

Prevalence of intolerance to food additives among Danish school children

Fuglsang G, Madsen C, Saval P, Østerballe O. Prevalence of intolerance to food additives among Danish school children.
Pediatr Allergy Immunol 1993; 4: 123–129. © Munksgaard 1993.

The prevalence of intolerance to food additives was assessed in a group of unselected school children aged 5–16 years. A study group of 271 children was selected on the basis of the results of a questionnaire on atopic disease answered by 4,274 (86%) school children in the municipality of Viborg, Denmark. The children in the study group followed an elimination diet for two weeks before they were challenged with a mixture of food preservatives, colourings and flavours. The challenge was open and the additives were prepared as a fizzy lemonade. If the open challenge was positive, a double-blind placebo controlled challenge with gelatine capsules was performed. The study included 281 children, 10 were excluded, and the remaining 271 children were given the open challenge (98 healthy controls and 173 with atopic symptoms). The open challenge was negative in all 98 healthy control children who had not reported any atopic symptoms. Of the 173 children reporting present or previous atopic disease 17 had a positive open challenge. Of these 17 children 1 experienced gastrointestinal symptoms, 13 reacted with aggravation of atopic eczema, and 3 with urticaria. Twelve of these 17 children went through the double-blind challenge which was positive in 6 cases. Five of these 6 children had positive reactions to synthetic colourings and 1 to citric acid. No serious reactions were seen. Based upon calculations of the results from this study and an earlier multicenter study in children referred to hospital clinics, the prevalence of intolerance to food additives in school children is estimated to be 1–2%.

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Key words: intolerance; food; additives; child;
prevalence

Received: October 25, 1992

Accepted: February 8, 1993

So far children's intolerance to food additives has only been studied in selected groups of patients. Therefore the frequency of intolerance to additives in a non-selected population of children is not known. Parents often suspect food additives as a causative factor for hypersensitivity reactions in children. Thus, in a recent survey of 335 children referred to hospital allergy clinics, we found that 2% to 7% reacted to challenges with food additives with atopic symptoms, whereas 23% of the parents to these children suspected that their child reacted to food additives with symptoms (1).

The literature only provides details of one single mass survey of the prevalence of intolerance to food additives in the diet (2). In that study Young et al. estimated a prevalence of 0.01–0.23% upon the basis of a questionnaire forwarded to 18,582 children and adults.

In order to supplement the knowledge we gained from our earlier study on children referred

to hospital allergy clinics (1), the present study was set up to evaluate the frequency of intolerance to food additives in children who had not been referred to allergological examination. The survey included children with atopic symptoms, as well as a control group of children without atopic symptoms.

Patients and methods

All 4,952 five to 16-year-old school children in a Danish municipal district (Viborg) were given a questionnaire. They were asked about present (i.e. within the preceding year) and earlier hypersensitivity reactions, the kind of symptoms, how they had been diagnosed (by parents or general practitioner). Furthermore, the parents were asked whether they knew the cause of the child's hypersensitivity or which factors they suspected as a cause of the adverse reaction. Finally, they were

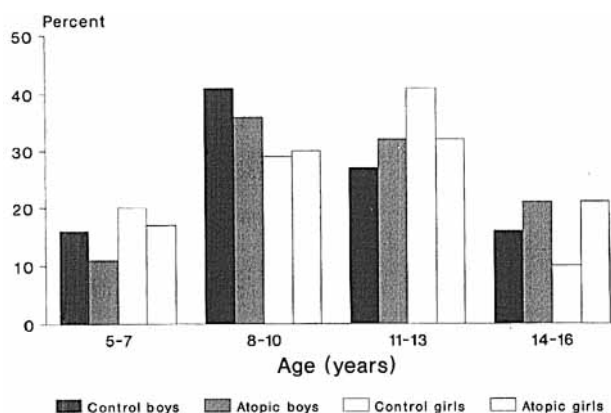


Fig. 1. Distribution of age and sex in the challenged atopy and control group.

also asked whom they had consulted (physicians or alternative therapists) because of the atopy suspicion. The results of the questionnaire are reported by Saval et al. (3).

The two groups of children that we wanted to examine for intolerance to food additives were chosen on the basis of the questionnaire: a group of children with atopic symptoms – the atopy group, and a group of healthy children – the control group. Statistical considerations regarding the sample size indicated that a sample of 100 healthy children and 200 children with atopic symptoms was required to ensure that important differences between the prevalence of a positive reaction in these two groups of children were not overlooked. These calculations were based on a 5% level of significance, 20% risk of Type II error, and assumed that the true prevalence in the two groups were 1% and 10%, respectively.

