FETO-MATERNAL INTERACTION OF ANTIBODY AND ANTIGEN TRANSFER, IMMUNITY AND ALLERGY DEVELOPMENT

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CONTENTS

INTRODUCTION

Although the human infant is immunologically complete at birth, the levels of immunoglobulins present are only a small fraction of those in adulthood. Through placental transfer, immunoglobulin G (IgG) passes from the mother to her fetus. The newborn infant receives secretory immunoglobulin A (sIgA) and, to a much lesser extent, IgG from colostrum and mature human milk. This phenomenon of passive immunity is vital for the infant's defence system against pathogenic microorganisms and potential allergens. In some infants, often those born into a family with a history of allergy, this harmonious state of affairs can be disrupted. In this case the infant may already be sensitized to allergens transferred *in utero* from the mother *via* the placenta. Furthermore the breast fed infant may suffer hypersensitivity to human milk born allergens derived from foods the mother has eaten during lactation.

In this review we examine the part played by feto–maternal interactions in the immunological development of the infant. In particular the development of tolerance is explored and the possible mechanisms involved when an infant becomes hypersensitive to food proteins or other allergens. The usefulness of maternal elimination diets, as a

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prophylactic measure in the prevention of the development of adverse reactions to foods including allergy in infants, is assessed.

DEFINITIONS

Over the past decade a better understanding of the classification of adverse reactions to environmental substances has led to clearer definitions. Ferguson (1992) has described the terms for the various syndromes and diseases associated with reactions to foods. One of the problems associated with defining the word 'allergy' is that it can be used to describe a different condition in different countries (Brostoff & Gamlin, 1990). The accepted definition of a food allergy in the United Kingdom is that it is a form of food intolerance that has an immunological basis, and that there is evidence of an immunological reaction mediated by an antibody or T-lymphocytes or both. Mechanisms involved in allergic reactions can be further subdivided into four types (Bleumink, 1983), although in any particular disease state more than one mechanism may operate. There are five different immunoglobulin (Ig) classes: IgA, IgD, IgE, IgG and IgM. Some of the immunoglobulin classes have a further subclass division, e.g. IgG1–IgG4. Atopy is associated with high circulating levels of IgE in response to common environmental allergens and individuals with atopic disease may or may not develop one or more of the following: asthma, hay fever, eczema (Savin, 1993). The atopic phenomenon is known to be familial. Aas (1989) contends that symptoms associated with an allergic reaction depend on the degree of reactivity of the involved tissue receptors and of the effector cells.

Current knowledge of mechanisms related to allergic reactions is poor, and several mechanisms may interact. Although it is beyond the scope of this article to detail our understanding of all possible mechanisms, it is of interest to note that the risk of developing an immediate or delayed allergic reaction is higher in infants and children compared with adults. This implies that developmental factors operative during gestation and after birth are likely to play an important, though as yet poorly understood, role in the development of allergic disease (Strobel, 1988).

INCIDENCE

A comprehensive review of immunological hypersensitivity and other untoward effects related to the chemical composition of foods has highlighted the difficulty of assessing the incidence of these conditions and the lack of a definitive clinical test to diagnose allergy (Wood, 1986). There are, however, studies that have attempted to quantify the incidence of many of these conditions. It has been estimated that 10% of the childhood population have an atopic constitution (Wood, 1986), and that the prevalence of atopic diseases is increasing in North West Europe (Croner, 1992). There is evidence to suggest that the incidence of atopic eczema is rising in Britain (Ferguson & Watret, 1988). The incidence of allergic reactions to food in the paediatric population is variously estimated to be in the range 0·5–6·0% (Chandra & Prasad, 1991).

FETO-MATERNAL RELATIONSHIP

The ability to mount an antibody response and an immune T-cell mediated response, as shown by allograft rejection, is reasonably well developed by birth. Antibody levels, except that of IgG, are low in the absence of an intra-uterine infection. The transfer of antibodies,

antigens and cells from the mother to the fetus and infant *via* the placenta and breast milk respectively is of great significance in the immunological development of the child.

PLACENTAL ANTIBODY TRANSFER

The mother and fetus possess a unique relationship *via* the placenta. In addition to the essential function of supplying the fetus with nutrients and oxygen, and removing any waste, the placenta affords a degree of protection to the fetus by the transfer of antibodies and specific cells and preventing the transfer of toxins and potentially harmful substances. The placenta is also involved with metabolism and endocrine secretion (Hurley, 1980).

The only known immunoglobulin class that is transferred across the placenta is IgG. The fragment crystallizable portion of IgG plays a major role in the transport process (Gitlin *et al.* 1964). The transfer of IgG is believed to be achieved *via* an active transport mechanism (Harlow & Lane, 1988) which involves a receptor mediated transcytosis of IgG across the syncytiotrophoblast, and a transcellular pathway through the endothelium (Leach *et al.* 1990). There is evidence that this transfer begins at approximately 20 weeks of gestation (Leach *et al.* 1990).

