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THE INCIDENCE OF THYROGLOBULIN ANTIBODIES AND THYROID ENLARGEMENT IN A GENERAL PRACTICE IN NORTH-EAST ENGLAND

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SUMMARY

Antibodies to thyroglobulin in a titre of 1:25 or more were found in 16·2% of women and 4·3% of men between the ages of 21 and 80 years in a random sample of the population from a general practice in the north-east of England. The incidence of antibodies was highest in the seventh decade in both sexes. High antibody titres (1:78125 or more) were found in 4·6% of women and 1·6% of men and it is suggested that this may represent the incidence of diffuse thyroiditis in the population.

Significant thyroid enlargement was found in 12% of women and 0·9% of men, the corrected incidence of goitre obtained by averaging the frequency of goitres in each decade between 21 and 80 years was 8·9% and 0·9% respectively.

Antibodies to thyroglobulin are found in the circulation of 80% of patients with Hashimoto's disease, usually in high concentration and less frequently and usually in lower titre in myxoedema and thyrotoxicosis and in some patients without clinical thyroid disease (Roitt & Doniach, 1960).

Studies on the frequency and distribution of thyroglobulin antibodies have been confined to hospital patients or to certain selected groups of the population. Because of the variable selection factors operating in previous studies it seemed necessary to examine the frequency and distribution of thyroglobulin antibodies in a random sample of the population. In this paper we report our findings in a general practice in the north-east of England and compare them with the results of other studies. The opportunity was also taken to assess thyroid size in the same patients.

PATIENTS, MATERIALS AND METHODS

The patients we investigated belonged to a general practice of about 5750 patients at New Herrington near Newcastle upon Tyne in the north-east of England. Patients to be included

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in the study were selected at random from the practice list arranged in alphabetical order. Every tenth patient over the age of 21 years on 21 November 1962 was chosen. If the choice fell on a patient under 21 years then the following patient was selected, i.e. the eleventh, and if the eleventh patient was under 21 years then the preceding patient, i.e. the ninth was chosen. In this way a sample of 576 patients, about one-tenth of the practice and rather more than one-tenth of those over the age of 21 years was obtained. We excluded patients under 21 years as we felt that they would be less likely to co-operate in having blood taken for antibody testing.

Blood was taken from each patient and tested for thyroglobulin antibodies by the tanned red cell test using the formolized sheep cell preparation supplied by Burroughs Wellcome. We are indebted to Dr S. G. Owen for the performance of the test. Serial five-fold dilutions of an original 1:5 dilution of sera were made to estimate the titre of antibodies. For the purpose of this survey, titres of 1:25 and greater were considered positive.

Thyroid enlargement was classified by the method of Kilpatrick *et al.* (1963) (Table 1).

TABLE 1. Classification of degree of thyroid enlargement (Kilpatrick *et al.*, 1963)

	On inspection	On palpation
Stage 0	Not visible	Not palpable
Stage 1	Not visible	Palpable but less than 40 g
Stage 2	Visible	Palpable but less than 40 g
Stage 3	Visible	Palpable and more than 40 g

A goitre is regarded as a thyroid gland showing stage 2 or 3 enlargement. Uniformity of classification was achieved by the authors examining many hospital patients together before the survey was begun.

Of the 576 patients, 273 were males and 303 females. We were unable to trace fifty-seven patients, thirty-six men and twenty-one women because of inaccurate addresses, or their having left the district. This left available 519 patients, 237 men and 282 women of whom fifty (nineteen men and thirty-one women) refused investigation for various reasons, the frequency of refusal tending to be greater in older patients. In all, 469 of the 519 patients available participated in the survey, an acceptance rate of 92% in men and 89% in women, giving a mean figure of 90%. Apart from the exclusion of patients under 21 years the sample was random, and patients with thyroid disease were not excluded.

RESULTS

Tables 2 and 3 show the age distribution of the patients studied and the incidence of antibodies in each decade. All results are analysed in decades 30–39, 40–49 and so on apart from the 9-year period from 21 to 29 years.

Circulating antibodies to thyroglobulin were found in forty women and twelve men, incidences of 15·9% and 5·5% respectively. The corrected incidence averaging the frequencies in each decade was 16·2% in women and 4·3% in men, a female–male sex ratio of 3·8:1.

