

Natural history of atopic dermatitis in childhood: an updated review and personal experience of a five-year follow-up

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The natural history of atopic dermatitis (AD) in children is not well-known; only a few studies have been performed in children (1-3).

The reported estimates of patient improvement vary widely, between 17 and 90% of the cases (Table 1), probably due to different selection criteria (1-13). Most authors quote 40-50% improvement at 13-15 years of follow-up (1, 4, 5, 8, 10-13). The different studies on the natural history of AD suggest the following predictive factors: severe (widespread) or "reverse pattern" skin lesions (2, 3, 8, 10-13); late (2) or early (12, 13) onset; family history of atopy (3, 10-13); female (2, 12, 13) or male (3) sex; association with respiratory allergy (3, 10-13); no association with food hypersensitivity.

Prevalence of respiratory allergy in AD varies between 30-55% of the patients (3, 4, 8-13). When AD was associated with cow's milk (CM) and/or egg hypersensitivity (44-90% of the patients), improvement and food tolerance were achieved 2-5 years later (1, 14-16). In children with hypersensitivity to other foods (cereals, fish, etc.), food tolerance was achieved later (14-16).

Sampson et al. (1) showed that the outcome of AD was more favorable when the patients lost the food hypersensitivity.

The aim of the present study was to investigate the natural history of AD in children with food hypersensitivity.

MATERIAL AND METHODS

During 1981-1982, 68 children affected with AD and food hypersensitivity were selected in

the present prospective study. All the children fulfilled the criteria of Hanifin & Lobitz for the diagnosis of AD (17). The following parameters were evaluated at the first examination: age; family history of atopy (parents and/or siblings with asthma, rhinitis or AD); duration of breast feeding; age of onset and severity score of AD; respiratory allergy (asthma and/or rhinitis or oculorhinitis); skin tests (SPT) for casein, lactoalbumin, ovalbumin, house dust, *Dermatophagoides pteronyssinus*, *Alternaria tenuis*, *Lolium perenne* and *Parietaria officinalis* (Lofarma, Milan): mean diameters of erythema and wheal reactions were recorded. Wheal reactions 3 mm greater than the negative control were considered positive; total IgE levels (Phadebas IgE PRIST®), were considered positive if > 2 SD for age; IgE (Phadebas RAST®) to casein, lactoalbumin, egg (albumen), *D. pteronyssinus*, *Alternaria tenuis*, *Lolium perenne* and *Parietaria officinalis* were considered positive if higher than 0.35 PRU/ml.

The diagnosis of food hypersensitivity was made as follows: a 4-week diagnostic elimination diet was prescribed. If AD occurred when the child was only given milk, CM and dairy products were excluded. If AD appeared when egg and wheat were also given, these foods were also excluded. Other foods were eliminated only because of a precise anamnestic indication. Nutritionally adequate CM substitutes were employed: Soy-protein formula (Isomil, Abbott), or Rezza's diet (18) prepared as follows: lamb's meat (100 g), rice flour (70 g), olive oil (40 g), calcium (300 mg), water up to 1 liter. Wheat-free pasta and bread were given (Schär, Merano, Ita-

Table 1
Natural history of AD: retrospective (R) and prospective (P) studies

Authors	Year	Subjects	Study	Patients (No.)	Follow-up (years)	Improvement (% of patients)	Respiratory allergy prevalence (%)
Vowles et al.	55	adults	R	84	13-22	45	50
Meenan	59	adults	R	42	14-27	58	n.r.
Burrows et al.	60	adults	R	29	9-12	17	nr.
Roth et al.	64	adults	R	220	20	29-40	55
Stifler	65	adults	R	40	21	70	20-50
Musgrove et al.	76	adults	R	99	15-17	42	30
Vickers	80	adults & children	P	2000	5-20	90	n.r.
Van Hecke et al.	81	adults	R	50	20	38	60
Rystedt	85	adults	P	955	24	38-60	32-60
Sampson et al.	85	adults & children	P	113	1-2	40	n.r.
Queille-Roussel et al.	85	children	P	200	7	26	34

n.r. = not reported.

ly) when the child was sensitive to wheat. Oral hydroxyzine (Atarax, UCB; 0.7 mg/kg/die) was also administred if necessary, as well as low strength topical steroid (Vaspit, Schering).

