individualised, and some patients may be deemed more suitable for haemodialysis.

HYPERTENSION, DIABETES AND RENAL DISEASE

Diabetic nephropathy was felt, until recently, to be more prevalent in patients with Type I than Type II diabetes. This is now recognised not to be the case and a significant public health problem looms. The prevalence of Type II diabetes is rising in an ageing population; patients with proteinuria are surviving much longer—to the point of developing end-stage renal disease—and this will undoubtedly place a considerable burden on end-stage renal disease programmes.

The previous view that diabetic nephropathy was less prevalent in Type II diabetes may have been an artifact due to a shorter survival in this group. In Erfurt (formerly in East Germany), 45 per cent of Type II patients died within 4 years of diagnosis. In Heidelberg (formerly in West Germany) the survival has been improving, possibly due to better control of hypertension and correction of other risk factors for vascular disease. Since German re-unification the proportion of Type II diabetic patients accepted onto chronic dialysis has increased dramatically in (former) East Germany, a trend observable also in the rest of Germany, Europe and the USA (where Type II diabetes accounts for between 50 and 80 per cent of all cases of end-stage renal failure).

Renal morphological changes observed in biopsies taken from Type II diabetics with nephropathy are more heterogeneous than in patients with Type I diabetes. In a series of 52 proteinuric patients with Type II diabetes typical changes of diabetic glomerulosclerosis were reported in only 19, with 16 showing chronic non-specific changes and 17 showed glomerular disease superimposed on diabetic glomerulosclerosis. In this series, as in others, changes of chronic ischaemia were prominent. Type I patients are reported as showing increased glomerular size; this is also the case with Type II diabetes in Pima Indians, who have large glomeruli even before the onset of diabetes.

In similar fashion to Type I patients, there seem to be a number of factors predicting the onset and progression of diabetic nephropathy. A positive family history of nephropathy or cardiovascular disease increases the risk of developing nephropathy in Type I and Type II patients, as does poor glycaemic control, poor control of blood pressure (BP) and (not well demonstrated until recently) a smoking habit. There seems to be an additional benefit in using ACE inhibitors to control BP in Type II patients as well as in Type I patients, but this benefit seems (at least in some studies) to be more marked when BP is not brought down to low levels.

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THE NATURAL HISTORY OF AUTOIMMUNE THYROIDITIS: HOW NORMAL IS AUTOIMMUNITY?*

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In 1912 Dr Hakuru Hashimoto described 4 women in whom the thyroid gland appeared to have been transformed into lymphoid tissue, *lymphomatosen veranderung*.[1] Despite the dramatic pathological changes (Fig 1), all 4 women were clinically euthyroid and presented simply with a swelling in the neck. Subtotal thyroidectomies were performed and it appears that all the patients became hypothyroid post-operatively, 'waxing and waning oedema'.[1] This early description of autoimmune thyroiditis raises several questions. What would have happened if Dr Hashimoto had not intervened? Would the women still have become hypothyroid? If not, would the *lymphomatosen veranderung* have ever come to attention had they had not developed visible goitres? And if it is possible to have lymphocytic infiltration of the thyroid without clinical sequelae, in what percentage of the apparently healthy population is this process occurring?

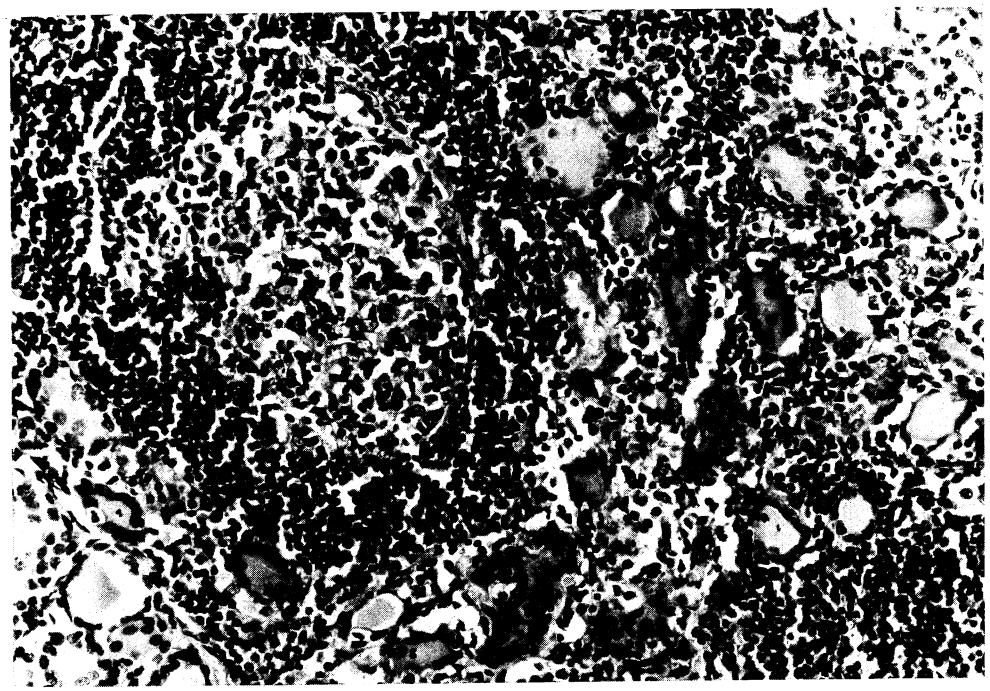

FIGURE 1

Histology of Hashimoto's disease showing dense lymphocytic infiltrate (courtesy of Dr E. Sheffield).

