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Allergenicity of Orally Administered Immunoglobulin Preparations in Food-Allergic Children

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ABSTRACT. Passive immunization by the oral administration of immunoglobulin preparations derived from bovine milk, chicken egg, and human sera has been proposed as a method for the prevention and treatment of enteric diseases. However, the allergenic potential of these proteins may be a factor limiting their widespread use for disease prevention. An in vitro study with sera from milk- and egg-allergic children was performed to determine whether these immunoglobulin preparations have allergenic potential. Protein extracts of milk, bovine immunoglobulin, egg white, human immune globulin, and five egg yolk antiviral immunoglobulin preparations were bound to nitrocellulose paper. These preparations were probed for specific IgE binding with sera from milk- and egg-allergic patients. Of 22 milk-hypersensitive patients, 16 had specific IgE binding against the bovine immunoglobulin preparation. Of 28 egg-allergic patients 15 had specific IgE binding against one or more of the egg yolk-derived antiviral chicken immunoglobulins. Control sera were negative against the milk and egg preparations. Western blot analysis confirmed that milk- and egg-allergic patients had IgE-specific antibodies for bovine and chicken immunoglobulin molecules. Therefore, the removal of contaminating proteins from milk and egg antibody preparations would be unlikely to eliminate their allergenic potential. In contrast, sera from milk- and egg-allergic patients displayed no detectable IgE binding to human immunoglobulin preparations. These data indicate that the administration of antibody preparations derived from bovine and chicken sources may lead to severe allergic reactions in milk- or egg-sensitized patients and to sensitization in some nonallergic individuals. On the other hand, it is likely that human immunoglobulin preparations can be administered to such patients with a minimal risk of IgE-mediated reactions. *Pediatrics* 1991;87:208-214; *immunoglobulin preparations, food allergy.*

Gastrointestinal infections remain important causes of morbidity in developed countries and major causes of mortality in the developing world. The development of an effective, practical modality for the prevention or treatment of a wide range of diarrheal diseases thus represents a major therapeutic goal. Active immunization may not prevent enteric diseases in young infants and in children and adults rendered immunocompromised by congenital or acquired immunodeficiency syndromes, malignancy, or immunosuppressive chemotherapy because of their inability to generate an effective immune response. For these reasons, passive immunization has been suggested. Because the organisms replicate within the lumen of the gastrointestinal tract, it would be logical to administer the immunoglobulins by the oral route. These performed antibodies are given by mouth with the intent of neutralizing their respective microbial pathogens within the gastrointestinal tract. Several recent studies have demonstrated reduced morbidity after the administration of immunoglobulins derived from bovine milk, chicken egg, and human serum to passively protect individuals from rotavirus, cryptosporidium, enterotoxigenic diarrheal diseases caused by *Escherichia coli*, and neonatal necrotizing enterocolitis.¹⁻⁶

However, the allergenicity of immunoglobulin preparations derived from animals needs to be examined before their widespread use can be recommended. There are limited data available on the allergenicity of bovine immunoglobulin and no previous studies have investigated the allergenicity of chicken egg immunoglobulins in humans. The rationale for concern that the bovine and egg preparations may be allergenic is twofold. First, milk and eggs are two of the most common antigens responsible for food hypersensitivity in children.⁷ In ad-

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dition, there are substantial levels of bovine immunoglobulins in raw and pasteurized milk, indicating the potential for a high degree of exposure in the population.⁸ The second concern with oral administration of these preparations is that their use is likely to occur during infancy at a time of relative gut-associated lymphoid tissue immaturity or during diarrheal episodes when the gastrointestinal mucosal barrier that protects against trans-mucosal passage of intraluminal antigens is impaired.^{9,10} Both situations may be ideal conditions for sensitization to food antigens.

Immunoglobulin is the principal antimicrobial substance in these oral preparations and must be the preparation's minimal protein component if it is to have potential efficacy.^{5,8} Therefore, the aim of this study was to determine whether milk- and egg-allergic patients have specific IgE antibodies directed against immunoglobulin preparations isolated from bovine milk, chicken egg yolk, and human sera. Furthermore, studies were conducted to document that the specific immunoglobulin fraction in question is being recognized and that the binding is not due to contamination from other proteins.