The majority of the IgG transfer occurs in the third trimester. This presents a potential problem for the prematurely born infant as the time available for antibody transfer is reduced compared with that for the full term infant. Premature infants do not obtain the full benefit of maternal IgG antibodies to help protect them against potentially life threatening infections or the development of possible allergies (Papadatos *et al.* 1970). Babies born with intra-uterine growth retardation also have low levels of IgG. The growth retardation is due to impaired placental transfer of nutrients to the fetus and there is also impaired transport of IgG (Papadatos *et al.* 1970). The level of IgG found in infants who are small-for-gestational-age is significantly less than that of those who are of the same gestational age but of normal weight. However the levels of IgG in the small-for-gestational-age infant are still greater than those of infants of the same body weight who are born prematurely.

Studies of IgG levels in premature infants and aborted fetuses show that fetuses of less than 20 weeks' gestational age have IgG levels under 1 g/l (Hobbs & Davis, 1967). At 16 weeks, IgG1 may be detected in fetal serum, followed by IgG2 and IgG3; IgG4 is detected by 22 weeks (Chandra, 1976). Fetuses or premature infants of less than 32 weeks gestational age usually have an IgG level of less than 4 g/l. The levels of IgG antibodies at full term are usually above 14 g/l (Chandra, 1976). After 32 weeks of gestation, total IgG concentrations in the mother and fetus are similar, and at birth IgG levels in cord blood of a full term infant tend to be higher than the corresponding paired maternal samples (Kohler & Farr, 1966; Carlsson *et al.* 1976; Iikura *et al.* 1989; Lovegrove, 1991; Lovegrove *et al.* 1994).

Fig. 1 shows results from a study of 20 normal mothers and their offspring of cows' milk β-lactoglobulin IgG antibody levels in maternal and cord serum samples (Lovegrove, 1991). The concentration of cows' milk β-lactoglobulin IgG antibodies in cord serum was higher compared with the concentration in the maternal serum. The same relationship was found if the levels of total IgG were compared. This implies that IgG antibodies are actively transported from mother to fetus across a concentration gradient. Maternal and cord serum antibody levels were found to be significantly correlated.

The significance of this antibody transfer is not clearly understood. It affords a degree of passive immunity for the first 3 months of the infant's life. Gill *et al.* (1983) demonstrated that immunization of the mother at 5–9 months of pregnancy with tetanus toxoid produced

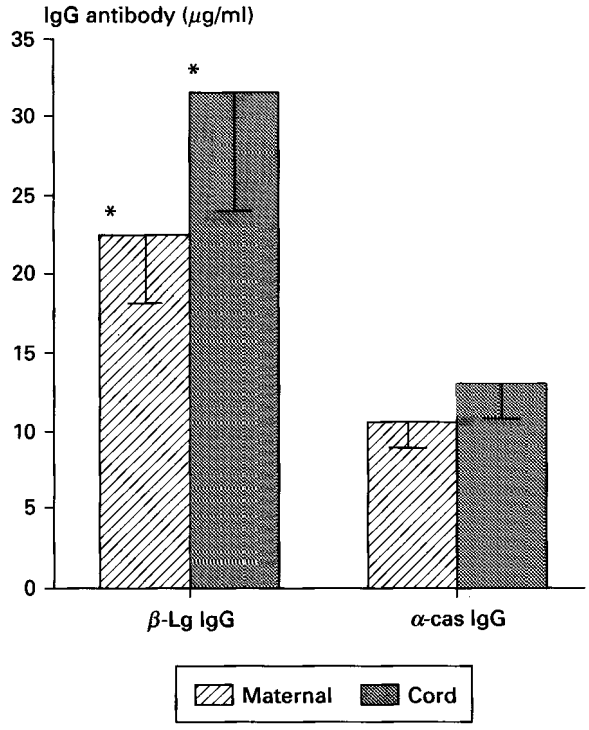

Fig. 1. Cows' milk β-lactoglobulin IgG antibody levels in maternal and cord serum samples. Cord serum β-lactoglobulin IgG levels were significantly higher than maternal serum β-lactoglobulin IgG levels ($P < 0{\cdot}05$). Modified from Lovegrove (1991). β-Lg, β-lactoglobulin; IgG, immunoglobulin G; α-cas, α-casein.

active immunization of the fetus. The importance of maternally derived IgG antibodies as a protection against neonatal infection is supported by the finding that there is a correlation between low levels of type-specific serum antibodies and the risk of sepsis with type III group B *Streptococcus* (Baker & Kasper, 1976; Baker *et al.* 1981; Oxelius *et al.* 1983).

The significance of the transfer of IgG antibodies *via* the placenta and the subsequent development of allergy is less clear. Casimir *et al.* (1985) reported that a high level of IgG antibodies to β-lactoglobulin in cord blood protected against the development of cows' milk protein allergy in the infant. Another study, however, showed an association between increased cord blood total IgG antibody levels and later development of atopic disease (Iikura *et al.* 1989). In contrast, Høst *et al.* (1992) found no association between cord blood total IgG and IgG subclass antibody levels against β-lactoglobulin and bovine whey and the risk of cows' milk protein allergy development in the infant. The discrepancies in these studies may be explained by different definitions of the term allergy, diagnostic criteria and the specificity of the IgG quantified. Therefore the association of maternally derived IgG antibodies in relation to the development of allergies is far from certain.