*A Croom Lecture delivered at the Symposium on *Antecedents of Adult Disease: the Paediatric Time Bomb* held in the College on 20 October 1995.

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Organ-specific autoimmune disease is easier to study in the thyroid than in any other organ for several reasons—the gland is readily accessible, subtle changes in thyroid function are easily measured and sensitive tests for thyroid autoantibodies have been available for over 30 years. Nonetheless, it has become apparent that large numbers of healthy individuals need to be studied over long periods of time, over 20 years, to address the questions raised by Dr Hashimoto's cases. The answers, therefore, are only just beginning to be known with any certainty. A remarkable picture is emerging of a process which begins in late childhood affecting such a high percentage of females that it might almost be described as 'normal', and progresses slowly but inexorably throughout adult life. Evidence from studies published over 30 years ago combined with very recent data support such a picture of the natural history of autoimmune thyroiditis. This has implications for our understanding and treatment of autoimmune diseases in general.

PREVALENCE OF THYROIDITIS IN POST-MORTEM STUDIES

In 1962, Williams and Doniach reported a study of thyroid histology in 724 consecutive post-mortems performed at the Hammersmith Hospital.[2] Remarkably, 45% of all females and 19% of all males aged over 20 years were found to have lymphocytic infiltration in their thyroid glands. Higher degrees of 'thyroiditis' were seen in fewer individuals as might be expected, but >10 lymphocytic foci per cm^2 were nonetheless present in 22% of females and 6% of males and >40 foci per cm^2 in 5–10% of females and 1–5% of males.[2] A second, larger post-mortem study of 2,040 individuals performed at a different time (1975–1992) and in a different part of the world (Johns Hopkins Hospital, Baltimore, USA) reproduced these findings almost exactly (Table 1). In the American series, over 100 thyroids were examined in each of the age groups 1–9 yrs, 10–19 yrs and 20–29 yrs. Significant degrees of lymphocytic infiltration were present amongst the teenagers and by their twenties, white females had thyroiditis rates approaching 40%. Little further increase in the prevalence of thyroiditis was seen until the eighth decade of life. Rates were 2–3 times higher in females than in males and also 2–3 times higher in whites than blacks.[3] Comparison with the epidemiology of clinical thyroid disease (see below) is required to appreciate the significance of these observations.

TABLE 1

Incidence of thyroid lymphocytic infiltration in post-mortem studies. Data shown are for all degrees of lymphocytic infiltration combined.[2,3] Around 40% of all women have some thyroid lymphocytic infiltration.

	Okayasu et al. 1994	*Williams & Doniach 1962*
White females >20 years old	41·4%	45%
White males >20 years old	20%	19%
Black females >20 years old	17·5%	
Black males >20 years old	8.5%	

INCIDENCE AND PREVALENCE OF CLINICAL THYROID DISEASE

Table 2 shows data from 8 published studies of the prevalence of hypothyroidism.[4–11] All of these are from iodine sufficient areas. Under such circumstances almost all spontaneous hypothyroidism is caused by autoimmune thyroiditis[12] and hence the results provide a good approximation of the rate of clinically significant disease due to autoimmune thyroiditis. Comparing studies involving in excess of 200 subjects, the prevalence of hypothyroidism appears to be in the range 0·3–1·7%, typically around 1%. A recent prospective study of the incidence of new hypothyroidism in females from the Whickam Survey indicates that clinical disease rarely develops below the age of 45 years (9% of cases) with 51% of new cases presenting between the ages of 45 and 64 years (Fig 2).[13] Women are affected 5–7 times more frequently than men.[13]

Comparison of these data with the post-mortem studies indicates that lymphocytic infiltration is up to 40 times more common than clinical disease. Even the prevalence of heavy lymphocytic infiltration (>40 foci/cm^2) is more than 5 times that of clinical hypothyroidism. Note also that the prevalence of hypothyroidism in males appears disproportionately low (half the rate of thyroiditis but one fifth the rate of hypothyroidism). Of particular interest, the appearance of clinical disease in females appears to be delayed by 20–30 years (age >45 years) when compared to the appearance of lymphocytic infiltration (age >20 years).

Caution must be applied in combining results from different population groups, in comparing incidence and prevalence figures, and in making conclusions about the natural history of a condition from cross-sectional studies. Nonetheless, the post-mortem and clinical data taken together do suggest a process that begins with lymphocytic infiltration in late teenage and early adulthood and takes 20 years or more to progress to clinically significant thyroid destruction. Furthermore, it appears that only a small proportion of those with subclinical thyroiditis, perhaps less than one in ten will progress to clinical disease in their lifetime. This would imply a large reservoir of subclinical disease in the population that might be detectable by subtle tests of thyroid function or the presence of thyroid autoantibodies. Cross-sectional studies of the prevalence of such markers confirm this.