MATERIALS AND METHODS

Sera were obtained from 22 milk-allergic and 28 egg-allergic pediatric patients who had documented immediate hypersensitivity reactions to the implicated food allergen. These patients were referred to the Pediatric Allergy Clinic because of severe atopic dermatitis and/or a history of allergic reactions to food. Food hypersensitivity in these patients was documented by double-blind placebo-controlled oral food challenges, as previously published.^{7,11} Challenges were considered positive only when objective symptoms developed: cutaneous = urticaria or erythematous morbilliform rash involving greater than 5% of body surface area; gastrointestinal = vomiting and/or diarrhea; upper respiratory = conjunctival erythema and tearing, nasal pruritus, rhinorrhea, and sneezing; and lower respiratory = audible wheezing by auscultation or at least a 20% decrease in 1-second forced expiratory volume. All challenges were performed in the Johns Hopkins Hospital Pediatric Clinical Research Center. Informed consent was obtained for each subject, and all procedures were approved by the Institutional Review Board for Human Investigation. Control sera were obtained from 5 nonatopic individuals, a peanut-allergic atopic patient, and an atopic patient not allergic to food but with a markedly elevated serum IgE concentration (18 249 ng/mL).

Preparation of Extracts

Three grams of egg white or whole milk was added to 30 mL of phosphate-buffered saline in sterile centrifuge tubes. The tubes were placed on a test tube rotator overnight in the cold room (4°C). The tubes were then spun at 2500 × g for 10 minutes and the supernatants were removed and placed in sterile tubes. Aliquots of supernatants were then microcentrifuged at 17 000 × g for 15 minutes to clarify the extract. The supernatants were filter sterilized sequentially through Millipore 0.45-μm and 0.22-μm filters.

Immunoglobulins

The human immune globulin used in the study was a stock vial of Immune Globulin Intravenous 5%, pH 4.25 (Cutter Biological, Berkeley, CA).

The antiviral chicken egg yolk immunoglobulin preparations were obtained from the eggs of chickens that were immunized with 10 μg of purified virus virions (rotavirus strain-WA, rotavirus A strain SA 11, and adenovirus type 40) as described previously.⁵ The immunoglobulins were isolated from the yolks by the method of Jensenius et al.¹² (The influenza A strain Bangkok and respiratory syncytial virus strain long yolk preparations were kindly provided by Dr Marc van Regenmortel, Strasburg, France.)

The bovine milk immunoglobulin preparations were purified by NH₄SO₄ precipitations from bovine colostrum using previously described methods.⁸ The bovine colostrum contained rotavirus antibodies, presumably due to natural infection with bovine rotaviruses.⁸

Protein determination of the nine immunoglobulin extracts was performed using the Bio-rad protein assay (Bio-rad Labs, Richmond, VA).

Immunodot Blots

Details of this method have been published previously.¹³ Briefly, 10 μg of each immunoglobulin extract was bound to nitrocellulose paper before incubating with patients' sera. After washing, blots were incubated with affinity purified goat anti-human IgE conjugated with alkaline phosphatase (Kirkegaard and Perry Laboratories, Gaithersburg, MD), developed, and analyzed by determining the optical density for each dot with a densitometer (Macbeth reflection densitometer, model 922). The optical density value was then converted to reflectance density. A reflectance density reading of 1.0 or greater was considered positive.

Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis

Details of this method have been published previously.¹³ Briefly, 25 μ g of each immunoglobulin extract was loaded and resolved in a discontinuous sodium dodecyl sulfate-polyacrylamide gel electrophoresis system as described by Dreyfuss et al.¹⁴ After protein fractions were electrotransferred to nitrocellulose blots, they were probed with patient sera for antigen-specific IgE binding to the protein bands. Bound human IgE was identified with affinity purified, biotinylated goat anti-human IgE (Kirkegaard and Perry Laboratories). The biotinylated goat anti-human IgE had been further purified by running it over a CNBr Sepharose 4B (Sigma Chemical, St Louis, MO) human IgG column to remove any anti-idiotypic activity that may be directed against determinants on human IgG. The blots were then reacted with an enzyme solution and developed.

Identification of bovine milk immunoglobulins was performed on a Western blot panel by probing with 1:1000 dilution of recombinant protein G-peroxidase conjugate (Zymed Labs, San Francisco, CA), which has been shown to bind bovine γ -globulin, for 1 hour, and developing with 3,3'-diaminobenzidine. The chicken egg immunoglobulins were confirmed by probing a panel with a 1:400 dilution of alkaline phosphatase-labeled goat anti-chicken IgG (Southern Biotechnology Associate, Birmingham, AL) for 2 hours and then developing.