Maternal antibodies, in addition to providing passive immunity for a limited period, may be able to enhance infant antibody production when present in small amounts (Levi *et al.* 1969; Dawe *et al.* 1971), thus playing a role in advancing immune competence in the infant. In addition to maternally derived IgG antibodies, the passage of intact maternal lymphocytes *via* the placenta to the fetus has also been implicated (Mohr, 1972). Although lymphocytes traverse the placenta in small numbers and are viable for a short time only,

they might play a role in passing information to the fetal cells or recruiting fetal cells during an immune reaction.

PLACENTAL ANTIGEN TRANSFER

During gestation the developing fetal immune system has the protection of the maternal environment. The placenta provides a physical barrier, selectively preventing the passage of potentially damaging agents from reaching the fetus. However, clinical evidence is accumulating which suggests that antigens may pass across the placenta in a form which could elicit an immune response in the developing neonate. This was initially suggested when reports of shared neonatal and maternal infections were observed at birth (Gill, 1973).

Pathogenic antigens are not the only ones which are involved in shared sensitization in the mother and infant. Antigens which are non-pathogenic are also involved (Leiken & Oppenheim, 1971). Common allergens such as grass pollen, ragweed, moulds and dust have been implicated in shared sensitization (Kaufman, 1971; Hashem, 1972). Indirect evidence for placental antigen transfer was presented by Ratner (1922) and by Van Asperen *et al.* (1983) implicating intra-uterine sensitization in infants in whom the first contact with a specific food led to allergic symptoms.

Evidence for the placental transfer of antigens including foods (egg and bovine proteins) in rabbits was documented as early as 1902 by Ascoli. Stronger evidence for this placental antigen transfer was provided when maternally derived food proteins, β-lactoglobulin, gliadin and hens' egg ovalbumin were quantified in cord blood samples of atopic and non-atopic mothers (Lovegrove *et al.* 1991; Morris, 1991). Transfer of potentially harmful antigens across the placenta seems somewhat surprising as the placenta is believed to be a protective barrier for the developing fetus. However, the transfer of food derived antigens across other physiological barriers, for example the intact gut mucosa, has been well documented in healthy adults (Paganelli & Levinsky, 1980; Husby *et al.* 1986; Lovegrove *et al.* 1993*a*), in individuals suffering from eczema (Jackson *et al.* 1981) and in individuals with cows' milk protein allergy (Jackson *et al.* 1981; Heyman *et al.* 1988; Husby *et al.* 1990; Schrander *et al.* 1990).

The significance of the transfer of antigens from mother to fetus appears in some cases to be associated with the development of tolerance in the fetus (Firer *et al.* 1987). Tolerance is defined as the inability of an individual to produce a specific antibody in response to an ingested antigen and is the most important protective, homeostatic function of the gut associated lymphoid tissues. Its induction is probably the most important factor preventing development of food allergy in animals and humans (Ferguson & Watret, 1988). However, the transfer of antigens may in some cases be associated with unwanted sensitization, which could have important clinical implications regarding possible fetal sensitization and subsequent allergy development (discussed below).

HUMAN MILK ANTIBODY TRANSFER

Discussion of the physiology of gut maturation with respect to permeability to macronutrients, e.g. proteins, is beyond the scope of this review. The timing of the reduction of permeability to proteins has been determined with some degree of certainty in experimental animals (e.g. mice and rats) and also domestic animals (e.g. pig) but not as yet in humans (Mehrishi, 1976). Until the reduction in permeability to proteins occurs, the

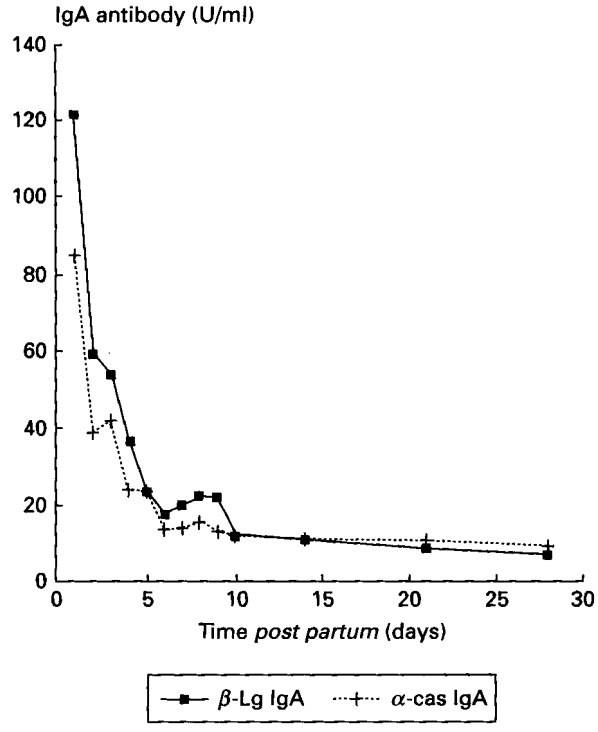

Fig. 2. Cows' milk β-lactoglobulin and α-casein specific IgA breast milk antibody levels for a 28 day period postnatally. Significant reduction in β-lactoglobulin and α-casein specific IgA levels from day 1 to 5 ($P < 0{\cdot}001$). Modified from Lovegrove, 1991. β-Lg, β-lactoglobulin; IgA, immunoglobulin A; α-cas, α-casein.

infant is immunologically immature, and the transport of maternal immunoglobulins *via* breast milk makes a very important contribution to an infant's immunocompetence.

