

Early intervention for the prevention of atopic dermatitis

Hide DW. Early intervention for the prevention of atopic dermatitis.
Pediatr Allergy Immunol 1997; 8: 7–10. © Munksgaard 1997.

Based on a lecture given to the European Society for Pediatric Allergy and Clinical Immunology.

Diseases associated with atopy are increasing throughout the world. Individuals appear to have a genetic predisposition to atopy which is then provoked by environmental influences. Ingested or inhaled allergens provoke an antibody response and a state of sensitization. In many but not all sensitized individuals subsequent exposure to allergen will provoke a release of histamine and other mediators from sensitized mast cells and produce clinical signs of an allergic reaction in the target organ or throughout the body. At the present time one approach to the prevention or reduction of such reactions appears to be the identification of the high-risk infant and then preventing or limiting exposure to the potentially allergenic protein materials in the child's diet or immediate environment.

This paper outlines the problems of identifying high-risk infants and comments on the success claimed in the intervention studies that have been undertaken. The possible hazards to mothers and infants of dietary exclusion are emphasized and the provision of appropriate medical and dietetic support are regarded as of paramount importance. Although more studies are needed, the Isle of Wight intervention programme offers hope to families at high-risk of atopy that the problem can be reduced for the next generation.

D.W. Hidet

Director, Asthma and Allergy Research Centre,
St Mary's Hospital NHS Trust, Newport,
Isle of Wight, United Kingdom

David W. Hide, Director, Asthma and Allergy
Research Centre, St Mary's Hospital NHS Trust,
Newport, Isle of Wight, PO30 5TG,
United Kingdom.

†We very much regret that Dr. David Hide died
during the preparation of this research paper for
publication.

Key words: aero-allergy; allergy prevention; atopy;
food allergy

Received November 11, 1996
Accepted January 10, 1997

For at least 60 years a view has been held with varying degrees of conviction that it may be possible to influence the expression of some forms of atopic disease by reducing the exposure of the infant, or perhaps even the foetus, to potentially antigenic material. Initially this exposure has been exclusively to food considered allergenic. More recently early aero-allergen exposure has been implicated and attention directed towards possible means of limiting this.

It is perhaps salutary to recognise that in spite of this area of investigation attracting considerable attention few would claim that it has yet been established beyond doubt that allergic disease can be prevented. In this paper some of the difficulties in providing such proof will be identified but it will be argued that there is now evidence to validate an approach to the prevention of atopic disease by allergen avoidance in infancy.

The often-quoted paper of Grulee and Sandford (1), which purported to show a difference of 7 times in the frequency in which atopic dermatitis (AD) occurred in the formula-fed compared with breast-fed infants was the first to claim that breast feeding sub-

stantially reduced the risk of atopic dermatitis. That message remains widely believed to this day although large population studies have not been able to confirm such a protective effect. Indeed some have actually shown more atopic dermatitis among the children of breast-feeding mothers. The explanation is that there is doubt about the validity of the diagnosis of AD in many of the instances and, more importantly, the population of breast feeding mothers differs in many respects from the population which chooses to formula feed. None of the confounding factors, of which the socio-economic are the most important, were taken into account and they have been ignored in many of the subsequent studies which supposedly compare the outcome of breast v bottle feeding. The truth is that it is not possible to compare the two feeding methods in the precise way that a drug trial of two forms of therapy would be undertaken. There cannot be a random allocation to breast or bottle, and obviously there can be no blinding of method.

Another major difficulty has been identifying infants at high risk of AD and other atopic disorders. Although hopes have been raised that the gene

carrying the predisposition to atopy had been identified (2) such optimism appears premature with other laboratories generally failing to confirm the Oxford work (3).

Clearly the family history is important and Zeiger states that the family history will give a 40% sensitivity and 80% specificity for predicting atopic disease later in childhood (4). We had hoped that there would be some serological method for identifying the high-risk newborn and for some years the measurement of IgE in cord blood seemed to fulfill that role. Unfortunately we and others (5, 6) concluded that cord IgE was inferior to knowledge of the family history as a predictor of atopic disease in later childhood (specificity 92% at one year, sensitivity 8.5%; specificity 90% at two years, sensitivity 12%). There is hope that current research into levels of interferon-gamma (IFN- γ) measured in cord blood mononuclear cells may provide a predictive test for risk of atopy as IFN- γ is reduced in high-risk families (7, 8).

