

Children with Atopic Eczema. I: Clinical Response to Food Elimination and Subsequent Double-blind Food Challenge

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SUMMARY

The role of foods in the exacerbation of atopic eczema was studied by offering a food elimination diet and subsequent random order, double-blind food challenges to 91 eczematous patients, [49 males and 42 females, median age 4.5 years (range 0.5-15)]. Eczema improved in 49 of 66 (74 per cent) (skin score fall ≥ 3) after stopping cows' milk, eggs and various other foods, with significant decreases in erythema, excoriation, lichenification and extent of eczema.

One hundred and ninety-four food challenges were given to 64 patients who had shown objective or subjective improvement. Eczema and associated symptoms were significantly worse after cows' milk and tomato compared with placebo. Egg did not worsen eczema, but 48 per cent of 44 challenges were incomplete, mainly due to hypersensitivity reactions and challenge refusal. The longer a food had been avoided, the less likely was the chance of a positive food reaction. Clinical history did not predict response to dietary manipulation.

A standard elimination diet avoiding cows' milk, egg, tomatoes and possibly colours and preservatives should help up to three-quarters of patients, and is easy to implement with the help of a dietician. This diet may be considered in all children with moderate or severe eczema.

INTRODUCTION

The role of foods in atopic eczema is controversial. Several authors [1-7] have described improvement in childhood eczema on a restricted diet (especially free of dairy products), although the reported proportion of patients improved by such a diet has ranged from 2 per cent [8] to 100 per cent [4]. These observations have been complemented by the results of open food challenges, which have caused exacerbation of eczema in between 7 per cent (egg challenges [9]) and 80 per cent (normal diet after an elemental diet [7]) of patients, although fewer than 50 per cent of patients have reacted in most studies. The few closed double-blind randomized studies reported have shown milk and egg [10] and various foods [11] to

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exacerbate eczema in some 70 per cent and 60 per cent of paediatric eczematous patients, respectively. However a recent similar study in adults and children showed diet to have no significant effect on eczema [12]. Interpretation of the studies is complicated by differences in populations studied, especially differences in age and severity of eczema, and by the natural history of eczema, a chronic disease with fluctuating course and tendency to improve with increasing age.

The purpose of this study was to test the hypothesis that dietary food elimination in childhood eczema would improve the condition in at least some patients, and to determine by double-blind food challenges whether food reintroduction would cause exacerbation. Immunological changes in the patient group are detailed in the following paper.

PATIENTS AND METHODS

CLINICAL FEATURES OF PATIENT GROUPS

Ninety-one children with atopic eczema, defined by typical appearance and distribution for age, pruritus, chronic or relapsing dermatitis and either evidence of personal or familial atopy or other specific clinical features [13], were recruited to the study from paediatric or allergy clinics (56), or volunteered by their parents after a request for patients made through the Eczema Society Magazine, Exchange (35). The eczema was variable in severity: some patients were seen for the first time while others had persistent problems despite intensive treatment. There were 49 (54 per cent) males and 42 (46 per cent) females, all born in Britain; 73 (80 per cent) were Caucasian, nine (10 per cent) Asian and nine (10 per cent) other. Patients were aged 0.42 to 15 years old (median age 4.5) but 58 per cent of the group were aged between 2 and 7 years; 74 (81 per cent) had an atopic first-degree relative. Social classes (OPCS 1980 [14]) 1 and 2 were over-represented: 39 (43 per cent) as compared with the normal population (32 per cent in the 1981 Census [15]); 22 (24 per cent) were in class 3, six (7 per cent) in class 4 and 5, and 24 (26 per cent) other, mainly single parents. A similar over-representation of socio-economic classes 1-3 was seen in eczematous children during the follow up of the 1970 British Births survey [16].

Not all of the 91 patients recruited and used for analysis of clinical features answered all questions. Seventy-eight were seen before and after 3-4 weeks of food elimination, and were also the source of the 64 patients used for challenges: adequate pre- and post-elimination data were available in 66 of these 78. Sixty-four patients underwent between one and nine sequential food challenges, each lasting 4 weeks: the sex, ages and other demographic and clinical features of these patients were similar to those of the entire group.

FEEDING HISTORY

Sixty-eight of 89 (76 per cent) were breast-fed, but the median duration of exclusive breast feeding was <1 month, range 0-15 months. Cows' milk had been given to 87 patients, starting from birth to 30 months (median <1 month). Solids were begun at a median age of 3.5 months (range 1-7). A reaction to foods on weaning, including vomiting, skin reddening or urticaria, diarrhoea, itch or exacerbation of eczema was reported in 49 of 88 (56 per cent) patients, associated particularly with egg (in 30 per cent), cows' milk (19 per cent), tomato (10 per cent), colours or chocolate (8 per cent), fish (7 per cent) and apple (6 per cent).