To make a more accurate estimate of the overall prevalence of intolerance in the entire child population, we have used the results from our earlier study on the school children examined at hospitals allergy clinics with the same challenge method and asked same questions of suspicion to food allergy – the hospital group.

Atopy group

The children in this group suffered from present or earlier atopic symptoms. They had not earlier been examined at a hospital allergy clinic. Stratified sampling was used to ensure an equal distribution of children with rhinitis, atopic eczema, and urticaria, and an equal distribution of children with and without suspected intolerance to food additives. We tried to exclude children who only suffered from asthma because the frequency of intolerance to food additives had been thoroughly examined in this group of children in our earlier study (1).

Control group

The control group consisted of children who had never experienced symptoms of atopy. The children in this group were selected so that their age distribution corresponded to that in the atopy group (Fig. 1). For both groups only parents and children who were willing to undergo a dietary period followed by challenge were included.

Hospital group

The present study only included children who had not been examined for allergic symptoms at hospital. In our earlier study (1) 335 children, examined for allergic symptoms at hospitals allergy clinics, were examined and challenged with the same method as in the present study i.e. questionnaire, clinical examination and open and double-blind challenges. For 261 of these children the distribution of age, sex and symptoms was the same as for the 378 school children, who in the present study had answered that they previously had been examined at hospital allergy clinics. On the basis of this we have used the challenge results from the 261 children in the earlier study to estimate the prevalence of intolerance to food additives in the group of 378 school children.

Challenge method

We used the same challenge method as in our earlier study (1), (Fig. 2). All children who agreed to participate in the survey were instructed by a dietician in how to follow an additive-free diet for a period of two weeks. The eliminated additives were natural and synthetic colouring's, preservatives, and flavours. The amounts of preservatives to be used for the high challenge dose was taken from the investigation entitled: dietary habits in Denmark (4) and The Danish National Food Agency list of approved additives (5). The amounts were calculated as the median consumption of the food additives in adults (mg/kg

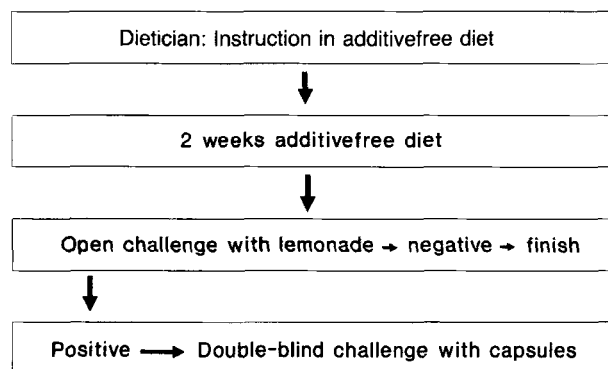


Fig. 2. Flowchart of methods.

Table 1. Content of the open challenge doses "lemonade", high dose

The additive suspensions were prepared as a concentrate and were, just prior to challenge, mixed with carbonated water to a final volume of 100 ml each. The low dose concentration was 1/10 of the high dose.

	Green lemonade	mg/100 ml	Red lemonade	mg/100 ml
Preservatives (capsule 1)	Sulfites	12	Benzoic acid	45
	Sorbic acid	100	Propionic acid	100
Synthetic colours (capsule 2)	Tartrazine	18	Ponceau 4R	1.5
	Quinoline yellow	2.5	Azorubine	7.5
	Patent blue	2.0		
	Sunset yellow	2.5		
Natural colours (capsule 3)	Turmeric	2.5	Beta-carotene	6.0
	Annatto	1.6	Chantaxantine	1.0
			Beetroot colour	5.5
Acids	Citric acid	40	Citric acid (capsule 4)	60
Flavours	Anethole	10	Orange oil	10
	Ethylvanillin	10	Lemon oil	10

bodyweight) extrapolated to a bodyweight of 30 kg. The amounts of flavours to be employed were determined on the basis of palatability. Citric acid and sugar was added to improve the taste of the lemonades. The amount of additives in the high challenge dose is equivalent to the additive content of approximately 500 g of (medium coloured) candy, 1 l soft drink and 30 g of rye bread.