This and other work that has suggested there is some inter-uterine programming of the high-risk foetus has questioned the assumption of an optimum time in the neonatal period for any intervention measures. This has been regarded as a 'window of immunological immaturity' when the neonate was supposedly at his or her most vulnerable to sensitisation.

The rationale for this belief has been that although the foetus is known to produce endogenous IgE from the end of the first trimester it has not usually been possible to identify specific IgE in cord blood. Although studies to try and limit any possible foetal exposure to food antigens have been few and limited to the third trimester of pregnancy only one study has suggested that this approach reduced AD in high risk infants (9). The study by Faith-Magnusson et al. (11), with a five year follow-up, failed to show any reduction in atopy, or level of IgE or number of positive skin prick tests, in children whose mothers had restricted their diet of the more antigenic foods, compared with a control group. Nevertheless recent suggestions that there may be significant intra-uterine programming have reopened this debate. Possibly efforts to date have not taken the intra-uterine dietary restriction back far enough into the gestation of the infant. It could even be appropriate to start an intervention programme before conception, but this has not been established and the potential hazards of subjecting both mother and foetus to an inadequate diet are too serious to contemplate until there is more evidence to support this approach.

At present the working hypothesis is that the new-born infant has not been exposed to food or aero-allergen *in utero* to the extent that would pro-

duce a significant specific IgE response. If these children then are followed through infancy and early childhood there is a steady rise in total IgE. Moreover many will develop specific IgE, demonstrable by skin prick testing or Radio-allergosorbent test (RAST). In the first months these will usually be to ingested allergens, milk, egg, etc. but from one year onwards the numbers showing overt sensitisation to aero-allergens will increase steadily. Thus an allergen avoidance programme which concentrates on the early months of extra-uterine life might prevent or limit such sensitisation and the consequent development of atopic disease. This has been termed prevention of primary sensitisation and the results of such intervention have been reported by several workers in Europe and North America. The studies have varied in detail and most can be criticised in some respect. The allocation to mode of feeding, as has been stated, is impossible to randomise – other than in the exceptional series reported by Lucas et al. of extremely premature infants who could be allocated to breast milk or formula (13). However, some of the other studies apparently did not randomise their infants to intervention or control groups – thus allowing confounding factors into the equation.

Ideally the follow-up of the infants should be carried out with the recording paediatrician blind as to whether the child was in the active or control group. There is also some difficulty in ascertaining the diagnosis of atopic disease in the several studies as they have varied diagnostic criteria and often there is no attempt to confirm the atopic status by skin prick testing or measuring specific levels of IgE. These caveats having been made it has to be said that such studies are extremely difficult to undertake. They require a high level of commitment by the participating families, and very close supervision by the investigators and supporting staff.

The studies have attempted to identify pregnancies at high-risk of producing an atopic infant. The intervention group has then been subjected to some dietary manipulation. In three studies the maternal diet was first restricted in the later months of pregnancy and foods were then controlled for the lactating mother. In the others the prophylactic programme commenced at birth. If the infant was to be breast fed maternal diet usually avoided the potentially antigenic foods, such as dairy products, eggs, nuts and fish and weaning was delayed. Alternatively the infants were given a so-called hypo-allergenic formula which was one of a number of either partially or extensively hydrolysates. All these studies have recently been reviewed in some detail by Zeiger (4). In spite of the different methodologies some general conclusions can be drawn from the studies to date. Apart from Chandra's work, the evi-

Table 1. Allergy in children in intervention ($n=58$) and control groups ($n=62$)

	One Year		(percentage) Two Years		Four Years	
	I	C	I	C	I	C
Intervention/Control						
Total allergy	13.8	40.3	29.3	58.0	32.6	54.8
Def. allergy (symptoms + SPT)	3.5	9.7	5.2	25.8	8.6	30.6
Asthma	6.9	19.4	15.5	27.4	24.1	35.5
Atopic dermatitis	6.9	19.4	13.8	24.2	13.8	24.2
Allergic rhinitis	-	-	4.2	11.3	10.3	17.7
Food intolerance	3.5	11.3	12.1	17.7	5.2	11.3
Positive skin prick test	3.5	9.7	5.2	25.8	13.8	33.9

dence suggests that dietary intervention which starts at the 28th week is ineffective in preventing atopic disease. This implies either that significant sensitisation does not occur during the third trimester - or that intervention needs to be started earlier in pregnancy.