The unique properties of human milk have received much attention over the decades; it is believed to be the most appropriate food for a normal healthy infant. In addition to the provision of energy and nutrients human milk also contains components such as lactoferrin, lysozyme and antibodies, the levels of which depend on a number of factors, of which maternal nutritional status is the most important (Hennart *et al.* 1991). The predominant antibodies in breast milk are sIgA antibodies with lower levels of IgG and IgM (Hanson & Winberg, 1972; Ahlstedt *et al.* 1975; Jatsyk *et al.* 1985). The breast milk sIgA in the gut of the suckled infant appears to be involved with blocking adhesion of potential pathogens to mucosal epithelial cells and complexing with potential pathogens to facilitate their clearance (Slade & Schwartz, 1987). It has recently been reported that breast milk sIgA antibodies benefit the infant by activating infant monocytes *via* receptors (Padeh *et al.* 1991), in addition to stimulating gastrointestinal humoral immunogenic development (Koutras & Vigorita, 1989). These factors illustrate some of the benefits of breast milk over formula milk to the immunologically immature infant.

The transferred sIgA antibodies act against a wide variety of microorganisms and their products, as well as harmless substances such as food proteins (Machtinger & Moss, 1986; Ladjeva *et al.* 1989). Fig. 2 shows the change in the concentration of specific IgA antibodies against cows' milk β-lactoglobulin and α-casein in breast milk from twenty normal healthy women (Lovegrove, 1991). The initial mean value for β-lactoglobulin specific IgA

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(121 U/ml) fell, so that by day 5 *post partum* the mean value was 24 U/ml and by day 28 the mean value was 7 U/ml. This represents a typical profile over time for milk specific sIgA antibodies in breast milk (Cruz & Arévalo, 1985). Earlier, work by Carlsson *et al.* (1976) reported a similar profile for sIgA against other antigens such as *Escherichia coli*. However Cruz & Arévalo (1985) did not confirm this; the profile they reported showed no regular pattern with time in the concentration of sIgA against *E. coli*.

An increased risk of developing an adverse reaction to foods in infants has been reported to be associated with a lack of sIgA antibodies specific to food antigens in maternal breast milk, although the mechanism of this action is not clear (Hanson *et al.* 1977; Machtinger & Moss, 1986; Renz *et al.* 1990). It has been postulated, however, that to quantify maternal breast milk sIgA antibody levels may act as an important screening technique for the identification of high risk infants. Infants born to women who present with low levels of breast milk sIgA may have a higher risk of allergy development than those infants born to women who present with average levels of breast milk sIgA (Machtinger & Moss, 1986; Lovegrove, 1991). This is an interesting concept that requires further research, and may prove to be an easy, non-invasive screening technique for infants potentially at risk for the development of adverse reactions to food or other allergy symptoms.

The levels of sIgA antibodies in mature breast milk are approximately 20 times those of IgG (Jatsyk *et al.* 1985). Recent research shows that the latter are principally responsible for surface phagocytosis in the infant, a function not associated with sIgA. This action of the IgG antibodies illustrates their invaluable benefit to the infant (Avery & Gordon, 1991).

In addition to preventing the development of allergy, antibodies transferred from the mother to the infant are believed to contribute significantly to the prevention of infantile infection (Carlsson *et al.* 1976; Hanson *et al.* 1977; Cruz & Arévalo, 1985; Machtinger & Moss, 1986).

Human colostrum and mature milk also contain a variety of cells. Most of these cells are neutrophilic granulocytes and macrophages. Their numbers decrease sharply after the fourth day and more gradually thereafter over several months (Ogra & Ogra, 1978). These cells include short lived and long lived cells, antibody forming cells, primed (memory) cells, and unprimed cells. It seems likely that some of these cells exert a protective role in the gastrointestinal tract of the newborn infant, and that others penetrate the circulation of the recipient newborn infant.

HUMAN MILK ANTIGEN TRANSFER

The presence of antigens in breast milk, both in individuals who have a genetic predisposition to allergy development and those who do not, is undisputed. More than 75 years ago Talbot (1918) reported that eczema in a 3-week infant was due to chocolate eaten by the mother who is breast feeding. Jakobsson & Lindberg (1978) showed that infantile colic could often be relieved by removing cows' milk from the mother's diet. Lifschitz *et al.* (1988) showed that removal of cows' milk from the mother's diet resolved all allergic symptoms previously encountered by her infant. More recently the direct quantification of food antigens in breast milk has been performed by a number of groups. The presence of antigens in breast milk has been reported thus: ovalbumin (Kilshaw & Cant, 1984; Morris, 1991); β-lactoglobulin (Kilshaw & Cant, 1984; Jakobsson *et al.* 1985; Axelsson *et al.* 1986; Machtinger & Moss, 1986; Cavagni *et al.* 1988; Høst *et al.* 1988; Lovegrove, 1991); and gliadin (Troncone *et al.* 1987; Morris, 1991). Using sensitive immunoassays, levels of antigens have been reported to be in the range 0·2–800 ng/ml. The levels vary greatly, and are influenced by the specific food protein assayed, the type of assay used, inherent individual variation and, to a much lesser extent, the dietary intake of the individual.

