Prevention of Atopy—Current Concepts and Personal Experience

Luisa Businco and Arnaldo Cantani

Recent advances in knowledge of the innate mechanisms of mucosal immunity and their potential role in mucosal infections, food allergies, and other disorders that may be immunologically mediated have important implications for the development of rational therapeutic strategies. In addition, it is increasingly apparent that the mucosal immune system has powerful regulatory mechanisms that allow it to react selectively to substances found in the mucosal environment.[1]

This chapter reviews our understanding of the immunological mechanisms concerned with the mucosal immune system, especially as they apply to preventive measures. We also shall discuss the results of our recent studies.

Mucosal Immune System

The prominence of IgA in mucosal secretions and its abundance in adjacent tissues suggest its crucial role in local resistance. Secretory IgA (sIgA), which may be considered the hallmark of the mucosal immune system, is largely derived from IgA precursor B lymphocytes found in abundance in gut-associated lymphoid tissue (GALT) and in bronchus-associated lymphoid tissue (BALT).[2] The major sources of these cells are Peyer's patches and bronchial lymphoid tissue.

It has been shown that IgA-bearing cells generated in GALT travel by lymphatics to mesenteric lymph nodes (MN) where they divide and differentiate. From the MN, cells proceed via the thoracic duct to the blood, when they appear to home selectively to the lamina propria of various mucosal surfaces, principally in the intestine, to become IgA plasma cells.[3] However, it is not yet clear whether repeated antigen stimulation or particular T cells (or both) play the predominant role in driving B cells to become IgA producers.[4,5]

The gastrointestinal tract has a unique role in relation to food allergic diseases. The development of mucosal immune responses to dietary as well as to microbial and other environmental antigens represents a first line of defense against the penetration of these antigens. It is generally agreed that the intestinal mucosa is immature in the newborn period at a time when it is exposed to a wealth of macromolecular antigens.[6] It also has been shown that large molecules can reach the circulation via persorption, thus coming into contact with other parts of the body where nonspecific damage might occur,[7] especially in at-risk infants.

The majority of gut lymphocytes are T cells and, like all T cells, derive from precursors that are in the thymus.[8] More immediate precursor cells are stimulated by antigens in the lymphoid tissue, such as the Peyer's patches. Their cycle is analogous to the differentiation pathway of the precursors of intestinal IgA-producing plasma cells from B cells, which are also stimulated in the Peyer's patches. The functional properties of the gut T cells have been extensively studied.[9-11] The terminal maturation of B cells is controlled in a positive fashion by helper T cells and macrophages that present not only antigens but also many polyclonal activators, including pokeweed mitogen, to B cells. A separate network of T cells, called suppressor T cells, regulates the maturation of B cells in a negative fashion. As the precursors of suppressor T cells emerge from the thymus, they are activated into the final effectors of suppression by interaction with antigens or mitogens as well as with inducer or activator cells.[5,8,12] Helper and suppressor T-cell subsets are not static but remain in a state of dynamic balance via a number of complex circuits.[13] The helper T-cell subset provides help for B cells and at the same time induces a set of suppressor T cells. The suppressor T cells in turn inhibit the antibody response. This process has been called feedback suppression.[14]

In both animals and humans, the majority of intraepithelial T cells have a suppressor/cytotoxic phenotype rather than a helper-inducer one. In contrast, human lamina propria T cells have mainly a helper/inducer phenotype.[15] It may take years to analyze how this complex environment affects the cellular interactions and regulatory events that determine the immune response in GALT.