When the skin lesions cleared-up, a challenge test in open fashion was performed under appropriate supervision. A drop of CM or egg emulsion was put on the child's lip. If no reaction occurred after 5 min, 5 ml of CM or egg emulsion were given. After a further 30 min, 100 ml of CM or half a boiled egg were given. The child remained under supervision for 4 h. The same procedure was followed for other food challenges. All reactions were scored on a standardized scoring chart previously described (19).

If no immediate reaction occurred, the food was allowed in the normal diet, and the parents carefully observed the child's skin. To verify the development of tolerance to the offending foods, the challenge test was repeated every year and the severity of skin lesions was assessed. Based on the challenge test, a therapeutic elimination diet, excluding the offending foods, was given independently of IgE and/or skin test response. All the patients were followed up every year, or more frequently if the symptoms were severe.

After 5 years the following parameters were considered: age; severity score of AD; develop-

ment of food tolerance; duration of symptoms (in months); respiratory allergy (asthma and/or rhinitis); psychological problems (stammering, enuresis, onicophagia, etc.). Twelve children of the 68 discontinued for a variety of reasons.

Of the 56 children (32 boys and 24 girls) remaining in the study, 7 had no total IgE determi-

Table 2
Clinical features of the 56 children at the first examination

Age (median)	3 y (4 mo - 10.58 y)	
Age of AD onset (median)	3 mo (1 mo - 5 y)	
Severity score (mean)	17 (2-78)	
	No.	%
Sex:		
Boys	32	57
Girls	24	43
Family history of atopy	23	41
Distribution of skin lesions:		
Typical	43	77
Not-typical or widespread	13	23
Respiratory allergy	19	34

nation, 1 child had no SPT and/or IgE to food allergens; 12 had no SPT and/or IgE to inhalant allergens. In 10 children the challenge test was not performed, due to the history of severe anaphylactic reaction (egg in 7 patients and CM in 3 patients).

Analysis of the data was estimated using the Chi-square and Student's t-test. The Fisher exact probability test was employed when necessary.

RESULTS

The clinical features of the 56 children at the first examination are shown in Table 2. The median age was 3 years (range: 4 mo – 10.58 y). The median age of onset of AD was 3 mo (range: 1 mo – 5 y) before the 4 mo of life in 27 babies (48%); between the 4 to 6 months in 10 babies (18%); and after 6 mo in 19 babies (34%) (Fig. 1). The mean severity score of AD was 17 (range 2–78). A family history of atopy was found in 23 patients (41%). The skin lesions were typical in 43 children (77%) and widespread or atypical (reverse pattern) in 13 (23%); 19 patients (34%) were affected with respiratory allergy (asthma and/or rhinitis).

Fig. 2 shows the age of the first CM formula feeding in the 56 children with AD. CM formulae were given since birth in 23 cases (41%), before the 3 mo in 18 cases (32%), and after 3 mo in 15 cases (27%). Total IgE levels were > 2 SD for age in 39/49 children (80%) (GM: 127 IU/ml; range: 5–3900 IU/ml); positive SPT and/or RAST were found in 45/55 children (82%). SPT and/or RAST to inhalant allergens were positive

