

# Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs

Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs.

*Pediatr Allergy Immunol* 1998; 9: 13–19. © Munksgaard 1998.

**Background:** The role of exclusion diets in the management of atopic eczema in young children is uncertain. This randomised controlled trial evaluates the effect of excluding egg from the diet in young children with atopic eczema and sensitivity to eggs. Fifty-five such children were randomised either to a 4-week regimen, in which mothers were given general advice on care of eczema and additional specific advice from a dietician about an egg exclusion diet (diet group), or to a control group in which general advice only was given. Both groups continued conventional topical treatment. Disease activity was assessed by estimates of the surface area affected by eczema and by an arbitrary severity score. Possible egg sensitivity was identified by RAST before randomisation and after the trial by double-blind placebo-controlled egg challenge. **Results:** The mean reduction in surface area affected by eczema was significantly greater ( $p=0.02$ ) in the group receiving dietary advice (from 19.6% to 10.9% area affected) than in the control group (from 21.9% to 18.9%). A significant improvement also occurred in severity score ( $p=0.04$ ): from 33.9 to 24.0 units for the diet group compared with a decrease from 36.7 to 33.5 in the control group. The study suggests that advice on the dietary exclusion of eggs is useful as part of the overall management of young children with atopic eczema and sensitivity to eggs.

**Rosemary Lever<sup>1</sup>,  
Carolyn MacDonald<sup>1</sup>,  
Pauline Waugh<sup>2</sup>, Tom Aitchison<sup>3</sup>**

Departments of <sup>1</sup>Dermatology and <sup>2</sup>Dietetics,  
Royal Hospital for Sick Children, Glasgow

<sup>3</sup>Department of Statistics, University of Glasgow,  
United Kingdom

Rosemary Lever, Department of Dermatology,  
Royal Hospital for Sick Children, G3 8SG Glasgow,  
UK

**Key words:** atopy; eczema; eggs; food hypersensitivity

Received August 30, 1997

Accepted January 21, 1998

Although atopic eczema has a strong genetic component (1), important environmental factors cause eczema to flare: bacterial infection of the skin, viral illness and contact with domestic pets are three common examples. Food allergy may be another, particularly in infants and young children (2–4), though the role of exclusion diets in the management of atopic eczema is still uncertain (5–7). We have investigated, in a randomised controlled trial, the effect of advice on excluding eggs from the diet of young children with evidence of egg sensitivity and atopic eczema.

## Methods

### Selection of patients

Over a 4-year period, 62 young children were selected as having possible egg sensitivity from ap-

proximately 600 children presenting with atopic eczema to one of two consultants running paediatric dermatology outpatient clinics at the Royal Hospital for Sick Children, Glasgow. Parents of the 600 referrals were asked about possible adverse reactions to food and whether particular foods had been excluded from the child's diet. A full blood count including a white cell differential count and routine RAST screen (for specific IgE to egg, milk and others) was checked in all the children at presentation.

None of the 62 children entering the study was randomised until optimal control of the eczema had been achieved with conventional topical treatment and the child was on stable maintenance treatment using only mild to moderate potency topical steroids (British National Formulary 3–4). The clinical scores at presentation and at entry are shown in Table 3. The mean time from presentation to entry was 3.5 months.

Table 1. Clinical details and investigations

|                              | Diet group<br>(diet advice) | Control group<br>(no diet advice) |
|------------------------------|-----------------------------|-----------------------------------|
| n=                           | 28                          | 27                                |
| <i>Clinical details</i>      |                             |                                   |
| Girls: boys                  | 11: 17                      | 16:11                             |
| Age of presentation (months) | 11.3±1.4*                   | 17.2±2.2                          |
| Age of onset (months)        | 2.8±0.7                     | 2.4±0.5                           |
| <i>History</i>               |                             |                                   |
| Adverse reactions to egg     | 1                           | 5 + 1 CU**                        |
| ARD-asthma                   | 1                           | 7                                 |
| <i>Family history</i>        |                             |                                   |
| Positive atopy               | 14                          | 14                                |
| First degree relative        | 13                          | 10                                |
| <i>Investigations</i>        |                             |                                   |
| Eosinophils                  | 952±137                     | 686±121                           |
| Specific IgE to eggs         | 8.2±1.8                     | 12.4±4.1                          |

\* Mean ± standard error of mean.