Recent Advances in Mucosal Immunoregulatory Mechanisms

Of the immunoregulatory mechanisms characteristic of the mucosal immune system, the best known involves the formation of suppressor T cells after oral administration of antigens.[16] An important feature of this suppressor cell response is that it may be immunoglobulin class-specific. Consequently, the suppression may affect largely IgM or IgG responses rather than IgA responses. Evidently a dual activation of helper cells for the IgA system and suppressor cells for IgM and IgG synthesis occurs.[16]

In studies analyzing the regulation of mitogen-induced Ig synthesis, it was found that cloned T cells act as switch cells that induce IgM B cells (and only these cells) to differentiate into IgA B cells. Furthermore, cells bearing IgA, but not cells secreting IgA, are produced under the influence of the IgA switch

T cells. Additional and different helper cells are necessary for terminal differentiation into IgA secreting cells.[17]

A second mechanism of mucosal immunoregulation may involve nonspecific induction of suppressor T cells. In particular, it has been shown that bacterial endotoxin or lipopolysaccharide (LPS) in the gastrointestinal lumen can induce a nonspecific suppression of mucosal immune responses.[18] It has been proposed that in the normal gastrointestinal tract, LPS either induces suppressor cells directly, or it induces activation of cells, eg, B cells and macrophages, which in turn induce feedback suppressor T cells.[18] The exact significance of these observations and their relation to the phenomenon of oral tolerance is speculative at present.

Physiological Uptake of Macromolecules

The initial events in the process of macromolecular transport in the small intestine appear to be the adsorption and subsequent endocytosis of antigens by the microvillous membrane. Soluble proteins interacting with the surface of the gut stimulate the invagination of that surface to form small vesicles. After invagination, macromolecules are transported within larger, membrane-bound phagosomes. Intracellular digestion occurs when lysosomes combine to form phagolysosomes. However, some macromolecules may bypass this digestive process to be released into the intercellular space by an exocytotic process and to be taken up into the circulation. Alternatively, macromolecules may cross the tight-junction barrier between cells and diffuse into the intercellular space.[19] Under normal conditions, macrophages and plasma cells present in the lamina propria of the small intestine or Kupffer's cells in the liver (fixed reticuloendothelial cells) located adjacent to the portal circulation interact with absorbed antigens acting as a secondary line of defense against the penetration of antigens into the circulation.[20] Normally, the transport of molecules results in no ill effects because of these defense mechanisms. However, when excessive quantities of antigens enter the body because of interferences with intracellular capacity to digest them, or when secondary defenses are lacking or diminished, antigens may enter the circulation and contribute to clinical diseases[6] as will be discussed later.

Recently, a specialized epithelial cell known as a membranous or microfold (M) epithelial cell, has been described overlying GALT in the ileum of several species, including humans.[7,21] It has been speculated that the M cell, which has few short microvilli and no lysosomes to digest antigens that pass through,[21] may be the route whereby intestinal antigens are transported to the tissue B and T lymphocytes[15] that are present in the dome epithelium of Peyer's patches.[9] There antigen recognition occurs. The sensitized B cells then move to the regional lymph nodes, undergo maturation and ultimately seed along the mucus epithelium of many tissues, including mammary glands.[4]

However, a crucial role of the M cell as the access route for induction of intestinal mucosal immune and hypersensitivity reactions has not been confirmed. In particular, neither food proteins nor other environmental antigens have been actually shown to use the M cell as the route of access to the lymphoid tissue.[7]

Factors Modulating Antigen Uptake

Immunological Factors

Current concepts of the mucosal immune system not only suggest that IgA is the principal immunoglobulin produced locally in the wall of the intestine but also that there is a specialized mucosal immunoregulation mechanism acting via secretory IgA. Intestinal antibodies capable of inhibiting bacterial adherence may represent an important advantage in establishing an indigenous gut bacterial flora. In addition, secretory IgA that complexes with cholera toxin can prevent toxin from binding to receptors on intestinal microvillus membranes and thus interfere with the active secretion associated with toxigenic diarrhea.[20]

Intestinal antigens also become rapidly associated with antibodies present in the glycocalyx; immune complex formation prevents migration of antigen to the cellular membrane surface and interferes with pinocytosis by enterocytes. Moreover, immunocomplex formation within the intestinal lumen may trigger the release of goblet-cell mucus, which can interfere with further antigen penetration across the mucosal barrier.[22]

Nonimmunological Factors

While immune responses constitute a specific mucosal defense system, a heterogeneous group of nonimmunologic factors are said to participate in protecting the gastrointestinal barrier. Taken individually, they are incapable of mounting a controlled response, whereas their combined action contributes to the overall protection of the gut mucosa. An outline of these factors will follow.

