

Coincidence of immune-mediated diseases driven by Th1 and Th 2 subsets suggests a common aetiology. A population-based study using computerized General Practice data

C. R. Simpson*†, W. J. A. Anderson†‡, P. J. Helms*, M. W. Taylor§, L. Watson¶, G. J. Prescott**, D. J. Godden†† and R. N. Barker‡‡

*Department of Child Health, ‡Department of Thoracic Medicine, §Department of General Practice and Primary Care, University of Aberdeen, ¶Department of Public Health, Grampian Health Board, **Department of Public Health, University of Aberdeen, Aberdeen, ††Highlands and Islands Health Research Institute, Inverness and ‡‡Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK

Summary

Background The recent rise in the prevalence of immune-mediated diseases has been attributed to environmental factors such as a lack of microbial challenge, or dietary change, that deviate the overall balance between mutually antagonistic subsets of T helper (Th) cells.

Objective An alternative proposal is that recent environmental changes have resulted in an immune system that is more likely to produce both Th1 and Th2 responses against benign antigens. The prediction of this hypothesis, that Th1 and Th2-mediated diseases are not mutually exclusive, and may be positively associated, is tested here in a whole population.

Methods Data from General Practices participating in the Scottish Continuous Morbidity Recording (CMR) project were used to determine the coincidence of the major Th2-mediated atopic diseases; asthma, eczema and allergic rhinitis, with the Th1-mediated autoimmune conditions; type I diabetes, rheumatoid arthritis and psoriasis. We also identified the prescription rates of inhaled therapy for asthma in patients with Th1-mediated disease.

Results There was a significant increase in the risk of presenting with a Th1-mediated autoimmune condition in patients with a history of allergic disease (standardized prevalence ratio (95% confidence interval) 1.28 (1.18–1.37)). Likewise, the standardized prevalence ratios of presenting with either eczema (1.67 (1.48–1.87)) or allergic rhinitis (1.22 (1.02–1.44)) were significantly increased in subjects with a history of Th1-mediated disease. There was a particularly strong association between current psoriasis and current eczema (standardized prevalence ratio of psoriasis in subjects with eczema 2.88, 95% confidence interval (CI) 2.38–3.45). There was also a significant increase in prescriptions for inhaled asthma therapy in patients with Th1 disease.

Conclusion It is concluded that Th1- and Th2-mediated diseases are significantly associated in a large General Practice population. This finding supports the proposal that autoimmune and atopic diseases share risk factors that increase the propensity of the immune system to generate both Th1- and Th2-mediated inappropriate responses to non-pathological antigens.

Keywords T helper cell, asthma, eczema, allergic rhinitis, diabetes, psoriasis, rheumatoid arthritis
Submitted 5 October 2000; revised 3 April 2001; accepted 30 June 2001

Introduction

The prevalence of many immune-mediated diseases is rising in Western societies [1–6], an increase which has been attributed to environmental factors [7,8]. The demonstration that CD4⁺ T helper (Th) cells drive many pathogenic immune responses has therefore led to a search for recent environmental changes that may have adversely affected such cells.

Th cell clones can be classified into distinct functional types on the basis of the cytokines they secrete, and it has become apparent that the differential activation of these helper subpopulations is important in immune-mediated disease [9–14]. Particular attention has been focused on the dichotomy between Th1 and Th2 cells, which are mutually antagonistic and characterized by the production of IFN- γ and IL-4, respectively. Many autoimmune diseases are driven by helper responses that are strongly dominated by the Th1 subset, and inducing a corresponding Th2 bias can prevent or ameliorate pathology in animal models [12,13]. IFN- γ , a Th1 cytokine, plays a critical role, not only in driving autoimmune inflammation and in helping B cells to produce autoantibodies, but also in initiating and perpetuating the response [9].

†These two authors made equal contributions.

Correspondence: Mr C. R. Simpson, Department of General Practice & Primary Care, University of Aberdeen, Westburn Road, AB25 2AY, UK.
E-mail: c.simp@abdn.ac.uk

In contrast, the pathogenesis of the atopic diseases; asthma, eczema and hayfever, depends on IL-4 produced by Th2 cells for the class switching of B cell responses to secrete IgE antibodies [15,16]. The antagonism between IL-4 and IFN- γ has lead to the belief that these responses are reciprocal [17].