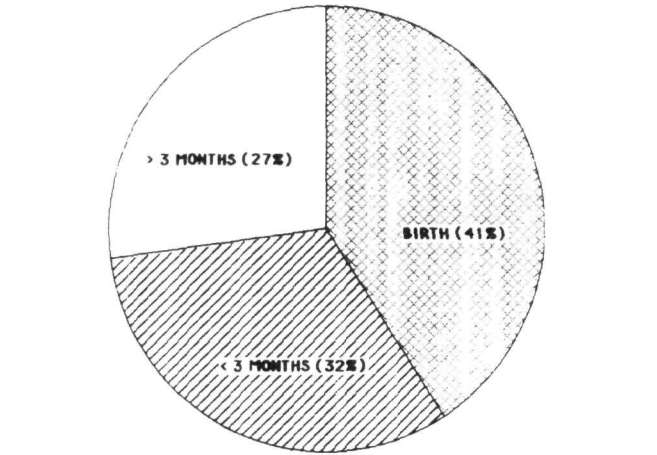


Fig. 2. Age of the first CM formula feeding in the 56 children with AD (follow-up to 5 y).

in 26/44 children (59%). The challenge test with the offending foods was positive in 42/46 children (91%). The main offending foods were: CM and egg in 40% of the children; CM alone in 14% of the children; egg in 14% of the children; wheat in 2% of the cases (Fig. 3); multisensitivity (especially towards CM, egg and wheat) in 29% of the patients. Overall, 10/56 (18%) were sensitive to wheat.

At the last follow-up, the median age of the children was 6.75 y (range: 4.16–14 y). Skin lesions cleared-up in 32 children (57%), persisted in 24 children (43%) (Fig. 4). Forty-five percent of the children completely lost the food hypersensitivity, 11% achieved a partial tolerance, 20% remained hypersensitive. There was no difference in the median age of these 3 groups. The tolerance to CM was achieved at the median age

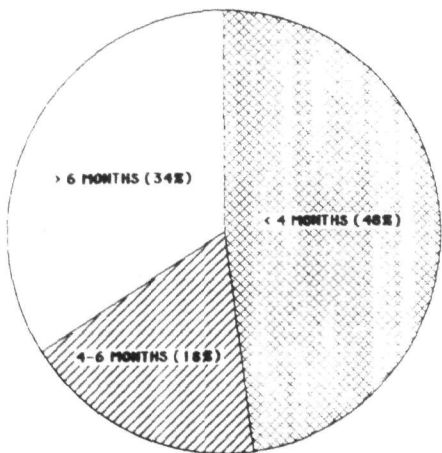


Fig. 1. Age of onset of atopic dermatitis in the 56 children.

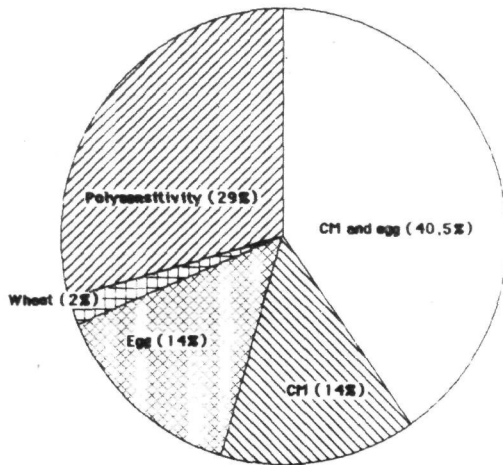


Fig. 3. Foods inducing positive challenges in the children with AD (follow-up to 5 y).

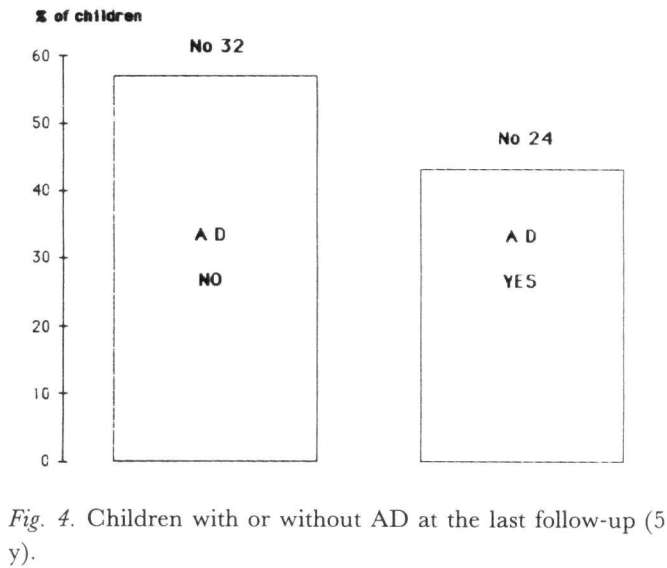


Fig. 4. Children with or without AD at the last follow-up (5 y).