For many decades, the importance of mucus in intestinal immunity has been known. Before bacteria can become a problem, mucus secreted by the goblet cells engulfs viable organisms, thus accelerating their elimination. Moreover, it appears that peristalsis, aided by mucus secretion, can result in removal of most foreign bodies that enter the small intestine.[23] A rise in intestinal goblet cells numbers in primary *Nippostrongylus brasiliensis* infections has been demonstrated.[24] Other evidence suggests that the goblet cell mucous coat covering the epithelial surface of the gastrointestinal tract may represent an important protective barrier against the penetration of microorganisms, toxins, and antigens present in the external environment of the lumen.[23] In addition, gastric mucus has been demonstrated to reduce the binding of toxins to epithelial cell receptors.[25] However, it is known that factors such as hormones, aging, and malnutrition can affect the molecular structure of the mucins produced. How this is achieved or the consequences of mucin structural differences has not been so far elucidated.

In addition to goblet-cell mucus, a number of other nonimmunological factors are required to adequately control macromolecular digestion and absorption at the mucosal surface.

Recent studies indicate that the glycocalyx is an active metabolic compartment that aids in the control of bacterial adherence to epithelial surfaces and interferes with attachment and uptake of antigens and enterotoxins.[26] In the neonatal stomach, low levels of gastric acid and pepsin limit gastric proteo-

lysis, while the water in secretions acts as a diluent, thus reducing the concentration of antigen.[27]

Peristaltic movements ensure that antigens, indigenous flora, and intestinal mucus are rapidly mixed, thus constituting an additional factor in controlling proliferation of bacteria within the small intestine. Impaired peristalsis, on the other hand, allows bacterial overgrowth. Peristalsis also decreases adherence of macromolecules and their engulfment by enterocytes.[28] Moreover, pancreatic enzymes adsorbed to the surface of the small intestine enhance the breakdown of antigen–antibody complexes within the glycocalyx compartment of the gastrointestinal surface, thereby diminishing the antigens available for persorption by intestinal epithelial cells.[23]

As already mentioned, reticuloendothelial cells of the liver phagocytize the noxious substances that may enter the portal circulation. The Kupffer's cells may act as a filter to deter transport into the systemic circulation. Furthermore, normal bacterial flora is promoted by lysozyme, bile salts, and specific antibodies. The normal flora protects the host by competitively inhibiting colonization with potentially harmful organisms.[22] In conclusion, decreased adherence as well as increased breakdown of macromolecules result in less availability of these antigens for adsorption to the microvillus surface and uptake via the mucosa.

Factors Enhancing Antigen Uptake

The risk of developing allergic symptoms to foods is due in part, at least, to enhanced absorption of macromolecules as a result of increased permeability of the gut during the first weeks of extrauterine life.[29,30] Passage of small amounts of these molecules induces little ill effect in most healthy adults.[20] Under normal circumstances, sIgA constitutes the first line of defense against ingress of foreign protein at the mucosal level.[31] It must be remembered, however, that sIgA is virtually undetectable at birth, possibly due to the almost nonexistent antigenic sensitization in utero. By four weeks of age, however, 92% of infants have been found to have increasing amounts of salivary IgA levels.[32] Recent studies have demonstrated that sIgA antibody levels remain relatively low only during the first six months of life.[33] In contrast, serum IgA levels increase more slowly and peak adult levels are not attained until about 10–12 years of age.[34] Thus there is a transient immunological gap during childhood, which is possibly related to enhanced macromolecular transport.