During the period with the additive-free diet, the occurrence of symptoms were recorded in a diary. Furthermore, at the end of the period, the parents were asked whether they felt that the diet had caused any changes in the atopic symptoms of the child. Finally compliance with the diet was recorded.

The child was examined by the investigator prior to each challenge. Objective findings in the skin were recorded, and symptoms (itching, irritation) described. Rhinitic symptoms (nasal stenosis, sneezing, or nasal discharge) were also recorded. If the child suffered from asthma the peak-flow was measured. The child was challenged immediately after the objective examination. Independent of the symptoms recorded during the dietary period, all children in both groups were given an open challenge with lemonades containing a mixture of the excluded additives (Table 1). All children were given a red and green lemonade containing a low concentration of additives. The volume of each drink was 100 ml. The challenge was followed by an objective examination every hour for three hours, and if there was no reaction or a doubtful reaction, the child was challenged with a lemonade that contained ten times as high concentration of additives as in the first one. This

challenge was also followed by an objective examination every hour, for three hours. All challenges, objective examinations and recordings were performed by the same pediatrician (GF) at the school health office. Symptoms which appeared later than 3 h after the high dose challenge were recorded by the parents, and their findings were confirmed by the investigator on the following day.

If the challenges provoked any symptoms within 24 h after the open challenge, the child was encouraged to continue with the diet to confirm the findings under double-blind conditions.

Gelatine capsules containing the same additives in the same quantities were used for the double-blind challenge (Table 1). The substances were masked in opaque, ferric oxide coloured gelatine capsules, with one group of additives in each capsule. Preservatives, synthetic colours, natural colours and citric acid were given on 4 separate days (Table 1). Placebo capsules were included in the randomization on 2 challenge days. The result of the challenge was recorded by the parents, who were aware that the capsules had been chosen at random. If the child reacted on low dose lemonade the double-blind challenge was performed with low dose capsules only. On special request from the parents one child was given both low and high dose provocation even if she had reacted on the low dose lemonade.

The code was not broken until after the entire challenge was completed, so that the challenge was double-blind. In the case of equivocal results the challenge were repeated in a new random order including placebo capsules. As it was impossible to mask the flavours in capsules, the challenge with

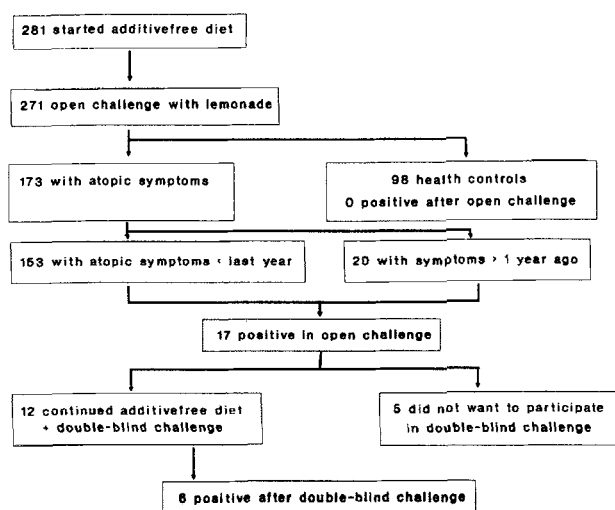


Fig. 3. Flowchart of results.

flavours was performed as an open challenge using two suspensions. The study was approved by the Human Research Committee. Informed consent was given by the parents before entering the study.

Results

4,952 questionnaires were sent out. 4,274 (86.3%) were answered. 1,052 children (24.6%) had present atopic symptoms (within the last year), and 555 children (13.0%) reported atopic symptoms in the past. 2,667 children (62.4%) had never had

atopic symptoms. Details about age, sex and symptoms are presented in the article by Saval et al. (3). Distribution of age and sex in the atopy and control groups are shown in Fig. 1. In all 281 children started on diet without additives (Fig. 3), 10 were excluded: 1 because the diet was broken, 2 were ill on the challenge day, and 7 children because they had consulted an allergy clinic. Upon the basis of the questionnaire 173 children were included in the atopy group because they reported present atopic symptoms. However, 20 of these children had only had symptoms in the past. Yet we decided to include them in the atopy group so that this group comprised 153 children with present and 20 with past symptoms. The remaining 98 children studied were healthy controls.

The distribution of symptoms in the 153 children with symptoms within the last year, was: atopic eczema 39.9%, rhinitis 34.6%, and urticaria 22.9%. The remaining 2.6% had other symptoms. None of the control children reported any changes in the dietary period. 34 children in the atopy group reported an improvement in their symptoms during the diet period.