TABLE 2. Age distribution and incidence of antibodies in women

Age (years)	No. of patients	No. with thyroglobulin antibodies	Percentage of women with antibodies
21–29	45	2	4·4
30–39	66	12	18·2
40–49	41	5	12·2
50–59	39	8	20·5
60–69	36	9	25·0
70–79	18	3	16·7
80–89	6	1	16·7
Total	251	40	15·9

TABLE 3. Age distribution and incidence of antibodies in men

Age (years)	No. of patients	No. with thyroglobulin antibodies	Percentage of men with antibodies
21–29	26	0	0
30–39	46	2	4·4
40–49	60	5	8·3
50–59	47	2	4·3
60–69	23	3	13·0
70–79	13	0	0
80–89	3	0	0
Total	218	12	5·5

TABLE 4. Titres of thyroglobulin antibodies at different ages in women

Age (years)	Titre of antibodies (reciprocal)								
	25	125	625	3125	15625	78125	390625	2000000	>2000000
21–29	—	2	—	—	—	—	—	—	—
30–39	5	2	1	—	—	1	1	1	1
40–49	1	—	2	—	—	1	—	1	—
50–59	3	1	1	—	3	—	—	—	—
60–69	4	1	—	—	—	—	—	1	3
70–79	—	—	—	—	2	—	—	—	1
80–89	—	1	—	—	—	—	—	—	—

TABLE 5. Titres of thyroglobulin antibodies at different ages in men

Age (years)	Titre of antibodies (reciprocal)								
	25	125	625	3125	15625	78125	390625	2000000	>2000000
21–29	—	—	—	—	—	—	—	—	—
30–39	1	1	—	—	—	—	—	—	—
40–49	1	1	1	—	—	—	—	—	2
50–59	—	1	—	—	—	—	—	—	1
60–69	1	—	1	—	—	—	—	—	1
70–79	—	—	—	—	—	—	—	—	—
80–89	—	—	—	—	—	—	—	—	—

TABLE 6. Incidence of thyroid enlargement

Age group (years)	No. of patients examined		Stage 1		Stage 2		Stage 3	
	M	F	M	F	M	F	M	F
21–29	26	45	1	0	1	8	0	0
30–39	46	66	2	4	1	7	0	4
40–49	60	41	0	2	0	2	0	1
50–59	47	39	0	0	0	5	0	2
60–69	23	36	0	0	0	0	0	1
70–79	13	18	0	0	0	0	0	0
80–89	3	6	0	0	0	0	0	0
Total	218	251	3	6	2	22	0	8
%	46·5	53·5	1·4	2·4	0·9	8·8	0	3·2
Grand total	469		9		24		8	

TABLE 7. Percentage of different age-groups with goitre (stages 2 and 3 combined)

Age (years)	Male	Female
21–29	3·9	17·8
30–39	2·2	16·7
40–49	0	7·3
50–59	0	18·0
60–69	0	2·8
70–79	0	0
80–89	0	0

The incidence of antibodies was greatest in the seventh decade in both sexes. The titre of antibodies in the different age groups is shown in Tables 4 and 5. High levels of antibodies were found in a number of patients without clinical thyroid disease.

The total numbers of patients with thyroid enlargement is shown in Table 6. Table 7 shows the percentage of patients with goitre in the different age groups. The figure shows the

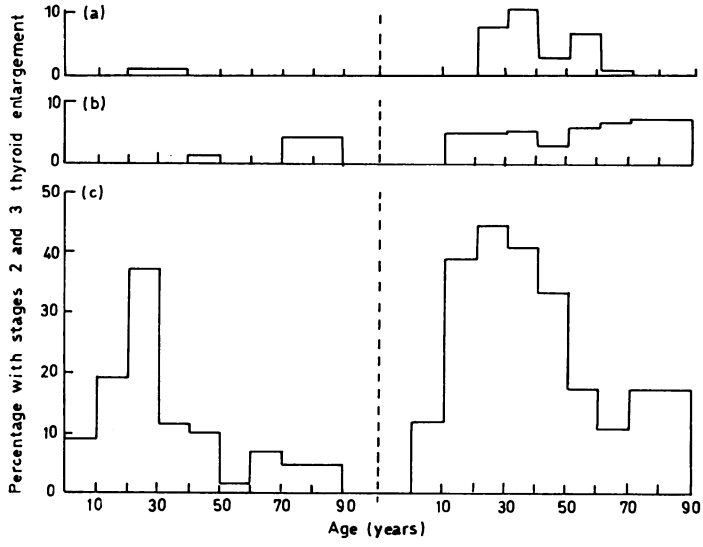

FIG. 1. Incidence of stages 2 and 3 thyroid enlargement at New Herrington (a) compared with that at Ormiston (b) and Sheffield (c) (Kilpatrick *et al.*, 1963). Left, male; right, female.