ASSOCIATED SYMPTOMS

Patients commonly had asthma (58 of 91; 64 per cent), rhinitis (53; 59 per cent) and urticaria (48; 53 per cent). Foods exacerbated eczema in 51 patients (56%), asthma in six of 58 (10 per

TABLE 1. *Foods reported to cause symptoms: percentage of patients who reported that a food was associated with either eczema or urticaria.*

Eczema	Frequency ^a	(%) ^a	Urticaria	Frequency	(%)
Egg	26	(28.6)	Egg	22	(24.4)
Cows' milk	26	(28.6)	Colours	12	(13.3)
Colours	12	(13.2)	Nuts	10	(11.1)
Tomato	7	(7.7)	Tomatoes	6	(6.7)
Fish	6	(6.6)	Orange	5	(5.6)
Goats' milk	6	(6.6)	Fish	5	(5.6)
Cheese	6	(6.6)			
Chocolate	5	(5.5)			
Wheat	5	(5.5)			
Other	26	(20.0)	Other	28	(22.0)
Total no. foods		125		88	
Total no. patients		(91)			(90)

^a Frequency = number of food related incidents; (%) = number of food related incidents/number of patients $\times 100$.

cent), urticaria in 43 of 48 (90 per cent) and rhinitis in three of 53 (6 per cent). The foods that caused most problems were egg and cows' milk (Table 1). Egg was associated with eczema in 26 of 91 (29 per cent), urticaria in 22 of 90 (24 per cent) and symptoms at weaning (including rashes and vomiting) in 27 of 88 (30 per cent) (data not shown). Cows' milk also induced eczema in 26 of 91 (29 per cent), although the 26 were not all the same as those reporting eczema following consumption of eggs. Cows' milk caused symptoms at weaning in 17 of 88 (19 per cent). Asthma was said to have been provoked by cows' milk, eggs, nuts and chocolate. Urticaria was seldom associated with cows' milk, but other foods were of comparable importance in apparently causing urticaria or eczema exacerbations (Table 1).

PRE-STUDY DIET AND FOOD PREFERENCES

Fifty-two per cent (47 of 91) of eczematous children were completely avoiding at least one food at the start of the study, particularly egg (28 of 87; 32 per cent) cows' milk (11 of 87; 13 per cent), and nuts (nine of 87; 10 per cent). Others were limiting certain foods, such as taking egg only infrequently or in small amounts in cooking.

Food preferences among patients were similar to those of 26 non-atopic control children attending an outpatient clinic except that dislike of eggs was more common in eczematous children: 18 of 87 (21 per cent) compared to two of 26 (8 per cent) of controls (χ^2 4.67, $p < 0.05$). Food preferences were compared with food challenge outcome.

METHOD OF CLINICAL ASSESSMENT, FOOD ELIMINATION AND CHALLENGE

General Management

Before entering the trial patients were given general advice, including use of emollients and antipruritics, and any topical steroid treatment was usually left unchanged. The study began when there was no further improvement on this 'orthodox' medical treatment. Associated conditions such as asthma, rhinitis and food-related gastrointestinal symptoms were treated

as necessary during the study. A patient given systemic corticosteroids for asthma during the study was excluded from the analysis.

Food Elimination

Patients were begun on a diet when the eczema was stable. Complete avoidance of cows' milk, eggs and certain other foods according to a history of food intolerance (past or present) and skin prick test results was achieved with advice from a dietician. The skin was assessed at this visit (initial) and at least 3 weeks after elimination. This second assessment, just prior to the first challenge, was the 'elimination' visit. The change in eczema over the 'elimination period' was found by comparing skin scores at the two visits.

Food Challenges

Of the 78 patients reviewed after food elimination, 64 patients took part in food challenges, and the others were not challenged because the eczema was no better (five) or for social or geographical reasons (nine).

A total of 194 food challenges were given (one to nine per patient): these consisted of the food disguised in a vegetable or fruit puree (active), or the puree alone (placebo) given from coded tins (by courtesy of Heinz Co. Ltd.). Quantities of foods given daily in challenges were: cows' milk 58 g; hens' egg 26 g; tomatoes 14 g; wheatflour 5 g; orange/apple juice 34 ml; cocoa 3 g; rice 5 g; soya flour 15 g; lentils 15 g. Active challenge and placebo were indistinguishable. Parents were asked to discard tins at the end of each week. Each challenge food or placebo was given as one tin daily for one week, and the order was randomized with a washout week in between. The challenge was considered complete only if at least half a tin was eaten on at least four out of seven days. Results of completed challenges were analysed together with incomplete challenges where a severe eczematous or immediate skin reaction had curtailed the challenge. If an apparent skin reaction to the challenge had not cleared, or in the event of intercurrent illness, the next challenge was delayed. Foods given for challenge had been avoided for between 3 weeks and over a year before challenge (median length of avoidance 4.6 months). The plan of each challenge sequence is shown in Fig. 1.

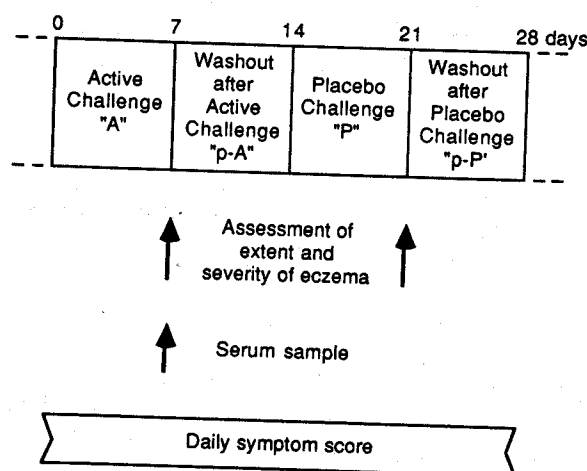


FIG. 1. Plan of a single challenge

Clinical Assessment

Diary cards were kept by parents and patients during challenge and washout weeks. Daily symptom scores were made (0-3) for itch, sleep disturbance, the daily antipruritic use, and of number (and type) of corticosteroid applications. The symptom scores were compared during active and placebo weeks (analysing the active minus placebo paired scores), and during the active and placebo washout weeks. For each challenge the day when symptoms began or increased was recorded; at the end of a challenge the day when symptoms began to decrease was noted. These times were compared for active and placebo challenges.

