

A joint meeting of the Irish Section and the Reproduction and Development Group of the Nutrition Society was held at Dublin Institute of Technology on 1–3 September 1999

Symposium on ‘Growing up with good nutrition: a focus on the first two decades’

Food allergy and nutrition in early life: implications for later health

Ranjit Kumar Chandra

Memorial University of Newfoundland, Janeway Child Health Centre, St John's, Newfoundland A1A 1R8, Canada

Allergic diseases are a common cause of illness in most industrialized countries. Diet during early childhood is an important determinant of the development of allergy, particularly in high-risk infants who have a parental history of atopy. Maternal avoidance of highly-allergenic foods during pregnancy and lactation, prolonged exclusive breast-feeding, the use of a hydrolysed milk formula, and delayed introduction of dairy products, eggs, fish, nuts and soyabean are associated with a lower incidence of allergic symptoms and signs. These beneficial effects are observed for as long as 18 years of age. Similarly, nutrition and physical growth are important factors that influence immunocompetence and morbidity due to infections. Small-for-gestational age low-birth-weight infants show prolonged impairment of cell-mediated immunity, antibody responses and phagocyte function. Recent studies indicate the beneficial effect of moderate amounts of Zn given in the first 6 months of life. Thus, diet and nutrition in early life are crucial for the development of allergic and infectious disease throughout childhood and into adulthood.

Food allergy: Low-birth-weight infants: Immune responses: Infection

The critical importance of nutrition in the maintenance of optimal health is not in dispute. It is also recognized that adverse influences in early life have a prolonged, and in some instances permanent, effect on susceptibility to illness. It follows that dietary factors during gestation and early childhood are of immense importance in shaping health in later life. In the present selective review the paradigms of food hypersensitivity and of immunocompetence are used to illustrate the potential role of diet in early life for health and illness later on.

Food allergy

In most industrialized countries allergic disease has emerged as a common cause of illness and even mortality in children. The prevalence of allergic disorders has been reported to have increased in the past 10–15 years (Taylor *et al.* 1984; Burney *et al.* 1990). The contributing factors for this increase are unclear. The construction of air-tight highly-insulated homes, decline in breast-feeding in some groups, early introduction of solid foods and a change in the occurrence of infectious disease may play a role. A second

reason for the current interest in allergic disease stems from health-care costs of treating those individuals with allergy. The treatment of allergic diseases, such as eczema, asthma, hay fever and gastroenteropathy, has considerable economic as well as other consequences that are more difficult or impossible to assess in monetary terms, e.g. absence from school, social isolation, emotional distress, curtailed participation in sports etc.

These epidemiological and economic data have stimulated efforts aimed at prevention, such as exclusive breast-feeding, maternal avoidance of common allergenic foods, use of a hypoallergenic formula, delayed introduction of allergenic solid foods and lessening of exposure to dust mites, animals, and tobacco smoke. Although such interventions have been successful (Arshad *et al.* 1992), it is almost impossible to distinguish and analyse the importance of each individual prophylactic measure. For this reason, it is important to conduct studies in which only one variable, such as the type of infant feeding formula, differs between groups. This recommendation was emphasized by the American Academy of Pediatrics Subcommittee on Nutrition and Allergic Disease (Kleinman *et al.* 1991).

Abbreviations: AGA, appropriate-for-gestational age; Ig, immunoglobulin; SGA, small-for-gestational age.

***Corresponding author:** Dr R. K. Chandra, fax +1 709 778 4191, email rchandra@morgan.ucs.mun.ca

Identification of high-risk newborn infants

In order to attempt vigorous interventions for the prevention of allergy and to ensure parental motivation, it is useful to identify the infant at high risk of developing atopic disease. If one parent has atopic disease, the risk of developing allergies in the offspring is about 37 %. If both parents are affected, this risk increases to about 62–85 %, depending on whether the mother and father have dissimilar or similar clinical disease. Besides family history, if cord-blood immunoglobulin (Ig) E is elevated, there is a higher risk, irrespective of positive or negative family history. Conversely, with low cord-blood IgE the risk is relatively lower. Similarly, those infants who develop atopic disease in childhood show a reduction in the number of CD8+ suppressor cells, particularly the lymphocytes with $\gamma\delta$ T-cell receptor, in the first few days of life, again irrespective of family history. This reduction in CD8+ suppressor cells may occur because of the important immunoregulatory role of these cells in IgE production (Chandra & Baker, 1983; Chandra, 1995). If these and other tests are combined, there is improved prediction, both positive and negative. In the presence of biparental family history, elevated cord-blood IgE and reduced CD8+ T-cells, the positive predictive value is approximately 92 %.