The total amount of antigen in milk varies according to the antigen measured. So, for example, Harmatz *et al.* (1986) and Telemo *et al.* (1986) reported, in rodent models, that significantly less bovine serum albumin and bovine γ globulin were present in the breast milk compared with ovalbumin and β-lactoglobulin. These differences may be explained by preferential clearance of antigens into maternal tissue other than mammary glands, or by the existence of specific transport mechanisms for certain proteins in the mammary gland (Harmatz *et al.* 1986; Telemo *et al.* 1986).

The presence of antigens, including food antigens, in breast milk is not restricted to atopic individuals, and is therefore a natural occurrence. A possible explanation for the existence of antigens in breast milk could be the development of oral tolerance in the suckled infant (see below). Exclusive breast feeding does not prevent some infants from allergy development, suggesting a possible disadvantage of this antigen transfer (Hattevig *et al.* 1989). It is probable that antigens transferred to the infant *via* breast milk may have the ability to sensitize the high risk infant, resulting in subsequent allergy development (Jakobsson & Lindberg, 1978; Cant *et al.* 1985; Machtinger & Moss, 1986; Lifschitz *et al.* 1988). It has been speculated that since the antibody titre to numerous dietary substances decreases with age and reaches a stable low level at about 40–50 years for most individuals, the eventual development of oral tolerance could be the result of continued antigen absorption (Rothberg & Farr, 1965; André *et al.* 1975).

DEVELOPMENT OF TOLERANCE IN THE NEONATE

Typically, oral (intestinal) exposure to foods or other foreign protein antigens either induces systemic immunological hyporesponsiveness (oral tolerance) or sensitizes the immune system, possibly by gut associated lymphoid tissue. The acquisition of tolerance to foods is a multifactorial process and is coregulated by genetic influences.

Cramer *et al.* (1974) suggested several mechanisms by which the maternal environment may influence the immunological development of the offspring, none of which, the authors claimed, need be mutually exclusive: first, the passage of maternal antibody *via* the placenta with alteration of fetal immune response by specific antibody; secondly, the passage of immunological information products, such as transfer factor, from mother *via* the placenta; thirdly, active migration of sensitized maternal lymphocytes to the fetus, with proliferation and participation in the immune response or recruitment of fetal lymphocytes for specific response; lastly, the transplacental passage of antigen to the fetus and direct sensitization of its lymphocytes. In addition to the above mechanisms of maternal influence, maternal anti-idiotype IgG antibody transfer has been implicated as being the most likely stimulus in the fetus for the production of antibodies to allergens before birth (Hanson *et al.* 1989; Hahn-Zoric *et al.* 1993).

For ethical reasons many studies investigating the immunological mechanisms of oral tolerance development have been performed in animals. Using rodent animal models, different groups have studied the role of the liver in modulating the immune response to dietary antigens (Thomas *et al.* 1976), have implicated suppressor T-cells in Peyer's patches (Ngan & Kind, 1978), and have investigated circulating complexes of dietary antigen and antibody (André *et al.* 1975). Pathirana *et al.* (1981) reported the importance of perinatal exposure to dietary proteins in the induction of tolerance to food antigens in rabbits. More recently investigators have attempted to evaluate, in humans, the role and integrity of the gastrointestinal mucosa in the host response after oral antigen exposure (Walker-Smith, 1992; Businco *et al.* 1992). To extrapolate evidence derived from animal experiments to man is questionable, but the placental transfer of maternally derived antigens and their role in immune tolerance induction seems a plausible theory. Strobel (1992) (Table 1) has

Table 1. *Factors which influence the induction and maintenance of systemic immunologic hyporesponsiveness (oral tolerance). Modified from Strobel (1992)*

- Genetic background
- Nature of antigen (soluble, particulate, replicating)
- Dose of antigen
- Frequency of administration
- Age (maturity *v.* immaturity) at first antigen exposure
- Immunologic status (virus infection, gastroenteropathy)
- Previous dietary exposure of the mother
- Antigen transmission *via* breast feeding

suggested factors which could be important in determining whether the antigen will induce stimulation or tolerance.

Although acquisition of tolerance is usual, it is known that some infants become sensitized to certain antigens. Miller *et al.* (1973) demonstrated for the first time the capability of the fetus to synthesize IgE as early as 11 weeks in lung and liver, and at 21 weeks in the spleen. Elevated cord serum total IgE antibody levels have been implicated as a risk factor for the development of allergy or intolerance to food or other substances (Høst *et al.* 1992). Cord serum total IgE levels are now routinely used as a screening tool in studies investigating 'at risk' infants (Arshad *et al.* 1992). Reagins (antibodies responsible for anaphylactic reactions), presumably IgE, are known not to cross the placenta (Kuhns, 1965), so IgE present in cord serum is probably derived from the fetal circulation as long as blood mixing has not occurred at birth. Synthesis of IgE in the fetus may be due to a number of factors none of which has been elucidated.

The mechanisms involved in the development of tolerance or sensitization in the neonate have been reviewed by Strobel (1992). Results from studies in rodents suggested that perinatal antigen exposure was more likely to prime the immune system rather than to induce tolerance, and that continuous feeding beyond the critical neonatal period may lead to induction of tolerance (Strobel, 1992).

