pneumonia, organism unspecified or *Pneumocystis carinii* pneumonia; most of the remainder were conditions known to be associated with but not specific to AIDS.

As the excess deaths were calculated only from the beginning of 1985, although some deaths due to AIDS are known to have occurred before then, the number underestimates the total deaths due to AIDS since the syndrome was first recognised in the United Kingdom. The 1984 baseline was adjusted to take account of the small increase in the population estimates of men in each succeeding year.

Some of the excess deaths may not have been associated with HIV infection. If this were so the increase in deaths is difficult to explain, particularly as about 90% of them occurred in men who had never been married, and these men represent only 40% of men aged 15-54. The deficit of deaths due to causes other than those possibly related to HIV infection suggests that the selection was generally appropriate. The deficit of deaths among women aged 15-54 emphasises the difference in the change in mortality between the sexes.

Infection with HIV may predispose to the development of clinical conditions that are not currently recognised as being associated with the virus. As the number of deaths after HIV infection increases analysis of other conditions mentioned on death certificates stating AIDS or HIV infection as the underlying cause of death and of trends in deaths attributed to other causes may help to identify a wider range of clinical manifestations.

Of the total 495 estimated excess deaths in men, in only 198 was the cause of death coded as AIDS by this office, leaving an estimated 297 coded as other causes. AIDS or HIV infection is therefore considerably understated as the cause of death. This is confirmed by

the number of cases of AIDS reported to the Communicable Disease Surveillance Centre in which AIDS was not recorded on the death certificate. In some cases the correct diagnosis may not have been made at the time of death or the doctor may not have wished to mention AIDS on the certificate and did not subsequently send this information to this office. The increase in mortality rate in men who had never been married may be due to some manifestation of HIV infection other than the syndrome recognised as AIDS. Accurate reporting of the underlying cause and other conditions present at the time of death is necessary if illness not currently known to be associated with HIV infection is to be identified.

I am indebted to my statistician colleagues at this office, Michael Day and Tim Devis, for their invaluable help in preparing this paper.

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Graves' disease: immunological and immunogenetic indicators of relapse

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Abstract

The use of measurements of antibody to the thyroid stimulating hormone receptor and HLA-DR3 phenotype for predicting relapse of hyperthyroidism in patients with Graves' disease receiving medical treatment is controversial. Fifty eight new patients with Graves' disease were followed up prospectively for up to 96 months after treatment with antithyroid drugs for 12 months. The presence of antibody to the thyroid stimulating hormone receptor before the start of treatment, measured as immunoglobulins inhibiting binding of thyroid stimulating

hormone, was not associated with relapse. Patients who remained positive for antibodies after treatment tended to relapse within six months, but no relation with long term relapse was found. HLA-Cw7 but not HLA-DR3 was significantly associated with relapse. The presence of HLA-DR4 was significantly associated with remission and with absence of antibodies to thyroid stimulating hormone receptor. HLA-DR4 may therefore protect against relapse of thyrotoxicosis by immunomodulation triggered by antithyroid drugs, which results in the synthesis of antibodies to the thyroid stimulating hormone receptor being inhibited.

Introduction

Graves' disease is characterised by hyperfunctioning of the thyroid, which is caused by antibodies to the thyroid stimulating hormone receptor.^{1,2} The natural course of the disease includes periods of spontaneous remission and recurrence.³ After treatment with thionamide drugs about 40-60% of patients relapse.^{3,5} The ability to predict recurrence is important as treatment by operation or with iodine-131 may be better for such patients. As relapse of hyperthyroidism is probably mediated immunologically^{1,2} there may be immunological factors that are of prognostic value. Graves' disease is associated with the histocompatibility antigen HLA-DR3.^{2,6} Initially, the presence of HLA-DR3 and of antibody to the thyroid

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stimulating hormone receptor antibody at the end of treatment, alone and in combination, were reported to be predictors of short term relapse^{2,6,8}; most workers, however, have been unable to relate long term outcome to the presence of HLA-DR3.^{2,6,9-11}

We followed up 58 new patients with Graves' disease prospectively. The long term outcome after a 12 month course of antithyroid drugs was evaluated for a possible association with antibody to the thyroid stimulating hormone receptor and the full array of HLA-A, B, C, DR, and DQ antigens.

Patients and methods

From January 1978 to December 1979 we treated 58 new patients (44 women and 14 men, aged 15-76) with Graves' disease. The diagnosis was based on the history, results of physical examination, and laboratory determinations of thyroid state including serum thyroxine and triiodo-

occurring within 48 months. Each patient was followed up for at least 48 months.

