

Clinical aspects of atopic dermatitis

K. Thestrup-Pedersen

Department of Dermatology, Marselisborg Hospital, University of Aarhus, Denmark

Summary

Atopic dermatitis (AD), or atopic eczema, is the most common, chronic inflammatory disease among children in industrialized countries. We still lack knowledge of its pathophysiology and in particular the role of allergy as both an eliciting factor for disease expression and for disease activity. This article describes the clinical symptoms of the disease and its qualitatively different aspects. AD cannot be understood as being induced by one factor only, e.g. allergy, and this is important when planning treatment strategies. It is also important to realize the very wide range of disease intensity: from subclinical, or latent AD, in which only a few symptoms are present and thus which prevents a clear diagnosis of AD, to its most severe forms including erythroderma. Its unknown aetiology, the wide range in symptomatology, and the fluctuating course (including the many eliciting factors) form the background for our diagnostic and therapeutic difficulties of atopic eczema. AD is prevalent in childhood, but the atopic trait continues, not only for later respiratory allergies, but also for skin diseases in adulthood (such as AD itself or the frequent irritant contact dermatitis of the hands). A child with an acute and first attack of AD is therefore a challenge to the child, its parents and – certainly – to the doctor. However, after stressing the chronicity of the disease, it is equally important to assure the parents that this disease is, in most cases, controllable through correct treatment and that it has a good prognosis: It is not a 'life sentence', but a controllable disease in an otherwise healthy child.

Introduction

Although many physicians must have known 'atopic dermatitis' (AD) for centuries, it was not until 1892 that E. Besnier focused attention on the disease entity by describing this very itchy skin condition in three teenage boys.¹ In the first part of the 20th century the Danish dermatologist Nexmand published his thesis on 100 patients with AD seen at the Finsen Institute in Copenhagen,² all with lifelong, severe disease. Nexmand also documented that only 1.3% of all patients seen at the Finsen Institute carried a diagnosis of 'Prurigo Besnier' as it was usually called in Scandinavia. This low incidence is in sharp contrast with the latter part of

the 20th century. An increase of AD was clearly demonstrated by Schultz Larsen, who observed that the incidence increased from 3% among children born in the 1960s to 12% among children born in the late 1970s.³ A questionnaire study in 1993 gave a cumulative prevalence of AD among 0–7 year-old children of 18.7%.⁴ It was also observed that 5.6% of all children born in 1984–1986 in the city of Aarhus, Denmark, had been seen by a dermatologist, who diagnosed AD.⁴ In 1998 the same authors found a prevalence of AD of almost 23% among 0–15-year-old children, and of 18.5% among the 0–7 year-old age group (A B Olesen *et al.* Personal communication). Thus, the incidence of AD appears not to have increased in the 1990s.

It is noteworthy that several studies demonstrate our difficulties in establishing a diagnosis of AD. Thus, a recent questionnaire study among schoolchildren in Denmark, Germany and Sweden showed the respective prevalences of AD to be 23%, 10% and 15% respectively.⁵ These

Correspondence: K. Thestrup-Pedersen, Department of Dermatology, Marselisborg Hospital, University of Aarhus, DK-8000 Aarhus C., Denmark. Tel.: +45 89491852. Fax: +45 89491850. E-mail: ktp56@hotmail.com

Table 1 The Hanifin and Rajka diagnostic criteria for atopic dermatitis.⁸

Major criteria
Pruritus
Dermatitis affecting flexural surfaces in adults and the face and extensors in infants
Chronic or relapsing dermatitis
Personal or family history of cutaneous or respiratory atopy
Minor criteria
<i>Features of the 'atopic face':</i> facial pallor or erythema, hypopigmented patches, infraorbital darkening, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, and anterior neck folds
<i>Triggers of atopic dermatitis:</i> foods, emotional factors, environmental factors, and skin irritants such as wool, solvents, and sweat
<i>Complications of atopic dermatitis:</i> susceptibility to cutaneous viral and bacterial infections, impaired cell-mediated immunity, immediate skin-test reactivity, raised serum IgE, keratoconus, anterior subcapsular cataracts.
<i>Others:</i> Early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermatographism, perifollicular accentuation

A diagnosis of AD is made when three of four major and three minor symptoms are present.

differences must be significantly different although the authors do not mention this. A recent study of 5-year-old pre-school children in Göteborg and Kristiansstad in Sweden, performed in the fall of 1997 and conducted by two experienced dermatologists, found the incidence of AD in Göteborg to be 6.2% and that in Kristiansstad to be 14.2%.⁶ Other studies have shown very wide variation in atopic diseases all over the world.⁷ Based on these facts, it is fair to ask the question: Can we diagnose AD?