of 3.5 y, while the median age for tolerance to egg was 4 y and, wheat, 4.5 y.

There was a significant difference ($P < 0.05$) in the age of onset of AD in the group with tolerance (median: 3 mo) and in the group without tolerance (median: 9 mo). Furthermore 28 children (50%) had respiratory allergy at the last follow-up; 21 patients (37%) developed asthma, 2 (4%) rhinitis, and 5 patients (9%) developed asthma and rhinitis (Fig. 5).

The 56 patients enrolled in the trial were divided into two groups: those with persisting AD (24 patients) and those with improved AD (32 patients). There was a significant relationship between the outcome of AD and the age of onset of the skin lesions (Fig. 6). In the group with improved AD, 25/32 children were (78%) < 6 mo old at age of onset. However, in 12/24 children (50%) with persistent AD, the age of onset was after 6 mo ($P < 0.05$).

There was a significant relationship between the outcome of AD and the skin lesion distribution at the first examination (Fig. 7). Among the 32 children with improvement, 29 (91%) had typical skin lesions at the first examination, while 10/24 children (42%) with persistent AD had atypical or widespread skin lesions ($P < 0.005$). A significant relationship was found between the outcome of AD and the development of food tolerance (Fig. 8). In the improved group of children with positive challenge test, 95% achieved a complete or partial tolerance to the offending foods, while 50% with persistent AD did not lose the food hypersensitivity ($P < 0.005$).

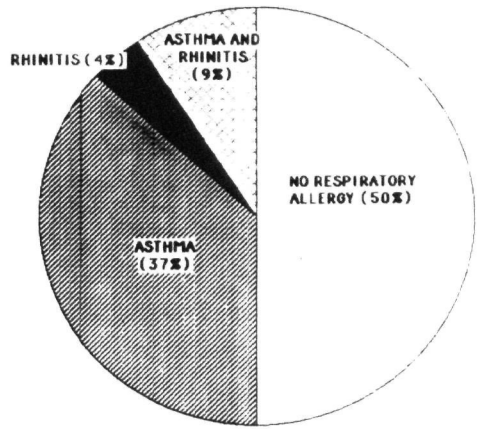


Fig. 5. Respiratory allergy prevalence in the 56 children with AD at the last follow-up (5 y).

No significant differences between the two groups were found regarding family history of atopy, sex, severity score of AD, association with respiratory allergy, total and specific IgE on SPT positivity. Among the improved children, 21% had hypersensitivity to 3 foods, while 40% of the children with persistent AD had hypersensitivity to 3 foods ($P = \text{n.s.}$).

In addition, we divided the children into two other groups: those with respiratory allergy (asthma and/or rhinitis), and those without respiratory allergy at the last follow-up. The two groups had similar median age (6.16 y and 6.25 y). There was a significant relationship between the respiratory allergy prevalence at the last follow-up and the positivity of SPT and/or IgE to inhalant allergens at the first examination (Fig. 9). Among the 18 children without respiratory allergy, 7 (39%) had positive SPT and/or RAST to inhalant allergens. However 19/26 children

