates, were collected on 87% of the total sample.

This study has estimated the annual incidence of spontaneous hypothyroidism over twenty years to be 3·5 per 1000 in women and 0·6 per 1000 in men. At the first survey the definition of overt hypothyroidism was based on clear clinical findings as well as biochemical criteria. In the follow-up survey the definition of a new case was on an intention-to-treat basis by the general practitioner. All new cases fulfilled clear biochemical criteria and the majority had symptoms consistent with hypothyroidism but none were clinically obvious at follow-up. The annual risk of developing hypothyroidism in women is 4·3% when both anti-thyroid antibodies are present and serum TSH is raised. This has confirmed the data from the four-year follow-up of a sub-sample of women in the Whickham Survey cohort in whom overt hypothyroidism had developed at a rate of 5% per year (Tunbridge *et al.*, 1981). Either alone however was not associated with an increased risk at four years. The current study has demonstrated that the presence of anti-thyroid antibodies or raised serum TSH alone was associated with a highly significantly raised risk of developing hypothyroidism at twenty years. It has also demonstrated that, independent of age, the higher the serum TSH above 2mU/l, the greater is the prognostic significance for the development of overt hypothyroidism in subjects with or without anti-thyroid antibodies (Fig. 4).

Other incidence data for hypothyroidism are available only from short follow-up studies (Hawkins *et al.*, 1980; Nyström *et al.*, 1981). A four-year follow-up of 22 selected young and middle-aged women with asymptomatic autoimmune thyroiditis found that overt hypothyroidism developed at a rate of 7·3% per annum, increasing to 10% per annum in those who initially had serum TSH values greater than 19 mU/l (Gordin & Lamberg, 1975; 1981). A

follow-up of 437 healthy women aged 40–60 years found that in those who initially had a normal serum TSH, 24% of anti-microsomal antibody positive women developed an elevated serum TSH (> 4·2 mU/l) ten years later, compared with 3% in the anti-microsomal antibody negative group (Geul *et al.*, 1993). Serum TSH levels in the upper part of the normal range (between 2·0 and 4·2 mU/l) also appeared to be predictive in this study. Studies in elderly subjects have confirmed the prognostic significance of positive anti-thyroid antibodies and raised serum TSH in this age group (Lazarus *et al.*, 1984; Rosenthal *et al.*, 1987; Parle *et al.*, 1991; Sundbeck *et al.*, 1991).

The present study has important implications for the recommendation of treatment of asymptomatic women with markers of thyroid disease, i.e. subclinical hypothyroidism. Not only is the presence of raised serum TSH and anti-thyroid antibodies associated with a significant risk of developing hypothyroidism, but it has also been suggested that there may be additional beneficial effects of thyroxine therapy upon lipid measurements in subclinical hypothyroidism (Franklyn *et al.*, 1993). In view of the annual risk of developing hypothyroidism of approximately 5%, most clinicians already treat those subjects who have both raised serum TSH and anti-thyroid antibodies, providing no contraindication is present. If a raised serum TSH alone is found the annual risk of developing hypothyroidism is 2·6%. This can be discussed with the subject. The theoretical risks of lifelong thyroxine therapy (Toft, 1993) can be balanced against the need for regular long-term follow-up in the expectation that one-third of such women will become hypothyroid within twenty years. If anti-thyroid antibodies alone are found then a check of thyroid function approximately every 3–5 years is recommended.

In the current study, 21% of the women who were aged 55–65 years at follow-up (and who were therefore aged 35–45 years at first survey) had developed anti-thyroid antibodies, their appearance coinciding with the menopause. It has been suggested in a survey of unselected pregnant women in South Wales that the prevalence of post-partum thyroiditis is 5–9%, with one quarter of affected women in prospective studies developing permanent thyroid impairment within 4 years (Othman *et al.*, 1990). The facts that the mean age of onset of spontaneous hypothyroidism in the women of the Whickham sample was 60 years and that parity documented at first survey was not associated with significant odds of developing hypothyroidism suggest that post-partum thyroiditis was not a significant aetiological factor for the development of hypothyroidism in this cohort. Parity at first survey however may not be indicative of final parity.