All 271 children from the atopy and control group were challenged with lemonade. None of the 98 control children reacted positively to the challenge. Of the 173 challenges in the atopy group there were 17 reactions, of which 3 were observed after the low concentration. Five children with positive open challenge did not want to continue

Table 2. Patients with positive reactions after challenge

Pt. nr.	Age	Sex	Symptom	Double blind	Causing additive	Clinical suspicion	Effect of diet
1*	13	F	A.E.	Neg		Citrus fruit	-
2	13	F	G.I.	Neg		Colour	-
3	7	M	Urt.	Neg		Colour	-
4	12	M	Urt.	Neg		Colour	-
5	13	M	A.E.	Pos	Citric acid, Flavour citrus	Colour	+
6	9	F	A.E.	Not done		Citrus fruit Colour Citrus fruit	+
7	5	F	A.E.	Not done		Colour	+
8	16	M	A.E.	Pos	Synt. C Flavour	Colour	-
9	7	F	A.E.	Pos	Flavour citrus	-	+
10*	9	F	A.E.	Not done		Colour	-
11	13	M	A.E.	Not done		-	-
12	11	F	A.E.	Pos	Synt. C	Colour	-
13	14	F	A.E.	Not done		Colour	-
14	7	F	A.E.	Pos	Synt. C	Colour	+
15	16	F	A.E.	Pos	Preserv.	Preserv. Colour	+
16*	15	F	Urt.	Pos	**Synt. C **Flavour citrus	Colour Preserv.	+
17	13	M	A.E.	Not done		Cacao	-

All had reactions after high dose. * reaction after low dose lemonade. ** reaction after low dose capsule/flavour. Abbreviations: A.E.: Atopic eczema; Urt: Urticaria; G.I.: Gastrointestinal symptoms; Synt. C: Synthetic colour.

Table 3. Distribution of patients – predictive parameters

The figures in the table shows the basis for the calculations of the prevalence.

Hosp.	Susp.	A.E.	No.	Prov.	Pos.	% Pos
Y	Y	Y	27	–	–	20*
Y	Y	N	33	–	–	9.4*
Y	N	Y	86	–	–	2.0*
Y	N	N	232	–	–	3.4*
N	Y	Y	80	28	9	32
N	Y	N	143	36	5	13.9
N	N	Y	309	39	2	5.1
N	N	N	697	70	1	1.4
Never atopy			2667	98	0	
Total			4274	271	17	

Abbreviations: Hosp.: Evaluated for atopic disease at hospital allergy clinic; Susp.: Suspicion to food additives causing symptoms; A.E.: Atopic eczema; No.: Number of children; Prov.: Number of children in the present study; % Pos: Percent positive reactions after open challenge (lemonade); Y: Yes; N: No; *: Children evaluated at a hospital allergy clinic (results from our earlier study).

with the blind challenge. The remaining 12 children were challenged double-blindly. Six of these had positive reactions (Fig. 3). In addition one child reacted to the flavours. This was recorded as an open challenge. Details of the positive reactions are given in Table 2.

One child experienced gastrointestinal symptoms. Sixteen children reacted to the open challenge with skin symptoms, (13 with a worsening of atopic eczema, and three with urticaria). In the double-blind challenges most reactions were caused by synthetic colouring (four). Three patients reacted after open challenge with citrus flavour. One patient reacted to both citrus flavour and citric acid capsules. No serious reactions were seen.

Only 3 of the 17 positive lemonade-challenged children had no prior suspicion towards food additives. In comparison 6.6% of all the children who answered the questionnaires, 18% of the 1,052 who reported atopy within the last year, and 37% of the 173 from the atopy group suspected intolerance to food additives.

The distribution of the lemonade-positive children in the total study population is given in Table 3. In the table the children have been divided into subgroups upon the basis of the occurrence of atopic eczema and suspicion of intolerance to food additives since only these two factors were found to be predictive for a positive lemonade provocation. Furthermore, the population was divided into children who had and who had not been evaluated at a hospital allergy clinic. The results from the children evaluated at a hospital clinic have been

taken from our earlier study on this population (1). These results are marked with an asterix. Assuming that for each subgroup the estimated proportion of positive reactions found in the study can be applied to the whole subgroup, the prevalence in the total population is estimated to be 2% (SD 0.7%). This estimate presupposes that the prevalence in the subgroup of children who had never had atopic symptoms is 0%. If instead the incidence in this group is assumed to be 0.5% or 1%, the prevalence in the total population becomes 2.3% or 2.7% respectively (SD 0.7%).

