

Prediction and Prevention of Atopic Allergy

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It is now generally accepted that atopic allergy has a multifactorial etiology and that atopic sensitization ensues from contact between a genetically predisposed subject and an allergen. Obviously, there are great differences in the genetic predisposition (1, 3, 14, 26). Sensitization may take weeks or years: the sensitization time is the product of genetic factors, allergenicity, dosis and time of exposure. Different adjuvants, including infections, may well play an important role in humans as well as in animals (23, 44, 92). With extreme exposure probably everyone may become sensitized and produce antibodies of the IgE class (76). As external factors are important for sensitization, hope arises that atopic disease may be prevented by avoiding different allergens or adjuvants.

With an apparently increasing incidence of atopic disease in industrialized communities (71), during the last decades, interest has been focused on methods for prediction and prevention of atopic disease before sensitization has occurred or any symptom of the sensitization has developed (15, 29). Screening programmes have been discussed and heavy preventive measures have been instituted in infants and/or nursing or even pregnant mothers – not without risks. Published results are difficult to interpret as different groups and regimens have been investigated (81); most studies were not blinded. The purpose of the present review is to scrutinize such results and to allow for a discussion on this important field of medicine.

Fundamentally, *prediction* of atopic symptoms in apparently healthy subjects may be performed using the same methods as for establishing such a diagnosis (Fig. 1) as elaborated below:

1. Family history of atopic disease – immediate and/or remote,
2. case history – unspecific symptoms indicating a high risk for atopic allergy,
3. clinical findings – unspecific indicators of a possible atopic constitution,
4. eosinophils in blood – high in allergy as well as in certain infections,
5. total serum IgE-concentrations – high in allergy, parasitosis and certain other infections,
6. specific IgE antibodies against common allergens in blood, skin or mucous membranes – may be detected in the pre-symptomatic stage, and

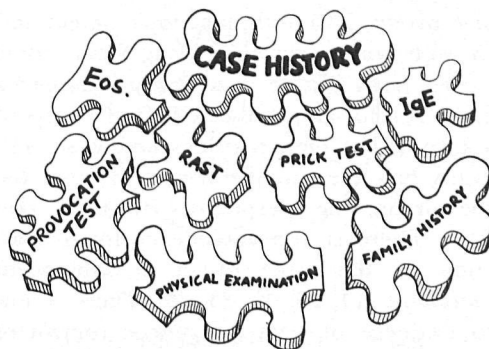


Fig. 1. Diagnostic and predictive methods.

7. number of circulating T cells and markers for T suppressor cells – low in atopic diseases.

Prediction by family history

It has been known for centuries that asthma tends to run in families. A genetic relationship exists between asthma and hay fever, vasomotor rhinitis and atopic eczema (1, 26, 83). In cases of atopic disease, a high incidence of a positive immediate family history is found (50–70%) although not significantly higher than in children without atopic disease (49). The symptoms of atopic disease begin at an earlier age when both parents rather than only one of them suffer from atopic disease; children with a family history develop their atopic symptoms at a lower age compared to children without such a family history (95). Data from twin studies indicate a genetic influence also on the severity of atopy as measured by the number of organs affected (14); later results support these findings (49); a combination of atopic diseases in a parent increased the incidence in the children from 18 to 38% (50). Some degree of an atopic family history (immediate or remote) was found in 58% of newborn infants in Sweden (Croner & Kjellman, to be published) indicating that genetic markers for atopy are very common. Evidence supports a polygenic transmission rather than dominant with failing penetrance; a higher incidence of atopic disease has been found with higher number of close relatives with such disease (45, 49, 83). The incidence in 7-year-old-children (49) was about 10% with no atopic parent, 20% with one atopic parent and 42% with both parents suffering from atopic diseases. Such disease in a sibling indicated a further risk for atopic disease before 7 years of age (30%). The highest risk existed when both parents had their atopic symptoms from the same organ, e.g. respiratory tract or skin (72%). There is also a tendency towards affection of the same organ in subsequent generations (14, 26, 49, 83, 85). There is now also evidence of separate genetic control of total IgE, specific IgE and tissue hyperreactivity (65, 85). The expression of the disease is thus

determined by several genetic factors. Furthermore, different predisposing factors, partially submitted to genetic influences, have been identified (86).

Prediction by case history and clinical findings

Ascertainment is a major problem in allergology as practically every symptom or sign of atopic disease may be seen in non-atopic subjects. Wheezy bronchitis is common, especially in infancy. With *recurrent episodes of bronchitis* there is a higher likelihood of developing asthma (22), higher when there is allergy in the family or coexisting eczema in the infant; nine of 53 (17%) first-time-wheezers were later classified as suffering from bronchial asthma as compared to 10 of 28 (36%) with recurrent wheezing. Laboratory tests such as total IgE and/or blood eosinophils were helpful to find cases with subsequent asthma (see below).

Croup is another common disease in early childhood, precipitated by viral infections. In children with *multiple episodes of croup* a highly significant correlation to allergy was found by Zach et al. (97): allergy was found in 33 of 57 such cases 9 years after hospitalisation for recurrent croup as compared to seven of 53 cases where croup occurred only once. Furthermore, airways hyperreactivity was associated with recurrent croup. Cases with recurrent croup were distinguished from those with one episode by onset at a younger age and familial predisposition. A similar association between recurrent croup and allergy was recently described (55).