Breast-feeding and maternal diet

Some of the reasons why breast-feeding reduces the occurrence of atopic disease are: reduced exposure to food proteins that would be present in formulas; improved maturation of the intestinal barrier thereby reducing the absorption of macromolecules; reduced frequency of infection which can act as an adjuvant; finally, the presence of anti-inflammatory factors and anti-idiotypic antibodies in human breast milk.

Our cumulative data, shown in Table 1, confirm the partial protective effect of breast-feeding for as long as 18 years of age. Three points need emphasis. First, the benefits are obvious in those infants who were at high risk because of family history or elevated IgE, or both. Second, the protection is greater with more prolonged breast-feeding, i.e. more than 4 months. Third, even among those infants who are exclusively breast-fed for that length of time, there is still a significant ($P < 0.5$) incidence of atopic disease. This finding led us to consider the role of maternal diet during pregnancy and during lactation.

Saariinen & Kajosaari (1995) have recently published the results of a prospective follow-up study until 17 years of age. They observed the highest prevalence of obvious atopy in the group with little or no breast-feeding, and concluded that breast-feeding is prophylactic against atopic eczema, food allergy and respiratory allergy throughout childhood.

Table 1. Influence of breast-feeding on cumulative incidence (%) of allergic disease: follow-up for 18 years

Group ...	Low-risk	High-risk
Breast-fed: Irrespective of duration	5.8	33.4
< 4 months	3.6	24.3
> 4 months	8.6	56.7

To examine the effect of maternal diet, mothers with a positive history of atopy in themselves or their husbands were recruited before 10 weeks of pregnancy. They were randomly divided into either the dietary precautions group, with avoidance of milk, eggs, fish and peanuts during the rest of pregnancy, or assigned to the control group with no dietary precautions. Infants not breast-fed were given a cow's-milk formula. The infants were followed for 18 months. Among thirty-five breast-fed infants whose mothers took precautions during pregnancy, five developed eczema. Of the thirty-six breast-fed infants whose mothers did not take these dietary precautions, eleven developed eczema (Chandra *et al.* 1986). These differences were significant ($P < 0.05$). The severity of eczema was assessed by a scoring system that takes into account the extent of skin involvement, its type and severity. The eczema score was lower in the affected infants whose mothers took dietary precautions during pregnancy. Interestingly, the lower eczema score was seen both for breast-fed and formula-fed infants. Apparently-different results were obtained in a Swedish study (Lilja *et al.* 1988). However, in this study the foods avoided were milk and eggs only, and also only during the last trimester of pregnancy, long after the fetus could have been sensitized.

Antigens derived from maternal dietary foods do come through into breast milk. If mothers omit common allergens from their diet, the frequency of breast-milk samples positive for milk and egg proteins is decreased, only three of twenty samples were positive compared with fifteen of sixteen in controls (Chandra *et al.* 1986).

Breast-fed infants of mothers who had a history of atopic disease in themselves or their husbands or a previous child were randomly divided into two groups: dietary precautions by the mothers, who avoided milk, egg, fish and peanuts; controls with no precautions. Breast-fed infants whose mothers took dietary precautions during lactation had a markedly reduced occurrence of atopic eczema (22 %) compared with the controls in whom the incidence was double (44 %). The severity of eczema judged by a scoring system was also less in the experimental group. Similar results were obtained in a study conducted in Linköping, Sweden (Hattevig *et al.* 1989).

The beneficial role of 'hypoallergenic' infant formula has been the subject of much work and debate. The consensus was described in a recent symposium (Reiger *et al.* 1998). Our study is described here as an example of the results generally obtained in such research using a hydrolysed formula.

A group of 216 infants whose mothers had elected not to breast-feed were randomized to receive exclusively a partial-whey-hydrolysate formula or a conventional cow's-milk formula or a soya-milk formula until 6 months of age. Seventy-two high-risk infants breast-fed for ≥ 4 months were also studied. Follow-up until 5 years of age showed a significant lowering in the cumulative incidence of atopic disease in the breast-fed and the whey-hydrolysate groups compared with the conventional cow's-milk group ($P < 0.001$). Soya-milk formula was not effective (Table 2). The occurrence of both eczema and asthma was lowest in the breast-fed and whey-hydrolysate groups, and was comparable in the cow's-milk and soya-milk groups.