Given the associations between particular Th subsets and autoimmune and atopic diseases, considerable effort has been expended in the search for environmental factors that bias the entire immune system in favour of either Th1 or Th2 responses [18,19]. For example, based on the increasing prevalence of atopy, and evidence that small families and first-born children [20] in developed countries suffer more from atopic disease, a lack of microbial challenge is thought to be important in increasing the prevalence of atopy. This 'hygiene hypothesis' [8] proposes that reduced exposure to infection allows an overall bias towards Th2 responses *in utero* and early infancy to persist and thereby encourage the production of IgE antibodies against ingested and inhaled allergens [18,19]. Dietary changes in the intake of ω -3 and ω -6 fatty acids have also been implicated in the rising incidence of atopic disease, and are thought to have an effect on the same axis [7]. However, the development of many autoimmune diseases has also been attributed to an overall Th1 bias caused by these same environmental changes. Thus, type I diabetes and autoimmune thyroid disease are increasing in incidence in children [4,5,21,22], and type I diabetes is more common in small families [23] and in first-born children [24]. In addition, ω -3 fatty acids, which are thought to protect from atopy, have been said to protect against both psoriasis and rheumatoid arthritis [25,26]. Thus, the current focus on factors that deviate the immune system as a whole towards Th1 or Th2 domination has produced apparently contradictory evidence. To resolve this paradox, we propose that recent environmental changes have increased susceptibility to immune-mediated disease, not by polarizing the entire Th compartment, but by allowing both Th1 and Th2 responses to otherwise benign antigens to go unchecked. Thus, the same environmental factors could contribute to the development of both atopic and autoimmune disease. The aim of this study was to test this hypothesis, which predicts that Th1- and Th2-mediated conditions should not be mutually exclusive, and indeed that these types of disease should be positively associated. The study took advantage of continuously collected General Practice data from the Scottish Executive Department of Health supported Continuous Morbidity Recording (CMR) project [27] to determine the coincidence of the atopic diseases (asthma, eczema and allergic rhinitis) with Th1-mediated autoimmune disease (type I diabetes, rheumatoid arthritis and psoriasis).

Methods

Patient database

Electronic records of all morbidity and repeat prescribing for all patients registered in April 1999 in 47 practices from the Scottish CMR project. CMR General Practices were recruited so that they represented the age/sex and rural/urban mix of the Scottish population with 252 538 registered patients on the census date [27].

Th1- and Th2-mediated disease classification

Diseases were included in the analysis if they were widely accepted as either Th1- or Th2-mediated and if their diagnosis could be clearly defined in a General Practice setting. Definitive doctor diagnoses and symptoms are coded in CMR according to Read 2.0 hierarchical classifications [28]. The Th1-mediated diseases included in the analysis were type I diabetes (Read code C10 and below) diagnosed between the ages of 5 and 30 years in order to exclude type II diabetics, and psoriasis (Read code M16 and below) and rheumatoid arthritis (Read code N04 and below) diagnosed at any age. The Th2-mediated diseases studied were asthma (Read code H33 and below), eczema (Read code M11, M12z) and allergic rhinitis (Read code H17, Hyu 2).

The 'current disease' group includes those patients who presented at least once in the study year (April 1998 to April 1999) with the defined diagnosis. The 'disease ever' population included any patient with a previous or current diagnosis. Prevalence rates for both Th1 and Th2 disease in the general population were compared with the respective rates in those with current and ever Th1 or Th2 disease. This analysis was repeated to find any association of Th1 and Th2 disease in those in the general population who had presented to their General Practice at least once in the study year ($n = 192\,284$).

Statistical analysis

In order to compare the prevalence rates of the conditions in diseased (Th1 and Th2) and general populations, it was necessary to standardize for the potentially different demographic structures of these populations. The prevalence rates were calculated for the conditions within each sex-age band stratum of the diseased population. For each stratum of the general population it was possible to calculate an expected number of observations assuming that the prevalence rates were the same in both populations. The total number of cases observed were compared with the total number expected under this assumption, to provide the indirect sex-age standardized prevalence ratio for the condition in the diseased and general populations. These standardization methods and those for the confidence intervals displayed are described by Coggon and by Altman et al. [29,30]. In addition to systemic associations we also looked for organ-specific associations, specifically for the association between psoriasis and eczema, both diseases of the skin, and for associations between the prescription of inhaled therapy for asthma (β_2 agonists and/or inhaled corticosteroids) and Th1 disease. The prescription of an inhaled corticosteroid was used as a surrogate for asthma severity and identified as low- ($< 800\ \mu\text{g}$ per day) or high-dose ($> 800\ \mu\text{g}$ per day).