Colics in early infancy are often caused by food, sometimes even by maternal food residuals in breast milk (38). Twenty-three of 66 infants on human milk were proven not to tolerate when the mother ingested cow's milk (39). These milk intolerant infants had a higher incidence of a family history of atopic disease (12/23) than the remaining infants suffering from colics (10/43), indeed as high as in atopic diseases. Thus, infantile colics with proven food intolerance seem to be associated with the atopic constitution.

Many signs of an atopic constitution may be found at the clinical examination of a child suffering from atopic disease (64). Such signs are allergic "shiners", skin folds on the lower eyelid and follicular hyperkeratosis. They are helpful when establishing a diagnosis but they seem to be rare in the absence of more specific atopic symptoms and signs. Thus, their usefulness in the prediction of atopic allergy seems to be limited.

Prediction by eosinophilia

Blood eosinophilia ($> 400/\text{mm}^3$) at wheezy bronchitis has been found to predict 12 of 16 (75%) subsequent cases of bronchial asthma and/or other atopic symptoms (22); however, five of 27 (19%) children classified as healthy later on also had eosinophilia.

Blood eosinophilia was also found in 33 of 132 (25%) children undergoing adenoidectomy for recurrent episodes of otitis (51); eosinophilia, high serum IgE and/or positive skin tests were found in 13 of 19 (68%) children who later on developed specific symptoms of atopic allergy. Recently, Dry et al. (13) demonstrated cord blood eosinophilia of significant degree in offspring of atopic parents but they have not yet produced evidence of its predictive value. The level of blood eosinophils is easily influenced by other factors such as infection and pharmacotherapy; for the time being, the analysis of blood eosinophils does not seem to be particularly useful for predictive purposes.

Prediction by high serum IgE concentrations

IgE may be produced from the 11th week of gestation (70). IgE and IgE antibodies do not usually seem to cross the placental barrier (5, 40, 48, 60, 87). In the absence of parasitic disease, a high serum IgE concentration in a child usually indicates atopic disease. The majority of children, in a general population, suffering from atopic disease show high serum IgE levels (50). The production of IgE is submitted to genetic control in humans as well as in rats (4, 24, 65, 84, 96). In 1974, Foucard et

al. (22) showed that the risk for subsequent bronchial asthma or other atopic symptoms was significantly higher with high serum IgE levels in children suffering from first time "wheezy bronchitis". Hamburger and his group (73) found different patterns of development for serum IgE concentrations during infancy: in most infants these levels remained rather unchanged whilst a considerable increase occurred in some of the children who were found to develop atopic disease during the first 2 years of life. In a recent study by the same group (35), data have been interpreted to indicate that regulation of IgE is under the control of at least two unlinked genetic loci; serum IgE determination was recommended for the prediction of atopic allergy.

In a Swedish study (47) of 206 apparently healthy infants and children without an individual history of atopic disease, a more than tenfold increase (47% as compared to 3%) of subsequent atopic disease was found if the IgE level exceeded the geom. mean $+1$ SD limit in healthy subjects of the same age; symptoms developed within 18 months (mean: about 6 months) after the sampling. Extended studies in a total of 426 children of all ages (48, 50) showed that the development of atopic disease was preceded by a high serum IgE concentration in 28 of 40 (70%) children.

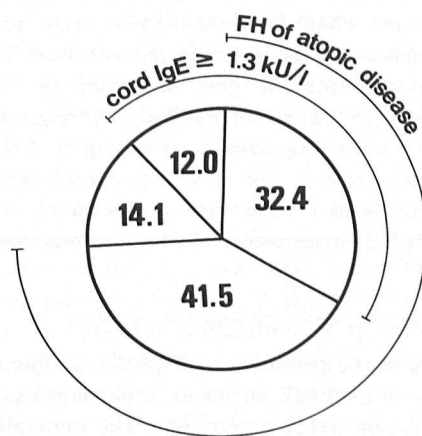


Fig. 2. Children with atopic disease before 18 months of age, identified by means of family history and cord blood IgE determination.

Table 1

WHO (1975): Prerequisites for screening

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1. Low level of risk and discomfort
 2. Few false positive and false negative
 3. Effective early treatment/prevention
 4. Sufficient medical facilities
 5. Reasonable cost/benefit
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Michel et al. (69) found detectable cord blood IgE concentrations in six of eight cases of subsequently obvious atopic disease and in 10 of 17 infants with possible such disease; in contrast, only 20 of 85 infants without such symptoms had detectable IgE at birth. Combined information on the cord blood IgE concentration and the family history was recommended for screening purposes.

In a series of 1701 newborn infants, high serum IgE concentrations (≥ 1.3 kU/l) in cord blood were followed by atopic symptoms before 1½ years of age in 70% (54) and before 4½ years of age in 82% (11). The combined effect of the family history and the cord blood IgE is presented in Fig. 2: 86% of infants with symptoms of atopic disease before 1½ years of age were identified by high IgE and/or a family history already at birth.

Studies by Dannaeus et al. (12) and by Businco et al. (63) have confirmed the predictive value of high serum IgE concentrations in newborn infants. However, it still remains to be proven whether a majority of significant atopic diseases may be predicted and hopefully prevented before a general screening programme can be recommended. Prerequisites for such screening have been set up by WHO (94); see Table 1. For special purposes before heavy preventive measures are instituted, cord blood IgE determination may be recommended.