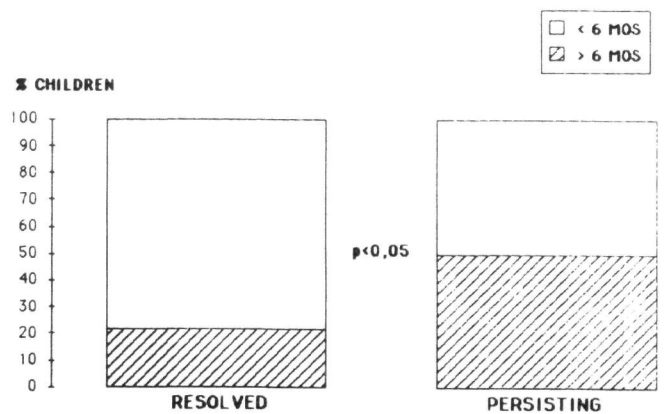


Fig. 6. Outcome of AD and age of onset of the skin lesions.

(73 %) affected with respiratory allergy at the last follow-up had positive SPT and/or RAST to inhalant allergens at the first examination ($P < 0.025$).

Tables 3 and 4 show the clinical parameters that several authors consider predictive factors regarding both persistent AD and development of respiratory allergy, and our own data.

DISCUSSION

The children of this prospective study were carefully selected. Most of them had a long history of AD. The median age of AD onset was 3 months, while the median age at the first examination was 3 years. This long course strongly indicates that the children suffered from AD with a severe outcome. This is not surprising because children with more severe diseases are referred to our clinic by paediatricians and dermatologists for further investigations.

The results of this prospective study confirm that AD is a complex disease. Although almost all the children had food hypersensitivity, as demonstrated by the elimination-provocation test and although at the last follow-up the children had a median age of 6.75 y, 43 % of them were still affected with AD. In addition, 50 % of the children developed respiratory allergy. These figures are in agreement with the data reported by others (1, 4, 5, 8-13).

Several studies have emphasized the relationship between CM formula feeding and development of atopic dermatitis (20-23). The prospective study by Queille-Roussel et al. (3) showed that CM formula feeding was an unfavorable fac-

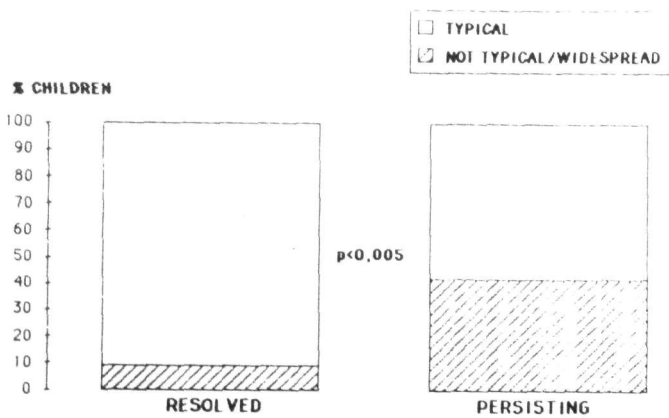


Fig. 7. Outcome of AD and skin lesion distribution.

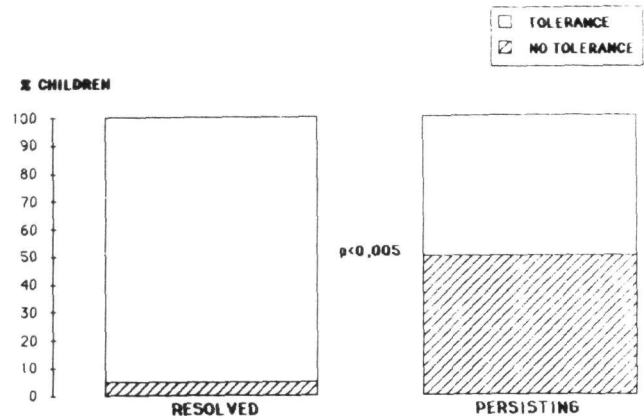


Fig. 8. Outcome of AD and development of food tolerance.