Autoimmune markers—Serum samples were taken before treatment and at regular intervals thereafter; in each sample the presence of antibodies to the thyroid stimulating hormone receptor, microsomal antibodies, and circulating immune complexes and thyroid function were determined. Antibodies to the thyroid stimulating hormone receptor were detected by assay of the ability of gammaglobulin fractions of the serum to inhibit binding of radioiodinated thyroid stimulating hormone to human thyroid plasma membranes.¹³ Results were expressed as an index of inhibition of thyroid stimulating hormone binding, and serum samples were considered to be positive when the index was below 68 (mean index for 96 normal subjects minus 2 SD).¹³ Microsomal antibody was measured by a standard haemagglutination assay (Fujirebio, Japan) and circulating immune complexes by an assay of binding of C1q.¹³

HLA typing—The major histocompatibility antigens at the HLA-A (n=21 with splits), B (n=46 with splits), C (n=7), DR (n=10), and DQ (n=3) loci were typed by the department of immunohaematology. The HLA-A, B, and C loci were typed according to the National Institutes of Health

TABLE I—Relation between variables studied and outcome. Values are numbers (percentages) of patients

	All patients (n=58)	Patients who relapsed (n=32)	Patients in remission (n=26)	Relative risk	p Value*
Antibody to thyroid stimulating hormone receptor present:					
Before treatment	33	21 (64)	12 (36)	1.45	0.22
After treatment	5	4 (80)	1 (20)	1.51	0.26
HLA-DR4 present	11	2 (18)	9 (82)	0.29	0.016
HLA-Cw7 present	30	22 (73)	8 (27)	2.05	0.009
Goitre (enlarged threefold or more)	11	8 (73)	3 (27)	1.42	0.24
Eye signs (class 2 or worse)	28	14 (50)	14 (50)	0.83	0.54

*χ² Analysis (2×2 tables).

thyronine concentrations, triiodothyronine resin uptake, and microsomal antibody titre. The size of the goitre was estimated by palpation. Thirty two patients, including four with asymmetric goitres, underwent thyroid scintiscanning to confirm diffuse uptake of radioactivity. Eye signs were scored according to the classification of the American Thyroid Association¹²; those in class 2 or worse were considered to be specific for Graves' disease and were found in 28 patients.

Antithyroid treatment (propylthiouracil 300 mg/day (38 patients), methimazole 30 mg/day (eight), or carbimazole 30 mg/day (12)) was given for a mean of 12.2 (SD 0.7) months as described before.¹³ When the patients became euthyroid, usually after two to six weeks, thyroxine (up to 150 µg/day) or thyroid (50-75 mg/day) was given in addition. Relapse was defined as the recurrence of symptoms and signs and biochemical evidence of hyperthyroidism; short term relapse was arbitrarily defined as that occurring within six months after the end of treatment and long term relapse as that

technique,¹⁴ and the HLA-DR and DQ loci by a two colour fluorescence lymphocytotoxicity assay,¹⁵ using a set of 200 highly selected serum samples. Five hundred and five healthy Dutch white subjects were randomly selected to serve as controls.

Statistical analysis—The relation between relapse and the index of inhibition of thyroid stimulating hormone binding, HLA specificity, size of goitre, and eye signs was evaluated by χ² analysis (2 × 2 tables)^{16,17}; p values were not corrected for the number of antigens tested except where specified.¹⁸

Results

Thirty four patients relapsed from two weeks to 96 months (median four months) after treatment, 32 within 60 months (figure). Two patients relapsed 64 and 96 months after treatment, respectively; they were regarded as being in remission for the analysis of long term relapse. Short term relapse occurred in 23 patients. None of the patients became hypothyroid after treatment.

Table I summarises the relation of certain clinical and immunogenetic variables with long term relapse. Before treatment 33 patients had antibodies to thyroid stimulating hormone receptor; the index of inhibition of thyroid stimulating hormone binding was significantly lower in these patients than in the 25 who did not have such antibodies (53.1 (SD) 11.7) v (83.2 (9.9), p<0.001, Student's *t* test). After treatment 53 patients did not have antibodies to the thyroid stimulating hormone receptor; five remained positive for these antibodies, and four of them relapsed within three months after treatment (odds ratio 3.57). The mean index of inhibition of binding of thyroid stimulating hormone initially was significantly lower in these five patients than in the 28 other patients who were antibody positive (44.6 (9.0) v (54.6 (11.6), p<0.001, Student's *t* test). The presence of antibodies to thyroid stimulating hormone receptor initially did not predict the occurrence of short term (p=0.44) or long term (p=0.22) relapse, whereas the presence of antibodies at the end of treatment was almost significantly associated with short term (p=0.056) but not long term relapse (table I). The prevalence of the HLA-B8 (36%) and HLA-DR3 (45%) phenotypes was appreciably increased in the patients compared with the normal population (23% and 25%, respectively). Short term relapse occurred in 23 patients and was associated with the absence of HLA-DR4 (22 patients, p=0.05) and, marginally, the presence of HLA-Cw7 (16 patients, p=0.053). Long term relapse was also significantly associated with the absence of HLA-DR4 (p=0.016) and the presence of HLA-Cw7 (p=0.009) (table I). It was striking