The extent and type of eczematous changes were assessed during all stages of the study by a single observer (KS) using a chart modified from that used by Atherton [10]. The body was divided into 20 areas, and the presence or absence of erythema, vesiculation, excoriation and lichenification was recorded in each, making a total possible eczema score of up to 80. The skin was scored at the beginning and end of the elimination period, and after each week of food challenge. (The coefficients of variation of the skin scores on a single subject within two 12-hour periods were 5.9 per cent [four assessments] and 4.2 per cent [five assessments].) The

TABLE 2. *Extent and severity of eczema at the initial and elimination visits in the 78 patients who attended for follow up, and decrease in skin score from initial to elimination visits compared in the 66 patients where paired data was available (Wilcoxon matched pairs signed rank test).*

	<i>Median no. of areas involved</i>			
	Initial assessment		After elimination	
	<i>n</i>	(range)	<i>n</i>	(range)
Skin areas with:				
Any eczema	10.5	(0-20)	9	(0-19)
Redness	7	(0-20)	1	(0-19)
Vesiculation	4.5	(0-18)	4	(0-13)
Excoriation	5	(0-19)	3.5	(0-14)
Lichenification	3.5	(0-19)	1.5	(0-15)
Summed scores	32	(0-80)	23	(0-67)
<i>Median skin score change</i>				
Elimination visit minus initial visit				
	<i>n</i>	(range)	<i>P</i>	
Skin areas with:				
Any eczema	-2	(-18 to +4)	<0.001	
Redness	-2	(-12 to +9)	<0.001	
Vesiculation	0	(-12 to +9)	NS	
Excoriation	-0.7	(-17 to +8)	<0.001	
Lichenification	-0.5	(-15 to +5)	<0.001	
Summed scores	-6	(-36 to +10)	<0.001	

initial severity of the eczema varied from mild to severe (Table 2); one patient without visible lesions was included because of a history of food-provoked eczema.

Statistical Analysis

Non-parametric statistical analysis was used in order to find whether dietary changes were associated with significant changes in eczema. Wilcoxon matched pairs signed rank test was used to compare skin scores before and after dieting. A similar method was used for paired data from active and placebo challenge periods, for each type of food challenge, and for both skin and symptom changes. The predictive value of initial data for the response to elimination and challenge was found using the Wilcoxon two samples test (Mann Whitney).

RESULTS

FOOD ELIMINATION

Seventy-eight patients attended for reassessment, 75 of whom had stopped eggs and 71 cows' milk. Other foods avoided included nuts (33), fish (28), food colours (20), tomatoes and wheat (18), citrus fruit (16), potato (14), soya and chocolate (13). Forty-seven per cent (34 of 74) of patients started the elimination diet in the months of May to July, when pollen allergy may have increased skin itching.

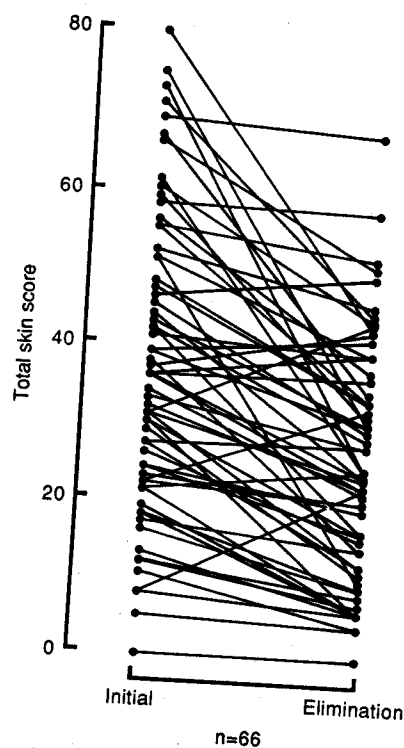


FIG. 2. Change in total skin score (sum of the number of areas involved with erythema, vesiculation, excoriation and lichenification) over the elimination period. In 66 patients with paired scores there was a significant decrease in the total score from the initial to elimination visit: $p < 0.001$ by Wilcoxon signed rank test.

Of the 78 patients, paired skin scores for the initial and elimination visits were available for 66. Using the arbitrary criterion of a fall in total skin score of at least 3, 49 of 66 patients (74 per cent) had improved. Paired analysis of skin scores showed that the fall over the elimination period was significant (Fig. 2, Table 2). A decrease occurred in the number of skin areas with any erythema, excoriation, lichenification or any eczema (extent of eczema) ($p < 0.001$, Wilcoxon signed rank test).

FACTORS INFLUENCING THE RESPONSE TO ELIMINATION DIET

Recurrent skin infection did not predict response: 25 of 31 patients reported to have had repeated skin infections improved, compared with 24 of 34 without such a history: the incidence of infection in the two groups was similar by χ^2 analysis. The age of onset of eczema was similar in improvers ($n=49$, median 0.25 years, range 0-7) and non-improvers ($n=17$, median 0.25 years, range 0.08-3); (Wilcoxon 2-sample test). Similarly age at elimination was comparable in improvers ($n=39$, median 4.09 years, range 0.42-15) and non-improvers ($n=15$, median 3.39 years, range 0.49-11.12). Improvement did not depend on the initial severity of the eczema. The skin score was similar for 39 improvers (median 37, range 11-73) and 15 non-improvers (32, 0-69) (Wilcoxon 2-sample test).

TABLE 3. Outcome of double blind challenges for cows' milk, egg, potato, orange, wheat, tomato and soy. Completed challenges, where at least half a tin was eaten daily for at least four of seven days during a challenge week, were only obtained for 52 per cent of attempted egg challenges, but higher proportions of other challenges were taken. Analysis of food challenge results includes only completed challenges.