tor for the development of AD. We emphasize that 86 % of the children in the present study were first given CM formulae before the age of 6 months. Furthermore, other authors stress that food hypersensitivity plays an important role in AD (1, 19, 23-37). Total IgE levels were higher than 2 SD for age in 80 %, and 82 % had positive SPT and/or IgE to food allergens. It was reported that in 80 % of AD patients with IgE-mediated allergy it is an important contributing factor (1, 25, 38). Sampson et al. showed that such patients generally have elevated serum levels of IgE antibodies directed against the relevant foods (37), and that such reactions are accompanied by increased amounts of circulating histamine (39). Atherton (40) stresses that the role of foods may be more important in the initiation of the disease than in its continuation. Some indirect support for this view could be provided by the finding that skin test reactivity to foods is particularly promi-

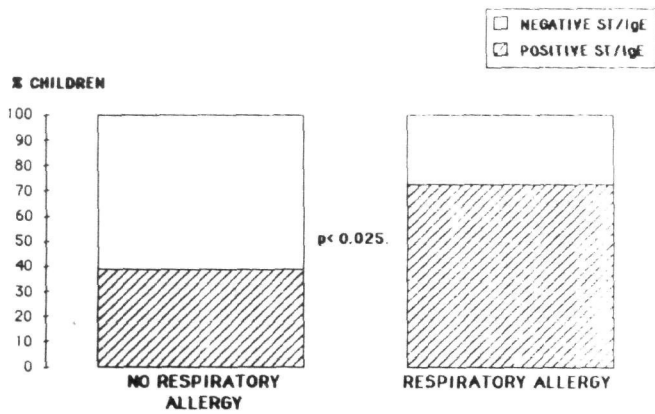


Fig. 9. SPT response and/or IgE to inhalants at the first examination and respiratory allergy prevalence at the last follow-up (5 y).

Table 3
Outcome of AD: Predictive unfavorable factors reported by the literature and personal data

Authors	Unfavorable factors	Personal data
Queille-Roussel et al.	Male	n.s.
Vickers Rystedt	Female	n.s.
Van Hecke et al. Musgrove et al. Rystedt Queille-Roussel et al.	Family history of atopy	n.s.
Rystedt	Early onset (<1 year)	n.s.
Van Hecke et al. Musgrove et al. Rystedt Queille-Roussel et al.	Respiratory allergy	n.s.
Sampson et al.	No food intolerance	n.s.
Atherton	Multisensitivity	n.s.
Vickers	Late onset (>1 year)	$P < 0.05$
Roth et al. Van Hecke et al. Musgrove et al. Vickers Rystedt Queille-Roussel et al.	Atypical or widespread skin lesions	$P < 0.005$
Not reported	Food tolerance not achieved	$P < 0.005$

nent in very young children with atopic eczema, becoming progressively less marked later (41). We would like to stress that 71% of the children had positive challenge only to 1 or 2 foods, 23% to 3 foods, and only 6% to more than 3 foods. These results again are in agreement with the study by Sampson et al. (1) which demonstrated that 80% of the children with positive food challenges reacted only to one or two antigens. It is frequently reported that children with AD are often allergic to a wide variety of foods (42, 43). The opinion is generally supported by the high number of positive SPT and RAST to foods found in children with AD. Although chil-

dren eat a wide variety of different food, CM, egg and wheat, which are the most common foods consumed in the Italian diet, accounted for more than 93% of the positive responses. These data should be taken into account to eliminate the nutritional problems of a too restrictive diet. According to Sampson et al. (1), foods frequently reported to induce hypersensitivity such as citrus fruits, chocolate, strawberries, did non elicit positive responses in our patients.

The tolerance to CM and egg was achieved at the median age of 3.5 y and 4 y, for those intolerant to 1–2 foods, respectively. The children with hypersensitivity to 3 or more foods achieved CM, egg or other food tolerance later, as already described (1, 14, 16, 44).

Of the children with improved AD and positive challenge test, 95% lost totally or partially the food hypersensitivity, while 50% of the children with persistent AD remained sensitive to the offending foods ($P < 0.005$). There was no difference in the development of food tolerance according to the age at the last follow-up. The median age of the children who lost the food hypersensitivity was 6.5 y. This was not significantly different from that of children with persistent hypersensitivity (7.16 y). These data are in agreement with those of Sampson et al. (1).