Treatment of hypothyroidism with thyroxine is associated with a decrease or disappearance of anti-thyroid antibodies (Jansson *et al.*, 1985; Takusu *et al.*, 1992). Ten women who had received thyroxine treatment for hypothyroidism since the first survey had lost anti-thyroid antibodies. In addition, 13 survivors (10%) had lost anti-thyroid antibodies, had not developed evidence of thyroid dysfunction and might be assumed to be false positives at the original survey. The methodology for the detection of anti-thyroid antibodies in the follow-up survey has increased sensitivity and specificity compared with the techniques used in the first survey. However, the laboratory results on the initial sample were confirmed on repeat testing and these subjects may genuinely have lost antibodies over twenty years. In other shorter longitudinal studies, one-third of subjects initially anti-thyroid antibody positive in a population survey no longer had detectable antibodies 6 years later (Hawkins *et al.*, 1980), whereas a five-year follow-up study of a sample of healthy elderly people aged over 70 years found that, despite significant fluctuations in antibody titre, all 51 subjects who were originally anti-thyroid antibody positive remained positive at follow-up (Lazarus *et al.*, 1984).

Incidence rates for hyperthyroidism in the community from large population studies average 0·1/1000/year in men and 0·4/1000/ year in women, but the age-specific incidence varies considerably (Furszyfer *et al.*, 1970; Mogensen & Green, 1980; Barker & Phillips, 1984; Haraldsson *et al.*, 1985; Berglund *et al.*, 1990). The peak age-specific incidence of Graves' disease was between 20 and 49 years in two studies (Furszyfer *et al.*, 1970; Mogensen & Green, 1980), but increased with age in Iceland (Haraldsson *et al.*, 1985) and peaked at 60–69 years in Malmö (Berglund *et al.*, 1990). The difference in mean incidence rates in women between these studies and the current study would suggest that many cases of hyperthyroidism may remain undiagnosed in the community if routine testing is not undertaken. The relatively small number of cases identified since the first survey did not allow a clear relation with age to be demonstrated. Other cohort studies in middle-aged and elderly women do however provide comparable data (Nyström *et al.*, 1984; Parle *et al.*, 1991; Sundbeck *et al.*, 1991). The assessment of thyroid function in survivors confirmed the lack of association between below normal serum TSH values (< 0·05 mU/l) and anti-thyroid antibodies found by Parle *et al.* (1991). The third generation serum TSH assay gave no diagnostic information in this group over and above that obtained from the original assessment by the second generation serum TSH assay.

The definition of goitre is based on a relatively imprecise clinical observation. The current study found that only 14% of women and no men with a goitre graded C at the first survey were found to have a goitre at follow-up. It has been

shown that the observer variation is greatest in deciding whether a thyroid that is palpable but not visible is normal (Grade B) or enlarged (Grade C) (MacLennan *et al.*, 1969). There is also considerable overlap between the five grades when compared with thyroid volume estimated by ultrasonography (Jarløv *et al.*, 1992). More recently, ultrasonography has been used in epidemiological studies to assess enlargement of the thyroid gland (Brander *et al.*, 1991; Hintze *et al.*, 1991; Nygaard *et al.*, 1993) and as a consequence the prevalence of goitre found is much higher than in studies where goitre size has been assessed by physical examination.

The decline in frequency of goitre with age demonstrated in cross-sectional surveys (Kilkpatrick *et al.*, 1963; Dingle *et al*, 1966; Tunbridge *et al*, 1977a) is confirmed by the present longitudinal study. In a twenty-year follow-up of a sample of a south-western United States population aged 11–18 years, spontaneous regression by the age of 30 years occurred in 60% of subjects who initially had diffuse goitres (Rallison *et al.*, 1991). In contrast, a retrospective study of a selected clinic population in Japan, found that diffuse goitres disappeared in only 5% of a subsample of 108 subjects after eight years of follow-up, and 7% of these subjects with goitre developed thyroid dysfunction (Hara *et al.*, 1993). The current study has shown that the presence of a 'simple' goitre is not predictive of any biochemical or clinical evidence of thyroid dysfunction over twenty years.

The aetiology of 'simple goitre' is complex. A dominant role in the pathogenesis has been attributed to TSH which is a potent stimulator of thyroid growth, whilst the presence of thyroid growth-stimulating immunoglobulins would suggest an autoimmune process (Stuber & Gerber, 1991). The current study found in women who developed goitre no association with serum TSH measured at either survey. However an association was found with anti-thyroid antibody status at follow-up but not at first survey. The inference is that these women have developed a goitre and become anti-thyroid antibody positive since the first survey but the order in which these events occurred is unknown.