TABLE 2

Prevalence of hypothyroidism. Summary of results from 8 separate cross-sectional studies of clinical hypothyroidism (low free T4).[4–11] Around 1% of women have hypothyroidism.

Study	*Age years*	*Number surveyed*	*Hypothyroid per cent*
Whickham 1977	>18	1494	1–1·5
Baldwin 1978	adult	1544	0·3
Lazarus 1984	>70	485	0·6
Sawin 1985	>60	2139	1·7
Rosenthal 1987	>60	258	0·8
Brochmann 1988 F	>70	113	1·2★
M	>70	113	0★
Falkenberg 1983	>60	1442	0·55
Parle 1991	>60	1210	1·5★

★Previous diagnoses excluded

PREVALENCE OF THYROID AUTOANTIBODIES AND SUBCLINICAL HYPOTHYROIDISM

Anti-thyroglobulin (Tg) autoantibodies were first identified in the serum of

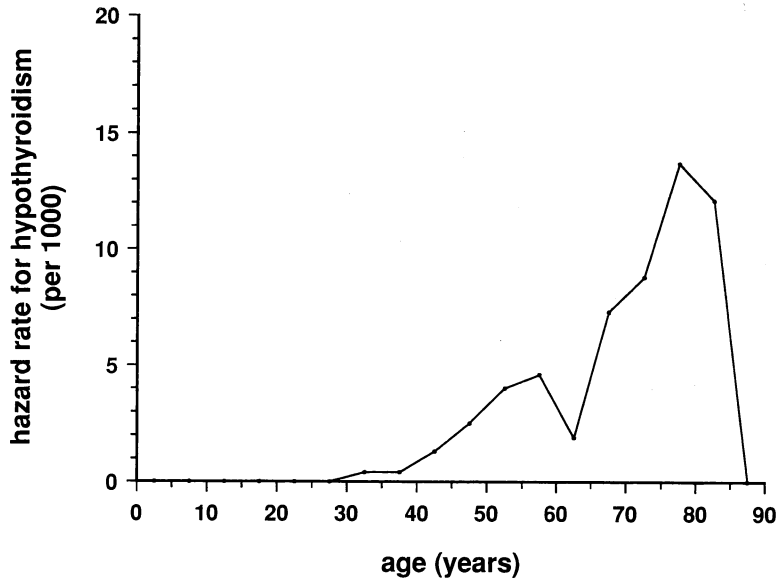

FIGURE 2

Incidence (hazard rate) of hypothyroidism in females by age in a prospective study (Whickham[13]). Development of clinical hypothyroidism was rare under the age of 45 years. (Reproduced from *Clinical Endocrinology* by permission of the authors. © Blackwell Science Ltd.)

patients with Hashimoto's disease in 1956.[14] Such antibodies are present in 59% of individuals with autoimmune hypothyroidism.[15] Antibodies to a thyroid-specific membrane bound antigen ('thyroid microsomal antigen, TMA') were identified in 1964[16] and shown in 1985 to be directed against the enzyme thyroid peroxidase (TPO), required for the synthesis of thyroid hormones.[17] Anti-TMA/TPO antibodies are more sensitive indicators of the autoimmune process than anti-thyroglobulin antibodies, being present in 95–99% of individuals with autoimmune hypothyroidism.[15,18] Thyroid-stimulating hormone (TSH) levels may also be used as an indicator of subclinical thyroid dysfunction since levels rise above normal (greater than 4 mU/L) prior to any fall in circulating thyroid hormone levels (T3, T4).

Tables 3 and 4 summarise data on the prevalence of subclinical autoimmune thyroiditis as assessed by the presence of anti-thyroid autoantibodies (anti-TMA and/or anti-Tg) or raised TSH levels.[4–8,10,19–24] Anti-thyroid antibodies are present in 10–15% of all adult females, with rates being 2–5 times lower in males (Table 3). Raised TSH levels >5 mU/L are seen slightly less commonly, being present in around 5–10% of females with higher degrees of thyroid failure (TSH>10 mU/L) in around 5% of women. Subclinical disease becomes more common with increasing age. In the study of Mariotti *et al.*, the percentage of individuals with anti-TPO antibodies increased 2–4 fold after the age of 60 with rates over 30% amongst females in their 70s and 80s (Fig 3).[20] Raised TSH levels also appear to be around twice as common above the age of 60 (Table 4).

These results are consistent with a 'pyramid' of severity of autoimmune thyroid disease (Fig 4) which may be summarised as follows. Amongst adult

females, approximately 40% have some lymphocytic infiltration in their thyroid and 10–15% have detectable thyroid autoantibodies, a similar figure to those with moderate thyroiditis (22%); 5–10% of women have evidence of early thyroid damage as signalled by a raised TSH, a comparable figure to the percentage with severe thyroiditis (5–10%). Clinical hypothyroidism, however, is only present in 1% of the female population.