The observed increase of AD may have many explanations, which will not be dealt with here. However, one contributing factor could be that the increased health industrial complex is partly responsible for the apparent increase of children with recognized AD: all children are in industrialized countries seen many times by health personnel; the small number of children in the families leads to a 'demanding parents syndrome', i.e. the child must be normal and not have dry, itchy skin.

Disease definition

Hanifin and Rajka were the first to establish a set of diagnostic criteria for AD, which are widely used (Table 1).⁸ The diagnosis of AD is based on three of four 'major signs' and three of '28 minor signs', many of them clinical signs, which should be obvious to observers. More recently the UK Working Party's

Table 2 The UK Working Party's Diagnostic Criteria for atopic dermatitis.⁹

Presence of an itchy skin rash within the past 12 months (obligatory) plus three or more of:
History of flexural dermatitis
Onset below the age of 2 years (only if child is over 4 years old)
Personal history of asthma or hay fever
History of dry skin
Visible flexural dermatitis

Diagnostic Criteria for AD was developed; these are simpler than Hanifin and Rajka's criteria.⁹ The 'minimum list of reliable discriminators for AD' consists of six parameters, which were found to be necessary and sufficient for diagnosis (Table 2). Interestingly, only one of these items is an 'objective physical sign', i.e. presence of flexural eczema; the other parameters relates to disease history. However, they have been validated^{10,11} not only in the UK, but in large investigations with both high sensitivity and specificity.¹² However, a recent study from Iran shows a quite different picture, in which sensitivity was found to be as low as 10%.¹³ The Iranian study has drawbacks,¹² but it again raises the relevant question: Can we diagnose AD?

There is one caveat in the British study: The diagnostic system is based on 'new cases of *typical* mild to moderate AD', which are then compared with 'age-matched controls with an inflammatory skin disease other than AD'. The British criteria are therefore developed from typical cases of AD. One could argue that 'atypical' cases of AD exist, i.e. patients with symptoms similar to AD, but who do not fulfil all criteria for the diagnosis. Teenagers with pityriasis alba on the upper arms or in the face with previous AD in their childhood will not be classified as having AD, but their propensity to develop this symptom rests on their atopic background.

AD has been suggested to be eczema and increased serum IgE only.¹⁴ This will exclude up to 40% of children to have inflammatory skin disease other than AD. It will also lead to situations, where a child with flexurable eczema and a total serum IgE of 349 kU/L (normal upper limit 350 kU/L) would not have AD, but would have it the following year, if the IgE value increased to 351 kU/L. Same child, two different diseases? Finally, a patient with AD and increased IgE in serum will continue to have the increased IgE even when the skin symptoms have resolved.

Factors underlying the disease

AD is the clinical expression of unknown changes giving rise to itching, changes in ectodermal tissue (skin)



Figure 1 Rather well-marked form of atopic eczema involving the scalp and the face.

leading to dryness, and a skin inflammation of cells from the immune system. The immune inflammation consists of activated T lymphocytes, eosinophils, increased numbers of dendritic cells and mast cells. It has recently been shown that even in clinically normal looking skin there is a doubling of the number of lymphocytes, indicating that latent AD does exist (A. R Ellingsen *et al.* Personal communication).

Keratinocytes appear to be normal although studies have indicated an increased release of the haematopoietic growth factor granulocyte-macrophage colony stimulating factor. The total lipids and ceramide levels are reduced and there is a changed composition of lipids which could explain the changed skin barrier of AD patients.^{15,16} The mesenchymal tissue (fibroblasts and collagen, etc.) seems to be unaffected although a changed vascular function is prominent.