Table 2. Cumulative incidence of allergic disease in high-risk infants followed until 5 years of age (from Chandra, 1997)

Group*	Total no.	No. affected†	Odds ratio‡ 95 % CI	χ^2	P§
Smilac	67	40	1.0		
Good Start	68	22	0.322, 0.159, 0.653	10.16	0.0014
Isomil	68	34	0.759, 0.384, 1.501	1.28	> 0.1
Breast milk	60	16	0.422, 0.200, 0.891	14.01	0.002

† χ^2 analysis of 4 × 2 contingency tables for multiple comparison, χ^2 18.68, df 3, $P=0.00032$. Two group comparisons showed Good Start v. Isomil, χ^2 4.37, $P<0.05$; Isomil v. breast χ^2 7.29, $P<0.01$; Good Start v. breast milk, χ^2 0.49, $P>0.1$.

‡ Calculated for the groups fed on Good Start or Isomil or breast milk, using Similac group as the reference group.

§ χ^2 analysis was carried out and P values calculated to assess differences between Similac and each of the other groups.

* Similac (cow's milk) and Isomil (soya-milk formula) were obtained from Ross Laboratories, Columbus, OH, USA. Good Start (whey hydrolysate) was obtained from Carnation, Glendale, CA, USA.

Similar significant differences were noted in the 18–60-month period prevalence of eczema and asthma ($P>0.1$). Eczema was less severe in the whey-hydrolysate group compared with the other groups. Double-blind placebo-controlled food challenges showed a lower prevalence of food allergy in the whey-hydrolysate group compared with the other formula groups. It was concluded that exclusive breast-feeding or feeding with a partial-whey-hydrolysate formula is associated with a lower incidence of atopic disease and food allergy. This approach was shown to be cost-effective in the prevention of allergic disease in children. A meta-analysis of all published studies came to a similar consensus (Baumgartner *et al.* 1998).

There are limited data on the effect of low birth weight on the incidence of allergic disease. These studies show that preterm and small-for-gestational age (SGA) infants with family history of atopy do have a significantly higher occurrence of allergic eczema, asthma and hay fever ($P<0.01$). Our observations are shown in Table 3.

Immunocompetence and risk of infection

The ontogenetic development of the immune system is a well-defined, almost stereotyped, event. The differentiation steps are largely genetically regulated, but some environmental influences, such as nutrition and infection, can affect this process. Differentiation and maturation of various types of cells that participate in the immune response progress at different rates. Moreover, antigenic differentiation may precede functional development by a substantial time period.

Low-birth-weight infants

The worldwide incidence of low birth weight, defined as weight less than 2500 g, varies considerably from one population group to another (from 8 % in some industrialized countries to as high as 41 % in some developing countries of Africa). In the industrialized countries the majority of low-birth-weight newborn infants are appropriate-for-gestational age (AGA) preterm, whereas in the developing countries, the majority of low-birth-weight neonates are SGA (Chandra, 1991). The aetiology of fetal growth retardation includes maternal malnutrition and infection, hypertension, toxemia, smoking, substance abuse, and 'placental insufficiency'. More than one factor is often at work.

Table 3. Odds ratios (OR) for the occurrence of allergic disease in low-birth-weight infants compared with full-term healthy infants

	OR	95 % CI
Preterm:High-risk	1.4	1.2, 1.7
General population	1.1	0.9, 1.8
SGA: High-risk	1.2	1.1, 1.9
General population	0.9	0.2, 1.6

SGA, small-for-gestational age.

Low birth weight is associated with a higher morbidity and mortality. While the overall proportion of infants who died or were handicapped is similar in AGA and SGA groups, the AGA group are at higher risk of death in the immediate postnatal period, while the SGA group are at higher risk of morbidity in the first year of life (Chandra, 1991). Infection is one of the recognized causes of increased illness in SGA infants. Table 4 shows that upper- and lower-respiratory-tract infections are two to three times more frequent in SGA infants than in AGA infants. It appears that the morbidity pattern in the SGA group has a bimodal distribution, about two-thirds showing a near-normal rate of illness, comparable with that of healthy full-term infants, whereas one-third have an increased illness rate, almost three times that of the full-term infants. 'Stunted' SGA infants have a higher neonatal mortality, lower neonatal morbidity but a lower post neonatal morbidity compared with 'wasted' SGA infants.