Do the elements shown on the pyramid in Fig 4—thyroiditis, detectable thyroid autoantibodies, raised TSH and clinical hypothyroidism—represent a continuum with progression from the first stage to the last, albeit slowly, over time? Some support for this view comes from studies of the degree of overlap

TABLE 3

Prevalence of thyroid autoantibodies. Summary of results from 8 separate cross-sectional studies of thyroid autoantibodies (predominantly anti-TMA or anti-TPO).[4,5,10,19–23] In the study by Lazarus,[5] titres were measured by a colorimetric ELISA and a significant level taken to be greater than 2 standard deviations from the mean of normal controls (+2SD). Around 10–15% or women have thyroid autoantibodies.

	Age years	*Minimum titre*	*Females per cent*	*Males per cent*
Whickham 1977	>18	1/10	10·3	2·7
Barbato 1978	All	1/100	13·4	4·2
Hawkins 1980	Adult		9·8	2·8
Mariotti 1992	<50	1/100[1]	5·0[2]	
Mariotti 1992	60–69	1/100[1]	21·4[2]	
Geul 1993	40–60	1/10	11	
Aho 1985	40–64	1/160	18[2]	
Lazarus 1984	>70	+2SD	18·6[2]	
Brochmann 1988	>70	1/400	17·5	9·6

[1]anti-TPO antibodies. [2]males + females

TABLE 4

Prevalence of a raised TSH. Summary of results from 8 separate cross-sectional studies of TSH levels greater than 5 or 10 mU/L.[4–8,10,21,24] Data are shown as percentages of the whole population. Around 5–10% of women have a TSH greater than 5 mU/L, and around 5% have a level greater than 10 mU/L.

	Age years	*Females*		*Males*	
		>5	*>10*	*>5*	*>10*
Whickham 1977	>18	7·5		2·8	
Geul 1993	40–60	4·0			
Lazarus 1984	>70		(3·6)[1]		
Sawin 1985	>60		5·9		2·3
Rosenthal 1987	>60	16·2	4·2	9·5	3·5
Brochmann 1988	>70	9·3		6·0	
Bagchi 1990	>55	8·5		4·4	
Parle 1991	>60	11·6	4·4	2·9	1·2

[1]males + females

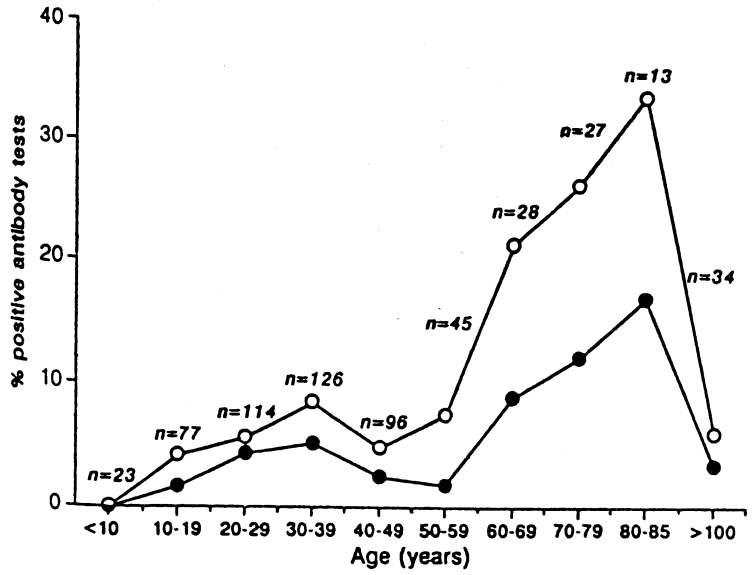

FIGURE 3

Prevalence of thyroid autoantibodies by age.[20] Filled circles anti-thyroglobulin antibodies. Open circles anti-TPO antibodies. Note that rates increase markedly after the age of 50. (Reproduced by permission of the authors. © The Lancet.)

between the presence of thyroid autoantibodies and raised TSH levels (Tables 5A and B).[4, 7, 8, 10, 21, 23] Only around 35% of females with circulating thyroid antibodies have evidence of organ damage in the form of a raised TSH. However, of females who already have thyroid damage (raised TSH), the prevalence of detectable thyroid autoantibodies correlates with the degree of thyroid dysfunction being around 50% when the TSH is >5 mU/L, 80–90% when the TSH is >10 mU/L and 95% when clinical hypothyroidism develops.

PROSPECTIVE STUDIES OF AUTOIMMUNE THYROIDITIS

Direct evidence that individuals with early indicators of autoimmunity progress 'up the pyramid' to clinical disease must be derived from prospective studies. The best known study of this type is the Whickham population study from North-East England. Over a 4 year follow-up period, no progression to hypothyroidism was seen in this study amongst women who initially had *either* circulating autoantibodies *or* a raised TSH level. However, amongst women with *both* antibodies *and* a raised TSH, 17·5% became clinically hypothyroid over this period.[25] Comparable results have been seen in other, smaller studies with rates of progression to clinical disease being higher in the elderly and in women with higher initial antibody and TSH titres (Table 6).[5, 7, 8, 21, 26, 27] In all of these studies, the number of men with markers of autoimmune disease that could be followed prospectively was too small for any meaningful conclusions.