So, the essentials of AD are: itching, epidermal (ectodermal) changes of lipids together with an inflammation created by the immune system,

The symptoms of AD

The atopic itch

This symptom is so prominent and constant that a nonitching rash excludes a diagnosis of AD. Despite intensive research the mediators causing the itch are not known. It is not histamine although it should be remembered that urticarial symptoms can form part of AD and if this happens, antihistamines will be helpful. The itch mediators are probably the result of ongoing biochemical reactions in the skin as cooling of the skin

relieves itching, whereas increased skin temperature makes it worse. Sweating, high bed temperatures or increased skin temperature from warm clothing including wool leads to increased itching in most patients. The itch is not constant, but comes in 'attacks' especially when the child gets tired in the afternoon or evening. Attacks of itch can be very severe and disturbing. Factors promoting cooling of the skin are helpful, i.e. light clothing or even almost no clothing for a short period of time, cool sleeping conditions, etc. It is advisable to use corticosteroids in the evening and emollients in the morning, because steroids have an itch-dampening effect. The atopic itch is visible indirectly through the many excoriations, which are a prominent clinical symptom of AD. The excoriations are located at areas of eczema, indirectly supporting that mediators are released from activated T cells and/or eosinophils and not from mast cells. Again, cholinergic urticaria or urticarial symptoms can form part of the AD complex.

The dry, atopic skin

Dry skin was found to be a common symptom among children with 'typical' AD.⁹ The decreased and changed lipid content of the skin is one contributing factor. In general, AD patients have a relative deficiency of their skin barrier: they have increased transepidermal water loss some also have reduced skin water content.¹⁵ Also, in the early years their skin barrier seems much less resistant to irritant exposures. Later in life occupational, irritant exposure of the hands is a significant factor in the development of irritant contact dermatitis on the hands, which occurs in up to 45% of adults with previous AD.¹⁷ Thus, hand eczema is the most common occupational disease in young persons below the age of 25 years¹⁸ and many of these relate to previous AD. Emollients are a very important part of treatment.

The atopic eczema

AD starts on the head with the development of dryness and redness of the skin accompanied by excoriations, which the child can induce after the first 2 months of life. It affects the scalp and cheeks and the skin folds on the neck (Figs 1 and 2). Infra-auricular fissures may be prominent. The tip of the nose and the perinasal areas are spared (Fig. 3). The eczema is usually not well-marked. It shows a diffuse spreading in the skin and it also shows a tendency for exacerbation within hours, which can then subside. It later spreads to the neck and extremities, where it can initially be localized on the external sides, but later develops in the flexural areas; the trunk can also be involved (Fig. 6). The



Figure 2 Five-year-old boy with pronounced folliculitis and eczema of the scalp. The lymph nodes on the neck were enlarged. Note hair loss due to infection and scratching.

napkin area is usually spared and it is not usual to see an affection of the palms or soles in early infancy. Lichenification of the skin is normally seen after the age of 3–4 years, because it is secondary to excessive scratching of the skin (Fig. 7). The figures illustrate children with AD. Adults with AD have symptoms similar to those of children. However, the fact that an adult continues to have eczema indicates that the patient has severe AD, which affects approximately 10% of patients. Rarely, the eczema becomes universal although palms and soles are rarely affected, even in erythrodermic patients.

The atopic stigmata

The Hanifin and Rajka criteria (Table 1) includes a long list of clinical symptoms that are seen more frequently



Figure 4 Same patient as in Figure 3; well-marked eczema on several fingers from biting and saliva.

among AD patients than other inflammatory skin conditions. The British diagnostic criteria have excluded all of the 'minor signs' of Hanifin and Rajka because the British study showed that the symptoms were observed in less than half of typical AD patients. The Dennie-Morgan fold (Fig. 6) is seen very commonly among black children without skin disease and thus, the specificity of the minor signs for the diagnosis of AD is clearly diminished.

Still, each symptom may be present and reflect a reminiscent symptom of an atopic eczema, which has now more or less gone and where the symptom alone is not sufficient for a diagnosis of AD. There are certain 'patterns' of AD, which are more or less well characterized as associated with or being a variant of AD: the atopic winter feet (Fig. 8), well-circumscribed hand



Figure 3 Atopic dermatitis in a 1.5-year-old boy. Note the lines and slight eczema on lower eye lids, the 'tip-of-the-nose' sign being free of eczema, the running nose and the saliva on the chin.