Immune responses

SGA infants show atrophy of the thymus and prolonged impairment of cell-mediated immunity. These general findings have been observed in infants as well as in laboratory animals (Chandra 1975b, 1991; Moscatelli *et al.* 1976). In animal models of intrauterine nutritional deficiency, protein-energy malnutrition as well as deprivation of selected nutrients results in reduced immune responses in the offspring (Chandra, 1975c). Briefly, the number of T lymphocytes is reduced and their response to mitogens is decreased. Delayed cutaneous hypersensitivity to a variety of microbial recall antigens as well as to the strong chemical sensitizer 2,4-dinitrochlorobenzene is impaired. Serum thymic factor activity is reduced in SGA infants tested at 1 month of age or later (Chandra, 1980). In contrast to AGA low-birth-weight infants, who recover immunologically by about 2–3 months of age, SGA infants

continue to exhibit impaired cell-mediated immune responses for several months or even years (Chandra *et al.* 1977). This situation is particularly true of those infants whose weight-for-height is less than 80 % of standard values. The prolonged immunosuppression in some SGA infants correlates with clinical experience of infectious illness (Table 5; Chandra, 1991), and thus may have considerable biological significance.

Phagocyte function is deranged in low-birth-weight infants. There is a slight reduction in the ingestion of particulate matter and a significant reduction in both metabolic activity and bactericidal capacity (Chandra 1975a).

IgG from the mother acquired through placental transfer is the principal Ig in cord blood. The half-life of IgG is 21 d and, thus, all infants show physiological hypoglobulinaemia between 3 and 5 months of age. This hypoglobulinaemia is pronounced and prolonged in low-birth-weight infants (Chandra 1975a,b), because their level of IgG at birth is significantly lower than that of full-term infants ($P < 0.01$). There is a progressive rise in IgG concentration with gestational age and birth weight, especially in infants below 2500 g. All four subclasses of IgG are detected in fetal sera as early as 16 weeks of gestation, the major proportion consisting of IgG1 (Chandra, 1975c). In SGA low-birth-weight infants the cord blood levels of IgG1 are reduced much more than those of the other subclasses. Thus, the infant:maternal value is significantly low for IgG1 ($P < 0.05$) but not for IgG2. The number of immunoglobulin-producing cells and the amount of immunoglobulin secreted is decreased in SGA infants who are symptomatic, i.e. those who have recurrent infections. In the second year of life SGA infants show a marked reduction in IgG2 levels and often show infections with organisms that have a polysaccharide capsule (Chandra, 1986).

Table 4. Risk of respiratory infections in small-for-gestational-age infants expressed as odds ratio (OR) with reference to full-term healthy infants: follow-up until age 3 years

	OR	95 % CI
Upper-respiratory-tract infection	2.3	1.4, 3.0
Lower-respiratory-tract infection	2.9	1.7, 3.4

Table 5. Immunological findings in small-for-gestational-age low-birth-weight infants (from Chandra, 1991) Values are the nos. of infants with the abnormality, except for illness days, which are shown as means.

	Group 1 (n 25)	Group 2 (n 16)
Immunological dysfunction		
Illness days (100 child days; mean)	6	17*
Impaired cell-mediated immunity	16	14*
Decreased IgG	4	4
Decreased IgG2 level	5	7*
Reduced opsonic activity	7	9*

Ig, immunoglobulin.

Values were significantly different from those for group 1: * $P < 0.05$.

† Forty-one infants were divided into two groups: those who were relatively asymptomatic (group 1) and those often ill with infection (group 2).

In addition to careful attention to the amount and type of macronutrients, it may be useful to examine the benefit derived from extra amounts of selected micronutrients. There are some anecdotal observations that link additional doses of vitamins A and E and of Fe and Zn to enhanced immunity. Recent intervention studies indicate a significant benefit of Zn supplements for enhancing immunity and reducing the incidence of infection in both preterm AGA and SGA infants (Chandra, 1991, 2000; Hill, 2000).

Concluding comments

There are important interactions between early fetal and infant nutrition and subsequent health outcome in later life. First, exclusive breast-feeding, particularly if it is prolonged beyond 4 months, is associated with a reduced occurrence of allergic disease, especially in those infants whose parents have had atopic disease. The benefit is enhanced by selective exclusion of common allergenic foods from the mother's diet during lactation, and probably also during pregnancy. In the case of infants who are not breast-fed or require a supplement, the choice of an hydrolysate formula is distinctly better than a conventional cows'-milk formula or a soya-milk formula. In addition, delayed introduction of dairy products, eggs, fish and nuts is helpful. Second, fetal malnutrition, epitomized by SGA low-birth-weight infants, results in pronounced and prolonged impairment of several aspects of immunocompetence. This impairment is associated with an increased incidence of infection in the first few years of life.