Patients with selective IgA deficiency who lack sIgA and have very low levels of serum IgA are more easily exposed to the antigenic stimulus of food proteins that may penetrate the mucosa and lead to specific antibody formation.[35] It has been reported[36] that 59% of patients with selective IgA deficiency have circulating immune complexes, 50% have milk precipitins, 23% have precipitins to bovine serum, and 13% have precipitins to fetal calf serum. These patients also have an increased frequency of allergic disease.[37] Selective IgA deficiency is the most common form of primary immunodeficiency, as is evident in Table 1.[37]

Finally, other conditions can predispose to an enhanced permeability of macromolecules within the gastrointestinal tract. These include local antibody deficiency and disruption of nonspecific defense mechanisms.[20]

Table 1. Number and Percentage of Cases of Primary Immunodeficiency Registered until April 1982, in Italian Register for Immunodeficiency

Diagnosis	No. of patients	Percentage
SCID	45	5.64
PNP-deficiency	2	0.25
DiGeorge syndrome	8	1.00
T-lymphocyte defects	58	7.27
X-linked agammaglobulinemia	33	4.14
Common variable hypogammaglobulinemia	117	14.68
IgA defect	354	44.40
Selective IgG and/or IgM defect	22	2.76
Hypogammaglobulinemia with hyper IgM	5	0.62
Immunodeficiency and short limbed dwarfism	6	0.75
Ataxia telangiectasia	50	6.27
Wiskott–Aldrich syndrome	14	1.75
Hyper IgE syndrome	12	1.50
Chronic granulomatous disease	12	1.50
Complement defects	13	1.63
Phagocyte disorders (phagocytosis chemotaxis, killing defect)	27	3.38
Chronic mucocutaneous candidiasis	19	2.38
Registered cases	797	

We shall now discuss the influence of antenatal and postnatal factors that might affect sensitization to allergens and subsequent allergies. In many instances, these predisposing factors can be identified, thus revealing the cause or the mechanism of atopy, besides suggesting a means for its prevention.

Predisposing Factors

Genetic Factors

Current information suggests that genetic factors play a paramount role in the development of atopy. It has been known for centuries that children with a parental history of atopic disease are at a high risk for the development of atopic symptoms at an earlier age. It has been found that if one parent is affected, the chances of an offspring being affected approach 50%, and if both parents are affected, this figure increases to 66%.[38] This compares to a much smaller proportion of affected children born of parents with no atopic disease.[39] Recent prospective studies have demonstrated that exclusive, prolonged breastfeeding during the newborn period and early infancy exerts a prophylactic effect on the development of atopic diseases in children at risk according to family history. In these children, atopic disease also may be postponed or its course may be less severe.[40]

Environmental Factors

In addition to genetic controls, different environmental factors seem to play a role in promoting allergic sensitization and the subsequent development of atopy. A review of these factors will follow.

Time of Birth. It has recently been suggested that the type of atopic sensitization, which may also manifest itself during later life, is dependent on the month of birth. In 1976, Soothill et al[41] found that the exposure to particular antigens during the neonatal period was strongly associated with the subsequent development of allergy. They found evidence of an increased incidence of children with positive skin tests to *Dermatophagoides pteronyssinus* among those born in September and October. In Great Britain, the maximal risk of sensitization to *Dermatoph.* is associated with this particular birth season.

Several studies have analyzed the dependence of the sensitization on the month of birth. These studies have demonstrated a significantly higher incidence of sensitization to pollens in children born in March–May, and to mites in children born in September–October.[42-44] Early in life, there may be a physiological deficit in the mechanisms acting to the exclusion and elimination of antigens[6] that, in connection with the season and place of birth, may represent a transient period of vulnerability to adverse environmental factors, predisposing to the atopic sensitization. Moreover, a high incidence of atopic diseases has been evidenced in immunodeficient patients.[45] Taken together these observations suggest that transient immunodeficiency may underlie much childhood allergy. In this regard, Juto et al[46] have recently reported that in a group of babies with a short duration of breastfeeding and early weaning to cow's milk, an altered T-cell function was detectable before the onset of allergic manifestations. These studies indicate that atopic disease is associated with imbalances between subpopulations of T cells.[47]

The implication of these observations is that exposure to allergens in early extrauterine life when the infant is known to be particularly vulnerable to penetration by harmful intraluminal substances[6,41,48] is accompanied by a high probability of sensitization and the subsequent development of atopic disease.