The studies have been more successful in showing a reduction in AD using both partial and extensively hydrolysed formulas or breast feeding with maternal diet restricted. A reduction in cows' milk allergy (CMA) / intolerance has also been observed but there has been no recorded improvement in respiratory manifestations of atopy, specifically asthma. Zeiger draws attention to a convergence of prevalence rates between the intervention and control children as they are followed later in to childhood (12). However, there is little doubt that AD and also probably CMA are reduced in infancy when they can give rise to great distress to child and family. The long-term results of many of these investigations are awaited but Mallet and Henocq have demonstrated reduced AD at 4 years of age (15).

Knowledge of some of these studies, and an increasing conviction of the major sensitising role of the house-dust mite, *Dermatophagoides pteronyssinus* encouraged us to extend the intervention programme to include environmental measures. Population studies on the Isle of Wight had demonstrated that the dust mite was the aero-allergen of greatest consequence for our atopic patients. Ideally one would prevent exposure to grass pollen, furry animals, passive smoking and other related factors but this was impractical within the context of a prospective, controlled study. Thus a high-risk population was identified which was randomly allocated to a prophylactic or intervention and a control group. The intervention group followed a dietary and environmental programme. The control group were fed normally by breast or bottle and no environmental modifications were recommended.

The results of the Isle of Wight study at one and two years have been reported (14, 15) and the four year figures are now available (16).

In summary, high-risk families were enrolled before the birth of their next infant and allocated to intervention or control groups. High-risk implied two first degree relatives with atopy, either both parents or one parent and a sibling, or one parent and a high level of cord IgE. In all 136 mothers and infants fulfilled the criteria and entered the study. For various reasons 16 dropped out in the early weeks - leaving 120 - 58 intervention infants and 62 in the control group. All have been seen at 1, 2 and 4 years with no further withdrawals.

The intervention group of infants was either breast-fed with mother avoiding dairy products, eggs, fish and nuts and supplementing feeds if necessary with soya-based protein hydrolysate (Aptamil HA, Milupa UK). If the child was to be formula fed he/she received Aptamil HA from birth. The commonly antigenic foods were not introduced into the infant's diet until 9 months - and then in a controlled manner. Close dietetic supervision was maintained and lactating mothers received vitamin and calcium supplements.

Infants in the control group were fed by breast or standard cows' milk formula with conventional weaning advice.

Both groups of infants slept on polyvinyl-covered mattresses but the bed-room and living room carpets and upholstered furniture in the homes of intervention infants were treated on four occasions with an acaricide, Acarosan, (Crawford Chemicals, UK). Dust samples were analysed for *Der p 1* before and three monthly during treatment in the intervention homes and at 0 and 9 months in the control homes.

Table 2. Control v intervention groups at four years-regression analysis. Odds ratios (95% confidence limits)

$n=120$	
Total allergy	2.7 (1.2-6.1)**
Definite allergy	5.6 (1.8-17.9)***
Positive skin prick test	3.7 (1.3-10.0)
Atopic dermatitis	3.4 (1.2-10.1)*

* $p < 0.05$, ** $p < 0.02$, *** $p < 0.005$.

Apart from the supervision of the dietitian both groups were monitored by the research nurse and research fellow. At the 1, 2 and 4 years assessment the children were seen by a consultant paediatric allergist unaware of whether the children had been in intervention or control groups.

The results are summarised (Table 1). The data was examined by logistic regression analysis to allow for confounding factors. At 12 months there was significantly more total allergy, asthma and atopic dermatitis in the control group. By two years, and again at four, there was significantly more total and definite allergy (symptoms plus positive skin test), and atopic dermatitis. The disadvantage to the control group identified by the regression analysis at four years is summarised (Table 2).