In 1995, the 20 year follow-up report of the Whickham cohort was published (Table 7).[13] Whereas after 4 years, no progression to clinical hypothyroidism was detectable in individuals with either antibodies or a raised TSH alone, after 20

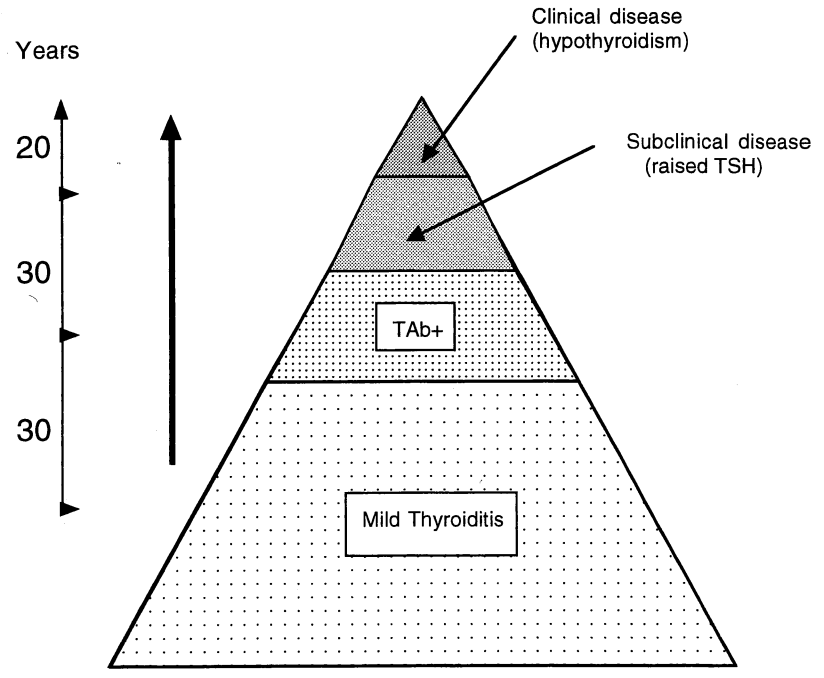

FIGURE 4

The 'Disease Pyramid' in autoimmune thyroiditis. Up to 45% of women have lymphocytic infiltration of the thyroid ('mild thyroiditis'), 10–15% are thyroid autoantibody positive (TAb+), 5–10% have a raised TSH (50–90% of whom are also TAb+) but only 1% have clinical hypothyroidism. Continuous progression of the disease 'up the pyramid' is proposed. Estimated half-times in years for progression between stages (time taken for the half-cohort to progress) are shown on the left-hand axis. The half time for progression from mild thyroiditis to clinical disease is estimated to be 80 years.

years 27% and 33% respectively of such women had developed hypothyroidism. Furthermore, the number of women with both markers that had become hypothyroid had increased from 17·5% at 4 years to 55% at 20 years (Table 7).[13] As suggested previously by the smaller studies, the risk of progression to hypothyroidism correlated with the initial TSH and the presence of thyroid autoantibodies.

A comment should be made on the study of Rallison *et al.* (Table 6).[26] This is the only large, long-term follow-up study in children (aged 11–18). The study was performed to monitor the effect of nuclear testing in Nevada, USA, on childrens' thyroid function. It followed 3,122 children, 1,962 from the nuclear test area and 1,160 controls from the state of Arizona. No specific effect of exposure to low-dose radiation was seen but in the group overall, 34% of children initially diagnosed as having 'thyroiditis' (firm goitre ± thyroid antibodies ± a raised TSH) became hypothyroid within 20 years.[26] Since the exact criteria for diagnosing 'thyroiditis' were not stated and no subgroup analysis was performed (goitre only, antibody positive only, raised TSH only, etc) only limited conclusions can be drawn. However, this study does suggest that teenagers and young adults are not protected from the disease progression seen in older individuals, particularly if they have sufficiently intense disease at the outset.

PROSPECTIVE STUDIES OF EUTHYROID GOITRE

The data reviewed above suggest that in the 10–15% of all women who have serum markers of thyroid autoimmunity progression to clinical disease does occur at a detectable, albeit very slow, rate. However, a further 30% of women probably have minor degrees of lymphocytic infiltration without serum markers. Is progression 'up the pyramid' of disease detectable in this cohort as well?

Studies of this population are limited by the difficulty of detecting lymphocytic infiltration of the thyroid in healthy individuals in the absence of serum markers. However, a palpable or visible goitre was reported in around 25% of women and 6% of men under the age of 55 in the Whickham survey.[4] Many of these individuals were negative for serum markers leading to a diagnosis of 'simple goitre'. Fukino *et al.* performed fine needle aspiration biopsies on 37 Japanese patients with 'simple goitre' and found 50% to have evidence of lymphocytic infiltration.[28] Since the prevalence of lymphocytic infiltration in Japanese in post-mortem studies is only around 20%,[3] this suggests that the presence of 'simple goitre' in non-iodine deficient countries may be a crude marker for lymphocytic infiltration. Long-term follow-up studies of 'simple goitre' might therefore be of interest.

In the Whickham survey, 231 women (26%) initially had a palpable or visible goitre, compared with only 49 (5·4%) after 20 years.[13] Of this cohort, 8 developed hypothyroidism and 2 thyrotoxicosis. However, on further analysis the authors concluded that simple goitre was 'not predictive of any biochemical or

TABLE 5A and B

Overlap between thyroid autoantibodies and subclinical hypothyroidism.