Prediction by specific IgE antibodies in blood

Control of the production of specific antibodies, but not of total IgE, seems to be partially associated with the HLA system (65). The radio allergosorbent test (RAST) allows the determination of low concentrations of circulating antibodies. Such antibodies indicate that sensitization has

taken place. The clinical evaluation should be: specific atopic allergy at present, in the past (especially with antibodies against food antigens) or in the future; such antibodies may probably also be found in patients never suffering from allergic symptoms (21): a positive RAST test was found in 12 of 27 (44%) wheezing infants with a subsequent diagnosis of bronchial asthma or other allergy but in only one of 35 (3%) children classified as healthy at the follow-up. IgE antibodies against pollen are occasionally found 2 years before symptoms of allergic rhinitis appear (Kjellman, unpublished): seven of 13 new cases of hay fever had specific IgE antibodies already during the preceding autumn. However, these seven and another two cases were also found to have high levels of total IgE. Hence, total IgE determination should be preferred for the purpose of prediction.

Prediction by specific IgE antibodies in skin and/or mucous membranes

If properly performed, with good extracts and great skill, skin tests, preferably performed as prick tests, offer great advantage in the etiological diagnosis of allergy. However, there is a high incidence of positive skin tests also in subjects without symptoms of allergy. Among relatives of asthmatics, 40% have been found to show positive skin tests (83). Seventeen per cent of adolescents in Finland without a history of atopic disease were skin test positive (31). In a number of such cases, the individual has probably been skin tested in a presymptomatic stage; such a statement is supported by several findings: Foucard (21), investigating infants suffering from bronchitis, found one or more positive skin tests in five of 19 subsequent asthmatics and in two of 35 children classified as healthy at follow-up. Chambers & Glaser (9) followed 68 allergic subjects with a positive ragweed pollen test but no overt pollinosis: 53% of them developed ragweed pollinosis, mostly within 10 years after the test; the highest incidence was found in patients under 16 years of age at the skin testing (63%). Hagy & Settupane (32), when studying 614 college students, found a ten times higher incidence of

new hay fever (18%) in students with a positive pollen skin test but without a history of allergy as compared to students with a negative test (1.7%).

A positive skin or RAST test seems to be able to give double information from a predictive aspect: 1) the subject has a *general* tendency for acquiring sensitization, and 2) *specific* sensitization against a given allergen is under progress in the subject. Such information should of course be used in order to prevent further sensitization. However, skin testing does not seem suitable for general screening.

A positive provocation test, mostly with a rather low degree of sensitivity, is rather often found in allergic subjects in the absence of overt symptoms during exposure to that particular allergen. It is probable that the finding in a number of such patients indicates a risk of subsequently overt allergy but we seem to lack information on this subject.

Prediction of atopic disease by T cell determination

Juto (42) demonstrated that a low number of circulating T cells (< 40%) at 1 month of age was followed by clinical symptoms indicative of atopic disease significantly more often than a normal number of T cells. Furthermore, infants with low T cells who were fed cow's milk developed higher serum IgE concentrations than breast-fed children (43). However, T cell determinations are too laborious and expensive to be useful for screening purposes.

In conclusion, there are several ways to achieve predictive information concerning atopic allergy. Of these, a carefully taken family history, although submitted to several sources of error, allows a rather precise prediction as to the general risk for development of atopic disease as well as the type of subsequent disease and even the offending allergen(s). The individual history is of predominant importance. Of *in vivo* and *in vitro* tests, the serum IgE determination with a test suitable for low concentrations, such as the Phadebas IgE PRIST® or Phadezym IgE PRIST®, may be added under certain conditions but is not yet recommended for general

screening purposes. Before such a recommendation should be given it remains to be proven that a majority of severe atopic diseases may be predicted, e.g. by cord blood analysis. Furthermore, there must be general agreement as to preventive measures in children at risk of developing atopic disease. A review of possible ways for prevention will follow.

Basic mechanisms in atopic sensitization

Knowledge about fundamentals of atopic sensitization is necessary in order to be able to institute preventive measures. The mechanisms are yet only partially understood, but there is some evidence that in man, as in mice, there are "high responders" and "low responders" regarding production of IgE (35, 65).

Genetic factors seem to be of the utmost importance for the development of atopic disease. Extended insight into these factors should be of great value for genetic counselling; in my opinion, parents of severely affected children as well as adolescents who have suffered from severe atopic disease – e.g. multifocal atopic disease of early onset, bronchial asthma with reduced psycho-social function or severe itching eczema disturbing the nights' sleep – should have the right to be informed about genetic factors. As always, such information must be given carefully, with a permissive and positive attitude, leaving full choice to the individual; it should also include a summary of present experience of preventive measures during pregnancy, neonatal period and early infancy (see below).

Time of birth. Björkstén & Suoniemi (6) found in males, but not in females, a significant difference in the month-of-birth distribution between patients allergic to pollen (and epithelia) and the general population of Finland; increased numbers of allergic subjects were born in March-May and September-November. Robert & Carron (77) found, among 667 children suffering from grass pollen allergy in southern France, that one out of three children below 6 years of age at the investigation were

born in April and May – a significantly higher incidence in comparison with local births in general. Similarly, Morrison Smith & Springett (72) found evidence of a higher proportion of children with asthma (total number: 1715) born between May and October than would be expected. Children with a positive skin test reaction to mites (*Dermatophagoides pteronyssinus*) were overrepresented among those born in the period May–October. Finally, Kemp (46) found a significantly increased incidence of grass pollen sensitivity by skin test in children reaching the age of 3 months during the time of exposure to grass pollen. Björkstén et al., in a second study (7), estimated that elimination of early birch pollen contacts could have reduced the prevalence of birch pollen allergy by 28% in subjects 0–19 years of age.