TABLE 8. Observer variation in ninety-three patients

Degree of thyroid enlargement found by P.D. and A.F.	Degree of thyroid enlargement found by R.H.			
	Stage 0	Stage 1	Stage 2	Stage 3
Stage 0	73	2	3 (1*)	0
Stage 1	0	1	2	0
Stage 2	4 (3*)	1	4	0
Stage 3	1	1	0	1

* Number of patients in given category who were pregnant or had recently been pregnant at the time of one of the examinations.

incidence of stages 2 and 3 thyroid enlargement compared with that found at Ormiston and Sheffield by Kilpatrick *et al.* (1963). It can be seen that the incidence of goitre at New Herrington was slightly greater than that at Ormiston but much less than that in Sheffield. The surveys are probably comparable since the criteria for thyroid enlargement were the same but variations between different groups of observers are always difficult to assess.

Observer variation in the survey

Almost 2 years after the patients had been examined by the general practitioners (P.D. and A.F.), ninety-three patients (fifty-nine women and thirty-four men) between the ages of 24 and 40 were examined by another observer (R.H.). The second examination was carried out independently without knowledge of the previous examination and the patients were chosen randomly.

The results are shown in Table 8. There was agreement in 85% of cases despite the lapse of time between the two examinations. In four women the discrepancy could be accounted for by one of the examinations having been made during or shortly after pregnancy. (Thyroid enlargement is common during pregnancy; Crooks *et al.*, 1964.) The incidence of goitre (stages 2 and 3 thyroid enlargement) in this sample was 18·6% in women and 3% in men (P.D. and A.F.), and 15·3% in women and 3% in men (R.H.), compared with the overall incidence of 17·3% in women and 3% in men for patients of the same age in the

TABLE 9. Thyroid abnormalities noted in antibody positive patients in sample of ninety-three patients

	Thyroglobulin antibody titre	Thyroid abnormality recorded
Women	1:125	Left lobe slightly enlarged and nodular
	1:125	Isthmus and left lobe just palpable and firm
	1:125	No thyroid enlargement
	1:625	Nodule 1 cm diameter in isthmus
	1:390625	Thyroid easily palpable on left
Men	1:25	Thyroid definitely enlarged on left side

whole survey. The incidences found by both observers are not significantly different from one another or from the practice as a whole, confirming that there was no bias in the selection of cases for observer variation.

Although there was no correlation between the presence of goitre and thyroid antibodies in the survey as a whole, in the sample of ninety-three patients examined by one of us (R.H.) minimal abnormalities of the thyroid were detected in all but one of the patients with antibodies as shown in Table 9. These abnormalities usually consisted of undue firmness, nodularity or asymmetry of the gland.

DISCUSSION

Data about the frequency and distribution of thyroglobulin antibodies in the general population have not previously been available. Reports of studies of control populations selected in various ways have been made by several workers (Hackett, Beech & Forbes, 1960; Hill, 1961). Most of the control patients were selected because of admission to hospital but some specimens were obtained from blood donors and from laboratories carrying out routine blood grouping or Wasserman testing. The incidence of thyroid autoimmunity in the population obtained from these selected series requires confirmation by investigation of a random sample of the population such as we report here.

The series published by Hackett *et al.* (1960) showed an incidence of antibodies of 26·7% in women and 9·3% in men but a titre of 1:10 was accepted as being positive compared with 1:25 in our study. Hackett's specimens were obtained from patients selected in a number of ways, for example by admission to a Professorial medical unit on which there was an interest in autoimmunity. Sera from cases of systemic lupus erythematosus and other collagen diseases were included as well as specimens showing abnormal electrophoretic patterns. Again patients with clinical thyroid disease were excluded from their series. Their higher incidence of antibodies can probably be explained by selection bias and the lower titre accepted as positive. Titres of 1:10 and lower are less reproducible and subject to observer variation in reading the test.