RESULTS

Immunodot Blots

Probing for specific IgE binding, 16 (73%) of 22 milk-hypersensitive patients with positive bovine milk Immunodot blots had a corresponding positive bovine immunoglobulin Immunodot blot. There were no patients who had a negative bovine milk and a positive bovine immunoglobulin Immunodot blot (Fig 1).

Fifteen (54%) of 28 egg-hypersensitive patients with positive chicken egg white Immunodot blots for IgE had a corresponding positive Immunodot blot to one or more of the five chicken egg yolk-derived antiviral immunoglobulin preparations rotavirus-WA, rotavirus A SA-11, influenza A-Bangkok, adenovirus type 40, and respiratory syncytial virus-long. As in the case of the above studies, there were no patients with negative chicken egg Immunodot blots and a corresponding positive egg antiviral Immunodot blot (Fig 2). All control sera were negative for specific IgE binding against the bovine and chicken egg extract Immunodot blots.

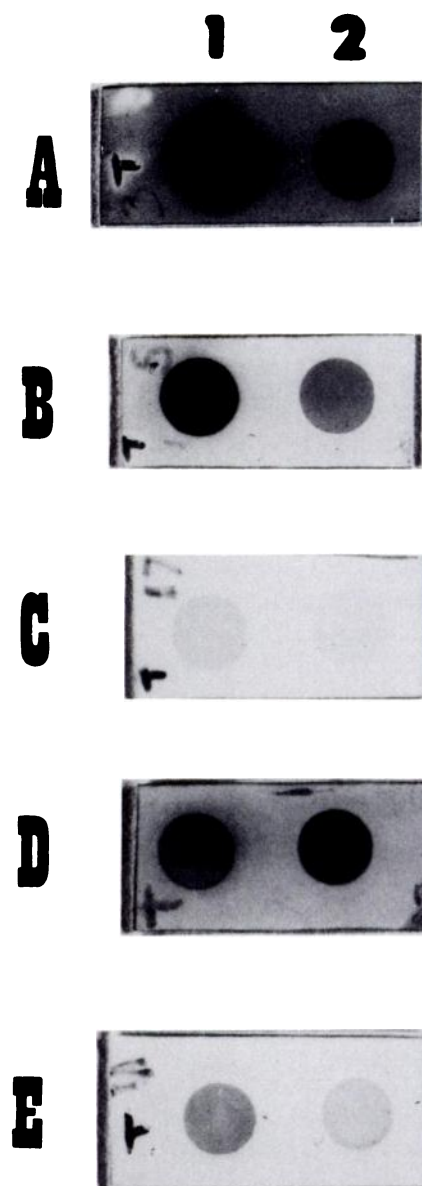


Fig 1. Representative bovine Immunodot blots probed with sera from five milk-allergic patients. Ten micrograms of protein extract was loaded per dot and developed for specific IgE binding. Column 1, defatted bovine whole milk extract; 2, bovine immunoglobulin extract. Representative reflectance densities (≥ 1 recorded as positive): (A) 1 = 77, 2 = 39; (B) 1 = 48, 2 = 5.2; (C) 1 = 1, 2 = 0.4; (D) 1 = 5.2, 2 = 13; (E) 1 = 3.8, 2 = 1.

Sera from all of the milk- and egg-hypersensitive patients as well as sera from control subjects failed to demonstrate specific IgE binding against the human immune globulin Immunodot blots (reflectance densities all less than 0.03).