Prenatal Factors. Several studies suggest that infections and maternal food or drug intake may be important determinants of risk for developing atopic allergy. It has been recently reported that IgE concentrations were high in cord blood if the pregnant mothers had been administered progesterone. However, these elevated levels were not associated with an increased development of atopic diseases in the infants born to these mothers.[49] Newborn IgM levels also were not related to subsequent allergies.[49]

Can a child come into the world with atopy? Although the research in this field is scarce, some experimental and clinical observations indicate that an intrauterine sensitization is possible.

As early as 1928, Ratner demonstrated intrauterine sensitization to cow's milk proteins in guinea pigs and speculated on analogous sensitization in humans.[50] Many years later, it was found that synthesis of IgE in utero occurs as early as the 11th week of gestation.[51] In addition, it was also demonstrated that the fetus is capable of producing specific IgE antibodies to food allergens that were ingested by the mother during pregnancy. Actually, antibodies to cow's milk and soybean proteins have been detected in both the amniotic fluid and cord blood.[52-54] Because the mothers were RAST-negative to these allergens, it follows that the antibodies had been synthetized by the fetus. Several investigators have observed that sensitization in utero is a distinct

possibility. Therefore, they recommend that atopic women not ingest excessive amounts of potentially allergenic foods such as egg and cow's milk during pregnancy.[55-60]

Pediatricians sometimes observe anaphylactic reactions occurring after an infant's first exposure to a food allergen.[54,55,61] Such reactions are now attributed to intrauterine sensitization.

In conclusion, experimental and clinical data suggest that infants can be born with atopy. However, further studies are needed to clarify the mechanisms of antenatal sensitization, and especially which food antigens are most likely to cross the placental barrier and whether the controlled ingestion of these foods by the mother during pregnancy can prevent or minimize sensitization of the fetus.

Cigarette Smoking. Among the environmental factors favoring the development of atopic disease, cigarette smoke plays a major role. Evidence is accumulating that there is a connection between parental smoking habits and atopic disease in children.

Recently, it has been observed that atopic symptoms begin earlier in children of parents who smoke.[62] Moreover, immunologic studies corroborate these findings. Reports of higher IgE levels in adult smokers[63] and in infants of smoking atopic parents[64] support the view that immunologic abnormalities may be relevant, although they may be effects rather than causes. The issue of whether smoking acts largely by irritating the respiratory mucosa,[65] facilitating both the penetration of antigens and the spread of infection, or by a direct action on the immune system has yet to be resolved. All current results suggest the importance of environmental controls. Thus there are grounds to forbid smoking not only in an allergic child's home but also in the house of children at risk for the development of allergic disease. In addition, parents should not expose their children to smoke in other confined spaces, such as the family car. Not only is tobacco smoke an irritant, but it may lead to an increased susceptibility to respiratory viral infections.[66] Another recent report indicates that adult smokers contract influenza with undue frequency.[67]

The rates of influenza also are elevated in smokers' children.[67,68] Because these infections often induce asthma, a vicious circle may be initiated, especially in winter months when virus transmission is facilitated: parents' smoking → viral respiratory infections → asthma in the child. Perhaps only a vigorous prohibition of smoking can interrupt this circle.

Environmental Factors. As mentioned earlier, the infant's environment during the first six months of life has the potential of provoking allergic sensitization. Children living in rural districts may have increased pollen and animal contacts, and thus may manifest atopic symptoms at an earlier age.[62]

The importance of environmental control has recently been reevaluated. It has been demonstrated that avoidance of provoking antigens in infancy can not only lead to freedom from allergic disease but also can reduce bronchial hyperreactivity present in asthmatic patients.[69] We interpret these observations as having great practical relevance. Specific hyperreactivity represents the Achilles' heel of asthmatic children. In the light of evidence showing that

bronchial hyperreactivity is ameliorated when environmental allergenicity is reduced, it is possible to consider that bronchial hyperreactivity may be secondary to allergy, at least in children. It has been suggested that repeated bronchospasm might damage bronchial muscles and nerves, thus leading to nonspecific hyperreactivity. It also has been postulated that release of mediators from mast cells in response to an IgE-mediated mechanism might contribute to the development of bronchial hyperreactivity.[70]