Challenge outcome	Cows' milk <i>n</i> (%)	Egg <i>n</i> (%)	Potato <i>n</i> (%)	Orange <i>n</i> (%)	Wheat <i>n</i> %	Tomato <i>n</i> %	Soy <i>n</i> %
<i>Double blind challenges</i>							
1 Complete	37 (67)	23 (52)	7 (70)	7 (70)	5 (62)	6 (86)	5 (71)
2 Complete but < 7 tins -severe reaction	0	1 (2)	0	0	0	0	0
3 Incomplete:							
Allergic reaction/ severe eczema	1 (2)	2 (5)	1 (10)	0	1 (13)	0	1 (14)
Severe reaction in placebo week	0	1 (2)	0	0	0	0	0
Total challenges analysed (1-3)	38	27	8	7	6	6	6
<i>Other double blind challenges</i>							
4 Incomplete:							
'Lapses'	6 (11)	4 (11)	1 (10)	2 (20)	0	1	0
Vomiting	1 (2)	1 (2)	0	0	0	0	0
Refusal	5 (9)	8 (18)	0	1 (10)	0	0	0
5 Excluded (illness, grass, urticaria etc.)	5 (5)	4 (11)	0	0	2 (25)	0	1 (14)
Total attempted double blind challenges	55	44	10	10	8	7	7

GROWTH VELOCITY

Patients on a restricted diet were measured using a Harpenden stadiometer at intervals of 4–12 months during the study. The longest interval was used to calculate the growth velocity. The median growth velocity for 32 patients with complete data lay on the 50th centile (ranging from below the third to above the 97th), indicating normal overall linear growth. Three of five patients with low growth velocities were prepubertal asthmatics aged 9–10 years, a group known to suffer from maturational delay [17]; growth velocity below the tenth centile was only seen in patients with asthma.

FOOD CHALLENGE

Sixty-four patients were given between 1 and 11 food challenges. Analysis of challenge results was confined to completed challenges, each food type being analysed separately. Challenge details are shown in Table 3; only double blind challenge outcomes 1–3 were analysed. Skin scores after each 7-day challenge were compared with those after the placebo challenge. Other double blind challenges attempted were sunset yellow (21), rice (four) chocolate (six), lentil (two), carrot (one) and apple (one), making a total of 176 double blind challenges, and there were 18 additional open challenges (including five cod), making a total of 194 challenges. Five challenges were not given because of a previous severe reaction (three to egg, one cod, one lentil).

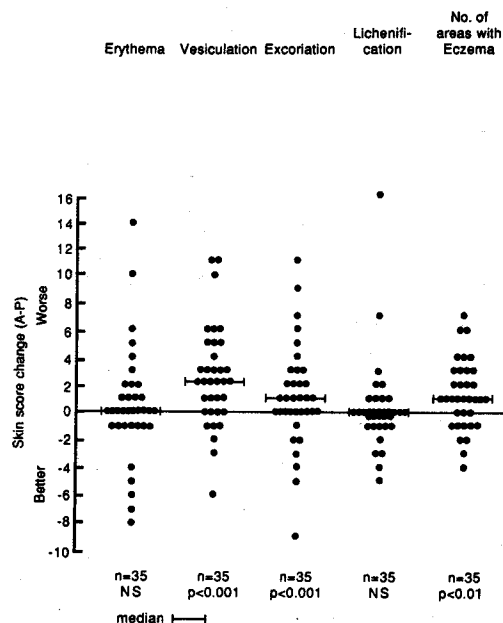


FIG. 3. Thirty-five completed cows' milk challenges: differences in skin score at the end of cows' milk challenge week (A) and of placebo challenge week (P) compared using Wilcoxon signed rank test. Cows' milk challenge was followed by a significant increase in vesiculation, excoriation and extent of eczema.

Cows' Milk

Thirty-seven challenges with cows' milk were completed and analysed: one challenge was curtailed because of a severe eczematous reaction and 17 further challenges were inadequate and excluded from statistical analysis (Table 3). There was worsening of eczema during the cows' milk challenge week compared to the placebo challenge, significant for extent of vesiculation ($p < 0.001$), excoriation ($p < 0.001$) and area involved by eczema ($p < 0.01$) (Fig. 3). Symptoms of itch ($p < 0.01$) and sleep disturbance ($p < 0.05$) and anti-pruritic use ($p < 0.02$) were also increased during the active challenge (Fig. 4; Table 4). The increased frequency of corticosteroid use persisted into the washout week after active challenge ($p < 0.02$). Symptoms tended to be greater in each challenge week than during its washout, but differences between active challenge washout and placebo were only significant for sleep disturbance ($p < 0.02$) and anti-pruritic use ($p < 0.01$).

The time of symptom change was examined within the active challenge and washout period (Fig. 5). Symptoms began to increase on the first challenge day in 35 per cent of patients and by the third day in 63 per cent. However, 10 per cent did not have increased symptoms until after the fourth day. Symptoms began to decrease on the first washout day in 40 per cent of patients, and over the next 8 days in 50 per cent. However 10 per cent of patients showed a decrease in symptoms during the active challenge after an initial deterioration.