Results

Table 1 shows the one year prevalence rates per 1000 patients by age and sex of the Th2-mediated atopic diseases; asthma, eczema and allergic rhinitis, and the Th1-mediated autoimmune diseases; type 1 diabetes, psoriasis and rheumatoid arthritis in the 252 538 registered patients of the general population.

The number of patients presenting in the study year with the Th2-mediated atopic diseases in the 252 538 registered patients, together with the 7881 registered patients with a history of Th1-mediated autoimmune disease and the standardized

Table 1. One year period prevalence rates per 1000 patients for Th1 and Th2 disease in the general population ($n = 252\,538$)

	Eczema		Allergic rhinitis		Asthma		Psoriasis		Rheumatoid arthritis		Diabetes	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
0–4	91	99	6	7	34	52	0	0	0	0	*	*
5–9	49	40	18	28	55	75	3	2	0	0	0	1
10–14	38	31	38	44	55	68	5	4	0	0	1	1
15–19	43	20	44	36	51	40	9	6	0	0	2	1
20–24	36	21	28	19	36	25	10	6	0	0	2	2
25–29	32	17	21	15	31	23	10	7	1	0	2	3
30–34	26	13	20	13	29	23	10	9	2	0	*	*
35–39	22	14	16	10	26	22	8	9	3	0	*	*
40–44	22	13	14	9	29	19	7	8	4	1	*	*
45–49	18	13	13	8	33	19	8	9	6	2	*	*
50–54	18	15	9	8	30	17	8	10	8	3	*	*
55–59	17	15	9	4	36	23	11	10	9	6	*	*
60–64	24	19	11	5	38	28	10	9	12	5	*	*
65–70	21	20	8	8	37	27	7	9	11	8	*	*
70–74	17	27	8	8	27	26	7	12	12	7	*	*
75–79	20	25	5	5	26	25	7	5	13	9	*	*
80+	17	26	3	4	17	25	4	2	8	2	*	*

*Type 1 diabetes > 4 years and < 30 years of age.

Table 2. One year prevalence ratio of asthma, eczema, allergic rhinitis and all atopy for subjects with Th1 disease (defined as diabetes between 5 and 30 years, psoriasis or rheumatoid arthritis)

	Total population ($n = 252\,538$)	Any Th1 disease ($n = 7881$)	Standardized prevalence ratio	95% confidence intervals
Asthma	8575	263	1.10	0.97–1.24
Eczema	7035	285	1.67	1.48–1.87
Allergic rhinitis	4094	136	1.22	1.02–1.44
All atopy	18307	643	1.32	1.22–1.43

prevalence ratio is summarized in Table 2. It can be seen that many individuals suffered from both types of disease, and that there was a significantly increased risk of presenting with a Th2-mediated allergic disease in patients who had a history of Th1-mediated autoimmune disease. The strongest association was between eczema and Th1-mediated disease, but there was also a significant increase in the standardized prevalence ratio of allergic rhinitis and a non-significant elevation of risk for asthma. While the prevalence of asthma was not significantly higher in subjects with Th1 disease, the prescription of inhaled asthma medication was greater (see Table 3).

Table 4 shows the one year prevalence of the Th1-mediated autoimmune diseases, the number of patients with a history of the atopic disease, and the standardized prevalence ratio of presenting with a Th1-mediated disease in those with a history of Th2-mediated disease. Again, it was apparent that these two types of disease were not mutually exclusive, and that they are in fact associated.

The analysis that was carried out to find associations of Th1 and Th2 disease in those in the general population who had presented to their General Practice at least once in the study year ($n = 192\,284$) (Tables 5 and 6), found that concomitance of Th1 and Th2 disease still occurred. No significant association between allergic rhinitis and Th1 disease occurred, however, all other results remained significant.

Further analysis aimed at demonstrating the organ-specific coincidence of disease revealed an increased standardized prevalence ratio of current psoriasis in those with current eczema (relative risk 2.88, 95% CI (2.38–3.45)).