Western Blots

We performed additional studies using polyacrylamide gel electrophoresis and electrotransfer to document that the human IgE reactions were di-

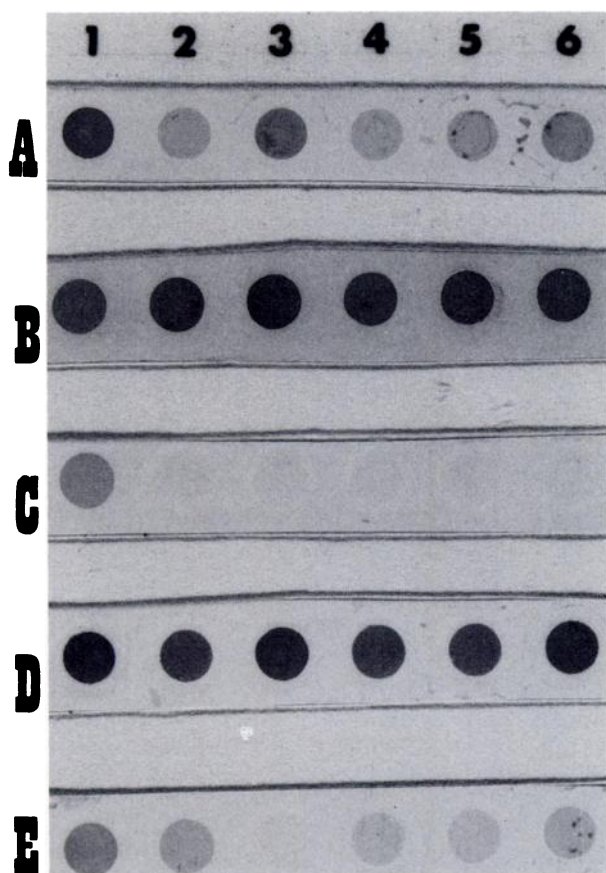


Fig 2. Representative chicken egg Immunodot blots probed with sera from five egg-hypersensitive patients. Column 1, chicken egg white extract; 2, chicken egg anti-rotavirus strain-WA extract; 3, chicken egg anti-rotavirus A strain SA-11 extract; 4, chicken egg anti-adenovirus type 40 extract; 5, chicken egg anti-influenza A-strain Bangkok extract; 6, chicken egg anti-respiratory syncytial virus-strain long extract. Representative reflectance densities: (A) 1 = 23, 2 = 2, 3 = 7.7, 4 = 1.3, 5 = 2.2, 6 = 4.5; (B) 1 = 11, 2 = 18, 3 = 25, 4 = 13, 5 = 16, 6 = 10; (C) 1 = 4.5, 2 = 0.03, 3 = 0.03, 4 = 0.03, 5 = 0.03, 6 = 0.03; (D) 1 = 65, 2 = 27, 3 = 43, 4 = 27, 5 = 25, 6 = 30; (E) 1 = 6, 2 = 3, 3 = 0.03, 4 = 1.0, 5 = 1.0, 6 = 1.7.

rected at bovine and chicken egg immunoglobulin molecules. A 13.5% sodium dodecyl sulfate-polyacrylamide gel in which the protein bands had been electrotransferred to nitrocellulose paper was stained with amido black. This Western blot revealed the representative protein bands and subunits of the six extracts (chicken egg white, chicken egg anti-rotavirus-WA, chicken egg anti-adenovirus type 40, bovine milk, bovine immunoglobulins, and human immune globulin) and their relative molecular weights (Fig 3).

Western blots probed with sera from milk-allergic patients had specific IgE binding of numerous proteins and protein subunits in the defatted whole bovine milk and bovine immunoglobulin lanes. Milk proteins recognized in the bovine milk lane

include bovine γ -globulin, α -casein, κ -casein, β -lactoglobulin, and α -lactalbumin. The dominant milk protein band recognized in the bovine immunoglobulin preparation appeared, by molecular weight and band intensity criteria, to be the heavy and light chains of bovine immunoglobulin with approximate relative molecular weights of 60 kd and 29 kd, respectively. A probable contaminant protein band corresponding to the molecular weight of β -lactoglobulin was also recognized (Fig 4). The protein band corresponding to the heavy and light chains of bovine immunoglobulins was confirmed by protein G binding; no other proteins or protein subunits in the other lanes demonstrated specific IgE binding.