All these results point to a connection between the time of birth and early exposure and they may be explained by the existence of an especially sensitive period at about 0–3 months of age. These findings tally with reports on different types of immune deficiency in infants with the atopic constitution (42, 66, 86); the study of human T suppressor function promises to be the most rewarding (44).

As a result of these findings, it may be adequate to inform a highly selected group of families with severe atopic disease including pollen sensitivity of the higher risk for allergy in children born during the period preceding the peak pollen exposition by 1–3 months.

Prenatal factors such as infections and maternal food or drug intake have been discussed as causes of allergic diseases in infancy. IgE levels were higher in cord blood if the mothers had been treated with progesterone but there was no increase in the development of atopic disease in these particular infants (68). There are astonishingly few reports on sensitization of newborns (45, 61, 62, 68), and in some of these, passive transfer is more probable than active sensitization. Many reports show that there is usually no crossing of the placenta to the foetus by maternal antibodies of the IgE class (3, 5, 40, 47). Prenatal infections could be important but neonatal IgM levels were not associated with

subsequent atopic disease (68). Many programmes include that the mother has to keep a diet during pregnancy, thereby avoiding foods which have given herself allergic symptoms – which seems reasonable. However, we are still lacking such information which would justify a general hypoallergenic food regimen during pregnancy.

Tobacco smoke seems to constitute a risk factor for atopic sensitization: Wittig et al. (95) found a significant influence on the age of onset of asthma and/or allergic rhinitis in 2190 patients; the symptoms started earlier if there was smoking in the family (mean 5.3 year) than in households without exposure to tobacco (mean 6.5 years). Furthermore, children exposed to smoke had more skin test reactions to pollen and lactalbumin.

These findings tally with recent reports on the effect of direct or indirect exposure to tobacco smoke on the serum IgE concentration: smokers showed higher IgE levels and a higher incidence of positive skin tests and/or positive RAST towards occupational allergen (98) and infants of smoking atopic parents developed higher serum IgE levels (53). It may be speculated, whether the effect is by damage to the airways mucosa, thus promoting penetration, or by direct influence on the immune system. All the same, a non-smoking environment should be advised especially for infants and young children at risk to develop atopic disease.

Environmental factors other than tobacco smoke were also found (95) to influence the age of onset of respiratory symptoms: children brought up in rural districts got their symptoms at an earlier age (3.8 years) than children in cities (6.5 years). Suoniemi et al. (89) showed that exposition to allergens, such as pollens and cat epithelium, during the first 6 months of life was a major risk factor for the development of positive skin tests and allergic disease in teenagers. Recommendations in many preventive programmes include an environment free from pets, and measures to diminish exposure to

animal products, mites and moulds (29) and such measures seem justified.

Infections during the first year of life requiring treatment by a physician are oftener reported in allergic than in non-allergic teenagers (89). Upper respiratory infections are frequently found to precede the first symptom of atopic sensitization but this could happen by mere coincidence due to the fact that such infections are so common, especially in this age period. However, Frick (23) found an association between the development of allergic disease and specified viral infections, such as RS virus and CMV. Increased levels of total IgE have been shown in certain infections, especially when B cells are affected as in mononucleosis (23). Recently, RS virus-specific IgE antibodies have been found (93) in the majority of 60 patients with wheezing but in only one of 19 patients suffering from RS virus infection without wheezing, indicating IgE-induction by the RS virus in genetically predisposed subjects. Endotoxins from *E. coli*, in bottle fed infants, are supposed to act in similar way (25). Exclusive breast feeding reduces hospital admissions for infections (17) and seems to protect against gastrointestinal infections (18) and colonisation with *E. coli* (25) as well as against RS virus infections (75) and should be recommended for these and other reasons (see below).

Early feeding seems to be of great importance: e.g. symptoms of bronchial asthma were found at an earlier age in children with a short period of breast feeding (58, 95). Eczema occurred more often in bottle fed infants (30). As expected there are also contradictory results (59).

Infants seem especially vulnerable to sensitization during the first week(s): children with allergy towards cow's milk had been exposed to such milk significantly more often (16 of 25) than a control group (19 of 47) without allergy (88). In human beings as well as in animals, there is an increased absorption of macromolecules through the intestine (90). Macromolecules are also absorbed later on, as a natural phenomenon. Maternal antibodies in the breast milk may give some protection against this absorp-

tion (36) before the maturation of the intestine and secretory immunoglobulin system is completed.

Late introduction of cow's milk (= prolonged breast feeding) was found to achieve lower antibody levels against whey proteins (57). Infants fed a casein hydrolysate for the first 3 months had lower hemagglutinin levels to subsequent milk or soy proteins than infants given these formulas since birth (16). However, feeding soy products during the first 4 months and then a cow's milk formula did not prevent the normal high peak of cow's milk antibodies obtained when starting on cow's milk from birth; the antibody levels had no obvious clinical correlation (67). A guinea pig model for determination of the sensitizing capacity of different food stuffs (McLaughlan 1981, personal communication) showed the superiority of a casein hydrolysate (Pregestimil®) to different cow's milk and soy preparations.

Clinical trials

The immunological advantages of human breast milk have been witnessed in many papers (56, 74, 75) and most described programmes for allergy prevention include recommendations on exclusive breast feeding for different time periods together with several other measures. Glaser & Johnstone (28) supplemented with a soy formula and withheld wheat, cow's milk and egg. The study group developed major allergic symptoms less often (15%) than a retrospective group of siblings (64%). In a second study, Johnstone & Dutton (41) included a control group of infants put on cow's milk already in the maternity ward; in the study group, advice was given against pets and dust. During the follow-up period of 13 years, 18% of the study group but 50% of the controls developed asthma; also the incidence of perennial (but not seasonal) rhinitis was reduced in the group on the diet.