\*\* Contact urticaria.

After the trial all parents were asked if they would consent to their child having a double-blind placebo-controlled food challenge to eggs to confirm egg sensitivity (8). Challenging children before randomisation would have been unwise: most parents, seeing a positive response to eggs, would not allow their child to enter a trial where the placebo group received no dietary advice on egg exclusion.

#### Randomisation and treatment

Detailed dietary histories were taken by the dietician (PW) from the parents of all 62 children. It is interesting that although all had raised specific IgE to eggs, only seven had a history suggestive of adverse reactions to eggs. No child was eating eggs as such; for example boiled or scrambled. However, all children were eating egg in hidden forms, usually in foods such as pasta, cakes, biscuits and sweets, although in some children the amounts eaten were small. The fact that almost all eggs eaten were in hidden form may explain why so few parents considered their children allergic to eggs. From the standpoint of the trial this was an advantage.

The 62 children were randomised by the dietician (PW) either to the diet group, and given a 4-week trial of an egg exclusion diet, or to the control group. Parents of children in the diet group were advised to exclude all foods containing eggs and were given lists of foods known to contain eggs and of egg-free foods. They were also helped with interpreting labels on foods, some of which mention egg specifically; others may mention ovalbumin and/or lecithin, both of which can be of egg origin. Parents of children in the control group were given no spe-

cific advice on avoidance of any particular item of food. During the 4-week period of the trial, topical treatment continued unchanged in both groups.

#### Assessment of eczema activity

This was assessed in two ways: (a) by estimating the area affected by eczema, expressed as a percentage of total skin area, using the 'rule of nine' (9) and (b) as a severity score in arbitrary units which assesses six clinical features (extent, erythema, oedema/papulation, oozing/crusts, dryness, lichenification) on a scale of 0–3 units at 16 body sites (9). Children were scored at their initial presentation, again immediately before the dietary treatment (entry/pre-study value) and on a third occasion after the 4-week dietary phase. During the trial, the children were scored by the same observer who was not aware of the child's dietary regimen. After assessment at 4 weeks, mothers of control group children were also given advice on an egg-free diet. This period of follow-up was not part of the formal comparison: it had no control group and observers were now unblinded. However, scores were assessed in 13 control children after a further 4-week period of active egg avoidance advice.

#### Statistical methods

As in the treatment of many other diseases, the potential for benefit may be greatest in patients whose disease is most marked at the outset. The changes (i.e. entry value minus the value 4 weeks into study) in surface area and severity score were each analysed, correcting for a child's entry value (i.e. of surface area or severity score respectively) by means of linear regressions. F-tests of the comparison of slopes of these regressions were carried out to allow the assumption of parallel regressions (for the diet and control groups) to be assessed. When these proved non-significant, standard analyses of covariance were carried out to compare the (adjusted) mean changes in surface area or severity score between the two groups as well as to assess the effect of the magnitude of eczema disease activity (i.e. pre-study value) on such changes.

As an alternative measure of each patient's inherent baseline, similar analyses of surface area and severity score were carried out using the mean for each patient, of the values at entry and at four weeks of each variable instead of the entry/pre-study value alone as a patient's 'baseline' value of the measure. This was done to avoid the possibility that the relationship between the change and pre-study value was simply a statistical artefact. This did not, in fact, prove to be so since the results from these analyses are even more conclusive in favour of a significant relationship between change and magnitude of eczema disease activity. However, the results presented

Table 2. Patient groups

|                        | Diet group (diet advice) | Control group (no diet advice) |
|------------------------|--------------------------|--------------------------------|
| RAST positive children | 32                       | 30                             |
| Defaulters             | 2                        | 1                              |
| Insufficient data      | 2                        | 2                              |
| Completed diet         | 28                       | 27                             |
| Challenge (DBPCFC)     |                          |                                |
| Positive               | 22                       | 20                             |
| Declined/defaulted     | 2                        | 4                              |
| Negative               | 4                        | 3                              |

below are in terms of the entry/pre-study value as this is a much more easily interpreted index of eczema magnitude.