The early age of onset of AD (< 6 mo) was significantly associated with the loss of food hypersensitivity ($P < 0.05$). According to several authors, both the age of onset of AD after the age 6 mo ($P < 0.05$) (2) and atypical or widespread

Table 4
Respiratory allergy: predictive unfavorable factors reported in the literature and personal data

Authors	Unfavorable factors	Personal data
Musgrove et al.	Male	n.s.
Musgrove et al. Van Hecke et al. Queille-Roussel et al.	Severe skin lesions	n.s.
Not reported	Positive skin tests and/or IgE to inhalant allergens at the first examination	$P < 0.025$

skin lesions ($P < 0.005$) (2, 3, 8, 10–13) are of significant value in predicting the persistence of AD.

Among the various parameters assessed for predicting the development of respiratory allergy, the only one which showed a significant predictive value was the response of SPT and RAST to inhalant allergens at the first examination. Thirty-nine percent of the children without respiratory allergy at the last follow-up had positive SPT and/or IgE to inhalant allergens at the first examination, while 73% of the children with respiratory allergy had positive response ($P < 0.025$).

Enuresis, stammering and onychophagia were present in 7–4–14% of the children, respectively, while in 5% enuresis and stammering were associated. But these percentages are similar to those found in the general population of children of the same age (45–48).

CONCLUSION

Although all the children selected for this study had food hypersensitivity, 43% of them were still affected after 5 years of follow-up, despite continuous pharmacological and dietary management thus stressing that atopic dermatitis is a multifactorial disease. The physical and psychological consequences of this chronic, itching disease are



Fig. 10. Ivano at the first examination (1 year old).



Fig. 11. Ivano (3 years old).

remarkable. To underscore how atopic dermatitis may strongly affect the quality of life of the affected children and how its natural history may be unusual, we would like to present the case history of one of our patients.

CASE HISTORY

Ivano experienced severe atopic dermatitis since age 1 year (Fig. 10). Elimination-provocation tests showed that Ivano was sensitive to egg, CM and wheat. It was very difficult for him to completely avoid these foods which are common items in the Italian cuisine. Therefore, despite

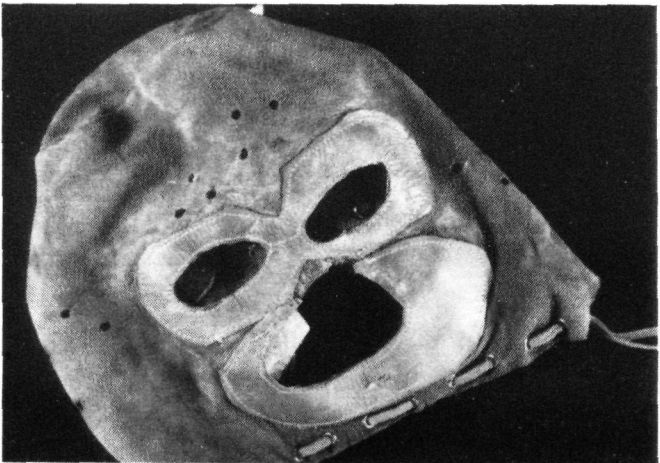


Fig. 12. Ivano's mask for playing with other children.



Fig. 13. Ivano, age 7, when AD cleared-up.

topical and systemic therapy, the skin lesions frequently relapsed (Fig. 11) and for this reason Ivano was rejected by his friends.

Then Ivano's father, a resourceful Italian craftsman, made a mask for hiding Ivano's face thus allowing his son to play with other children (Fig. 12).

However, strange enough, when Ivano was 7, the atopic dermatitis suddenly cleared-up (Fig. 13).

This moving history reminds us of the prolonged frustration and the psychological troubles suffered by both children with atopic dermatitis and the family during the long course of the disease.

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