Antigenic constituents of human milk or of alternative feedings for infants may be responsible for adverse reactions in a subset of infants with milk protein intolerance. These reactions include those commonly associated with atopy, such as angioedema, urticaria, wheezing, vomiting, and eczema. Pulmonary hemosiderosis, malabsorption with villous atrophy, and eosinophilic enterocolitis, perhaps mediated by immune complexes or T cells, have also been associated with the ingestion of cow's milk proteins and/or soy proteins in infant feedings. Colic, sleeplessness, and irritability are symptoms seen in almost all infants at some time during infancy, including those few infants with immune-mediated reactions to dietary antigens.

Determining that adverse reactions are, in fact, immune mediated is often difficult and is accomplished by an in vivo challenge with the potential offending antigen, together with in vitro confirmation of immunoreactivity to the challenge antigen. Double-blind challenge with purified dietary antigens is useful in relating symptoms to a specific antigen, but the results may be difficult to interpret if the appearance of symptoms is delayed beyond several hours in a young infant. In vitro testing is compromised by the presence of some form of immunoreactivity, such as hemagglutinating antibodies, to dietary antigens in a large percentage of infants without symptoms and by lack of standardization of clinical tests for cell-mediated reactions to dietary antigens.

Much effort also has been devoted to predicting in which infants immune-mediated reactions to dietary proteins will develop in advance of their introduction into the diet. Increased cord blood IgE concentrations and parental history of atopy place an infant at highest risk for atopic disease during infancy and early childhood. Efforts at prophylaxis for the development of immune-mediated reactions to dietary antigens in high-risk infants and at elimination of repeated reactions in infants with documented hypersensitivity have focused on (1) promoting human milk feeding while delaying the introduction of solid foods beyond 6 months of age, (2) using different protein sources, such as soy or goat's milk protein, and (3) altering the antigenicity of cow's milk protein through physicochemical alteration of the native protein antigens.

Whereas the value of human milk for mature infants is clear, its role in the prophylaxis of atopic disease has not been established. The conclusions of numerous studies, both pro and con, are weakened by failure to continue breast-feeding beyond 6 months, lack of strict diagnostic criteria for immune-mediated symptoms, and failure to control for observer and patient bias. Studies in which the efficacy of soy and goat's milk proteins were examined suffer from similar weaknesses but suggest that neither soy nor goat's milk proteins are wholly effective in the prophylaxis or treatment of adverse reactions to cow's milk proteins. These substitute proteins are clearly antigenic when tested in animals or healthy infants and have provoked adverse reactions in some cow's milk allergic infants.

Casein hydrolysate, digested in vitro by enzymatic hydrolysis, has been in use for more than 40 years for infants with defects in protein digestion and adverse reactions to intact cow's milk protein. More recently, heat-treated whey proteins and hydrolyzed whey proteins have been introduced for similar purposes. Some of these products, such as the casein hydrolysates, have been subjected to extensive preclinical testing (including sensitive immunoassays, gel permeation chromatography, and guinea pig immunization), which demonstrates nonantigenic peptides of <1,200 molecular weight. Enzymatic hydrolysates of whey have been subjected to similar preclinical testing, which reveals a final product that contains some peptides of >2,000 molecular weight. No published, well-controlled, double-blind studies exist to support the use of either casein or whey hydrolysates for prophylaxis or treatment of infants with milk hypersensitivity. Casein hydrolysate-containing formulas, however,
have been used routinely to treat infants with immune-mediated reactions to cow's milk, with only rare treatment failures. A whey hydrolysate formula recently has become available in the United States. Although clinical experience is limited, it suggests that this formula may be an acceptable alternative to cow's milk and soy protein formulas for infants who are intolerant, but not allergic, to cow's milk.

In summary, the development of atopic and other immune-mediated reactions to dietary antigens is a complex and incompletely understood process. The amount of antigen, age at introduction into the diet, nature of the antigen (egg, milk, wheat, etc), maternal immunity, integrity of the intestinal mucosal barrier, and heredity all play some role in determining immune responses (both priming and tolerance) to dietary antigens. Human milk and casein and whey hydrolysates may be useful in the prophylaxis or elimination of symptoms in sensitized infants, with hydrolysates of <1,200 molecular weight having theoretical advantages over other hydrolysates. There is no evidence to support the use of hydrolysate formulas for the treatment of colic, sleeplessness, and irritability. These common symptoms occur frequently in infants but rarely as a result of an immune-mediated reaction to cow's milk protein.

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