## Results

### Patient details

Sixty-two children entered the study (Table 2). Three defaulted, two from the diet group (D) and one from the control group (C), and the records of four were incomplete (2D, 2C). This left 55 who completed the dietary phase. Data from these form the basis of our analyses (Table 2). Seven of these children (4D, 3C) had a negative egg challenge and a further seven families declined or defaulted from the challenge (3D, 4C).

The diet group had more boys than the control group (Table 1) and control children were slightly older. Children of both groups had developed eczema early in life (Table 1). The diet group had slightly more extensive and more severe involvement than the controls at their initial presentation (Table 3). One child in the diet group and seven among the

controls had asthma (Table 1), possibly a reflection of the older age of the controls. Fourteen in each group had a positive family history of atopy; of these 13 in the diet group and 10 in the control group had atopy in a first degree relative.

### Investigations

Children of both groups had an eosinophilia; it was more marked in the diet group (mean  $952 \times 10^9/l$ ) than in the controls ( $686 \times 10^9/l$ ) but not significantly so. In contrast, eosinophilia was not found in an unselected group of 52 infants with atopic eczema aged less than 2 years (unpublished data).

### RAST screen

All subjects of both groups had a raised specific IgE to eggs, a criterion for entry to the study. The control group had a slightly but not significantly higher level of RAST titre to eggs than the diet group (Table 1). Low level positive RASTs to other food allergens (milk, wheat, soya and nut) were found but there were no significant differences comparing these allergens across the two groups.

### Changes in eczema during trial

#### Surface area affected

Figure 1A shows the changes in area affected by eczema between entry and the end of study 4 weeks later. Although increases and decreases occurred in both groups, more children in the diet group showed improvement: 25 (89%) vs 16 (59%) controls. The reduction in mean area affected was significantly greater in the diet group than in controls (2 sample t-test,  $t=2.08$ ,  $p=0.04$ ).

#### Severity scores

As shown in Fig. 1B, similar changes were seen in severity scores, and again improvement was greater in the diet group ( $t=1.99$ ,  $p=0.05$ ).

### Changes in eczema related to initial eczema scores

#### Surface area affected

In Fig. 2A, for each child, the change of surface area is plotted against the surface area affected at entry into the study. Generally, children from the diet group did better than the controls, and this improvement tended to be greatest in those with the largest affected area at the outset. Thus the slope of the fitted linear regression for the diet group tended to be steeper than that for the control group, although the slopes were not significantly different ( $p=0.13$ ). This lack of significance is

Table 3. Summary statistics

|                       | Diet group<br>n=28<br>Mean (sd) | Control group<br>n=27<br>Mean (sd) | 95% CI for mean difference<br>(diet-control group) |
|-----------------------|---------------------------------|------------------------------------|----------------------------------------------------|
| <i>% surface area</i> |                                 |                                    |                                                    |
| Presentation          | 30.5(18.5)                      | 27.0(18.0)                         |                                                    |
| Study entry           | 19.6(12.8)                      | 21.9(14.8)                         | (-9.8, 5.2)                                        |
| 4 weeks               | 10.9(10.8)                      | 18.7(15.3)                         | (-15.0, -0.6)                                      |
| Change                | 8.7(10.3)                       | 3.2(9.8)                           | (0.1, 10.9)                                        |
| <i>Severity score</i> |                                 |                                    |                                                    |
| Presentation          | 48.5(28.4)                      | 43.4(24.3)                         |                                                    |
| Study entry           | 33.9(15.3)                      | 36.7(19.0)                         | (-12.6, 6.1)                                       |
| 4 weeks               | 24.0(16.6)                      | 33.4(21.6)                         | (-19.8, 1.1)                                       |
| Change                | 9.4(12.3)                       | 3.3(10.5)                          | (-0.1, 12.3)                                       |