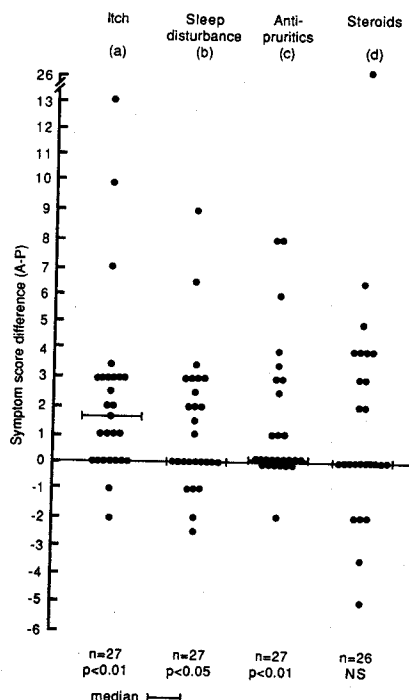


FIG. 4. Completed cows' milk challenges: difference in symptom score between active and placebo challenge weeks for (a) itch (b) sleep disturbance (c) antipruritic use (d) topical steroid use, compared in patients with full diary records (26-27) using Wilcoxon signed rank test. After cows' milk there were significant increases in recorded itch, sleep disturbance and use of antipruritics.

TABLE 4. Changes in symptom scores for 38 cows' milk and 27 egg random order, double blind challenges, comparing scores obtained during the week of food challenges (active), the week of placebo challenges, and their washout weeks using Wilcoxon signed rank test.

Score difference	Cows' milk				Egg			
	n	Median score increase			n	Median score increase		
	n	(range)	p		n	(range)	p	
<i>Itch score</i>								
Active minus placebo	27	1.4	(-2 to +12.5)	<0.01	21	0.8	(-4 to +12)	NS
Active washout (minus placebo washout)	15	0	(-7 to +6.5)	NS	18	0	(-3.5 to +11)	NS
Time of increase in itch (days after challenge onset)	26	0	(-3 to +7)	NS	21	0	(-3 to +7)	NS
Time of decrease in itch (days after end of challenge)	22	0	(-4 to +6)	NS	20	0.5	(-6 to +17)	NS
<i>Sleep disturbance score</i>								
Active minus placebo	27	0	(-6 to +9)	<0.05	21	0	(-5 to +3)	NS
Active minus its washout week	22	0	(-2 to +8)	<0.02	19	0	(-6 to +1)	NS
Placebo minus its washout week	20	0	(-4 to +5)	NS	19	0	(-2 to +3)	NS
<i>Score of antipruritic use</i>								
Active minus placebo	27	0	(-2 to +8)	<0.01	21	0	(-3 to +6)	NS
Active minus its washout week	22	0	(0 to +8)	<0.01	19	0	(-2 to +0)	NS
<i>Score of steroid applications</i>								
Active minus placebo	26	0	(-5 to +26)	NS	21	0	(-7 to +13)	NS
Time of decrease in use (days after end of challenge)	21	0	(-2 to +8)	<0.02	20	0	(-5 to +5)	NS

Egg

Egg challenges were frequently incomplete because of the high proportion of patients who refused, vomited or took inadequate amounts (17 of 47, 36 per cent) (Table 3). Three were not challenged because of previous angioedema following ingestion of egg. There was no significant difference in skin eczema scores (Fig. 6) or in symptom scores (Table 4) for completed challenges. Even when complete and incomplete challenges were analysed together there was no significant difference in eczema skin score or symptoms. Thus eczematous patients are commonly intolerant of egg, but where egg is tolerated there is no significant exacerbation of eczema.

order, double blind
(active), the week of
st.

score increase (range)	p
-4 to +12)	NS
-3.5 to +11)	NS

-3 to +7) NS

-6 to +17) NS

-5 to +3) NS

-6 to +1) NS

-2 to +3) NS

-3 to +6) NS

-2 to +0) NS

-7 to +13) NS

-5 to +5) NS

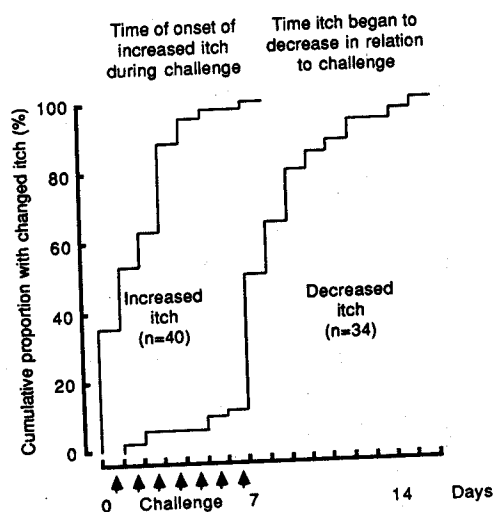


FIG. 5. Cows' milk challenges: time of onset of increase itch during active 7-day challenge; time of decrease in itch after stopping challenge. Itch mainly began to increase during the first 3 days of cows' milk and to decrease on the first 2 days after stopping challenges.

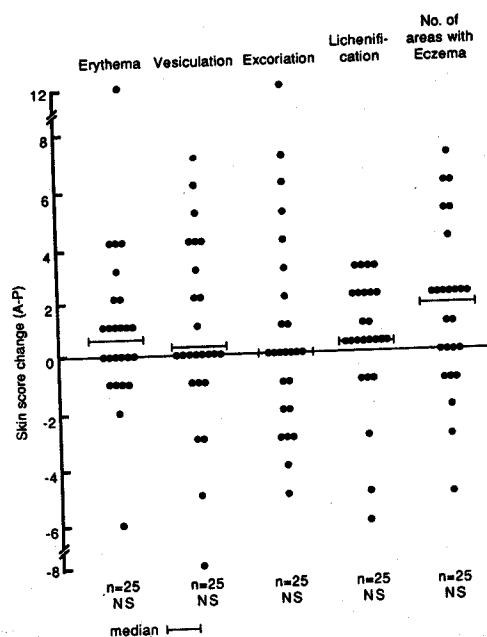


FIG. 6. Completed egg challenges: differences in skin score at end of egg challenge week (A) and end of placebo challenge week (P) compared using Wilcoxon paired samples signed rank test. The extent of eczema and of erythema, vesiculation, excoriation and lichenification did not change after egg challenge compared to placebo in the 25 who were able to complete the challenges.