A. Prevalence of a raised TSH (>5 mU/L) amongst individuals who are positive for serum thyroid autoantibodies (TAb+).[4, 10, 21, 23] Around 35% of TAb+ women have a raised TSH.

	Age years	*Females per cent*	*Males per cent*
Whickham 1977	>18	50	
Hawkins 1980	All	36[1]	
Geul 1993	40–60	23	
Brochmann 1988	>70	22	38

[1]males + females

B. Prevalence of detectable thyroid autoantibodies amongst women who have a raised TSH.[4, 7, 8, 21] At a TSH level >5 mU/L, around 50% of women are TAb+, while at a TSH level of >10 mU/L, the percentage of TAb+ women is 80–90%.

	Age years	*>5 mU/L per cent*	*>10 mU/L per cent*
Whickham 1977	>18	60	80
Geul 1993	40–60	48	
Rosenthal 1987	>60	23	90
Parle 1991	>60	46	81

clinical evidence of thyroid dysfunction over twenty years'. The only significant association found was between 'keeping a goitre' over this period and the presence of thyroid autoantibodies at the end of the follow-up period ($p=0{\cdot}012$).[13] In 3 other smaller and shorter follow-up studies of women with euthyroid goitre (Table 8),[29–31] significant progression to hypothyroidism was only seen in the group of Hayashi *et al.* who were all thyroid antibody positive initially.[30]

EVIDENCE THAT LYMPHOCYTIC INFILTRATION ALONE DOES PROGRESS TOWARDS CLINICAL DISEASE

As discussed above, women with very active disease—i.e. detectable thyroid antibodies and a raised TSH—have a half-time to hypothyroidism (when half the cohort will be hypothyroid) of around 20 years. For those with only one serum marker (raised TSH *or* autoantibodies), 25–30% progress in 20 years giving an estimated half-time to hypothyroidism of 50–60 years assuming exponential decay. It is therefore not surprising that progression from lymphocytic infiltration

TABLE 6

Progression in subclinical disease. Summary of results from 6 prospective studies of subclinical autoimmune thyroiditis, excluding the Whickham survey.[5, 7, 8, 21, 26, 27] TSH levels in mU/L. TAb = thyroid autoantibodies. The percentage of subjects developing clinical hypothyroidism and/or low T4 is shown. Progression rates vary from 0–100% and are clearly higher in the presence of TAb and with higher initial TSH levels.

	Age years	*Follow-up years*	*Comments*		*Hypothyroidism per cent*
			TAb	*TSH*	
Rallison 1991	11–18	20	'Thyroiditis'		34
Parle 1991	>60	1	+ve	5–10	18
			−ve	5–10	7
Lazarus 1994	>70	5	+ve	raised	2·2
			+ve	normal	0·4
Rosenthal 1987	>60	4	>1/1600	5–28	82
			0–1/1600	4–17	0
Gordin 1981	21–62	2–8	+ve	8–33	100
			+ve	2–8	0
Geul 1993	40–60	10	+ve	normal	24[1]
			−ve	normal	3[1]

[1]raised TSH at end-point.

TABLE 7

Progression in subclinical disease, the Whickham survey.[13, 25] Percentage of subjects (all female) developing clinical hypothyroidism after 4 and 20 years is shown. The disease is seen to progress significantly between these two time points.

	Percent hypothyroid	
	4 years	*20 years*
TAb+	<2	27
Raised TSH	<2	33
Raised TSH+TAb+	17·5	55

TABLE 8

Prospective studies of euthyroid goitre. Summary of results from three studies, excluding the Whickham survey.[29–31] Outcome is given as a percentage of subjects developing hyperthyroidism ('hyper'), positive thyroid antibodies (TAb+) or hypothyroidism ('hypo'). Significant progression to hypothyroidism is only seen in the group that were initially TAb+.

	Initial status	*Follow-up (years)*	*Outcome*
Hara 1993 ($n=108$)	TAb−	5–14	4% hyper, 10% TAb+, 1% hypo
Maeda 1993 ($n=11$)	TAb−	7	15% hyper, 0% hypo
Hayashi 1985 ($n=13$)	TAb+	10–20	3% hyper, 38% hypo

alone to clinical disease is difficult to observe even in 20 year follow-up studies. However, it would not be unreasonable to expect to see progression from lymphocytic infiltration to subclinical disease in a measurable period of time.

The practical problems of identifying asymptomatic individuals with lymphocytic infiltration and the length of follow-up required for meaningful results have meant that, other than the studies of euthyroid goitre described above, there are no data that directly address this issue. However, comparison of the prevalence of thyroid antibodies at different ages (Fig 3) with the prevalence of thyroiditis in post-mortem studies (Fig 5) provides some useful circumstantial evidence.[3, 20] While lymphocytic infiltration seems to reach significant levels above the age of 20 in women, the prevalence of thyroid antibodies only shows a rise after the age of 50 (Fig 5).[3, 20] It is therefore tempting to speculate that progression from thyroiditis alone to the production of detectable levels of thyroid antibodies takes around 30 years. If progression to clinical disease has a further half-time of 50–60 years, the reason that thyroiditis is common but hypothyroidism rare becomes apparent. In addition, the increase in thyroid antiboby prevalence and hypothyroidism with age becomes understandable (see timescale, Fig 4).