Infections. Viral infections frequently trigger asthmatic attacks in children. In the last few years, many studies have reported that infection with several viruses, including respiratory syncytial virus (RSV), parainfluenza (types 1–3), coronavirus, adenovirus, and cytomegalovirus may contribute to the development of allergic sensitization. In children of atopic parents, allergic sensitization accompanied by IgE synthesis began after viral upper respiratory infections, in concert with specific antibody responses to the virus.[53] Increased levels of IgE have been shown in various viral infections.[71,72] Recently, RSV-specific IgE antibodies have been found to be persistently present in patients affected by RSV infections.[73] A subsequent study from these investigators[74] demonstrated the association of high RSV-IgE titers and concentrations of histamine in the nasopharyngeal secretions of patients with wheezing caused by RSV infection. The authors suggest that the disease may be due to hyperproduction of RSV–IgE, which results in an enhanced release of histamine and other chemical mediators causing airway obstruction.

There are several mechanisms by which viral infections could stimulate IgE synthesis and thereby favor the development of an atopic disease. They could depress T-suppressor cells, which in turn allow increased IgE synthesis. In addition, their cytopathic effect on respiratory mucosal membranes might favor antigen penetration. Viruses might also accentuate the β-adrenergic blockade, thus enhancing IgE synthesis.[75] Moreover, RSV-induced lymphocyte production[76] might produce soluble factors that are chemotactic for basophils[77] and enhance antigen-induced histamine release from basophils.[78]

In conclusion, the studies so far reviewed afford an insight into the association between viral infections and IgE synthesis. In particular, these studies explain in part why RSV bronchiolitis in infancy is followed by asthma in about 50% of cases.[79,80]

Early Weaning. Early weaning seems to be of importance in subsequent sensitization to allergens. Several prospective studies done in different countries have demonstrated that early weaning is associated with an increased risk of atopic disease. On the other hand, prolonged breastfeeding exerts a prophylactic effect on the development of allergies, at least during the first years of life.[40] It may be argued that infants are at risk of developing atopy especially during the first weeks of life. This is shown by experimental and clinical studies that have demonstrated that macromolecules can cross the intestinal mucosa at any age, the absorption being greatest in early life.[29,30] Rothberg[30] reported that the absorption of bovine serum albumin in premature infants was higher than in older children. Eastham et al[48] were able to show that food protein macromolecules are absorbed more readily into the circu-

lation during the first three months of life than later. It is apparent from the foregoing that the neonatal intestine may absorb greater quantities of ingested protein antigens than the mature adult intestine, which suggests that the mucosal defense system that promotes exclusion and elimination of the antigens is immature. Morphological studies done on fetal intestinal cells of the monkey and of humans showed excessive uptake of large molecules by intestinal epithelial cells. The morphological features of these cells suggested a structural immaturity.[81,82] This structural and functional immaturity can persist beyond fetal life into the neonatal period where new exposures come from without in the form of bacterial and food antigens.

During the early neonatal period, the human gastrointestinal mucosa develops in both structure and function, forming a defense system that is operational against the penetration of antigenic material in the intestinal lumen (bacteria, toxins, and antigens). However, due to the immunological gap—the transient lack of sIgA—and the functional immaturity of the intestinal tract, the mucosal barrier remains immature for varying periods of extrauterine existence and therefore protects the neonate incompletely.[6] Indeed one is struck by the relative ease with which the intestinal barrier can be penetrated, especially by bacteria. A vicious cycle of mucosal damage, increased antigen absorption, and atopic sensitization may thus be initiated.[23]

It is puzzling that the normal neonate lacks sIgA antibody activity during the first two weeks of life, when such immunity is of the utmost importance in dealing with a wealth of microbial, dietary, and other environmental agents. Nevertheless, while the machinery for mucosal immunity is developing, the ingestion of colostral and breast milk IgA affords protection.[27,83–85] The implications of these observations for the intestinal host defenses are obvious.