Order Effect

Cows' milk and egg challenge results were examined for an order effect. There was no greater likelihood of the first or second challenge week having a higher skin or symptom score.

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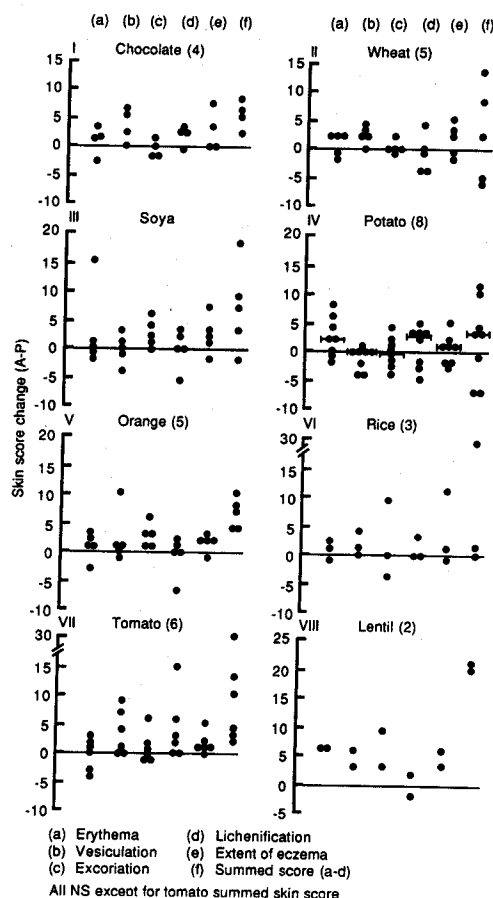


FIG. 7. Completed challenges with tomato (six), chocolate (four), wheat (five), soya (five), potato (eight), orange (five), rice (three) and lentil (two). For each food the skin scores were compared at the end of the active and placebo weeks. The summed skin eczema score was increased after tomato challenge ($p < 0.05$). Erythema (a), vesiculation (b), excoriation (c), lichenification (d), extent of eczema (e) and summed skin score a-d (f) did not otherwise differ where numbers permitted statistical analysis (Wilcoxon paired samples signed rank test).

Tomato

Six of seven double blind challenges with tomato were complete. The eczema summed skin score was increased ($p < 0.05$) after tomato challenge compared to placebo (Fig. 7), with no change in symptoms (Fig. 8). Open challenge reportedly exacerbated eczema in one patient.

Other Foods

Other double blind food challenges produced no significant changes in eczema skin scores (Fig. 7) or symptoms (Fig. 8) but the number of challenges for each food was too small for analysis; they suggest a trend to increased eczema. The results for potato and tomato challenges were also analysed together, since the plants are closely related. For 14 challenges (13 patients) eczema skin score changes were not significant, but itch was increased after the

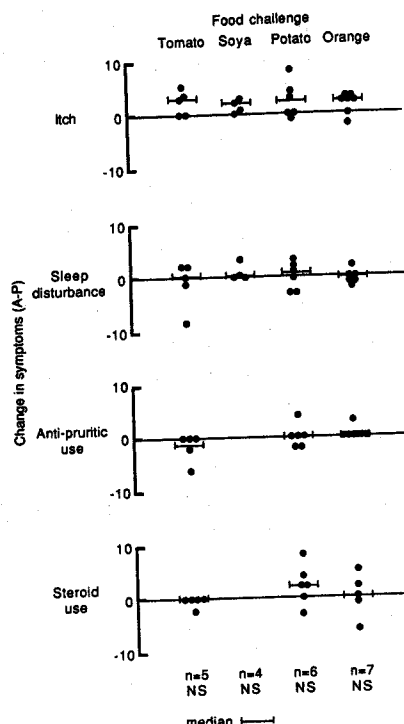


FIG. 8. Completed double blind challenges with tomato (five), soya (four), potato (six) and orange (seven) showing the difference in symptom scores between active challenge week and placebo for (a) itch, (b) sleep disturbance. Symptoms did not differ during active and placebo challenges where numbers were adequate for analysis (Wilcoxon signed rank test).

foods compared to placebo ($n=11$, median score increase 3, range -1 to 8, $p<0.05$, Wilcoxon signed rank test). Sunset yellow challenges (to be reported separately) caused itch but no change in eczema.

Timing of Challenges in Relation to Previous Food Elimination

The results of completed double blind challenges were analysed in relation to the length of time for which a food had been completely avoided prior to the challenge. Challenge results were described arbitrarily as positive if the sum of the score increases for erythema, vesiculation, excoriation and lichenification was increased by ≥ 3 after active challenge compared with placebo. The median time of avoidance of the particular food before challenge was 7.5 months for negative challenges and 3.5 for positive challenges. Figure 9 shows that the longer food had been avoided before the challenge was given, the more likely it was that the challenge would be negative.

Relationship Between Challenge Outcome and Response to Elimination Diet

The outcomes of food challenges were compared in patients with and without improvement on elimination diet. The 41 who improved were significantly more likely than 12 non-improvers to have at least one positive food challenge ($\chi^2=15.9$, $p<0.001$).