Figure 5 Same patient as in Figure 3; well-marked eczema of discoid type on the wrist. This is often indicative of impetiginized eczema.



Figure 6 Five pictures of an 8-year-old boy with almost universal eczema. Note lines below eyes and the eczema on the eye lids (a), neck folds (b), nonwell marked excoriated eczema on trunk (c), nummular lesions on femura (d), but without flexural eczema in knees (e).

eczema of infants with AD probably develop as a consequence of skin irritation from physical damage (biting) (Fig. 4) and saliva on the skin (Fig. 9); the nummular forms of AD seen in children and adults; the papular AD with a rather nonspecific eruption of excoriated papules without the usual flexural eczema and lack of other atopic stigmata but often increased IgE (Fig. 10); and the toilet-seat type of AD.

In adults 'head and neck' dermatitis is often seen and

can be quite severe (Fig. 11). This location of eczema gives strong suspicion to either allergic or irritant contact dermatitis as one sign of AD. As mentioned, up to 45% of adults who had atopic eczema in childhood will develop hand eczema, which in most cases is irritant contact dermatitis, starting as dryness of the hands, following by vesicular eruptions between the fingers and later spreading of the skin changes. Allergic contact dermatitis is not a major issue among AD patients as they are resistant to



Figure 7 Lichenization of the skin in an adult with severe atopic eczema.

development of type IV contact allergy. It is not possible to predict who will develop hand eczema and who will not, but the cumulative irritancy of the skin on the hands, both from occupational exposure and exposure at home (cooking, soap, bathing children, gardening, hobbies with chemicals) all add to this condition.

There is a rarer form of hand eczema, pompholyx or recurrent vesicular hand eczema of the palms and/or feet, which is known to be observed more frequently among persons with previous atopy.¹⁹ However, its exact relationship to AD vs. its relationship to contact allergies is disputed.

Skin infections and AD

Staphylococcus aureus can be found on the eczematous skin of 95% of patients with AD. It frequently gives

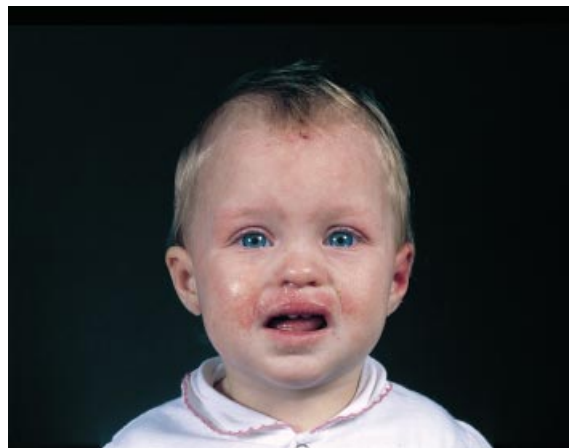


Figure 9 Facial atopic dermatitis. Note the lines and slight eczema on lower eye lids. Note also that the tip of the nose is free of eczema. The eczema is most pronounced on the upper lips because of running nose, saliva and physical contact caused by the use of a pacifier.

rise to impetigo, which are reasonably well-marked lesions that develop suddenly and grow with brown crusts, as opposed to scales, on top (Fig. 12). Also, eczema can become oozing as a sign of infection with *Staph. aureus*. Sometimes streptococci are found, but staphylococci are the most common cause of impetigo. There is much discussion about the significance of *Staph. aureus* for immune inflammation in atopic eczema as certain reports not only document that eczema can be induced by staphylococcal exotoxins,²⁰ but that a combination therapy with fusidic acid and hydrocortisone cream leads to significantly quicker symptom relief.²¹ However, other forms of therapy such as disinfecting the skin



Figure 8 Dermatitis plantaris sicca ('atopic winter feet').



Figure 10 Papulous atopic eczema in an adult.



Figure 11 Head and neck dermatitis. Note skin covered by the T-shirt is not affected by eczema.

and the use of systemic antibiotics do not always have a clear effect although they are used frequently.