The number of capsule challenges used in the double-blind challenge is given in Table 4. Four children showed a total of five positive reactions to synthetic colouring (one child reacted both to low and high dose) (Tables 2, 4). One child had a positive reaction to citric acid, and one to preservatives. There were no reactions to challenges with natural colourings. The positive reactions after challenge with capsules did not differ from the reactions after lemonade provocations.

When the validity of the capsule challenge was evaluated by cross tabulating the figures in Table 4, it was found that positive reactions to preservatives and citric acid did not occur more frequently than placebo reactions. For synthetic colouring there was a trend towards an increased incidence compared with placebo, but it was not significant. Six of 12 double-blind challenges were positive. If there were no false negative challenges in the lemonade provocation, and the twelve children in the capsule challenge were similar to the five who would not participate, the predictive value of a positive lemonade test is 50%. Therefore, the incidence of intolerance to food additives calculated on the basis of the blind challenges is estimated to be about 1%.

Discussion

The main finding was that the prevalence of intolerance to food additives in an unselected

Table 4. Number of capsules used in double-blind challenge

Additive	Result		Total
	+	–	
Synthetic colour	5	12	17
Natural colour	0	15	15
Preservatives	1	15	16
Citric acid	1	13	14
Total active	7	55	62
Placebo	1	24	25

+ positive reaction; – negative reaction.

population of Danish school children was 1–2%. This prevalence was markedly higher than that estimated by Young et al. (2) who reported an incidence of 0.01–0.23%. Young et al.'s results were based on a questionnaire and a clinical examination of selected groups. However, they only challenged 81 persons and they had no healthy controls in the challenged group. Furthermore, their study comprised both adults and children whereas our study only included children. Atopic eczema is far more frequent in children than in adults (6) and the vast majority of reactions in our study were skin reactions. The method of provocation also differed between the two studies. We used some different additives including flavours and a combined method of open and blind challenge. Our estimate was based on the results of both the open and the double-blind provocations because we had too few double-blind challenges to make an accurate assessment. However, based on the double-blind challenge a qualified estimate of the prevalence would be about 1%. We do not believe that our selection of patients with atopic eczema and urticaria for provocation test led to an overestimation of the prevalence because we adjusted for this selection in our prevalence estimate for the whole population.

The estimation of the prevalence was based on a stratification of the children into 9 strata Table 3. A more detailed stratification has also been applied. Furthermore, for the control group different values of the prevalence in the range 0% to 1% was used in order to evaluate the power of the final estimate. These alternative calculations all gave a prevalence estimate for the total population in the range of 1.9% to 2.7%. We therefore believe that the estimate of prevalence is reliable.

The design of the study where the provocation groups were selected by stratified sampling and the high responder rate (86.3%) minimized the risk of an important selection bias which could skew the results towards a high prevalence. This was supported by the findings in a drop-out investigation of the children who did not return the questionnaire (3). The urticaria group was smaller than the other groups because there was an insufficient number of children with this symptom. This did not influence the results since adjustments were made for this in the calculations.

It was not technically possible to mask the taste and smell of the flavours. Consequently, the lemonade provocations were not blind. Furthermore, in the present study we tried to make the challenges as accurate and reliable as possible by letting the same experienced researcher do all challenges and recordings. Though the lemonade challenges were not blind, the following findings

all suggest that the provocation method was reliable: there were no positive reactions among the healthy controls, the frequency of positive reactions seemed to be dose related and the frequency of positive provocations were similar to that observed in an earlier multicenter-study (1). It cannot be excluded however, that some of the positive reactions after high-dose lemonade were in fact late reactions after the low dose challenge 3 h earlier. If this was the case we would also expect a late reaction after the high-dose challenge with an exacerbation of symptoms 4–6 h after this challenge. This was not the case.

The markedly lower number of positive reactions after capsule challenges as compared with lemonade challenge could be due to the fact that the mixture of all the additives in the lemonade gave a higher number of reactions because of a synergistic effect of the mixture compared with the provocation with the additives given group by group in capsules on separate days. Furthermore, the direct contact of the additives with the oropharynx and oesophagus during lemonade provocations may also have been important for the development of symptoms. This contact does not occur with the capsules. Further studies are needed to evaluate that.