Relapse of Graves' disease after treatment in 58 patients and its relation to presence or absence of HLA-DR4 and Cw7.

that the two patients positive for HLA-DR4 who relapsed were also positive for HLA-Cw7 whereas the nine others positive for HLA-DR4, who did not relapse, were negative for HLA-Cw7. No significant relation was found between relapse or remission and HLA-DR3 ($p=0.25$) or HLA-DR2 ($p=0.17$), which is in linkage disequilibrium with HLA-Cw7, or any of the HLA-A, B, C, DR, and DQ phenotypes. Four of the five patients who remained positive for antibody to thyroid stimulating hormone receptor during treatment relapsed within three months after treatment; all four were negative for HLA-DR4, as might have been expected, and also, unexpectedly, for HLA-Cw7.

The absence of antibody to thyroid stimulating hormone receptors before the start of treatment was associated with the presence of HLA-DR4 ($p=0.028$) but not Cw7 ($p=0.81$) (table II). No relation was observed between microsomal antibodies or circulating immune complexes and any HLA phenotype.

TABLE II—Relation of HLA-DR4 and Cw7 with antibody to thyroid stimulating hormone receptor, microsomal antibody, and circulating immune complexes during treatment with antithyroid drugs

	DR4 (n=11)		Cw7 (n=30)	
	No of patients	Significance*	No of patients	Significance*
Antibody to thyroid stimulating hormone receptor:				
Present (n=33)	2	$p=0.028$	18	$p=0.81$
Absent (n=25)	9		12	
Microsomal antibody:				
Present (n=54)	10	$p=0.37$	26	$p=0.48$
Absent (n=4)	1		4	
Circulating immune complexes:				
Present (n=42)	7	$p=0.97$	23	$p=0.10$
Absent (n=16)	4		7	

χ^2 Analysis (2×2 tables).

The size of the goitre, which is an established risk factor for relapse, was found to be significantly greater in the patients who relapsed (2.35 (1.0 times normal size) than in those in remission (1.8 (0.6 times normal size) ($p<0.01$); eight of the 11 patients whose goitres were enlarged threefold relapsed within 48 months ($p=0.24$) (table I). The presence of eye signs could not be related to long term relapse ($p=0.54$), and the antithyroid drugs prescribed were not associated with relapse (data not shown).

Logistic regression analysis of data on HLA-Cw7 and DR4 specificities, threefold enlargement of the goitre, and the presence of antibody to the thyroid stimulating hormone receptor at the end of treatment showed that only HLA-Cw7 (estimated odds ratio 2.75, $p=0.003$) and HLA-DR4 (estimated odds ratio 0.36, $p=0.03$) were significant and independent risk factors.

Discussion

Our 58 patients were representative of all patients with Graves' disease as the rate of recurrence of thyrotoxicosis within four years after treatment (55%) and the prevalence of eye signs (48%), HLA-B8 (36%) and HLA-DR3 (45%) antigens, autoimmune markers such as antibodies to the thyroid stimulating hormone receptor (57%), microsomal antibody (93%), and circulating immune complexes (72%) compared favourably with those reported previously.^{2 4 6 9 13 19-22} The frequency of antibodies to the thyroid stimulating hormone receptor (57%) was lower than in our previous report (72%); we cannot explain this as the same assay was used in both studies.

Four of the five patients in our study who remained positive for antibody to thyroid stimulating hormone receptor during treatment relapsed. A similar association between antibodies during treatment and relapse has been reported in previous prospective studies.^{4 8 20 21} As in other prospective studies,⁷⁻¹¹ however, we found that the presence of antibodies before treatment did not predict relapse; this conflicts with claims based on retrospective studies.^{2 6} This difference in results may be due to an unwanted selection of patients but is not related to differences in duration of treatment or follow up.^{2 6 7} Enlargement of the goitre is a well known risk factor for

relapse^{4 22} and often influences the management of patients with Graves' disease.²² The goitre was significantly larger in patients who relapsed than in those remaining in remission. Eye signs were not associated with relapse or presence of antibodies.

Our finding that HLA-DR3 did not predict relapse confirms the results of three other prospective studies.⁹⁻¹¹ The association of relapse with the presence of HLA-Cw7 and of remission with HLA-DR4 has not been reported previously; table III shows the combined influence of these phenotypes. In patients positive for HLA-Cw7 the absence or presence of DR4 did not seem to alter the increased risk of relapse; patients with an HLA-DR4 positive HLA-Cw7 negative phenotype seemed to be protected against relapse; and in those negative for both HLA-Cw7 and DR4 the numbers of patients who relapsed or were in remission were similar.