In the series published by Hill (1961), 579 sera sent to a laboratory for routine Wasserman testing and 700 sent to the blood transfusion service for grouping were tested for thyroglobulin antibodies. The notes of all patients whose sera contained antibodies were examined and those with clinically observed thyroid abnormality were removed from the series. Because of the source of the sera the series was biased to include pregnant women, patients suspected of venereal disease, surgical admissions and patients from a radiotherapy unit. The size of the series and the diversity of the sources may well compensate in part for selection bias. Hill's incidence of antibodies at titres of 1: 25 or more was 7% in women and 1·5% in men, figures lower than those we obtained, possibly due to his selection bias and the insensitive method used to screen the sera for antibodies.

Antibodies were found about four times more often in women than in men, the results being similar to those in the two series mentioned before. This sex distribution is similar to that reported by Masi and his associates (1965) for the frequency of Hashimoto's disease at autopsy and for the clinical incidence of myxoedema and Graves' disease. Clinically apparent Hashimoto's disease shows a much greater female preponderance, ratios varying from ten to twenty females for every male. The reason for this discrepancy is not clear.

The highest incidence of antibodies was found in the seventh decade in both sexes. Hackett *et al.* (1960) and Hill (1961) also found the peak incidence in the seventh decade in women though the peak was rather earlier in men. Similarly Goudie, Anderson & Gray (1959) testing the sera of 486 hospital patients without clinical thyroid disease for complement-fixing thyroid antibodies found most positive reactions in women over 50 years of age. Similar findings have been recorded with respect to gastric-autoimmunity (Irvine *et al.*, 1965).

What then is the clinical implication of the finding of circulating antibodies to thyroglobulin and how does this correlate with the histological appearance of the thyroid gland?

Schade *et al.* (1960) have shown that in various thyroid diseases—Graves' disease, toxic adenoma and non-toxic nodular goitre, circulating antibodies to thyroglobulin are significantly associated with lymphocytic infiltration of the thyroid gland. Buchanan *et al.* (1962) also found a correlation between the positivity of the complement-fixation test and the degree of lymphocytic infiltration of the thyroid in patients with thyrotoxicosis. There seems no reason to doubt that the finding of circulating thyroglobulin antibodies in the general population is also correlated with lymphocytic infiltration of the thyroid. Our findings suggest, therefore, that between the ages of 21 and 80 years 16·2% of women and 4·3% of men are likely to have significant lymphocytic infiltration of the thyroid gland.

This incidence is remarkably similar to that of focal thyroiditis a necropsy reported by

Williams & Doniach (1962). They found more than ten foci of lymphocytic infiltration per square centimetre area of a 6 μ thick thyroid section in 22% of adult females and 6% of adult males. A definite rise in the percentage of females with thyroiditis was noted after the age of 50.

The titre of thyroid antibodies is related in most cases to the degree of lymphocytic infiltration in the thyroid (Buchanan *et al.*, 1962). The incidence of patients in this survey with high levels of thyroglobulin antibodies (1:78125 or greater) was 4·6% in women from 21 to 79 years and 1·6% in men. Again this frequency is similar to that reported by Williams & Doniach (1962) for diffuse thyroiditis (more than forty foci of lymphocytic infiltration per square centimetre) at autopsy. In their study 4·5% of women and 1·1% of men had this severe degree of lymphocytic infiltration of the thyroid. Such frequencies probably represent the incidence of diffuse thyroiditis in the population and would lend support for Masi's view that Hashimoto's disease is more common than previously believed (Masi, 1965).

The difficulties which beset goitre surveys have recently been discussed by Kilpatrick *et al.* (1963). The main problems are to decide the degree of thyroid enlargement which is to be considered abnormal and to allow for observer variation. In the present survey similar incidences of goitre were recorded by the different observers suggesting that the frequency of goitre which we record in this area is a valid one. Our results confirm the striking regional differences in thyroid enlargement shown by Kilpatrick *et al.* (1963) at Ormiston and Sheffield though they throw no light on the causes for these differences.

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