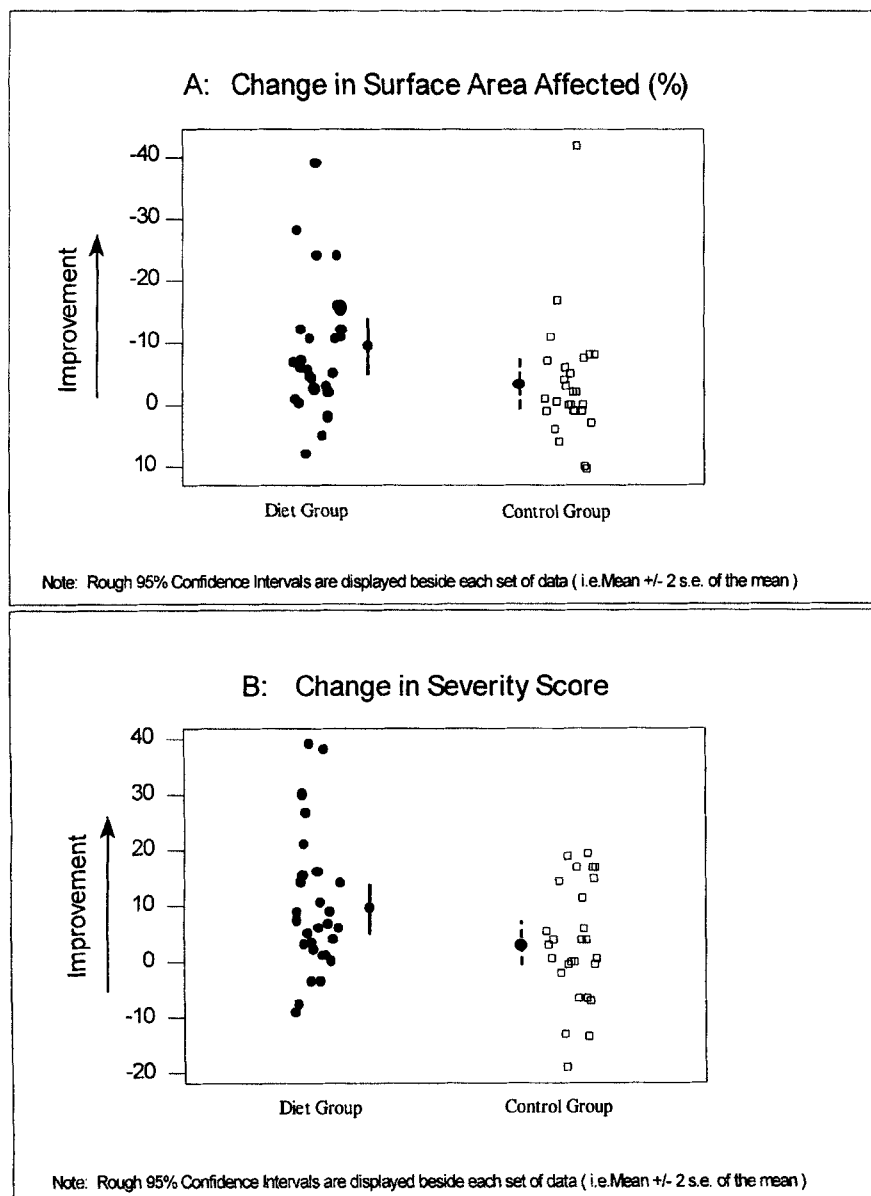


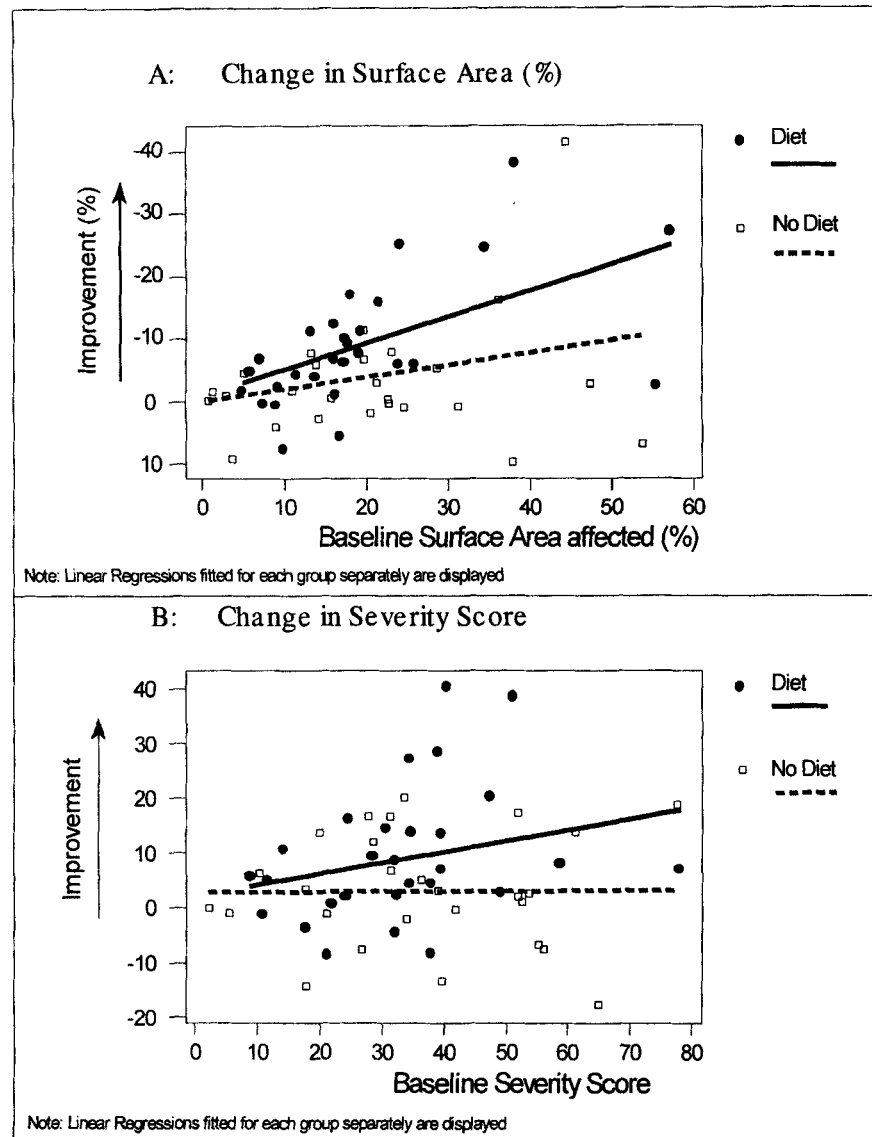
Fig. 1. Panel A: Individual patient changes in area (%) affected by eczema where change is pre-study minus value at 4 weeks. Upward change from zero is improvement, downward from zero is deterioration. Panel B: as for Panel A except that changes refer to eczema severity scores (in arbitrary units). Solid circles (●) represent patients in the diet group, open squares (□) patients in the control group.

heavily influenced by two patients quite different from the rest of the group: one a control with 40% involvement, whose eczema cleared almost completely during the study period, the other a diet group patient with marked involvement (53%), but showing no improvement. However, analysis of covariance (assuming lines of equal slope) did show a significant difference in favour of the diet group ( $p=0.02$ ) with an adjusted mean improvement of 9.0% (diet group) and 2.8% in controls at the mean pre-study value of 20.7%. A 95% confidence interval, for this *mean additional* (adjusted) improvement of the diet group over the controls is 11.2% to 1.2%. A summary of the data including both unadjusted means and confidence intervals is given in Table 3.