Western blots probed with sera from egg-allergic patients had specific IgE binding of numerous proteins and protein subunits in the chicken egg white,

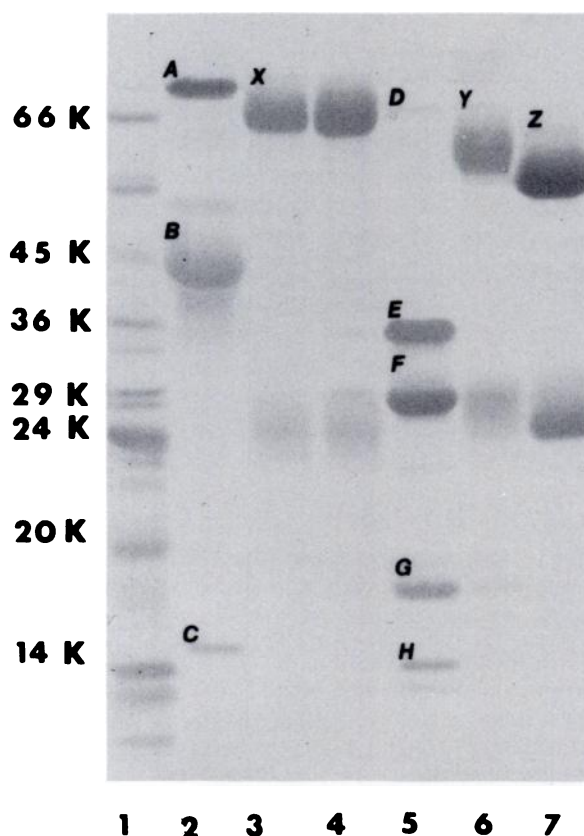
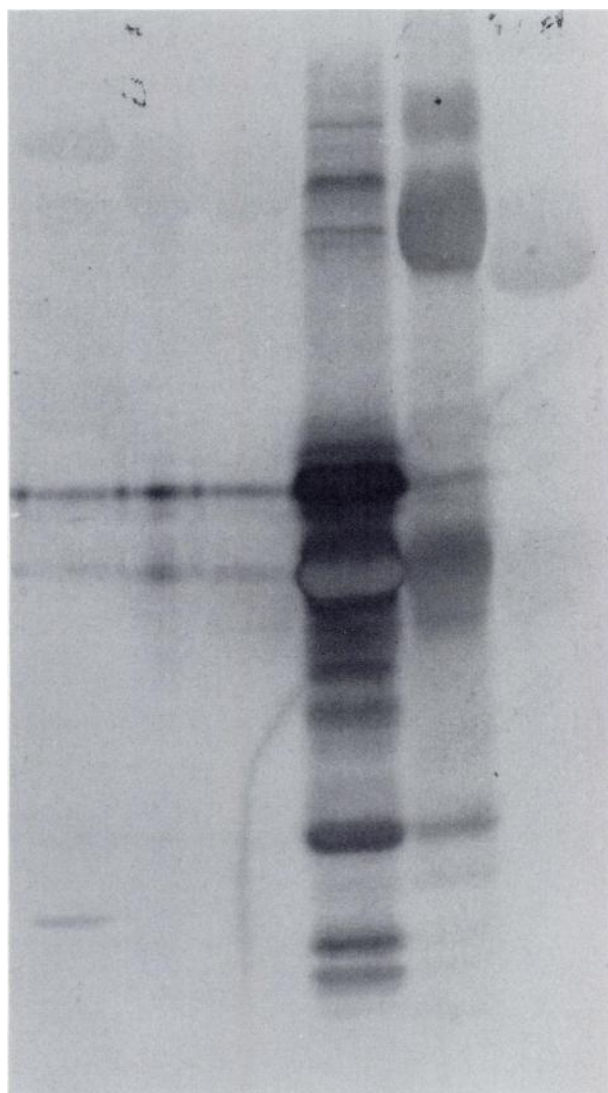


Fig 3. Amino black-stained Western blot of 13.5% sodium dodecyl sulfate-polyacrylamide gel electrophoresis run with 25 μ g of protein extract per lane. Lane 1, molecular weight markers; 2, chicken egg white; 3, chicken egg anti-rotavirus strain-WA; 4, chicken egg anti-adenovirus type 40; 5, defatted whole bovine milk; 6, bovine immunoglobulin; 7, intravenous human immune globulin. Protein bands: A, conalbumin; B, ovalbumin; C, lysozyme; D, bovine γ -globulin; E, α -casein; F, κ -casein; G, β -lactoglobulin; H, α -lactalbumin; X, chicken immune globulin; Y, bovine immunoglobulin; Z, human immune globulin.