References

- Arshad SH, Matthews S, Grant C & Hide DW (1992) Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* **339**, 1493–1497.
- Baumgartner M, Brown CA, Exl B-M, Secretin M-C, van't Hoft M & Haschke F (1998) Controlled trials investigating the use of one partially hydrolyzed whey formula for dietary prevention of atopic manifestations until 60 months of age: An overview using meta-analytic techniques. *Nutrition Research* **8**, 1425–1442.
- Burney PGJ, Chinn S & Rona R (1990) Has the prevalence of asthma increased in children? *British Medical Journal* **300**, 1306–1310.
- Chandra RK (1975a) Fetal malnutrition and postnatal immunocompetence. *American Journal of Diseases of Children* **129**, 450–454.
- Chandra RK (1975b) Levels of IgG subclasses, IgM and tetanus antitoxin in paired maternal and foetal sera: Findings in healthy pregnancy and placental insufficiency. In *Maternofoetal Transmission of Immunoglobulins*, pp. 77–90 [WA Hemmings, editor]. London: Cambridge University Press.
- Chandra RK (1975c) Antibody formation in first and second generation offspring of nutritionally deprived rats. *Science* **190**, 289–290.
- Chandra RK (1980) Serum thymic hormone activity and cell-mediated immunity in healthy neonates, preterm infants and small-for-gestational age infants. *Pediatrics* **67**, 407–411.
- Chandra RK (1986) Serum levels and synthesis of IgG subclasses in small for gestation low birth weight infants and in patients with selective IgA deficiency. In *Immunoglobulin Subclass Deficiencies*, pp. 90–99 [LA Hanson, T Soderstrom and V-A Oxelius, editors]. Basel: Kruger.

- Chandra RK (1991) Interactions between early nutrition and the immune system. In *The Childhood Environment and Adult Disease. Ciba Foundation Symposium* no. 156, pp. 77–88 [GR Bock and J Whelan, editors]. Chichester: Wiley-Interscience.
- Chandra RK (1995) Food allergy and atopic disease – Overview. *Clinical Reviews in Allergy and Immunology* **13**, 293–234.
- Chandra RK (1997) Five year follow-up of high risk infants with family history of allergy exclusively breast-fed or fed partial whey hydrolysate, soy and conventional cow's milk formulas. *Journal of Pediatric Gastroenterology and Nutrition* **24**, 380–388.
- Chandra RK (2000) Impact of iron and zinc deficiencies on immunity and risk of infection. In *Nutrition, Immunity and Infection* [R Suskind, editor]. New York: Raven Press (In the Press).
- Chandra RK, Ali S, Kutty KM & Chandra S (1977) Thymus-dependent lymphocytes and delayed hypersensitivity in low birth weight infants. *Biology of the Neonate* **31**, 15–18.
- Chandra RK & Baker M (1983) Numerical and functional deficiency of suppressor T cells precedes development of atopic eczema. *Lancet* **ii**, 1393–1394.
- Chandra RK, Puri S, Suraiya C & Cheema PS (1986) Influence of maternal food antigen avoidance during pregnancy on incidence of atopic eczema in infants. *Clinical Allergy* **16**, 563–569.
- Hattevig G, Kjellman B, Sigurs N & Kjellman N-I (1989) The effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clinical Allergy* **19**, 27–32.
- Hill A (2000) Zinc supplements in low birth weight infants. In *Nutrition, Immunity and Infection* [R Suskind, editor]. New York: Raven Press (In the Press).
- Kleinman RE, Bahna S, Powell GF & Sampson HA (1991) Use of infant formulas in infants with cow milk allergy. A review and recommendations. *Pediatric Allergy and Immunology* **2**, 146–155.
- Lilja G, Dannaeus A & Fälth-Magnusson K (1988) Immune response of the atopic woman and foetus. Effects of high- and low-dose food allergen intake during late pregnancy. *Clinical Allergy* **18**, 131–142.
- Moscatelli P, Bricarelli FG, Piccinini A, Tomatis C & Dufour MA (1976) Defective immunocompetence in foetal malnutrition. *Helvetica Paediatrica Acta* **21**, 241–247.
- Reiger C, Bauer CP, Koletzko B, Lantz MJ & Reinhardt D (1998) Ten years of food allergy prevention with partial whey hydrolysate HA formula. *Nutrition Research* **18**, 1327–1462.
- Saarinen UM & Kajosaari M (1995) Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* **346**, 1065–1069.
- Taylor B, Wadsworth J, Wadsworth M & Peckam C (1984) Changes in the prevalence of eczema since the 1939–45 war. *Lancet* **ii**, 1255–1257.