Evidence seems to indicate that antigen exposure in the fetus *via* the placenta, or in the infant *via* breast milk or formula milk can sensitize those who have a predisposition to the development of allergy. It therefore seems prudent to protect the high risk infant from exposure to foreign antigens by the elimination of antigen exposure.

HUMAN MILK AS A PROTECTION AGAINST ALLERGY

There is still controversy concerning the protective effect of breast milk as opposed to cows' milk formula, against the development of atopic diseases. Since the hallmark study of Grulee & Sanford (1936), which demonstrated that breast feeding compared to cows' milk formula ingestion reduced the development of eczema 7-fold in a group of 20000 infants, many dietary prevention studies have attempted to confirm their findings but they have produced conflicting conclusions.

Two extensive publications reviewed the role of breast feeding in protecting the infant from allergy development (Zeiger, 1987; Kramer, 1988). Zeiger discussed the large number of confounding variables and exposed weaknesses in the numerous studies reviewed. These included: timing and control of solid food introduction; lack of blind assessments of allergy development; failure to document compliance; lack of immunological documentation; differential environmental control measures in groups; high dropout rates; small sample

size; brief duration of breast feeding. Due to these confounding variables, comparison of the studies was, in many cases, inappropriate. However Zeiger concluded that breast feeding seemed to have a protective effect, compared with formula feeding, against infant allergy development.

Kramer (1988) evaluated 36 original studies published between 1936 and 1986 and sought to find whether those studies which confirmed a protective effect of breast feeding in the development of allergy were better conducted than those which reported no protective effect. Biological and methodological aspects of cows' milk exposure, outcome (allergic conditions) and statistical analysis were assessed. The author concluded that most studies had weaknesses in various areas, preventing direct comparison one with another, and went on to state that "the inconsistent findings, even among the better studies, prevents any firm inferences, although it seems likely that the results from the larger high-quality studies could be compatible with a large protective effect of breast feeding".

Feeding an infant human milk does seem to have some protective effect on infant allergy development, although even exclusive breast feeding does not eliminate the risk of allergy development (Jakobsson & Lindberg, 1978; Chandra *et al.* 1986). A possible explanation for the lack of conclusive evidence for the benefit of breast milk, compared with infant formula feeding, in the risk of allergic disease development is that in non-randomized trials atopic mothers are more inclined to breast feed their infants than are non-atopic mothers. Additionally, the possible influence of maternal dietary protein transfer to the infant *via* the placenta or breast milk has not, in the majority of studies, been considered.

So, although it appears that breast feeding may reduce the incidence of allergy during early childhood (Chandra *et al.* 1989; Morris, 1991), this protection seems to be lost at about 9 years of age (Pöysä *et al.* 1989, 1991). This theory was supported by Åberg *et al.* (1989), who reported a significantly lower cumulative incidence of allergic disease during the first three years of life in breast fed children with a double-parental history of allergy, compared with children having a history of allergy in one or in neither parent. However, at the ages of 7, 10 and 14 years, diet in infancy had no influence on the incidence of atopy, irrespective of parental status. These studies suggest that the effect of breast feeding is to delay the onset of allergic disease, rather than to decrease the overall risk of becoming allergic during childhood, but more strictly controlled studies are necessary to confirm this conclusion.

MATERNAL ELIMINATION DIETS

Before introducing the subject of maternal elimination diets it seems appropriate to highlight the problem of how to define the allergic condition from which an individual is suffering, in these types of studies. In most publications mothers are described as being 'atopic', although there is no evidence presented that the mothers have inherited the allergic condition. Strictly speaking the words 'atopy' and 'atopic' should be used only to refer to an inherited condition of adverse reactions involving the immune system (Savin, 1993).

There are reports of studies which have observed sensitization of infants by transferred food proteins (Van Asperen *et al.* 1983; Cant *et al.* 1985; Lifschitz *et al.* 1988). It would therefore seem that elimination of the suspect protein or proteins from the mother's diet during pregnancy, lactation, or both could reduce the risk of the infant developing an adverse reaction to foods.

The value of maternal dietary elimination in reducing or preventing the risk of allergy development in the infant during pregnancy and/or lactation has been studied. Owing to the restrictive nature of any dietary elimination regimen, the timing of dietary intervention

must be carefully defined for maximum benefit to the infant and minimum inconvenience to the mother. In 1986, Chandra and colleagues performed a study on 121 women who already had an offspring with an allergic condition. These women were randomly allocated into an antigen avoidance group or a control group. Milk, dairy products, egg, fish, beef and peanuts were eliminated from the diet throughout pregnancy and lactation in the food avoidance group. Infants born to mothers in this group had a reduced occurrence, and milder form, of atopic eczema compared with those infants in the control group. The benefit of a reduced exposure of infants to allergenic proteins during gestation and lactation was also observed by Zeiger *et al.* (1989), who reported a more ambitious programme. Mothers with a history of allergy followed a diet excluding milk, dairy products, eggs and peanuts during the last trimester of pregnancy and lactation. A casein hydrolysate formula was given to the infant at weaning, with the avoidance of solid food until the infant was 6 months of age. Despite this protocol, the accumulated incidence of atopic disease up to 36 months of age in the offspring treated prophylactically was: food allergy development, 14%; eczema, 12%; infectious asthma, 12%; allergic rhinitis, 7%. The authors concluded that the two most obvious factors responsible for the above findings were a genetic predisposition to allergy development and parental non-compliance.