2 3 4 5 6 7

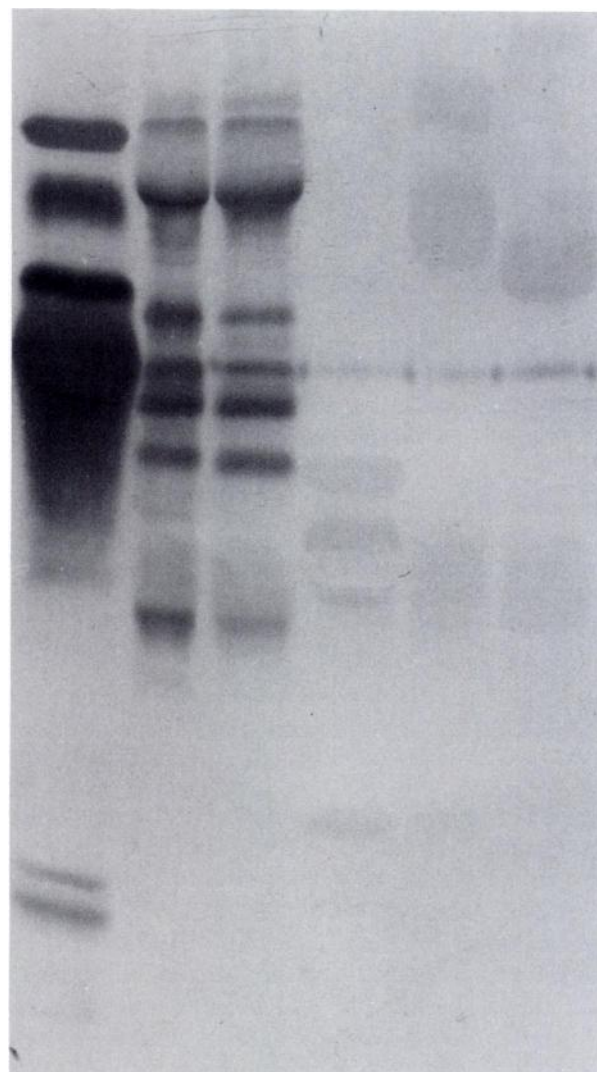
Fig 4. Western blot probed for specific IgE binding with sera from a milk-allergic patient. Lane 2, chicken egg white; 3), chicken egg anti-rotavirus strain-WA; 4, chicken egg anti-adenovirus type 40; 5, defatted whole bovine milk; 6, bovine immunoglobulin; 7, intravenous human immune globulin.

chicken egg anti-rotavirus-WA, and chicken egg anti-adenovirus type 40 lanes. As in the previous study, protein bands in the other lanes did not display specific IgE binding. Chicken egg proteins recognized in the egg white lane include conalbumin, ovalbumin, lysozyme, and ovomucoid (ovomucoid did not stain well with amido black and appears as a smear on Western Blots probed with sera because of its high [25%] carbohydrate content.¹⁵ The dominant chicken egg protein bands recognized in the anti-rotavirus-WA and anti-adenovirus type 40 lanes displayed molecular weights consistent with those of the heavy and light chains

of chicken egg immunoglobulins (Fig 5). The immunoglobulin nature of these bands was confirmed by reaction with goat anti-chicken IgG. On the other hand, no sera from milk- and egg-allergic patients reacted with human immune globulin or its subunits. Control sera (from donors described under "Materials and Methods") had no specific IgE binding against any of the protein bands in the six lanes on the Western blot.

DISCUSSION

Recent studies using immunoglobulins derived from bovine milk or chicken egg yolk to reduce the morbidity of infectious gastroenteritis have been



2 3 4 5 6 7

Fig 5. Western blot probed for specific IgE binding with sera from an egg-allergic patient. Lane 2, chicken egg white; 3, chicken egg anti-rotavirus strain-WA; 4, chicken egg anti-adenovirus type 40; 5, defatted whole bovine milk; 6, bovine immunoglobulin, 7, intravenous human immune globulin.

encouraging. Hilpert et al,¹ studying infants hospitalized for acute rotavirus gastroenteritis, found that those infants who received oral milk immunoglobulins prepared from rotavirus-hyperimmunized cows had a significant reduction in the duration of excreted virus. In another study, Tacket et al² achieved prophylaxis against experimentally induced traveller's diarrhea due to enterotoxigenic *E coli* in 10 volunteers who received prior oral administration of milk immunoglobulins from cows immunized with this agent *E coli*. Eibl et al³ concluded that the oral administration of a human immunoglobulin preparation may help prevent the development of necrotizing enterocolitis in low-birth-weight infants. Barnes et al⁴ administered human γ -globulin orally to low-birth-weight infants and found that it seemed to protect these neonates from diarrhea caused by rotavirus. Yolken et al,⁵ using immunoglobulins isolated from the eggs of hens immunized with purified rotavirus preparations, prevented the development of rotavirus gastroenteritis in experimentally infected animals.