This study has provided incidence data for thyroid disease over a twenty-year period for a representative cross-section of the population, similar to that of the United Kingdom in age, sex and social class. It has also allowed the determination of the significance of prognostic risk factors for thyroid disease first identified twenty years ago.

Acknowledgements

The authors wish to thank the people of Whickham and Dunston for participating in the follow-up survey; the General Practitioners and Practice Staff, and in particular those of Whickham and Dunston for their cooperation; the staff of Dunston Hill Hospital and Dunston Health Centre for their hospitality; the Medical Records Department staff of Queen Elizabeth Hospital Trust, Gateshead, Gateshead FHSA, and OPCS for their assistance; Mr A. McGill, Dr A. Fleetwood, Dr G. Spickett and the laboratory staff of the Biochemistry and Immunology Departments, Newcastle General Hospital for their collaboration; Dr H. Perrild and Mr E. Christiansen, Department of Clinical Chemistry, Copenhagen, Denmark for the urinary iodine analysis; Professor K.G.M.M. Alberti, Department of Medicine, University of Newcastle, for his support and encouragement.

Financial support was gratefully received from the following: Department of Health, Newcastle District Research Committee, Northern Regional Health Authority Small Grants Committee, and Novo-Nordisk Ltd. MPJV was generously supported by a Northern Regional Research Fellowship.

References

Baldwin, D.B. & Rowett, D. (1978) Incidence of thyroid disorders in Connecticut. *Journal of the American Medical Association*, **239**, 742–744.

Barker, D.J.B. & Phillips, D.I.W. (1984) Current incidence of thyrotoxicosis and past prevalence of goitre in 12 British towns. *Lancet*, **ii**, 567–570.

Berglund, J., Christensen, S.B. & Hallengren, B. (1990) Total and age-specific incidence of Graves' thyrotoxicosis, toxic nodular goitre and solitary toxic adenoma in Malmö 1970-1974. *Journal of Internal Medicine*, **227**, 137–141.

Brander, A., Viikinkoski, P., Nickels, J. & Kivisaari, L. (1991) Thyroid gland : US screening in random adult population. *Radiology*, **181**, 683–687.

DeGroot, L.J. & Mayor, G. (1992) Admission screening by thyroid function tests in an acute general care teaching hospital. *American Journal of Medicine*, **93**, 558–564.

Dingle, P.R., Ferguson, A., Horn, D.B. Tubmen, J. & Hall, R. (1966) The incidence of thyroglobulin antibodies and thyroid enlargement in a general practice in North-East England. *Clinical and Experimental Immunology*, **1**, 277-284.

Dunn, J.T., Crutchfield H.E., Gutekunst R. and Dunn A.D. (1993) Two simple methods for measuring iodine in urine. *Thyroid*, **3**, 119–123.

Falkenberg, M., Kågedal, B. & Norr, A. (1983) Screening of an elderly female population for hypo- and hyperthyroidism by use of a thyroid hormone panel. *Acta Medica Scandinavica*, **214**, 361–365.

Franklyn, J.A., Daykin, J., Betteridge, J., Hughes, E.A., Holder, R., Jones, S.R. & Sheppard, M.C. (1993) Thyroxine replacement therapy and circulating lipid concentrations. *Clinical Endocrinology*, **38**, 453–459.

Furszyfer, J., Kurland, L.T., McConahey, W.M. & Elveback, L.R. (1970) Graves' disease in Olmsted County, Minnesota, 1935 through 1967.*Mayo Clinic Proceedings*, **45**, 636–644.

Geul, K.W., van Sluisveld, I.L.L., Grobbee, D.E., Docter, R., de Bruyn, A.M., Hooykaas, H., van der Merwe, J.P., van Hermert,

A.M., Krenning, E.P., Henneman, G. & Weber, R.F.A. (1993) The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women : associations with serum lipids. *Clinical Endocrinology*, **39,** 275–280.

Gordin, A. & Lamberg, B-A. (1975) Natural course of symptomless autoimmune thyroiditis. *Lancet*, **ii,** 1234–1238.

Gordin, A. & Lamberg, B-A. (1981) Spontaneous hypothyroidism in symptomless autoimmune thyroiditis. A long-term follow-up study. *Clinical Endocrinology*, **15,** 537–543.