We want to stress that early supplements of cow's milk are often given in maternity hospitals without the mother's awareness. This is an unwise practice because supplementary feeds may be as sensitizing as full bottle feedings.[86] Experiments with an animal model have demonstrated that small quantities of oral antigens are more harmful than larger ones.[87] An elegant study by Roberts and Soothill[88] recently demonstrated that the postweaning IgE and IgG antiovalbumin antibody responses were greater in rat pups that had received a cow's milk-based supplementary feed than in litter mates that had not. Furthermore, they showed that the intestinal absorption of β-lactoglobulin was enhanced by the presence of ovalbumin in rats that had IgE antiovalbumin.[88] These data can be explained by the fact that reaginic antibody provokes an immediate hypersensitivity reaction in the gastrointestinal mucosa, thereby increasing gut permeability to β-lactoglobulin.[89] These results suggest that cow's milk supplements administered to rats may contribute in a nonspecific way to the atopic sensitization to other allergens. Sensitization to an allergen thus may favor the absorption of other macromolecules, increasing the risk of allergy. Finally, it is likely that similar mechanisms are operative in the human newborn.

Prevention by Dietary Manipulations

Dietary management based principally on exclusive breastfeeding and/or soy formulas in the first months of life to prevent allergy have provided encour-

aging results. Several prospective studies have confirmed this,[38,50,90-93] whereas several retrospective studies yielded contradictory results.[94-98]

In particular, all prospective studies reported an improvement in atopic disease rates using breast milk[90-92] or soy milk.[38] In addition, two retrospective studies reported an improvement in eczema[94] or asthma.[96] The remaining three studies observed no differences either using breast or cow's milk[97,98] or a combination of breast, soy, and cow's milk.[95]

In a recent prospective study,[40] we evaluated the prophylactic effect of prolonged breastfeeding on the development of allergic disease in 101 newborns of atopic parents. Thirty-four newborns were exclusively breastfed during the first six months of life, 26 received soy milk supplements with breastfeeding for an average of 1.5 months, and 41 were fed cow's milk from birth. The study design also included a strict dietary avoidance of cow's milk by the nursing mothers. In addition, in the breast- and soy-milk-fed infants, none were weaned to solid food for the first six months and only selected weanings were permitted up to nine months of age.

There were 6/34 breastfed, 6/26 soy milk fed, and 15/41 cow's milk fed infants who developed atopic disease during the two years of follow-up. Our prospective study confirms, therefore, that prolonged breastfeeding as well as breastfeeding supplemented with soy milk exert a protective effect on the development of atopic sensitization in newborns at hereditary risk for allergic disease.[40]

As mentioned earlier, three retrospective studies[95,97,98] failed to confirm this effect. Indeed, retrospective studies may yield controversial results due to various factors. In our view, it may be impossible for mothers to recall early supplementary feeds and/or former illnesses of their babies. In addition, atopic disease may be difficult to diagnose in young infants, especially in retrospect.

Thus there are grounds to recommend preventive measures at birth and even during pregnancy. Fortunately, because it would be unethical to require a feeding method against the mother's will, nature has provided a unique food that protects the infant, ie, human milk. It is now increasingly apparent that there are sound indications that breastfeeding is better than other methods of infant feeding. Proteins in breast milk are homologous and the likelihood of infant sensitization is minimal. A wide variety of humoral and cellular elements contained in breast milk may contribute to protection against enteric infections and to intestinal integrity.[83,90,97,99] Conversely, bacterial overgrowth has harmful effects on mucosal integrity, thereby enhancing the attachment of antigens to the intestinal epithelium. It has been demonstrated that breast milk protects against respiratory tract infections.[90] Viral infections often stimulate IgE synthesis.[71,72] There is an interesting study of infants at risk that shows the association between the development of allergenic sensitization and early infections.[53] Furthermore, IgE bound to epithelial cells has been demonstrated in the respiratory tract of infants with RSV-induced bronchiolitis,[73] a condition that is less frequent in breastfed infants.[38] Breast milk contains substances called mucosal growth factors that stimulate early maturation of the intestine and gut closure.[100] Closure of the intestine reduces the crucial period in which newborn infants are particularly vulnerable to infection and pathological absorption of macromolecules. The fecal flora of breastfed infants is characterized by a marked predominance of bifidobacteria