Discussion

The main result reported here is that Th1-mediated autoimmune and Th2-mediated atopic diseases are not mutually exclusive, but associated. This observation conflicts with the current rationale that these two types of condition are caused by domination of the entire immune system by either Th1 or Th2 responses, respectively. Rather, the association may support the hypothesis that Th1-mediated autoimmune and Th2-mediated atopic diseases share common environmental risk factors, which increased the likelihood of either Th1 or Th2 responses to otherwise benign antigens.

The significant concurrence between the autoimmune disease psoriasis and allergic eczema demonstrates that both Th1- and Th2-mediated immune pathology can co-exist in the same organ, exemplifying that the critical factors determining the type of Th response are likely to be antigen-specific, and not related to the immune system as a whole. The potential for psoriasis and eczema to coincide has been noted previously

Table 3. One year prevalence ratio (95% confidence interval) of a prescription of inhaled β_2 agonists, low-dose and high-dose inhaled steroids for subjects with Th1-mediated disease against the general population

	Total population (<i>n</i> = 252 538)	Any Th1 disease (<i>n</i> = 7881)	Standardized prevalence ratio	95% confidence intervals
β_2 agonist prescriptions	15249	569	1.15	1.05–1.24
Low-dose inhaled steroids	6838	255	1.19	1.05–1.35
High-dose inhaled steroids	2325	155	1.27	1.05–1.53

Table 4. One year prevalence ratio of diabetes between 5 and 30 years, psoriasis, rheumatoid arthritis and all Th1 disease for subjects with Th2 disease (defined as asthma, eczema and allergic rhinitis)

	Total population (<i>n</i> = 252 538)	Any Th2 disease (<i>n</i> = 52 986)	Standardized prevalence ratio	95% confidence intervals
Type I diabetes	128	35	1.05	0.73–1.47
Psoriasis	1836	668	1.86	1.72–2.01
Rheumatoid arthritis	824	161	1.16	0.99–1.36
Any Th1 disease	2892	703	1.28	1.18–1.37

Table 5. One year prevalence ratio of asthma, eczema, allergic rhinitis and all atopy for subjects with Th1 disease (defined as diabetes between 5 and 30 years, psoriasis or rheumatoid arthritis) for those patients who presented during the study year

	Total population (<i>n</i> = 192 284)	Any Th1 disease (<i>n</i> = 2762)	Standardized prevalence ratio	95% confidence intervals
Asthma	8575	107	0.98	0.80–1.19
Eczema	7035	139	1.80	1.52–2.13
Allergic rhinitis	4094	49	0.93	0.69–1.23
All atopy	18307	277	1.24	1.10–1.40

Table 6. One year prevalence ratio of diabetes between 5 and 30 years, psoriasis, rheumatoid arthritis and all Th1 disease for subjects with Th2 disease (defined as asthma, eczema and allergic rhinitis) for those patients who presented during the study year

	Total population (<i>n</i> = 192 284)	Any Th2 disease (<i>n</i> = 18 307)	Standardized prevalence ratio	95% confidence intervals
Diabetes Type 1	84	11	1.30	0.65–2.34
Psoriasis	1836	211	1.36	1.18–1.56
Rheumatoid arthritis	824	58	1.05	0.80–1.36
Any Th1 disease	2762	277	1.24	1.10–1.39

[31,32], although not all studies agree, some showing an inverse association [33,34]. Further evidence that Th1- and Th2-mediated diseases may share a common aetiology comes from close similarities in the epidemiology of these diseases. The increased prevalence of atopic disease has been attributed to a lack of microbial challenge (the 'hygiene hypothesis'), which has been claimed to bias the immune system towards Th2 responses. However, the same environmental influences could be blamed for the parallel increases in the prevalence of many autoimmune diseases that are mediated by Th1 cells. In particular, type I diabetes is rising in incidence [4–6], and is more common in affluent children and those in less crowded households [23]. In an animal model of type I diabetes, prior infection with mycobacterium, far from increasing the Th1 response, protects against disease [35]. Taken together, these observations

are inconsistent with the wide-spread notion that microbial challenge drives the entire immune system towards Th1 responsiveness. Similarly, the view that ω -3 fatty acids in the diet protect against Th2-mediated diseases by promoting Th1 polarization is contradicted by the findings that ω -3 fatty acids inhibit the antigen presentation by human monocytes in rheumatoid arthritis and multiple sclerosis [36], and are known to be therapeutic in psoriasis and rheumatoid arthritis [25,26].