Gow, S.M., Elder, A., Caldwell, G., Bell, G., Seth, J., Sweeting, V.M., Toft, A.D. & Beckett, G.J. (1986) An improved approach to thyroid function testing in patients with non-thyroidal illness. *Clinica Chimica Acta*, **158,** 49–58.

Hara, T., Tamai, H., Makuta T., Fukata, S., Kuma, K. & Nakagwa, T. (1993) A long-term follow-up study of patients with non-toxic diffuse goitre in Japan. *Clinical Endocrinology*, **39,** 541–546.

Haraldsson, A., Gudmundsson, S.T., Larusson, G. & Sigurdsson, G. (1985) Thyrotoxicosis in Iceland 1980-1982. An epidemiological survey. *Acta Medica Scandinavica*, **217**, 253–258.

Hawkins, B.R., Cheah, P.S., Dawkins, R.L., Whittingham, S., Burger, H.G., Patel, Y., Mackay, I.R. & Welborn, T.A. (1980) Diagnostic significance of thyroid microsomal antibodies in randomly selected population. *Lancet*, **ii,** 1057–1059.

Hintze, G., Windeler, J., Baumert, J., Stein, H. & Kobberling, J. (1991) Thyroid volume and goitre prevalence in the elderly as determined by ultrasound and their relationships to laboratory indices. *Acta Endocrinologica*, **124,** 12–18.

Jansson, R., Karlsson, A. & Dahlberg, P.A. (1985) Thyroxine, methimazole, and thyroid microsomal autoantibody titres in hypothyroid Hashimoto's thyroiditis. *British Medical Journal*, **290,** 11–12.

Jarløv, E.A., Hegedüs, L., Gjørup, T. & Hansen, M.J. (1992) Inadequacy of the WHO classification of the thyroid gland. *Thyroidology*, **4,** 107–110.

Kågedal, B., Månson, J.C., Norr, A., Sörbo, B. & Tegler, L. (1981) Screening for thyroid disorders in middle-aged women by computer-assisted evaluation of a thyroid hormone panel. *Scandinavian Journal of Clinical and Laboratory Investigation*, **41,** 403–408.

Kaplan, M.M., Reed Larsen, P., Cranzt, F.R., Dzau, V.J. & Rossing, T.H. (1982) Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. *American Journal of Medicine*, **72,** 9–16.

Kilpatrick, R., Milne, J.S., Rushbrooke, M., Wilson, E.S.B. & Wilson, G.M. (1963) A survey of thyroid enlargement in two general practices in Great Britain. *British Medical Journal* **i,** 29–34.

Lazarus, J.H., Burr, M.L., McGregor, A.M., Weetman, A.P., Ludgate, M., Woodhead, J.S. & Hall, R. (1984) The prevalence and progression of autoimmune thyroid disease in the elderly. *Acta Endocrinologica*, **106,** 199–202.

MacLennan, R., Gaitán, E. & Clinton Miller, M. (1969) Observer variation in grading and measuring the thyroid in epidemiological surveys. *Pan American Health Organisation Scientific Publication*, **193,** 67–77.

Mogensen, E.F. & Green, A. (1980) The epidemiology of thyrotoxicosis in Denmark. Incidence and geographical variation in the Funen region 1972–1974. *Acta Medica Scandinavica*, **208**, 183-186.

Nygaard, B., Gideon, P., Dige-Petersen, H., Jespersen, N., Solling, K. & Veje, A. (1993) Thyroid volume and morphology and urinary iodine excretion in a Danish municipality. *Acta Endocrinologica*, **129,** 505–510.

Nyström, E., Bengtsson, C., Lindquist, O., Lindberg, S., Lindstedt, G. & Lundberg, P-A. (1984) Serum triiodothyronine and hyperthyroidism in a population sample of women. *Clinical Endocrinology*, **20,** 31–42.

Nyström, E., Bengtsson, C., Lindquist, O., Noppa, H., Lindstedt, G. & Lundberg, P-A. (1981) Thyroid disease and high concentration of serum thyrotrophin in a population sample of women. *Acta Medica Scandinavica*, **210,** 39–46.

Office of Population Censuses and Surveys (1993) *1991 Census. Sex, Age and Marital Status: Great Britain.* London, Her Majesty's Stationery Office.