Of particular interest was the substantial difference in the number of children sensitised in the two groups as shown by skin prick testing. All children were examined with a battery of the common food and aero-allergens and eight children in the intervention group showed a total of 12 positive tests. In the control group 21 children showed 50 positive tests. The number of positive SPTs to all the aeroallergens tested as well as to the food battery was less in the intervention group but the difference in number of children sensitised to the house-dust mite was particularly impressive (3 vs. 15).

Thus it seems that it is possible to reduce atopic disease and sensitisation in early childhood. So far dietary manipulation appears to reduce AD. If environmental measures are added to the intervention programme, and these include an anti-dust mite programme if the mite is a relevant sensitizer in that population, and exposure to furry animals and passive smoking is topped, then there should be a reduction in respiratory tract allergy as well as aeroallergen sensitisation in patients with AD.

It is our hope that others will investigate this dual approach to allergen avoidance. The persisting benefit of the programme encourages us to advocate closely supervised management along these lines when advising high-risk families and their physicians on possible intervention measures.

References

- GRULEE CG, SANFORD HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 1936; 9: 223-5.
- HOPKIN JM. Genetics of atopy. *Pediatr Allergy Immunol* 1995; 6: 139-44.
- LYMPANY P, WELSH KI, COCHRANE GM, KEMENY DM, LEE TH. Genetic analysis of the linkage between the chromosome 11q and atopy. *Clin Exp Allergy* 1992; 22: 1085-92.
- ZEIGER RS. Secondary prevention of allergic disease: an adjunct to primary prevention. *Pediatr Allergy Immunol* 1995; 6: 127-38.
- HIDE DW, ARSHAD SH, TWISELTON R, STEVENS M. Cord serum IgE: an insensitive method for prediction of atopy. *Clin Exp Allergy* 1991; 21: 739-43.
- RUIZ RCG, RICHARDS D, KEMENY DM, PRICE JF. Neonatal IgE: a poor screen for atopic disease. *Clin Exp Allergy* 1991; 21: 467-72.
- WARNER JA, MILES EA, JONES AC, QUINT DJ, COLWELL BM, WARNER JO. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; 24: 423-30.
- TANG MLK, KEMP AS, THORBURN J, HILL DJ. Reduced interferon gamma secretion in neonates is associated with the subsequent development of atopy. *Lancet* 1994; 344: 983-5.
- CHANDRA RK, PURI S, SURAIYA C, CHEEMA PS. Influence of maternal food antigen avoidance during pregnancy and lactation on the incidence of atopic eczema in infants. *Clin Allergy* 1986; 16: 563-71.
- ODELRAM H, BJÖRKSTEN B, LEANDER E, KJELLMAN N-IM. Predictors of atopy in newborn babies. *Allergy* 1995; 50: 585-92.
- FAITH-MAGNUSSON K, KJELLMAN N-IM. Allergy prevention by maternal elimination diet during pregnancy - a 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992; 89: 709-13.
- ARSHAD SH, STEVENS M, HIDE DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23: 504-11.
- LUCAS A, BROOK OG, MORLEY R, COLE TJ, BAMFORD MF. Early diet of pre-term infants and development of allergic or atopic disease: randomized prospective study. *BMJ* 1990; 300: 837-40.
- ZEIGER RS. Dietary manipulations in infants and their mothers and the natural course of atopic disease. *Pediatr Allergy Immunol* 1994; 5(Suppl 1): 33-43.
- MALLET E, HENOCQ A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. *J Pediatr* 1992; 121: S95-100.
- HAKIM EA, HIDE DW, MATTHEWS S, et al. Prevalence of atopic disease and sensitisation to common allergens at the age of four years (Abstract). *Clin Exp Allergy* 1994; 24: 986.
- ARSHAD SH, MATTHEWS S, GANT C, HIDE DW. Effect of allergen avoidance on development of allergic disorders in infancy. 1992; 339: 1493-7.
- HIDE DW, MATTHEWS S, MATTHEWS L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994; 93: 842-6.
- HIDE DW, MATTHEWS S, TARIQ S, ARSHAD SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996; 21: 89-93.