TABLE III—Distribution of HLA-Cw7 and DR4 and relation with long term relapse or remission

	Cw7 positive, DR4 negative (n=26)	Cw7 positive, DR4 positive (n=4)	Cw7 negative, DR4 positive (n=7)	Cw7 negative, DR4 negative (n=21)
Patients who relapsed	20	3	0	11
Patients in remission	6	1	7	10

The significance found for HLA-DR4 and Cw7, however, was lost when, as is customary in analysis in applied immunogenetics,¹⁸ the p value was multiplied by the number of antigens tested. A relation between DR4 specificity and increased synthesis of microsomal antibody in postpartum thyroiditis has been described.²³ Previous reports showed that the prevalence of HLA-DR4 was not significantly decreased in patients with Graves' disease compared with the normal population.²⁴⁻²⁶ No data are available on patients who relapsed; our results suggesting a relation between the presence of DR4 and remission and the presence of Cw7 and relapse therefore need to be confirmed.

The presence of HLA-DR4 was also significantly associated with the absence of antibodies to the thyroid stimulating hormone receptor, whereas HLA-Cw7 specificity was not related to the presence or absence of antibodies or to other immunological variables. Notably, the four patients with antibodies to the receptor who relapsed were all negative for HLA-DR4 as expected but also for HLA-Cw7. The abnormal immune response in Graves' disease, which results in synthesis of autoantibodies against the thyroid stimulating hormone receptor, has been linked to the abnormal expression of HLA-DR and HLA-DQ on thyroid follicular cells²⁷ and is associated with HLA-DR3.⁶ The level of this antibody is known to decrease during antithyroid drug treatment.^{2 6-8 11 20 21} Recently, numbers of activated T suppressor cells were shown to increase and numbers of activated T helper cells to decrease during drug treatment; this resulted in reduced synthesis of thyroid auto-antibodies as indicated by lower serum titres.²⁸ Our data suggest an association between the HLA-DR4 phenotype and both the absence of antibody to the thyroid stimulating hormone receptor and permanent remission after treatment. The HLA-DR4 phenotype may perhaps be associated with immunomodulation, which is probably enhanced by antithyroid drug treatment: in such people lymphocytes might have a decreased rate of synthesis of auto-antibodies, which might eventually result in a higher chance of remission.

Our results support a recent hypothesis that some HLA antigens may promote the development of autoimmune disease whereas others may have a protective action.²⁹

In conclusion, HLA-Cw7, antibodies to thyroid stimulating hormone receptor at the end of treatment, and a large goitre were found more commonly in patients who relapsed. The presence of HLA-DR4 as well as the absence of antibodies was associated with remission. HLA-DR4 may protect against relapse of thyrotoxicosis, possibly by immunomodulation resulting in inhibition of synthesis

of pathogenic antibodies to the thyroid stimulating hormone receptor.

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Prevalence, concentration, and prognostic importance of proteinuria in patients with malignancies

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Abstract

Protein was found significantly more frequently in single urine samples from 504 patients with malignancy (290; 58%) than in 529 controls (119; 22%) ($p < 0.001$). Median protein concentration was greater ($p < 0.001$) in patients with neoplasia (0.14 g/l) than in controls (0.07 g/l). Actuarial analysis showed a median survival of 4.5 months in patients with proteinuria compared with 10 months in those without ($p < 0.001$). The association between proteinuria and shorter survival was statistically significant for patients with gut tumours, lung tumours, and tumours at other sites analysed

as a group. Patients with myeloma or urinary tract tumours were not studied.

In many patients with malignancy the presence of proteinuria may be associated with a substantially reduced survival time.

Introduction

Proteinuria, often heavy, is an infrequent but well recognised complication of many different malignancies.^{1,2} Histologically membranous nephropathy is most often present,^{3,4} but minimal change is typically found in patients with lymphomas.^{5,6} Tumour products were detected in glomeruli in a patient with colonic carcinoma,⁷ and tumour antigen was eluted from the kidneys of a patient with the nephrotic syndrome and malignant melanoma.⁸ Renal tissue obtained at necropsy from patients who had reticulo-endothelial tumours contained C3, immunoglobulins, and electron dense deposits in glomeruli,^{9,10} suggesting subclinical deposition of immune complexes. These observations were confirmed in patients who had died of gut tumours.¹¹

Low concentrations of proteinuria may be found in patients with advanced neoplastic disease¹² and extrarenal carcinomas.¹³ The Framingham study showed that proteinuria was associated with increased mortality after controlling for cardiovascular risk factors.¹⁴ The data are being examined to see whether proteinuria

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