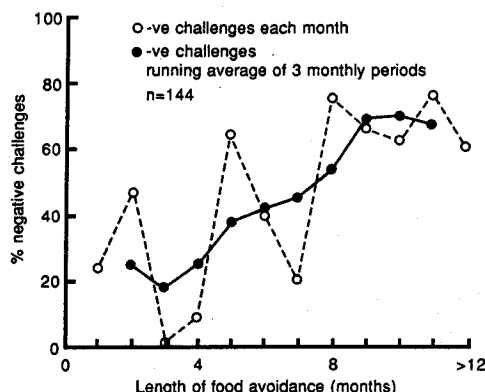


FIG. 9. Length of food avoidance before food challenge in relation to challenge outcome. The proportion of negative challenges is shown (i) in relation to the number of months for which a food given as challenge had been avoided (open circles) and (ii) in relation to the time a food had been avoided before challenge, as the running average of 3-monthly periods (closed circles). A challenge was increasingly likely to be negative the longer the food had been avoided before challenge. Variation reflects small numbers.

Food Like or Dislike

The outcome of a food challenge was compared for each food with the initial history that a patient either particularly liked or disliked that food. Using Wilcoxon two-sample tests it was found that challenge outcome, either as differences in itch or sleep disturbance between active and placebo weeks of challenge, was not affected by food preference.

DISCUSSION

This clinical study has shown that eczematous children often have a history of food-related symptoms and that elimination of certain foods (including cows' milk and egg) for 3–4 weeks resulted in an improvement in eczema in two-thirds of the children studied. The role of food avoidance in this improvement was supported by a series of random order, double blind food challenges in which cows' milk, tomato and other foods produced a worsening of eczema. Patients who had improved after dietary restriction were more likely to have at least one positive food challenge than those who showed no improvement, but positive challenge was less likely after prolonged elimination.

The study design, with daily symptom records, confirmed that repeated food challenges produce eczematous changes within 1 to 3 days [3,4]. By contrast, Sampson and McCaskill [11] noted a diffuse erythematous or morbilliform rash within a few hours of food challenges (double blind) and no later changes. Erythema and itch was also seen within 24 hours of food challenge in eczematous infants [5]. Adults have reported eczematous changes after single food challenges, often with urticaria prior to eczema [16]. This was an unusual event in our food challenges, as were immediate skin changes. The later changes seen after repeated challenges may reflect either a response related to food accumulation or a delayed response. Delayed food reactions may have a similar pathogenesis to the eczematous lesions that developed 48–72 hours after application of birch pollen to patients' skin [19]. Delays may have been due to slow penetration by the allergen or to the time taken for chronic

inflammatory cells to be recruited and cause tissue injury. Such delayed changes may be slow to resolve, and our study highlights the importance of an adequate washout period.

Sampson [20] reported associated non-cutaneous reactions after 71 per cent of 514 challenges, 43 per cent of which were gastrointestinal and 28 per cent respiratory. Apart from egg challenge, such associated symptoms were rare in our study, although a few patients had asthma, vomiting and diarrhoea within an hour, and some developed diarrhoea beginning up to 28 hours after challenge onset. It has been suggested that such delayed onset diarrhoea is non-IgE mediated [21].

In those children able to tolerate the challenges egg produced no significant increase in eczema or associated symptoms. This is in accordance with Meera's observations in children who were skin-prick test positive solely for egg, where only 7 per cent of ingestion of egg exacerbated eczema [9]. Egg caused urticaria in one-third of his patients, including the two who developed eczema. In our study 48 per cent of attempted egg challenges were incomplete, largely because of food refusal or intolerance. Similar difficulties in repeatedly challenging eczematous children with egg were found by Sedlis [22], who showed that egg exacerbated eczema in some, as in two other studies of patients with positive skin tests to egg [4, 23]. The high proportion of patients excluded from analysis in one study [10] may have been due to tolerance to the egg in the egg/cows' milk mixture used. We have shown that egg commonly causes hypersensitivity reactions in eczematous children without having a discernible effect on their eczema.

In this study, response to an elimination diet was not affected by the age of patients, whereas others [5, 6] have found that younger patients were more likely to respond. While a history of recurrent skin infections, severity of eczema or age at onset of eczema had no effect on our study outcome, Businco [6] found that patients with earlier age of onset of eczema tended to improve more with diet than those with late onset disease.

A history of food-induced eczema did not predict response to food challenge; this is in agreement with others [11]. Cows' milk and tomato, challenge with which exacerbated eczema, were among the foods most commonly reported by parents to exacerbate eczema, so history may be of value in planning diets, although the increasing tolerance to a food which develops after longer period of food avoidance complicates the evaluation of such a history. A history of pronounced food like or dislike did not correlate with challenge results, although there is anecdotal evidence that patients with other syndromes crave foods to which they have chronic adverse reactions [24].

The safety of food elimination diets in eczema has been questioned, both because of the risk of nutritional deficiencies, despite the involvement of dieticians [25], and the risk of adverse food reactions without warning [26]. Our patients were regularly reminded of the need to take calcium and other food supplements if required, and grew normally over the study period. Only one of the 64 patients challenged had a potentially serious hypersensitivity reaction with tongue swelling (to egg). He was known to have multiple food sensitivities and an indirect egg challenge (in maternal milk) had recently led to worsening of his eczema. It would seem sensible to avoid introducing potent allergens for several months to avoid the period of maximum sensitivity (Fig. 9). In highly allergic patients food reintroduction should probably take place in hospital.