Viral infections are common, not so much by human papillomaviruses, but *Molluscum contagiosum*, which can be quite extensive. Herpes simplex virus can induce eczema herpeticum, which develops quickly and dramatically and in which systemic antiviral therapy is required immediately. Herpes keratitis is a feared complication.

Fungal infections do not appear to be more common in patients with AD. The significance of the much discussed *Pityrosporum orbiculare* and its importance for head and neck dermatitis has recently been questioned.²² However, some patients do show clear improvement of symptoms when given specific therapy.

Table 3 Severity distribution of atopic dermatitis.

Reference	Mild	Moderate	Severe	Investigated (n)
Emerson <i>et al.</i> ²⁵	84%	14%	2%	290 children
Murphy <i>et al.</i> ²⁸	23%	44%	33%	183 children



Figure 12 Impetigo on cheek; note eczema in the surrounding skin.

The course of AD

It is important to realize that AD extends from being 'latent', i.e. with dryness and xerosis of the skin, accompanied by fluctuating itching. If a biopsy is performed an increase of lymphocytes will be seen in the skin. From this it can develop into the severe erythrodermic forms. Estimates of the distribution of severity of AD is shown in Table 3. The vast group of mild AD are those children who are rarely seen by dermatologists.

The fluctuation of disease intensity is quite extensive. Thus, children aged between 2 and 11 years were found to have a point prevalence of AD of 2.6% compared with a 1-year prevalence of 8%.²³

When does AD start and when does it disappear? It has been observed that approximately one-third of children express their disease within the first year of life, another one-third during the second year of life and roughly one-third during the third year.²⁴ In the majority of children the eczema disappeared in the age range of 7–11 years.²⁵ However other studies are less optimistic as 40% still have eczema as teenagers. This depends on the composition of the study population (see Table 3). The difficulties in assessing a prognosis is probably a combination of the large variation in disease severity with fluctuation of symptoms, and a lack of continued optimal topical treatment, which will lead to a different classification of disease severity.

AD and allergen avoidance

A major focus of discussion is the significance of allergens as



Figure 13 Facial atopic dermatitis in a boy who was strongly allergic to house dust mite allergen.

eliciting factors. Some investigations support that avoidance of house dust mites²⁶ and other allergens is beneficial (Fig. 13). However, other well-conducted studies do not support this view. The usual environmental allergens are very ubiquitous, and it is not possible to avoid them completely. It has recently been observed that even newborn children without AD can respond to environmental allergens, but they differ from AD children by having a different cytokine response, i.e. a Th-1 response.²⁷ The head and neck syndrome in teenagers or adults (Fig. 11) and hand eczema patients (Fig. 14) require thorough allergological investigations and not only allergens, but irritants (including plants) should be considered as eliciting factors. A list of eliciting factors is given in Table 4.

The future of the atopic child

How restrictive should advice be concerning the future



Figure 14 Irritant contact dermatitis on the hands of a young adult with previous atopic dermatitis.

Table 4 Factors known to elicit disease activity in patients with atopic dermatitis.

Physical factors	Sweating Warm surroundings (bed, clothing, working place) Physical irritation of skin (in children's clothing consider the brand label in the neck region) Climate
Psychological factors	Stress, i.e. work related, examinations, etc. (not evident in children)
Food items	Tomato and orange in children, handling of certain fresh vegetables Juice from fish, meat, etc. Saliva in small children
Allergens	House dust mite (10–25% exposed to high levels of antigen) Animal hair, pollen, plants Food (this topic is much debated — true type I allergies are very rare; whether type IV allergies are of importance is uncertain)
Other	<i>Staphylococcus aureus</i> and release of exotoxins ('superantigens')

of a child with AD? The majority of children with minor atopic eczema need no restriction in their daily life or concerning their future. Skin care is important, at least as a steroid-saving measure, and regular use of mild steroids must be accepted and conducted. Although long-term studies of the use of steroids in children are lacking, it is likely that even prophylactic use of steroids two to three times per week is very effective and beneficial. The teenager still having AD should be informed about the risks for hand eczema. However, although 45% may develop hand eczema, the remaining group will not, and if the young girl strongly wishes to become hair dresser, she may try — knowing the risks.