THE CONCEPT OF 'UNIVERSAL PROGRESSION' IN THE AUTOIMMUNE PROCESS

Our information on the natural history of autoimmune thyroiditis from the time of arrival of lymphocytes in the thyroid to the time of development of hypothyroidism is incomplete. However, I would argue that the available data are consistent with a process that slowly progresses to thyroid destruction in almost *all* women, given sufficient time ('universal progression'), rather than one that only advances in a subset of unfortunate individuals. Although never static, the process is so slow that only those women with higher initial disease activity are likely to develop clinical sequelae in a normal lifespan. It therefore remains true that the subset of women with serum markers of thyroid autoimmunity are at greatest risk of hypothyroidism—around a third of all those with thyroiditis—but the concept of 'universal progression' has important implications nonetheless.

Firstly, 'universal progression', if true, has implications for our understanding of the pathogenesis of autoimmunity. A biological explanation has to found to explain such an inexorably slow process. The contrast with protective immune responses against pathogens which usually become effective in 7–14 days and the

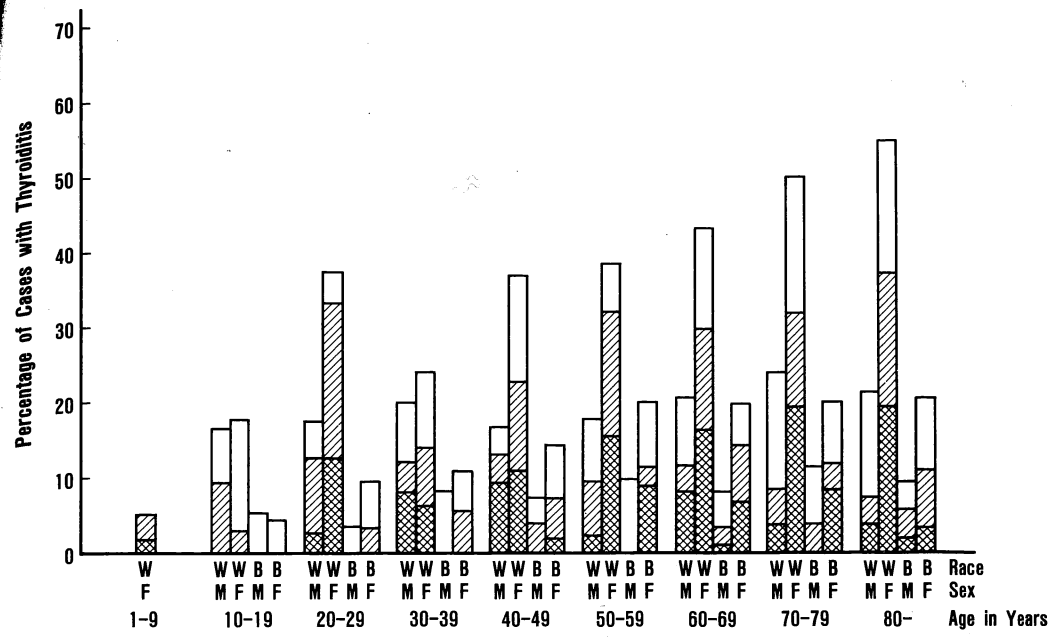

FIGURE 5

Prevalence of thyroid lymphocytic infiltration at post-mortem by age group.[3] W-white; B-black; M-male; F-female. Height of bar shows total percentage with thyroiditis, striped area shows percentage with moderate thyroiditis, cross-hatching shows percentage with severe thyroiditis. (Reproduced from the *American Journal of Clinical Pathology* by permission of the authors. © J B Lippicott Co.)

transit of lymphocytes through peripheral tissues which rarely lasts more than a few hours, if the lymphocytes are not actively engaged, is striking. Secondly, 'universal progression' has implications for our approach to treatment. Factors able to modify the speed of the process, even by small amounts, take on great importance. If the rate of progression could be halfed, the half-time to clinical disease could be lengthened to 40 years in those with both a raised TSH and autoantibodies, and 100 years in those with a single serum marker. A high percentage of clinical disease could thereby be averted altogether in a normal lifespan. Thirdly, a very slow rate of 'universal progression' suggests that to find the initiating events in the autoimmune process, we need to look in early adulthood/late childhood if not earlier. This is when lymphocytic infiltration begins, if it is going to happen at all, and progression continues from there on. Some brief comments on these three issues, in the light of current knowledge of thyroidology and immunology, are presented below.