Several factors need to be borne in mind when interpreting the study findings. Firstly, patients registered with CMR practices under-represent some rare but very deprived members of the population who may choose over-the-counter remedies to relieve symptoms. This may result in the underestimation of disease prevalence. Secondly, CMR practices may over-represent affluent areas within Scotland [27]. However, these

are the most appropriate populations to include since they are at highest risk of immune-mediated disease. Thirdly, it might also be said that the presence of one disease might increase the chance of the physician diagnosing a second disease. However, some of the associations presented in this study are strong, such as that between current eczema and current psoriasis, and therefore it seems unlikely that this provides a complete explanation. A further standardized comparison using those patients in the general population who had presented to their GP at least once in the study year showed little change from existing results. Fourthly, our presumption that inhaled β_2 agonists and inhaled corticosteroids are markers of a diagnosis of asthma may be an oversimplification. Our data has also shown (Table 1) that atopic and autoimmune diseases have different prevalences with age in that the former are more common in childhood in contrast to the latter which present predominantly in adulthood. Despite these differences in age at presentation we have shown that the two broad groups of diseases tend to aggregate rather than offering some degree of mutual protection as the TH1/Th2 paradigm would suggest. This is consistent with our suggestion that common environmental provoking factors may have contributed to the expression of both atopy and autoimmune disease in our population. Despite some apparent weaknesses, which may have diluted or confounded the results, we have found a consistent pattern that contradicts the current dogma and supports a common aetiology.

It remains possible that the environmental influence on the prevalence of Th1- and Th2-mediated disease in childhood acts at another site in the disease pathogenesis. Nevertheless, in contrast to the clear contradictions that emerge when it is assumed that risk factors for autoimmune and atopic diseases must act by polarizing the entire immune system towards Th1 or Th2 domination, all of the data can be reconciled by our hypothesis that such factors cause immune dysregulation [37]. The predictions of this hypothesis, that Th1- and Th2-mediated conditions should not be mutually exclusive, but positively associated, have been fulfilled by the current study. Thus, although experimental Th1 and Th2 responses are reciprocal, diseases mediated by each subset can co-exist in the same patient, and even in the same organ. Acceptance that Th1 and Th2 diseases may not be mutually exclusive, has important implications for future development of therapeutic and environmental interventions.

We believe that a prospective cohort study would provide an opportunity for a more thorough investigation of the association between the presence of Th1- and Th2-mediated diseases.

Acknowledgements

We would like to thank those involved with the Continuous Morbidity Recording project which is supported by the Scottish Executive's Information and Statistics Division. Colin Simpson is supported by an educational grant from Merck Sharp & Dohme, UK.

References

- 1 Anderson HR, Butland BK, Strachan DP. Trends in prevalence and severity of childhood asthma. *BMJ* 1994; 308:1600–4.
- 2 Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992; 304:873–5.
- 3 Britton J. Asthma's changing prevalence. *BMJ* 1992; 304:857–8.
- 4 Gardner SG, Bingley PJ, Sawtell PA, Weeks S, Gale EA. Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's-Oxford Study Group. *BMJ* 1997; 315:713–7.
- 5 Zhao HX, Stenhouse E, Soper C et al. Incidence of childhood-onset Type 1 diabetes mellitus in Devon and Cornwall, England, 1975–1996. *Diabet Med* 1999; 16:1030–5.
- 6 Rangasami JJ, Greenwood DC, McSporran B, Smail PJ, Patterson CC, Waugh NR. Rising incidence of type 1 diabetes in Scottish children, 1984–93. The Scottish Study Group for Care Young Diabetics. *Arch Dis Child* 1997; 77:210–3.
- 7 Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; 10:6–12.
- 8 Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999; 354 (Suppl. 2):SII12–SII15.
- 9 Elson CJ, Barker RN, Thompson SJ, Williams NA. Immunologically ignorant autoreactive T cells, epitope spreading and repertoire limitation. *Immunol Today* 1995; 16:71–6.
- 10 Horrocks C, Holder JE, Berth-Jones J, Camp RD. Antigen-independent expansion of T cells from psoriatic skin lesions: phenotypic characterization and antigen reactivity. *Br J Dermatol* 1997; 137:331–8.
- 11 Liblau RS, Singer SM, McDevitt HO. Th1 and Th2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. *Immunol Today* 1995; 16:34–8.
- 12 Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986; 136:2348–57.
- 13 Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; 7:145–73.
- 14 Robinson DS, Hamid Q, Jacobson M, Ying S, Kay AB, Durham SR. Evidence for Th 2-type T helper cell control of allergic disease in vivo. *Springer Semin Immunopathol* 1993; 15:17–27.
- 15 Ichikawa K, Baba M, Kawano Y, Noma T. Effect of interferon-gamma on HLA class 2 expression by antigen-presenting cells inducing Dermatophagoides farinae-specific interleukin-2 responsiveness of lymphocytes in asthmatic children. *Pediatr Allergy Immunol* 1994; 5:53–8.
- 16 Kuwabara N, Kondo N, Fukutomi O, Fujii H, Orii T. Methylation patterns of I epsilon region in B cells stimulated with interleukin 4 and Epstein-Barr virus in patients with a high level of serum IgE. *Eur J Immunogenet* 1995; 22:265–75.
- 17 Lin KL, Hsieh KH, Huang JH, Wang SY. Major histocompatibility complex (MHC) class II restriction, lymphokine production, and IgE regulation of house dust mite-specific T-cell clones. *J Clin Immunol* 1992; 12:271–80.
- 18 Holgate ST. The epidemic of allergy and asthma. *Nature* 1999; 402:B2–B4.
- 19 Holt PG, Macaubas C, Stumbles PA, Sly PD. The role of allergy in the development of asthma. *Nature* 1999; 402 (Suppl.):7.
- 20 Strachan DP, Harkins LS, Johnston ID, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997; 99:6–12.