A child with AD requires up to a half hour of skin care each day. The crying during the night-time will disturb the mother's sleep in particular. This may create tensions between parents and guilt complexes. All of these psychological aspects should be explained to and discussed with the parents.

References

- 1 Besnier E. Première note et observations preliminaires pour servir d'introduction à l'étude diathésique (in French). *Ann Dermatol Syphilogr* 1892; **4**: 634.

- 2 Nexmand P-H. Clinical studies of Besnier's prurigo. Copenhagen: Rosenkilde and Bagger, 1948.
- 3 Larsen FS, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986; **15**: 487–94.
- 4 Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *Br Med J* 1997; **314**: 1003–8.
- 5 Schultz Larsen F, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol* 1996; **34**: 760–4.
- 6 Broberg A, Svensson A. Prevalence and severity scoring of atopic dermatitis. 1st Georg Rajka Symposium, Davos, 1998.
- 7 Williams HC, Robertson CF, Stewart AW *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999; **103**: 125–38.
- 8 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol (Stockh)* 1980; **92** (Suppl.): 44–7.
- 9 Williams HC, Burney PGJ, Hay RJ *et al.* The UK working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994; **131**: 383–96.
- 10 Williams HC, Burney PG, Strachan D, Hay RJ. The UK working party's diagnostic criteria for atopic dermatitis II. Observer variation of clinical diagnoses and signs of atopic dermatitis. *Br J Dermatol* 1994; **131**: 397–405.
- 11 Williams HC, Burney PG, Pembroke AC, Hay RJ. The UK working party's diagnostic criteria for atopic dermatitis III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–16.
- 12 Williams HC. Diagnostic criteria for atopic dermatitis. Where do we go from here? *Arch Dermatol* 1999; **135**: 583–7.
- 13 Firooz A, Davoudi SM, Farahmand AN, Majdzadeh R, Kashani MN, Dowlati Y. Validation of the diagnostic criteria for atopic dermatitis. *Arch Dermatol* 1999; **135**: 514–6.
- 14 Bos JD, Van Leent EJM, Smitt JHS. The millenium criteria for the diagnosis of atopic dermatitis. *Exp Dermatol* 1998; **7**: 132–8.
- 15 Di Nardo A, Wertz P, Giannetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol* 1998; **78**: 27–30.
- 16 Schäfer L, Kragballe K. Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. *J Invest Dermatol* 1991; **96**: 10–5.
- 17 Rystedt I. Atopic background in patients with occupational hand eczema. *Contact Dermatitis* 1985; **12**: 247–54.
- 18 Halkier-Sørensen L. Occupational skin diseases. *Contact Dermatitis* 1996; **35** (Suppl. 1): 1–120.
- 19 Lodi A, Betti R, Chiarelli G, Urbani CE, Crosti C. Epidemiological, clinical and allergological observations on pompholyx. *Contact Dermatitis* 1992; **26**: 17–21.
- 20 Strange P, Skov L, Lisby S, Nielsen PL, Baadsgaard O. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. *Arch Dermatol* 1996; **132**: 27–33.
- 21 Ramsay CA, Savoie JM, Gilbert M *et al.* The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. *J Eru Acad Dermatol Venereol* 1996; **7** (Suppl. 1): 515–22.
- 22 Broberg A, Faergemann J. Topical antimycotic treatment of atopic dermatitis in the head/neck area. A double-blind randomised study. *Acta Derm Venereol* 1995; **75**: 46–9.
- 23 Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. Prevalence of atopic eczema in the community: the Lothian atopic dermatitis study. *Br J Dermatol* 1996; **135**: 18–9.
- 24 Olesen AB, Ellingsen AR, Larsen FS, Larsen PØ, Veien NK, Thestrup-Pedersen K. Atopic dermatitis may be linked to whether a child is first- or second-born and/or the age of the mother. *Acta Derm Venereol (Stockh)* 1996; **76**: 457–60.
- 25 Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol* 1998; **139**: 834–9.
- 26 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**: 15–8.
- 27 Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly D, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999; **353**: 196–200.
- 28 Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* 1998; **139**: 73–6.
- 29 Murphy R, Williams HC, Duff GW, Cork MJ. Total and specific IgE and the definitions of atopy. *Br J Dermatol* 1999; **141** (Suppl. 55): 22–5.