Okamura, K., Ueda, K., Sone, H., Ikenoue, H., Hasuo, Y., Sato, K., Yoshinari, M. & Fujishima, M. (1989) A sensitive thyroid stimulating hormone assay for screening of thyroid functional disorder in elderly Japanese. *Journal of the American Geriatric Society*, **37,** 317–322.

Othman, S., Phillips, D.I.W., Parkes, A.B., Richards, C.J., Harris, B., Fung, H., Darke, C., John, R., Hall, R. & Lazarus, J.H. (1990) A long term follow up of post-partum thyroiditis. *Clinical Endocrinology*, **32,** 559–564.

Parle, J.V., Franklyn, J.A., Cross, K.W., Jones, S.C. & Sheppard, M.C. (1991) Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clinical Endocrinology*, **34,** 77–83.

Querido, A., Delange, F., Dunn, J.T., Fierro-Benítez, R., Ibbertson, H.K., Koutras, D.A. & Perinetti, H. (1974) Definitions of endemic goitre and cretinism, classification of goitre size and severity of endemias, and survey techniques. *Pan American Health Organisation Scientific Publication*, **292,** 267–272.

Rallison, M.L., Dobyns, B.M., Meikle, A.W., Bishop, M. Lyon, J.L. & Stevens, W. (1991) Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. *American Journal of Medicine*, **91,** 363–370.

dos Remedios, L.V., Weber, P.M., Feldman, R., Schurr, D.A. & Tsoi T.G. (1980) Detecting unsuspected thyroid dysfunction by the free thyroxine index. *Archives of Internal Medicine*, **140,** 1045–1049.

Rosenthal, K.J., Hunt, W.C., Garry, P.J. & Goodwin, J.S. (1987) Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. *Journal of the American Medical Association*, **258,** 209–213.

Small, M., Buchanan, L. & Evans, R. (1990) Value of screening thyroid function in acute medical admissions to hospital. *Clinical Endocrinology*, **32,** 185–191

Stuber, H. & Gerber, H. (1991) Pathogenesis of nontoxic diffuse and nodular goiter. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*, 6th edn (eds. L.M. Braverman and R.D. Utiger), pp. 1107–1118. J.B. Lippencott Company, Philadelphia.

Sundbeck, G., Lundberg, P-A, Lindstedt, G., Jagenburg, R. & Edén, S. (1991) Incidence and prevalence of thyroid disease in elderly women: results from the longitudinal population study of elderly people in Gothenburg, Sweden. *Age and Ageing*, **20,** 291–298.

Takusu, N., Yamada, T., Takusu, M., Komiya, I., Nagasawa, Y., Asawa, T., Shinoda, T., Aizawa, T. & Koizumi, Y. (1992) Disappearance of thyrotropin-blocking antibodies and sponta-

neous recovery from hypothyroidism in autoimmune thyroiditis. *New England Journal of Medicine*, **326,** 513–518.

Toft, A.D. (1993) Fine tuning of thyroxine replacement therapy. *Clinical Endocrinology*, **38,** 451–452

Tunbridge, W.M.G., Brewis, M., French, J.M., Appleton, D., Bird, T., Clark, F., Evered, D.C., Grimley Evans, J., Hall, R., Smith, P., Stephenson. J. & Young, E. (1981) Natural history of autoimmune thyroiditis. *British Medical Journal*, **282,** 258–262.

Tunbridge, W.M.G. & Caldwell G. (1991) The Epidemiology of Thyroid Diseases. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*, 6th edn (eds. L.M. Braverman and R.D. Utiger), pp. 578–587. J.B. Lippencott Company, Philadelphia.

Tunbridge, W.M.G., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Grimley Evans, J., Young, E., Bird, T. & Smith, P.A. (1977a) The spectrum of thyroid disease in the community: The Whickham Survey. *Clinical Endocrinology*, **7,** 481–493.

Tunbridge, W.M.G., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Grimley Evans, J., Young, E., Bird, T. & Smith, P.A. (1977b) Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clinical Endocrinology*, **7,** 495–508.

Vollset, S.E. (1993) Confidence intervals for a binomial proportion. *Statistics in Medicine*, **12,** 809-824.

World Health Organisation (1977) *International Classification of Diseases, 9th revision.* WHO, Geneva.