If the discrepancy between open and blind challenges were due to false-positive reactions after open challenge in general, one would expect an even distribution between positive reactions among low- and high-dose lemonade provocations. This was not the case. Unfortunately the validity of the double-blind provocation could not be evaluated thoroughly statistically because of the low number of capsule provocations.

In accordance with the findings in our earlier study (1) there was a discrepancy between the actual prevalence of intolerance to food additives (1–2%) and the number of parents who suspected additives to cause symptoms: 18% in the group with atopic symptoms within the last year and 6.6% of the entire population of school children. The latter compares well with the figure reported by Young (2), who found that 7.4% of the population, answering the questionnaire suspected problems with additives.

We did not find any reactions with rhinitic symptoms in children in the rhinitis group. Almost all reactions were seen in the group of children with urticaria and atopic eczema. Other studies have challenged children with atopic eczema and urticaria with food additives and found positive reactions after elimination-provocation trials (7–11). In a Danish study Østergaard (7) found that 8% of 62 children with atopic eczema had itching of the skin and/or eczema and urticaria after provocation

with food colouring. We found in our earlier study (1) that it was mainly children with skin symptoms among all children with atopic symptoms who reacted after challenge with the lemonade of mixed additives (11% of the children with atopic eczema and 18% of the children with urticaria). In comparison with these findings David estimated that about 5% of children with atopic eczema would react with exacerbation of their skin symptoms after ingestion of tartrazine or benzoic acid (12). However, no calculations were given.

The present study population was different from the children evaluated in the earlier studies. Most of our children with positive reactions in the present study had already suspected food additives to cause symptoms and the families themselves had solved the problem by eliminating the suspected additives from the food. Furthermore, none had severe reactions. This suggests that many families are capable of handling the problem themselves by gaining their own experience.

Conclusion

The prevalence of intolerance to food additives in unselected school children is estimated to be 1–2%. The vast majority of positive reactions are skin symptoms (worsening of atopic eczema and urticaria). Positive reactions are rare in children without any previous suspicion of intolerance to food additives. A lemonade challenge with a mixture of additives can be used as a safe and reliable provocation in an out-patient setting.

Acknowledgements

The authors wish to thank ALK, Denmark, for producing lemonades and capsules. The study was supported by grants from Lundbeck Research Foundation, National Food Agency of Denmark, Viborg County Research Foundation and Lions Club, Viborg, Denmark. The authors wish to thank Michael Væth, Ph.D., Institute of Mathematics, University of Aarhus, Denmark, for statistical assistance.

References

1. FUGLSANG G, MADSEN C, HALKEN S, JØRGENSEN M, ØSTERGAARD PA, ØSTERBALLE O. Adverse reactions to food additives in atopic children. *Allergy* (in press).
2. YOUNG E, PATEL S, STONEHAM M, ROONA R, WILKINSON JD. The prevalence of reactions to food additives in a survey population. *J Royal Coll Phys* 1987; 21: 241–7.
3. SAVAL P, FUGLSANG G, MADSEN C, ØSTERBALLE O. Prevalence of atopic disease among Danish school children. *Pediatr Allergy Immunol* 1993; 4: 117–22.
4. HARALDSDOTTIR J, HOLM L, JENSEN JH et al. Dietary habits in Denmark (Main results). *Levnedsmiddelstyrelsen* 1986 nr. 136. (In Danish, summary in English).
5. List of approved food additives. (The positive list). National Food Agency of Denmark, 1985.
6. RYSTEDT I. Prognostic factors in atopic dermatitis. *Acta Derm Venerol* 1985; 65: 206–13.
7. ØSTERGAARD PA. The incidence of intolerance to colouring agents in children with eczema. *Ugeskr Læger* 1986; 148: 711–4.
8. BEVER HP, DOCX M, STEVENS WJ. Food and food additives in severe atopic dermatitis. *Allergy* 1986; 44: 588–94.
9. SUPRAMANIAM G, WARNER JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986; 18: 907–9.
10. IBERO M, ESEVERRI JL, BARROSO C et al. Dyes, preservatives and salicylates in the induction of food intolerance and/or hypersensitivity in children. *Allergol Immunopathol* 1982; 10: 263–8.
11. KEMP J, SCHEMBRI G. An elimination diet for chronic urticaria of childhood. *Med J Aust* 1985; 148: 234–5.
12. DAVID TJ. Food additives. *Arch Dis Child* 1988; 63: 582–3.