Brown et al. (8) and Halpern et al. (33) could not find a significant decrease when giving soy instead of cow's milk nor was there definite evidence on the protective effect of human milk; however, symptoms started at an earlier

age in children on cow's milk (33). Furthermore, cow's milk allergy was more often found in children fed cow's milk (1.8%) than soy allergy when the children had been fed a soy formula (0.5%). Also others have failed to find a protection from the use of soy products (52).

Breast feeding exclusively during the first months is supported by several recent papers (10, 34, 37, 43, 63, 66, 78, 79). In some of these studies, lower IgE levels were found in breast fed as compared to formula fed infants (43, 66, 78, 79). Even a very short period of breast feeding seems worthwhile (37) with regard to the development of bronchial asthma. There is no "safe" age after which foreign proteins are tolerated and could be given without risk for the "allergic breakthrough" (44). Human breast milk may also contain allergens from the food of the nursing mother; especially cow's milk, wheat and egg have been shown to provoke allergic symptoms in breast fed infants (27, 91). It has also been speculated that the small amounts of allergen in human milk may be ideal for induction of IgE mediated allergy (20, 27, 92). However, before general recommendations are given as to a "hypoallergic" diet to mothers giving their breast milk to high risk infants, much more information must accumulate; on the other hand, when there are symptoms of possible allergic etiology in the breast fed baby, temporary elimination of suspected allergens from the mother's diet should be included in the investigation.

A recent paper (19) suggests that with an earlier introduction and a higher number of supplemental foods there is an increasing incidence of allergic symptoms, especially when there is a family history of atopic diseases. Breast feeding seemed to be of less importance than the family history and the premature introduction of supplemental foods. Saarinen et al. (80) found a similar incidence of a positive provocation test (3%) at 3 years of age in children who avoided fish and citrus fruits to 1 year of age as in a similar group where these foods were introduced before 6 months of age, indicating that for a single foodstuff it may be possible to postpone but not to prevent the sensitization. For practical purposes, intro-

duction of one foodstuff at a time from 4–6 months of age may be recommended as there is no nutritional advantage from an earlier introduction (2). Exclusive breast feeding should be recommended whenever possible (82), preferably for 6 months, but at the same time we must offer alternative feeding when breast feeding is impossible or unwanted; it seems justified to recommend casein hydrolysate (instead of soy) for infants submitted to high risk for the development of atopic disease. This group may be estimated at 1.5% of all newborn children (49).

In conclusion, genetic counselling should be considered when there is severe atopic disease, providing a basis for full choice. Advice should be given on the safest periods of birth, on prolonged breast feeding and late introduction of supplemental food, on an environment free from tobacco smoke, pets and animal products during infancy. As yet, there is no possibility to induce tolerance in human beings (92) but further experiments in this field are welcome.

REFERENCES

1. Arsdel, P. P. van & Motulsky, A. G.: Frequency and inheritance of asthma and allergic rhinitis in college students. *Acta Genet.* 9, 101–114, 1959.
2. Barness, L. A.: On the feeding of supplemental foods to infants. American Academy of Pediatrics Committee on Nutrition. *Pediatrics* 65, 1178–1181, 1980.
3. Bazaral, M., Orgel, H. A. & Hamburger, R. N.: IgE levels in normal infants and mothers and an inheritance hypothesis. *J. Immunol.* 107, 794–801, 1971.
4. Bazaral, M., Orgel, H. A. & Hamburger, R. N.: Genetics of IgE and allergy: Serum IgE levels in twins. *J. Allergy Clin. Immunol.* 54, 288–303, 1974.
5. Bell, S. D. & Eriksson, Z.: Studies in the transmission of sensitization from mother to child in human beings. I. Transfer of skin sensitizing antibodies. *J. Immunol.* 20, 447–458, 1931.
6. Björkstén, F. & Suoniemi, I.: Dependence of immediate hypersensitivity on the month of birth. *Clin. Allergy* 6, 165–171, 1976.
7. Björkstén, F., Suoniemi, I. & Koski, V.: Neonatal birch-pollen contact and subsequent allergy to birch-pollen. *Clin. Allergy* 10, 585–591, 1980.
8. Brown, E. B., Josephson, B. M., Levine, H. S. & Rosen, M.: A prospective study of allergy in a pediatric population. *Am. J. Dis. Child.* 117, 693–698, 1969.
9. Chambers, V. V. & Glaser, J.: The incidence of subsequent ragweed pollinosis in symptom-free persons having