and a constantly acid pH,[101] which further protect these infants from excess penetration of antigenic macromolecules. One study, however, has not confirmed this finding, suggesting there is no difference in the fecal flora of breast- and formula-fed babies.[102] Finally, an immunoregulatory effect by breast milk cells has been reported.[103] It was postulated that a soluble mediator(s) of immunologic regulation was released by human milk cells and that this factor(s) explained, in part, the peculiar immunologic behavior of human milk cells in vitro. The factor(s) was released in greater amounts by colostral cells than by cells in mature milk, and human colostrum was thought to play a role in activating local immunity in the gastrointestinal tract of the newborn.

Recently, the relationship between E-rosette forming cells (ERFC), lymphocyte responsiveness and atopic disease was studied prospectively in 70 healthy newborn infants. Of these, 40 had positive heredity for atopic disease and 30 did not.[104] The study showed that heredity for atopic disease is commonly associated with low ERFC even before the infants develop any symptoms of allergy. The clinical relevance of these results was supported by the finding that in babies who received cow's milk based formulas serum IgE was significantly higher when there was a low ERFC count. These data could indicate that breastfeeding protects against allergy in infants at risk, namely those infants with positive heredity, and/or low ERFC counts, and/or high cord blood IgE.[105] Thus low numbers of ERFC are commonly found in early infancy in babies with a positive heredity for allergy before they have developed any clinical symptoms of allergy. Moreover, cow's milk-fed infants with ERFC deficiency appear to develop higher IgE levels and allergy symptom scores than normal infants, possibly because they lack normal IgE-suppressive mechanisms.[106]

Conclusions

Prophylaxis against atopy/food allergy appears to be best achieved by breastfeeding for as long as the mother is able to do so. In particular, exclusive breastfeeding should be encouraged for as long as possible when there is a history of allergy in immediate members of the family.

We have stressed[40] that when there is a high risk for allergy in offspring, the maternal diet during lactation should be modified to largely exclude potentially allergenic foods such as cow's milk. It also would be prudent to restrict the intake of cow's milk, egg, and perhaps other allergenic foods in the diet of pregnant women. We are continuing the follow-up of the 101 infants under study[40] in order to ascertain whether the protective effect of breast milk will guarantee freedom from allergy and for how long.

Another problem must be considered in feeding breast milk to children at risk. Indeed, a mother may be unable to supply adequate amounts of her own milk even with the help of pumping and manual expression. A mother also may not like nursing her baby. Banked human milk has been considered as an alternative, but this is not feasible everywhere. Therefore, an infant requiring human milk may not receive optimal feeding as long as necessary. In this case, our advice is to feed the baby at risk with appropriate milk

substitutes, among which soy milk appears to be a reasonable choice.[107] However, studies of soy-based formulas have yielded contradictory results.[48,59,95] Nevertheless, 26 of the 101 newborns in our study received soy milk.[40] It appears that the percentage of atopic disease in the soy-fed children is higher than in the breastfed group, but much less than in the cow's milk-fed infants (6/26 compared to 15/41 in the latter group). Hence, soy formulas may be preferable to modified cow's milk formulas, provided care is taken to provide adequate nutrition. Other preparations including those containing predigested or hydrolyzed proteins should be evaluated.

As concerns some atopic diseases, to postpone their onset may lessen the severity of symptoms and even guarantee freedom from atopic disease. It is known that certain atopic diseases such as intractable diarrhea due to cow's milk protein allergy and atopic dermatitis are more frequent in young infants, in whom the clinical manifestations are also more severe than in older children. In like manner, asthma is a very serious disorder during the first years of life. It should be stressed that early in life, dietary manipulations can be successful only if cow's milk and other supplements are truly excluded from the diet, as any deviation can obscure the presence of a prophylactic effect from these measures. Even if parents are presented with serious psychological or financial difficulties, this must be weighed against potential therapeutic benefit of dietary management. In conclusion, we stress again that an ounce of prevention is worth a pound of cure.

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