Lovegrove (1991) and Lovegrove *et al.* (1993*b*, 1994) studied a group of 38 mothers from 36 weeks gestation to 18 months *post partum*. They investigated the effect of a maternal milk free and milk product free diet (cows', sheep and goat) during late pregnancy and lactation on the incidence of eczema in the offspring. Women who presented with clinically diagnosed allergic conditions, defined for the purposes of this review as atopic, were randomly allocated to a prophylactic group, on a milk and milk product free diet (with calcium supplementation and a whey hydrolysate formula consumption advised, $n = 12$), or an unrestricted diet group ($n = 14$). These women were compared with a third group of non-atopic women on an unrestricted diet ($n = 12$). At 18 months of age, the incidence of eczema in the offspring of the atopic women on the unrestricted diet was significantly higher than in those of the atopic group prophylactically treated with the restricted diet ($P < 0{\cdot}005$); the eczema incidence in the infants in the prophylactic group was similar to that of the non-atopic women on an unrestricted diet. No significant differences were observed for β-lactoglobulin or α-casein IgG levels in cord serum or infant serum between the three groups of infants. However, there was a trend for infants born to atopic women on the unrestricted diet to have elevated serum cows' milk specific IgG antibody levels compared with serum levels from infants born to non-atopic women or to atopic women on a restricted diet.

Contrary to the findings of the studies described above, another group has reported that maternal dietary restriction during pregnancy and lactation had a limited effect on the atopic outcome of the infants (Lilja *et al.* 1989, 1991). This group investigated the immunological consequences and atopic outcome of a range of maternal dietary regimens on 163 infants born to atopic women. The diets ranged from high quantities of cows' milk (1 litre per day) and egg (1 per day) to low quantities of cows' milk and egg (although the diet was not completely free from these foods) during late pregnancy and lactation. This 'high' and 'low' antigen intake was in contrast to a total exclusion diet reported in most other studies. Results of the study showed that maternal intake of cows' milk and eggs did not affect total IgE antibody levels in the infants up to 18 months of age (Lilja *et al.* 1991) and dietary manipulation did not affect the development of atopic symptoms in the infants at 18 months *post partum* (Lilja *et al.* 1989). It is possible that the less than rigorous nature of the dietary regimen contributed to these inconclusive results.

The studies described above have observed varying degrees of benefit to the high risk infant in terms of the development of adverse reactions to foods resulting from maternal

dietary avoidance during pregnancy and lactation. Although the quantity of milk and eggs had limited effect on the development of allergy, in order to evaluate the importance of intervention in either pregnancy or lactation, studies have been conducted to investigate each period in isolation.

MATERNAL ELIMINATION DIET DURING PREGNANCY

Fälth-Magnusson & Kjellman (1987) and Fälth-Magnusson *et al.* (1987, 1988) conducted a study on 212 atopic women in Sweden. The women were randomly allocated to a diet group taking no cows' milk or eggs from week 28 until delivery, with extra calcium and casein hydrolysate formula consumption advised, or a control group following an unaltered diet. No significant differences were observed in specific cord blood IgE levels against cows' milk and eggs in either of the groups, although a significant decrease in maternal serum total IgG levels was observed in the group that complied with the restricted diet. The mothers' ingestion of cows' milk and egg during lactation did affect the immunological response of the infant to these antigens as the IgG levels were lower in the diet restricted infants compared with the control group. In addition the authors reported that the specific IgG levels to gliadin were lower in the diet restricted group than in the control group even though this food protein had not been restricted in the mothers' diets. However no protection was subsequently observed against the development of clinical signs and symptoms associated with allergy in infants up to 18 months of age.

Lilja *et al.* (1988), in an early publication of their longitudinal study, described above, investigated the effect of the consumption of various quantities of egg and milk protein in a maternal diet during the last trimester of pregnancy on the outcome of allergy in their offspring. Women ($n = 165$) with respiratory allergies and their infants were observed. Although the maternal serum total IgG antibody levels were reduced, due to the elimination of these foods from the maternal diet, the cord blood total IgE and total IgG antibody levels did not change significantly. They also observed no significant differences in the distribution of atopic disease among the infants in relation to maternal diet during pregnancy.

MATERNAL ELIMINATION DIETS DURING LACTATION

According to Jakobsson & Lindberg (1978), the removal of cows' milk from the mother's diet while she is breast feeding will 'cure' colic in her infant. Cant *et al.* (1986) reported that maternal dietery exclusion of cows' milk and eggs benefited some breast fed babies with eczema.

In an ambitious study undertaken by Chandra *et al.* (1989), mothers who were breast feeding their infants ($n = 97$) were randomly allocated to a restricted diet group avoiding milk, dairy products, eggs, fish, peanuts and soya ($n = 48$), or an unrestricted diet group ($n = 49$). Mothers who bottle fed their infants ($n = 124$) were directed to use cows' milk formula or soya formula or a casein hydrolysate. The incidence of signs and symptoms associated with an allergic condition was greatly affected by the infant formula used, with the incidence of eczema at 70%, 63% and 21% to cows' milk formula, soya formula and casein hydrolysate respectively. The authors also observed that eczema was less common and milder in babies who were breast fed and whose mothers were following the elimination diet.