- positive reactions to ragweed pollen extract. *J. Allergy* 29, 249–257, 1958.
10. Chandra, R. K.: Prospective studies on the effect of breast feeding on incidence of infections and allergy. *Acta Paediatr. Scand.* 68, 691–694, 1979.
 11. Croner, S., Kjellman, N.-I. M., Eriksson, B. & Roth, A.: IgE-screening in cord blood and development of atopic disease to 4½ years of age. Poster. XIV Nordiska Kongressen i Allergologi, Göteborg, 10–13 June 1981.
 12. Dannaeus, A., Johansson, S. G. O. & Foucard, T.: Clinical and immunological aspects of food allergy in childhood. II. Development of allergic symptoms and humoral immune response to foods in infants of atopic mothers during the first 24 months of life. *Acta Paediatr. Scand.* 67, 497–504, 1978.
 13. Dry, J., Leyndier, F., Abuaf, N., Luce, H. & Bernaille, J. M.: Blood cord eosinophilia (BCE) and family history (FH) of atopic disease. In Dehling, A. (ed.): *Advances in allergology and applied immunology*, p. 779. International Congress of Allergology, 10, Jerusalem 1979. Oxford 1980.
 14. Eastham, E. J., Lichauco, T., Grady, M. I. & Walker, W. A.: Antigenicity of infant formulas: Role of immature intestine on protein permeability. *J. Pediatr.* 93, 561–564, 1978.
 15. Edfors-Lubs, M.-L.: Allergy in 7000 twin pairs. *Acta Allergol.* 26, 249–285, 1971.
 16. Editorial. Towards prevention of allergy. *Lancet* i, 339, 1977.
 17. Fallot, M. E., Boyd, J. L. & Oski, F. A.: Breast-feeding reduces incidence of hospital admissions for infection in infants. *Pediatrics* 65, 1121–1124, 1980.
 18. Fergusson, D. M., Horwood, L. J., Shannon, F. T. & Taylor, B.: Infant health and breast-feeding during the first 16 weeks of life. *Aust. Paediatr. J.* 14, 254–258, 1978.
 19. Fergusson, D. M., Horwood, L. J., Beutrais, A. L., Shannon, F. T. & Taylor, B.: Eczema and infant diet. *Clin. Allergy* 11, 325–331, 1981.
 20. Firer, M. A., Hosking, C. S. & Hill, D. J.: Effect of antigen load on development of milk antibodies in infants allergic to milk. *Br. Med. J.* 283, 693–696, 1981.
 21. Foucard, T.: A follow-up study of children with asthmatoïd bronchitis. I. Skin test reactions and IgE: Antibodies to common allergens. *Acta Paediatr. Scand.* 62, 633–644, 1973.
 22. Foucard, T.: A follow-up study of children with asthmatoïd bronchitis. II. Serum IgE and eosinophil counts in relation to clinical course. *Acta Paediatr. Scand.* 63, 129–139, 1974.
 23. Frick, O. L.: Viral infections as triggers of allergy. In Steffen, C. & Ludwig, H. (eds.): *Clinical immunology and allergology*, pp. 283–292. Elsevier/North-Holland, Biomedical Press, 1981.
 24. Gerrard, J. W., Horne, S., Vickers, P., MacKenzie, J. W. A., Goluboff, N., Garson, J. Z. & Maningas, C. S.: Serum IgE levels in parents and children. *J. Pediatr.* 85, 660–663, 1974.
 25. Gerrard, J. W.: Breast-feeding: second thoughts. *Pediatr.* 54, 757–764, 1974.
 26. Gerrard, J. W., Vickers, P. & Gerrard, C. D.: The familial incidence of allergic disease. *Ann. Allergy* 36, 10–15, 1976.
 27. Gerrard, J. W.: Allergy in breast fed babies to ingredients in breast milk. *Ann. Allergy* 42, 69–71, 1979.
 28. Glaser, J. & Johnstone, D. E.: Prophylaxis of allergic disease in the newborn. *J. Am. Med. Assoc.* 153, 620–622, 1953.
 29. Green, A. R.: An updated assessment of the critical environmental factors involved in the prevention of allergic disease. *Ann. Allergy* 42, 372–383, 1979.
 30. Grulee, C. & Sanford, H. N.: The influence of breast and artificial feeding on infantile eczema. *J. Pediatr.* 9, 223–225, 1936.
 31. Haahtela, T. M. K.: The prevalence of allergic conditions and immediate skin test reactions among Finnish adolescents. *Clin. Allergy* 9, 53–60, 1979.
 32. Hagy, G. W. & Settupane, G. A.: Prognosis of positive allergy skin tests in an asymptomatic population. A three year follow-up of college students. *J. Allergy Clin. Immunol.* 48, 200–211, 1971.
 33. Halpern, S., Sellars, W. A., Johnson, R. B., Anderson, D. W., Saperstein, S. & Reisch, J. S.: Development of childhood allergy in infants fed breast, soy, or cow milk. *J. Allergy Clin. Immunol.* 51, 139–151, 1973.
 34. Hamburger, R. N.: Allergies in infants – perhaps they can be prevented. *Consultant* 19, 23–29, 1979.
 35. Hamburger, R. N., Melvin, D. & Street, D.: Development of antigen specific IgE antibody in low total IgE atopic individuals. *Clin. Res.* 28, 108A, 1980.
 36. Hansson, L. Å., Ahlstedt, S., Carlsson, B. & Fällström, S. P.: Secretory IgA antibodies against cow's milk proteins in human milk and their possible effect in mixed feeding. *Int. Arch. Allergy Appl. Immunol.* 54, 457–462, 1977.
 37. Hide, D. W. & Guyer, B. M.: Clinical manifestations of allergy related to breast and cow's milk feeding. *Arch. Dis. Child.* 56, 172–175, 1981.
 38. Jakobsson, I. & Lindberg, T.: Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet* ii, 437–439, 1978.
 39. Jakobsson, I.: Clinical and experimental studies on cow's milk protein intolerance in infancy. Dissertation, pp. 35–41, Malmö 1982.
 40. Johansson, S. G. O.: Serum IgND levels in healthy children and adults. *Int. Arch. Allergy* 34, 1–8, 1968.
 41. Johnstone, D. E. & Dutton, A. M.: Dietary prophylaxis of allergic disease in children. *N. Engl. J. Med.* 274, 715–719, 1966.
 42. Juto, P.: Immune responses, type of feeding and atopic allergy in infants. Umeå University, Sweden, Med. Diss. No. 57, 1980.
 43. Juto, P.: Elevated serum IgE in T cell-deficient infants fed cow's milk. *J. Allergy Clin. Immunol.* 66, 402–407, 1980.
 44. Katz, D. H.: The allergic phenotype: manifestations of "allergic breakthrough" and imbalance in normal "damping" of IgE antibody production. *Immunol. Rev.* 41, 77–108, 1978.
 45. Kaufman, H. S.: Allergy in the newborn: skin test reactions confirmed by the Prausnitz-Küstner test at birch.