#### Severity scores

Figure 2B shows, again for each child, the change in severity score plotted against severity score on entry to the study. This time the relationship is less clear. There is no significant difference in slopes between diet and control groups ( $p=0.22$ ), and the (assumed) common slope is not significantly different from zero ( $p=0.28$ ). However, a highly significant ( $p<0.001$ ) effect of baseline on severity was shown when the analysis used as baseline the *mean* of the severity scores at entry and 4 weeks. This form of analysis is arguably more reliable statistically (10). However, regardless of which form of analysis is used, the mean change in severity in the diet group from 33.9 to 24.0 was significantly greater ( $p=0.04$ ) than that in controls (from 36.7 to

Fig. 2. Panel A: relation between change of area (%) affected by eczema and area affected at baseline before randomised treatment begins. Panel B: as for Panel A except that changes and baseline value refer to eczema severity score (in arbitrary units). Solid circles (●) represent patients in the diet group, open squares (□) patients in the control group.



33.7). A 95% confidence interval for the mean (additional) improvement in severity score for the diet over the control group is 0.4 to 11.8 severity units. Again, a summary of unadjusted means and confidence intervals for the severity scores is given in Table 3.

#### Relation of affected surface area and severity score

Figure 3 shows the change in surface area plotted against change in the severity score (for this the component of the severity score which related to extent was excluded from the severity score). Generally, improvements in one related to improvements in the other. Most diet group patients showed an improvement in both variables, although two showed improvement in one but not the other. Perhaps more significant, only one diet group patient showed deterioration in both severi-

ty score and surface area affected. In contrast, five of the control group showed deterioration in both.

#### Post-trial observations on controls

Thirteen children in the control group had measurements made after conclusion of the randomised part of the trial. In these, the area affected had decreased slightly during the randomised trial from a mean of 22.6% at entry to 21.1% at the end of the trial. During the next 4 weeks, and when advice was given on egg exclusion, it fell further to a mean of 16.8%. Similarly, the severity score during these two periods fell from a mean of 40.8 at randomisation to 40.4 by the end of the randomised trial and then to 33.2 after the final 4 weeks of egg exclusion. These results also suggest that the diet has a beneficial effect, with results reaching significance when post-diet scores are compared with pre-study values

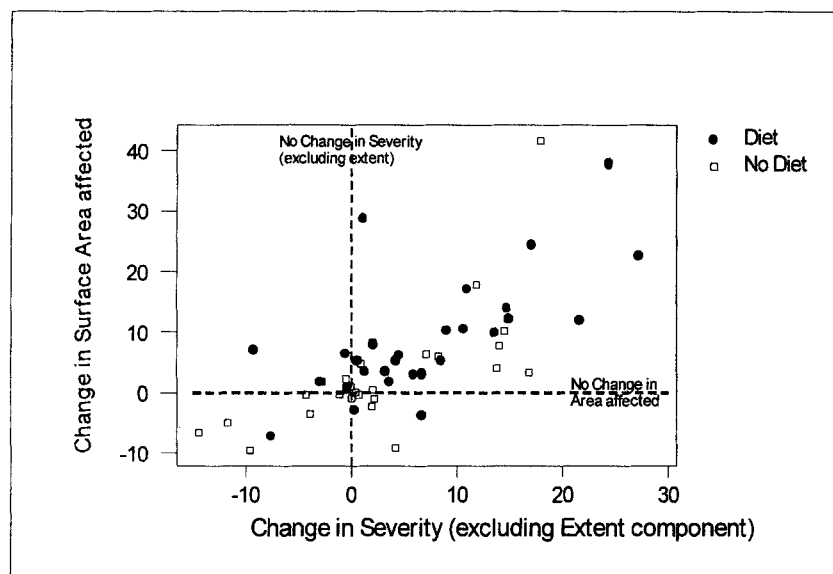


Fig. 3. Plot of the change in surface area affected against the change in severity score minus the component value for extent. Solid circles (●) represent patients in the diet group, open squares (□) patients in the control group.

Note: Patients in the upper right quadrant of the plot improved in both surface area affected and severity score over the study. Most of the diet group (●) are in this section of the plot. Patients in the lower left quadrant of the plot worsened in both variables over the study. In this section there is only one patient in the diet group but five controls.

(paired t-tests for % surface area,  $p < 0.04$ ; for severity score,  $p = 0.02$ ). However, it is important to note that these observations are for an uncontrolled and unblinded part of the study.