- 21 Green A, Gale EA, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 1992; 339:905–9.
- 22 Hunter I, Greene SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young. *Arch Dis Child* 2000; 83:207–10.
- 23 Patterson CC, Carson DJ, Hadden DR. Epidemiology of childhood IDDM in Northern Ireland 1989–94: low incidence in areas with highest population density and most household crowding. Northern Ireland Diabetes Study Group *Diabetologia* 1996; 39:1063–9.
- 24 Bingley PJ, Douek IF, Rogers CA, Gale EA. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. *BMJ* 2000; 321:420–4.
- 25 Cleland LG, James MJ. Rheumatoid arthritis and the balance of dietary N-6 and N-3 essential fatty acids. *Br J Rheumatol* 1997; 36:513–4.
- 26 Mayser P, Mrowietz U, Arenberger P et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial. *J Am Acad Dermatol* 1998; 38:539–47.
- 27 Simpson CR, Helms PJ, Taylor MW, Baxter-Jones ADG. Respiratory morbidity in Primary Care. A population based study, using practices from the Scottish Continuous Morbidity Recording Research Database. *Health Bull* 2001; 60:488–95.
- 28 Stuart-Buttle CD, Read JD, Sanderson HF, Sutton YM. A language of health in action: Read Codes, classifications and groupings. *Proc AMIA Annu Fall Symp* 1996, 75–9.
- 29 Altman DG, Machin D, Bryant TN, Gardner MJ. *Statistics with Confidence*. 2nd edn. London: BMJ Books, 2000.
- 30 Coggon D, Rose G, Barker DJP. *Epidemiology for the Uninitiated*, 3rd edn. London: British Medical Journal 1993.
- 31 Welp K, Gieler U, Stander M, Friederich HC. Concomitant psoriasis vulgaris and atopic dermatitis. A study of 1,065 patients with psoriasis. *Hautarzt* 1989; 40:496–500.
- 32 Williams HC, Strachan DP. Psoriasis and eczema are not mutually exclusive diseases. *Dermatology* 1994; 189:238–40.
- 33 Christophers E, Henseler T. Contrasting disease patterns in psoriasis and atopic dermatitis. *Arch Dermatol Res* 1987; 279 (Suppl.):S48–S51.
- 34 Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995; 32:982–6.
- 35 Martins TC, Aguas AP. A role for CD45RBlow CD38+ T cells and costimulatory pathways of T-cell activation in protection of non-obese diabetic (NOD) mice from diabetes. *Immunology* 1999; 96:600–5.
- 36 Hughes DA, Pinder AC. n-3 polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes. *Am J Clin Nutr* 2000; 71:357S–60S.
- 37 Lipscomb MF, Wilder JA. Immune dysregulation as a cause for allergic asthma. *Curr Opin Pulm Med* 1999; 5:10–20.