- Clin. Allergy 1, 363-367, 1971.
46. Kemp, A. S.: Relationship between the time of birth and the development of immediate hypersensitivity to grass-pollen antigens. *Med. J. Aust.* 1, 263-264, 1979.
 47. Kjellman, N.-I. M.: Predictive value of high IgE levels in children. *Acta Paediatr. Scand.* 65, 465-471, 1976.
 48. Kjellman, N.-I. M. & Johansson, S. G. O.: IgE and allergy in newborns and infants with a family history of atopic disease. *Acta Paediatr. Scand.* 65, 601-607, 1976.
 49. Kjellman, N.-I. M.: Atopic disease in seven-year-old children. *Acta Paediatr. Scand.* 66, 465-471, 1977.
 50. Kjellman, N.-I. M.: Immunoglobulin E and atopic allergy in childhood. *Acta Paediatr. Belg.* 30, Suppl. 7, 15-20, 1977.
 51. Kjellman, N.-I. M., Harder, H., Hansson, L.-O. & Lindwall, L.: Allergy, otitis media and serum immunoglobulins after adenoidectomy. *Acta Paediatr. Scand.* 67, 717-723, 1978.
 52. Kjellman, N.-I. M. & Johansson, S. G. O.: Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin. Allergy* 9, 347-358, 1979.
 53. Kjellman, N.-I. M.: Effect of parental smoking on IgE levels in children. *Lancet* i, 993-994, 1981.
 54. Kjellman, N.-I. M., Croner, S., Johansson, S. G. O., Eriksson, B. & Roth, A.: Serum IgE in newborn infants and its predictive value. XIth Congress of the European Academy of Allergy and Clinical Immunology, Vienna, October 6-10, 1981.
 55. Kjellman, N.-I. M.: Recurrent croup and allergy. *Arch. Dis. Child.* 56, 893-894, 1981.
 56. Klagsbrun, M., Neumann, J. & Tapper, D.: The mitogenic activity of human breast milk. *J. Surg. Res.* 26, 417-422, 1979.
 57. Kletter, B., Gery, I., Freier, S. & Davies, A. M.: Immune responses of normal infants to cow milk. II. Decreased immune reactions in initially breast-fed infants. *Int. Arch. Allergy Appl. Immunol.* 40, 667-674, 1971.
 58. Koivikko, A.: Childhood asthma in Finland. *Acta Allergol.* 29, 30-72, 1974.
 59. Kramer, M. S. & Moroz, B.: Do breast-feeding and delayed introduction of solid foods protect against subsequent atopic eczema. *J. Pediatr.* 98, 546-550, 1981.
 60. Kuhns, W. J.: Studies of immediate wheal reactions and of reaginic antibodies in pregnancy and in the newborn infant. *Proc. Soc. Exp. Biol. Med.* 118, 377-380, 1965.
 61. Kuroume, T., Oguri, M., Matsumura, T., Iwasaki, I., Kanbe, Y., Kawabe, S. & Negishi, K.: Milk sensitivity and soybean sensitivity in the production of eczematous manifestations in breast-fed infants with particular reference to intra-uterine sensitization. *Ann. Allergy* 37, 41-46, 1976.
 62. Levine, B. B.: Genetic factors in reagin production in mice. In Austen, K. F. & Becker, E. L. (eds.): *Biochemistry of the acute allergic reactions*, p. 1. Blackwell Scientific Publ., Oxford, 1971.
 63. Lucarelli, S., Frediani, T., Barbato, M., Marchetti, F., Pellegrini, G. & Businco, L.: The predictive value of serum IgE in newborns from atopic parents and influence of type of feeding. *Abstract. Ann. Allergy* 47, 121, 1981.
 64. Marks, M. B.: Physical signs of allergy of the respiratory tract in children. *Ann. Allergy* 25, 310-317, 1967.
 65. Marsh, D. G.: HLA and allergy. In Steffen, C. & Ludwig, H. (eds.): *Clinical immunology and allergology*, pp. 157-166. Elsevier/North-Holland, Biomedical Press, 1981.
 66. Mathew, D. J., Taylor, B., Norman, A. P., Turner, M. W. & Soothill, J. F.: Prevention of eczema. *Lancet* i, 321-324, 1977.
 67. May, C. D., Fomon, S. J. & Remigio, L.: Immunologic consequences of feeding infants with cow milk and soy products. *Acta Paediatr. Scand.* 71, 43-51, 1982.
 68. Michel, F. B., Bousquet, J., Greillier, P., Robinet-Lévy, M. & Coulomb, Y.: Comparison of cord blood immunoglobulin E concentration and maternal allergy for the prediction of atopic diseases in infancy. *J. Allergy Clin. Immunol.* 65, 422-430, 1980.
 69. Michel, F. B., Bousquet, J., Coulomb, U. & Robinet-Lévy, M.: Prediction of the "high-allergic-risk" newborn. In Johansson, S. G. O. (ed.): *Diagnosis and treatment of IgE-mediated diseases*, pp. 35-47. Excerpta Med. Amsterdam-Oxford-Princeton, 1981.
 70. Miller, D. L., Hirvonen, T. & Gitlin, D.: Synthesis of IgE by the human conceptus. *J. Allergy Clin. Immunol.* 52, 182-188, 1973.
 71. Morrison Smith, J., Hardin, K. & Cumming, G.: The changing prevalence of asthma in school children. *Clin. Allergy* 1, 57-61, 1971.
 72. Morrison Smith, J. & Springett, V. H.: Atopic disease and month of birth. *Clin. Allergy* 9, 153-157, 1979.
 73. Orgel, H. A., Hamburger, R. N., Bazalal, M., Gorrin, H., Groshong, T., Lenoir, M., Miller, J. R. & Wallace, W.: Development of IgE and allergy in infancy. *J. Allergy Clin. Immunol.* 56, 296-307, 1975.
 74. Pittard, W. B.: Breast milk immunology. A frontier in infant nutrition. *Am. J. Dis. Child.* 133, 83-87, 1979.
 75. Pullan, C. R., Tomas, G. L., Martin, A. J., Gardner, P. S., Webb, J. K. G. & Appleton, D. R.: Breast-feeding and respiratory syncytial virus infection. *Br. Med. J.* 281, 1033-1036, 1980.
 76. Rapaport, J. G.: Anyone may develop allergy. *Ann. Allergy* 36, 207, 1976.
 77. Roberts, J. & Carron, R.: Pollinose précoce des natifs du Taureau. *Rev. Française Allergol. Immunol.* 19, 153-155, 1979.
 78. Saarinen, U. M., Kajosaari, M., Backman, A. & Siimes, M. A.: Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* ii, 163-165, 1979.
 79. Saarinen, U. M., Björkstén, F., Knekt, P. & Siimes, M. A.: Serum IgE in healthy infants fed breast milk or cow's milk-based formulas. *Clin. Allergy* 9, 339-345, 1979.
 80. Saarinen, U. M. & Kajosaari, M.: Does dietary elimination in infancy prevent or only postpone a food allergy? *Lancet* i, 166-167, 1980.
 81. Sauls, H. S.: Potential effect of demographic and other variables in studies comparing morbidity of breast-fed and bottle-fed infants. *Pediatrics* 64, 523-527, 1979.
 82. Savilahti, Erkki: Cow's milk allergy. *Allergy* 36, 73-88,