## Discussion

Our study suggests that children with atopic eczema and sensitivity to eggs benefit from a regimen in which mothers are advised by a dietician to exclude eggs and egg products from their child's diet. Eczema improved significantly in the diet group, for the group as a whole and for most individuals within the group. In the control group there were only small non-significant changes. The diet group also showed significantly greater improvement at the end of the trial compared with the controls.

### Selection of patients

Because the question of efficacy of dietary treatment in children with atopic eczema is still unanswered, those most likely to respond to an exclusion diet were chosen. These were young, the majority under 2 years, and all with evidence suggestive of egg sensitivity. Young children were chosen because food allergy is predominantly a problem of early life (3). Sensitivity to eggs was a second condition of selection because removal of egg and egg protein from the diet can be achieved with careful advice and an egg-free diet is relatively simple for a mother to follow.

### Value of tests

All our children had a positive RAST to egg. RAST screening has its critics (11) but, in our experience, it

is useful in screening children of this age group since RAST in infants is usually negative. Skin prick tests are an alternative method of assessing specific IgE and are considered by some to be more sensitive (12). To confirm egg sensitivity, all 55 children completing the dietary phase were offered a double-blind food challenge to egg. The challenge test is recognised as the best available for identifying food allergy (13–15). In 41 of the 48 (85%) children with a positive egg RAST, the challenge was also positive. This supports the idea that a raised specific IgE to eggs has value in identifying possible egg allergy in young children with atopic eczema.

A history of food allergy given by the mother is not considered reliable by some (13) and this was our experience: only seven (11%) children in our study had a history of reacting adversely to eggs. This is not surprising since eggs, as such, are often refused and rarely, if ever, eaten by children with egg allergy. On the other hand, the dietician also established that all children in the trial ate egg in 'hidden' forms in foods such as pasta, baking and confectionery. The amount of hidden egg eaten varies from child to child and from time to time and this may account for variation in the severity of the eczema. It could be important where a child, strongly allergic to egg, has only mild eczema because little egg is being eaten. For these reasons, severity of eczema may not be useful in selecting children for studies of exclusion diets.

### Value of treatment

The importance of dietary treatment in atopic eczema is not agreed (6): some studies show benefit (16–23), others show little or none (5, 7, 24). These differences may reflect differences of trial design, age of children studied and the allergen or allergens

on test. Few controlled studies have been performed. One suggesting benefit was a double-blind cross-over study design testing exclusion of milk and eggs in children of median age 6 years (25). Another, also of egg and milk, suggested benefit in the younger children in the trial, although overall benefit was unclear (26).

On this study, seven children (11%) had a negative food challenge and were able to return to a normal diet although this percentage has been higher in other populations studied (13, 15). Although children with genuine food allergy should be on an exclusion diet, it is also important that children who are not food allergic are on normal unrestricted diets. Dietary treatment has risks: normal toddlers can become picky eaters, compliance with the diet may be a problem (7, 19) and restricted diets can be nutritionally inadequate (27, 28). Also, in highly sensitive food-allergic patients, restricted diets carry a risk of an anaphylactic reaction if the food is accidentally ingested (22, 29). Exclusion diets should not be undertaken lightly, and never without proper supervision by a dietician.

Long-term benefits of exclusion diets have been reported (14, 21). Egg-allergic children who remain on an egg-free diet for 2 to 3 years may become tolerant of egg (14). During this time, the eczema can remain under good control in some children. This may be important since restoration of an intact skin barrier might prevent the secondary sensitisation to the inhalant allergens which some have suggested occurs through eczematous skin (30).

Further studies of exclusion diets are needed in atopic eczema. Until the position is clearer these should target patients with an identified food allergy. A longer period of dietary exclusion than the one used here needs testing since improvement occurs gradually. Longer follow-up might produce a clearer distinction between control and diet groups.