Firstly, the biological explanation for the slow rate of progression of the autoimmune process may lie in the signals delivered to T lymphocytes by the target tissue. T lymphocytes (T cells) are known to play a central role in immune responses, controlling both antibody production and cell-mediated immunity. Over 50% of the lymphocytic infiltrate seen in autoimmune thyroiditis consists of T cells.[32] In 1983, it was observed that thyroid cells can express the molecules required to present their own autoantigens to T cells (Major Histocompatibility

Class II molecules),[33] and our own data suggest that they do so in autoimmune disease.[34] However, in recent years it has become apparent that the nature of the T cell response is strongly influenced by additional signals delivered by the antigen presenting cell, so-called 'costimulatory signals'.[35] While over 5 different costimulatory molecules have been identified on antigen presenting cells of haemopoetic origin,[36] none have yet been found on epithelial cells such as thyrocytes,[37] and the nature of T cell costimulation in this situation remains unknown. Conceivably, epithelial cells might express 'negative' costimulatory molecules, not seen on 'professional' antigen presenting cells, able to engage self-reactive T cells and down-regulate rather than accelerate their activity. The strength of these negative signals would then be a major determinant of the rate of the autoimmune process. Such molecules remain to be identified and a search for them should be an important target for research in this field.

Secondly, several factors are known which can precipitate hypothyroidism in some individuals with subclinical autoimmune thyroiditis and these may play a role in determining the rate of disease progression in the population as a whole. Pregnancy, or more particularly the post-partum period, causes transient hypothyroidism in up to 85% of women with thyroid autoantibodies.[38] Treatment with cytokines such as interferon alpha,[39,40] interleukin-2[41] or granulocyte-macrophage colony stimulating factor[42] generates thyroid autoantibodies in up to 20% of individuals and around 5% develop hypothyroidism. Excess iodine ingestion may also precipitate hypothyroidism,[43] as seen in patients given the iodine-containing anti-arrhythmic drug, amiodarone.[44] This last effect might explain why in Japan, where iodine intake is very high, autoimmune hypothyroidism is common although the prevalence of lymphocytic infiltration in the population is half that in Caucasians.[3] The relevance of all of these factors remains unproven,[13] but a reduction in iodine intake seems most likely to be able to significantly affect disease progression in a whole population.[45,46]

Finally, with respect to the initiating factors of the autoimmune process, our understanding remains very limited. Genetic factors may play a role, in view of the significant racial differences in the prevalence of lymphocytic infiltration.[3] The fact that much thyroiditis appears to start around the age of puberty, and the consistently higher rates in women than men suggest a role for sex hormones.

RELEVANCE OF STUDIES OF AUTOIMMUNE THYROIDITIS TO OTHER AUTOIMMUNE DISEASE

Thankfully, even when autoimmune thyroiditis does result in hypothyroidism, simple and effective treatment in the form of oral L-thyroxine is available. However, in other organ-specific autoimmune diseases, such as chronic active hepatitis, primary biliary cirrhosis, myasthenia gravis or insulin-dependent diabetes mellitus (IDDM), replacement therapy is not so straightforward and the need to develop treatments able to halt progression of the autoimmune process in the pre-clinical phase is much greater.

Information on the natural history and subclinical phases of these diseases is limited, but data from prospective studies of the development of IDDM in individuals with anti-islet cell autoantibodies are available. Relatives of IDDM patients who have high titres of anti-islet cells antibodies (>80 JDF units) as well as anti-insulin antibodies, progress to clinical disease with a half-time of 3–5 years.[47] However, amongst individuals who have lower titres of anti-islet cell

antibodies—e.g. < 20 JDF units—or who have only anti-insulin antibodies, less than 20% develop diabetes in 10 years consistent with a half-time to clinical disease of over 40 years.[47–49]

These results are very comparable with the progression rates and patterns seen in autoimmune thyroiditis. It therefore seems likely that advances in our understanding of disease progression in thyroiditis will be of immense value in developing immunointervention strategies in these other autoimmune diseases.

CONCLUDING REMARKS

In this article, I have attempted to synthesise the many and diverse studies on the epidemiology of autoimmune thyroid disease into a coherent picture of the natural history of the autoimmune process. Two pieces of information emphasised by recent studies have particularly influenced my thinking. The high prevalence of lymphocytic infiltration in the population has been known since 1962 but this information has largely lain dormant until confirmed by Okayasu *et al.* in 1994. Secondly, the slow but continuously progressive nature of the autoimmune process has been dramatically emphasised by the 20 year follow-up of the Whickham cohort published in 1995. Compared to the data available after 4 years of this study, the percentage of patients developing hypothyroidism who initially had one serum marker of subclinical disease had increased from 0 to 30% by twenty years, and where both a raised TSH and antibodies were present, this percentage had increased from 17·5% to 55%. This data combined with the high prevalence of lymphocytic infiltration in the population led to the hypothesis of 'universal progression': that the disease process is active and progressive at all stages although at such a slow rate that only those who reach the higher levels of the disease pyramid (Fig 4) in early adulthood will develop clinical sequelae by the time they die.

In these terms, autoimmune thyroiditis is 'endemic' in Caucasian female populations and almost as 'normal' as osteoporosis, atherosclerosis, osteoarthritis, latent viral infections or the ageing process itself. While these processes may not be altogether preventable, the key is to learn how to slow their progress sufficiently that they do not become clinically important within a normal lifespan. Developing these ideas and this approach in autoimmune thyroiditis may teach us how to avert clinical disease in other conditions, such as in insulin-dependent diabetes and chronic active hepatitis. Appreciating the nature of the beast is an important first step in any fight.

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