Hattevig and colleagues (1989, 1990) investigated the effect of a strict maternal elimination of milk, eggs, and fish during the first 3 months of lactation on 155 babies. The

cumulative prevalence of allergic manifestations up to 6 months of age was higher (28%) in the control babies compared to the elimination diet babies (11%; $P < 0{\cdot}05$). The elimination diet also improved the relationship between mild and severe atopic dermatitis. This difference was only transitory, for after 6 months the difference between the two groups had disappeared.

In a prenatal, randomized, control study of 120 infants with a family history of allergy and high cord blood IgE levels the prophylactic group avoided the consumption of milk, egg, fish and nuts during lactation (Arshad *et al.* 1992). As the presence of house dust mite in an infant's room is known to influence infant allergy development (Sporik *et al.* 1990), Arshad and colleagues also instructed the mothers in the prophylactic group to reduce the levels of house dust mite by vigilant house cleaning. The result of this combined regimen was to reduce the incidence of allergy by 50% within the first 12 months of the infant's life although long term follow-up was not reported.

Thus it appears that maternal dietary elimination during lactation, rather than in pregnancy, may afford some protection to the high risk infant. In the majority of studies in which elimination diets are used by mothers nursing high risk infants a significant decrease in the incidence and severity of atopic eczema and other allergic manifestations that occur during the first year of life are reported. Whether these diets will afford long term protection from the development of atopic disease in high risk individuals is unclear and requires further long term studies.

MATERNAL ELIMINATION DIETS AND NUTRITIONAL STATUS

Prophylactic elimination diets prescribed for mothers in pregnancy or lactation are not usually as rigorously enforced as those prescribed for adults with a suspected food allergy. Although no one specific food is required in a diet, individual foods (e.g. cows' milk) are useful sources of essential nutrients (e.g. calcium and riboflavin). Care must be taken to ensure that a nutritionally complete diet is consumed when any type of elimination diet is prescribed. Medical and/or dietetic supervision is essential.

In the dietary intervention study conducted by Lovegrove and colleagues (1994) in which atopic mothers excluded milk and milk products in the latter stages of pregnancy and during lactation, their energy and nutrient intakes were assessed by a 7-day weighed food intake and compared with the intakes of mothers following an unrestricted diet. The mean energy and nutrient intakes in both groups were similar with the exception of the lower mean daily intake of calcium in the diet-restricted group ($P < 0{\cdot}001$, Table 2). Indeed, none of the subjects in the diet-restricted group received, from a dietary source, a mean daily intake of calcium that reached the reference nutrient intake of calcium (700 mg/d; Department of Health, 1991). However, all women in this group were supplied with a calcium supplement (1 g/d derived from $CaCO_3$). One factor responsible for the high polyunsaturated to saturated (p:s) fat ratio in the diet restricted group was the omission of milk and milk products from their diet.

It is therefore important to monitor energy and nutrient intakes during any dietary restriction, and to give supplements where appropriate. Supplementation with calcium is usually carried out in studies where milk and milk products are eliminated from the diet (Fälth-Magnusson *et al.* 1987; Lilja *et al.* 1991; Lovegrove *et al.* 1994).

Table 2. *Daily energy and nutrient intake of atopic women in restricted diet group (diet) and women in unrestricted diet group (control) at approximately 36 weeks gestation calculated from seven day weighed food inventory. (Modified from Lovegrove, 1991)*

Nutrient	Control group ($n = 12$)		Diet group ($n = 14$)	
Energy (MJ)	10·0 (2·1)	[7·0–14·3]	8·9 (3·2)	[3·8–15·7]
Protein (g)	84 (19)	[50–122]	77 (29)	[34–151]
Carbohydrate (g)	300 (98)	[201–579]	285 (105)	[122–459]
Fat (g)	103 (22)	[67–151]	86 (40)	[33–172]
P:S ratio	0·20 (0·10)*	[0·12–0·40]	0·50 (0·20)*	[0·19–1·00]
Calcium (mg)	1261 (411)*	[860–2297]	434 (135)*	[236–667]

Values are given as mean (SD) [range].
P:S, polyunsaturated:saturated fat.
* Significant difference between diet and control groups ($P < 0·001$).

CONCLUSION

Parents who are known to be atopic should be made aware that their offspring may develop allergic symptoms. They may wish to minimize this risk by adopting certain strategies to decrease the chance of sensitizing the infant. One strategy that has been studied, and which appears to be successful, is for the breastfeeding mother to avoid foods which contain allergenic proteins. The benefit to the high risk infant of maternal dietary intervention during pregnancy is less evident. Some workers advise the avoidance of allergenic foods in the last two or three months of pregnancy to decrease the chances of sensitizing the infant *in utero*. There are other factors which also influence the development of conditions associated with adverse reaction to food and other environmental substances in infancy. These include the timing and types of weaning foods introduced into the infant's diet, inhaled airborne allergens and maternal smoking habits. As no single mechanism is sufficient to explain the many forms of reactivity which are present in this condition, it would appear that a simple means of preventing the development of allergy in infancy does not at present exist.

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