- 1981.
83. Schwartz, M.: Heredity in bronchial asthma. *Acta Allergol., Suppl. II*, 1952.
84. Sears, M. R., Chow, C. M. & Morseth, D. J.: Serum total IgE in normal subjects and the influence of a family history of allergy. *Clin. Allergy* 10, 423-431, 1980.
85. Sibbald, B., Horn, M. E. C., Brain, E. A. & Gregg, I.: Genetic factors in childhood asthma. *Thorax* 35, 671-674, 1980.
86. Soothill, J. F.: Some intrinsic and extrinsic factors predisposing to allergy. *Proc. R. Soc. Med.* 69, 439-442, 1976.
87. Stevensson, D. D., Orgel, H. A., Hamburger, R. N. & Reid, R. T.: Development of IgE in newborn human infants. *J. Allergy Clin. Immunol.* 48, 61-72, 1972.
88. Stintzing, G. & Zetterström, R.: Cow's milk allergy, incidence and pathogenetic role of early exposure to cow's milk formula. *Acta Paediatr. Scand.* 68, 383-387, 1979.
89. Suoniemi, I., Björkstén, F. & Haahtela, T.: Dependence of immediate hypersensitivity in the adolescent period on factors encountered in infancy. *Allergy* 36, 263-268, 1981.
90. Walker, W. A. & Isselbacher, K. J.: Uptake and transport of macromolecules by the intestine. Possible role in clinical disorders. *Progr. Gastroenterol.* 67, 531-550, 1974.
91. Warner, J. O.: Food allergy in fully breast-fed infants. *Clin. Allergy* 10, 133-136, 1980.
92. Weck, A. L. de: Suppression of IgE antibodies. *Dev. Immunol.* 14, 381-388, 1981.
93. Welliver, R. C., Wong, D. T., Sun, M., Middleton, E., Vaughan, R. S. & Ogra, P. L.: The development of respiratory syncytial virus specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N. Engl. J. Med.* 305, 841-846, 1981.
94. Wilson, J. M. G. & Jungner, G.: Principles and practice of screening for disease. WHO Publ. Health Papers, No. 34, 1968.
95. Wittig, H. J., McLaughlin, E. T., Leifer, K. L. & Belliot, J. D.: Risk factors for the development of allergic disease: Analysis of 2,190 patient records. *Ann. Allergy* 41, 84-88, 1978.
96. Wütrich, B., Baumann, E., Fries, R. A. & Schnyder, U. W.: Total and specific IgE (RAST) in atopic twins. *Clin. Allergy* 11, 147-154, 1981.
97. Zach, M., Erben, A. & Olinsky, A.: Croup, recurrent croup, allergy and airways hyper-reactivity. *Arch. Dis. Child.* 56, 336-341, 1981.
98. Zetterström, O., Osterman, K., Machado, L. & Johansson, S. G. O.: Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *Br. Med. J.* 283, 1215-1217, 1981.

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