## References

- SCHULTZ LARSEN F, HOLM NV, HENNINGSEN K. Atopic dermatitis: a genetic study in a population-based sample. *J Am Acad Dermatol* 1986; 15: 487-94.
- PRZYBILLA B, RING J. Food allergy and atopic eczema. *Semin Dermatol* 1990; 9: 220-5.
- GUILLET G, GUILLET M-H. Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 1992; 128: 187-92.
- SAMPSON HA, METCALFE DD. Food allergies. *JAMA* 1992; 268: 2840-4.
- MUNKVAD M, DANIELSEN L, HØJ L, et al. Antigen-free diet in adult patients with atopic dermatitis. *Acta Derm Venereol (Stockh)* 1984; 64: 524-8.
- ALLEN R. Role of diet in treating atopic eczema: dietary manipulation has no value. *Br Med J* 1988; 297: 1459-60.
- MABIN DC, SYKES AE, DAVID TJ. Controlled trial of a few foods diet in severe atopic dermatitis. *Arch Dis Child* 1995; 73: 202-7.
- BOCK SA, SAMPSON HA, ATKINS FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; 82: 986-97.
- LEVER R, HADLEY K, DOWNEY D, MACKIE R. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. *Br J Dermatol* 1988; 119: 189-98.
- CAMPBELL MJ, MACHIN D. Medical statistics; a common-sense approach. New York: J Wiley 1993: 130-2.
- DAVID TJ. Conventional allergy tests. *Arch Dis Child* 1991; 66: 281-2.
- SAMPSON HA, ALBERGO R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984; 74: 26-33.
- BURKS AW, MALLORY SB, WILLIAMS LW, SHIRRELL MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113: 447-51.
- SAMPSON HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988; 81: 635-45.
- BOCK SA, ATKINS FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Paediatr* 1990; 11: 561-7.
- JUTO P, ENGBERG S, WINBERG J. Treatment of infantile atopic dermatitis with a strict elimination diet. *Clin Allergy* 1978; 8: 493-500.
- BUSINCO L, BUSINCO E, CANTANI A, GALLI E, INFUSSI R, BENINCORI N. Results of a milk and/or egg-free diet in children with atopic dermatitis. *Allergol Immunopath* 1982; 10: 283-8.
- HILL DJ, LYNCH BC. Elemental diet in the management of severe eczema in childhood. *Clin Allergy* 1982; 12: 313-5.
- HATHAWAY JM, WARNER JO. Compliance problems in the dietary management of eczema. *Arch Dis Child* 1983; 58: 463-4.
- GRAHAM P, HALL-SMITH SP, HARRIS JM, PRICE ML. A study of hypoallergenic diets and oral sodium cromoglycate in the management of atopic eczema. *Br J Dermatol* 1984; 110: 457-67.
- PIKE MG, CARTER CM, BOULTON P, TURNER MW, SOOTHILL JF, ATHERTON DJ. Few food diets in the treatment of atopic eczema. *Arch Dis Child* 1989; 64: 1691-8.
- DEVLIN J, DAVID TJ, STANTON RHJ. Elemental diet for refractory atopic eczema. *Arch Dis Child* 1991; 66: 93-9.
- SLOPER KS, WADSWORTH J, BROSTOFF J. Children with atopic eczema I: clinical response to food elimination and subsequent food challenge. *QJM* 1991; 29: 2 677-93.
- VAN ASPEREN PP, LEWIS M, ROGERS M, KEMP AS, THOMPSON S. Experience with an elimination diet in children with atopic dermatitis. *Clin Allergy* 1983; 13: 479-85.
- ATHERTON DJ, SOOTHILL JF, SEWELL M, WELLS RS, CHILVERS CEDC. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; i: 401-3.
- NEILD VS, MARSDEN RA, BAILES JA, BLAND JM. Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 1986; 114: 117-23.
- DAVID TJ, WADDINGTON E, STANTON RHJ. Nutritional hazards of elimination diets in children with atopic dermatitis. *Arch Dis Child* 1984; 59: 323-5.
- DEVLIN J, STANTON RHJ, DAVID TJ. Calcium intake and cows' milk free diets. *Arch Dis Child* 1989; 64: 1183-4.
- DAVID TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984; 9: 983-6.
- CARSWELL F, THOMPSON S. Does natural sensitisation in eczema occur through the skin? *Lancet* 1986; ii: 13-5.