This study suggests that food elimination can be used safely in the treatment of eczematous children whose symptoms are poorly controlled by topical measures. Cows' milk, tomato and soy (if already used) can be stopped for a trial period of about 3 weeks. If improvement occurs on the diet the patient should be challenged some months later; each food should be given separately for several days, and the duration and separation of challenges must take into account the commonly delayed responses and the increase in food

challenge outcome. The food for which a food give had been avoided was not challenged. A challenge was given. Variation

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tolerance which is seen after a long period of food avoidance. Sampson [11] found that only 60 per cent of patients were still sensitive after 2 years avoidance and Hammar [4] found that only 33 per cent still responded to food challenge. The method of food processing for food challenge is also important. Heat denatured proteins have reduced allergenicity [27], and the sterilized tinned foods used in our study may have been less likely to induce eczema than uncooked foods taken in everyday life. Bowel absorption of large molecules may be increased in atopic children [28], although others did not find this [29], and intestinal permeability did not change in parallel with eczema improvement on a few food diet [30]. It is postulated that immune complexes containing proteins and their antibodies may be deposited in the skin, initiating mediator release, cell-mediated immune changes and tissue damage.

Clearly factors other than foods, including environmental changes (temperature, aeroallergens), intercurrent infections and psychological factors, have an important influence on eczema, all of which should be taken into account when investigating aetiological factors in eczema. Further investigations into the role of foods in eczema should involve studies of immunohistological changes in the skin when foods are given.

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REFERENCES

1. Hill LW. Sensitivity to cow's milk in infantile eczema. *J Pediatr* 1938; 12: 725-729.
2. Kesten B. Allergic eczema. *NY State J Med* 1954; 54: 2441-2448.
3. Stifter WC. Some challenge studies with foods (Conference on Infantile eczema). *J Pediatr* 1965; 66: 235.
4. Hammar H. Provocation with cow's milk and cereals in atopic dermatitis. *Acta Dermatovenereol* 1977; 57: 159-163.
5. Juto P, Engberg S, Winberg J. Treatment of infantile atopic dermatitis with a strict elimination diet. *Clin Allergy* 1978; 8: 493-500.
6. Businco L, Businco E, Cantini A, Galli E, Infussi R, Benincori N. Results of a milk and/egg free diet in children with atopic dermatitis. *Allergol Immunopathol* 1982; 10: 283-288.
7. Hill DJ, Lynch BC. Elemental diet in the management of severe eczema in childhood. *Clin Allergy* 1982; 12: 313-315.
8. Freedman SS. Milk Allergy in infantile eczema. *Am J Dis Child* 1961; 102: 106-111.
9. Meara RH. Skin reactions in atopic dermatitis. *Br J Dermatol* 1955; 67: 60-64.
10. Atherton DJ, Sewell M, Soothill JF, Wells RS. A Double blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; i: 401-403.
11. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. *J Pediatr* 1985; 107: 669-675.
12. Neild VS, Marsden RA, Bailes JA, Bland JM. Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 1986; 114: 117-123.
13. Hanifin JM, Lobitz WC. Newer concepts of atopic dermatitis. *Arch Dermatol* 1977; 113: 663-670.
14. Office of Population Censuses and Surveys. Classification of occupations 1980. A publication of the Government Statistical Services.

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1977; 113: 663-670.

0. A publication of

15. Office of Population Censuses and Surveys. Registrar General Scotland. Census 1981. National Report. Great Britain. Part 2.
16. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939-1945 war. *Lancet* 1984; ii: 1255-1257.
17. Hausple R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. *J Allergy Clin Immunol* 1977; 59: 200-206.
18. Benton EC, Barnetson RC. Skin Reactions to Foods in Patients with Atopic Dermatitis. *Acta Dermatovenereol* 1985; 114 (Suppl): 129-132.
19. Reitamo S, Visa K, Kahonen K, Kayhko K, Stubb S, Salo OP. Eczematous reactions in atopic patients caused by epicutaneous testing with inhalant allergens. *Br J Dermatol* 1986; 114: 303-309.
20. Sampson HA. The role of food allergy and mediator release in atopic dermatitis. American Academy of Allergy and Immunology, Postgraduate Course Syllabus 1987; pp. 51-60.
21. Minford AMB, Macdonald A, Littlewood JM. Food intolerance and food allergy in children: a review of 68 cases. *Arch Dis Child* 1982; 57: 742-747.
22. Sedlis E. Some challenge studies with foods conference on infantile eczema. *J Pediatr* 1965; 66: 236-238.
23. Sampson HA. Dermatological reactions secondary to food allergy. In *Proceedings of the XII International Congress of Allergology and Clinical Immunology* (ed. Reed CE), pp. 462-467, CV Mosby Co.
24. Randolph TG. Specific adaptation. *Ann Allergy* 1978; 40: 333-345.
25. David TJ, Waddington E, Stanton RHJ. Nutritional hazards of elimination diets in children with atopic eczema. *Arch Dis Child* 1984; 59: 323-325.
26. David TJ. Anaphylactic shock during elimination diets for severe atopic dermatitis. *Arch Dis Child* 1984; 59: 983-986.
27. McLaughlan P, Anderson KJ, Coombs RRA. An oral screening procedure to determine the sensitizing capacity of infant feeding formulae. *Clin Allergy* 1981; 11: 311-318.
28. Pike M, Heddle RJ, Boulton P, Turner MW, Atherton DJ. Increased intestinal permeability in atopic eczema. *J Invest Dermatol* 1986; 86: 101-104.
29. Du Mont GCL, Beach RC, Menzies IS. Gastrointestinal permeability in food-allergic eczematous children. *Clin Allergy* 1984; 14: 55-59.
30. 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: 1691-1698.