However, this study demonstrates that the majority of our children with challenge-proven milk and egg allergy have specific IgE antibodies directed against bovine immunoglobulin and chicken egg immunoglobulin, respectively. Previous information about the allergenicity of bovine immunoglobulin is limited, and it is not one of the milk proteins generally listed as allergenic. Bovine milk contains more than 20 protein fractions, and the relative allergenicity of most of these proteins has not been determined.^{16,17} In a case report study, one of six patients with gastrointestinal intolerance to milk, presumably of non-IgE-mediated etiology, experienced vomiting and weight loss with an oral challenge of bovine γ -globulin that had been obtained commercially from Armour Pharmaceutical Company.¹⁸ Bovine immunoglobulin is contained in the whey fraction and comprises 1% to 2% of the total protein in skim milk.¹⁹ Information on the allergenicity of chicken egg immunoglobulins is unknown. Anet et al²⁰ found that patients with a history of egg allergy had IgE directed against egg yolk in an in vitro assay, although the specific identity of the protein(s) recognized was not established. However, chicken egg immunoglobulins are actively secreted into the yolk during gestation.¹²

We have confirmed that patient IgE antibody binding is specific for the heavy and light chains of the immunoglobulin protein fraction, and therefore further purification of these bovine milk and chicken egg immunoglobulin preparations would not likely abolish their potential allergenicity. Furthermore, because reactivity was noted to both heavy and light chains of the immunoglobulin mol-

ecule, it is unlikely that the use of the Fab fragment or other immunoglobulin fragments will result in the total removal of allergenic potential. Oral challenges with the immunoglobulin preparations would need to be performed to document the in vitro evidence of specific IgE reactivity with sera from our food-allergic patients against the bovine and chicken egg immunoglobulin does indeed correlate with clinical hypersensitivity. However, it is likely that immunoglobulin-specific IgE reactivity in these milk- and egg-allergic patients would correspond to clinical hypersensitivity. In addition, the possibility of a γ -globulin hypersensitivity may be further increased because the bovine and chicken egg immunoglobulin preparations are being given in a purified form. Consequently, much larger quantities would be ingested compared with the amount normally consumed in milk and eggs.

Our studies demonstrated no evidence of specific IgE binding against human immune globulin among our milk- and egg-allergic patients nor among our control donors. There have been several studies using oral human immune globulin without evidence of adverse or allergic reactions.^{3,4,21} Presumably, the potential exists for an immunologically adverse reaction to occur with the administration of oral human immune globulin to a patient with undiagnosed IgA deficiency. However, the few case reports associated with anaphylactic reactions have all occurred after intravenous γ -globulin administration in patients with hypogammaglobulinemia presumably mediated by IgE anti-IgA antibodies.^{22,23} In addition, intravenous human immune globulin is now being used frequently for several other pediatric diseases such as Kawasaki's disease, neonatal sepsis, and idiopathic thrombocytopenia purpura without known adverse immunologic reactions.²⁴⁻²⁶ Therefore, human IgG can likely be administered orally to patients without significant potential for anaphylactic or other allergic reactions.

Based on our study results, one would not recommend the administration of bovine- or chicken egg-derived immunoglobulin preparations to known milk protein-allergic (ie, not lactose intolerant) or chicken egg-allergic patients until appropriate clinical challenge studies are completed. However, because of the high morbidity and mortality of these diarrheal diseases in infants of developing countries and among immunosuppressed patients, the potential risk of sensitizing these patients to milk and egg during infancy or an episode of gastroenteritis must be balanced against their potential benefit as determined by appropriately performed clinical trials.

Inasmuch as no IgE-mediated reactivity against

human immunoglobulins could be demonstrated in food-allergic children, the possible use of human immunoglobulins derived from serum or breast milk sources should be the subject of continued exploration. The recent development of methods for the production of human monoclonal antibodies²⁷ might markedly increase the practicality of using human antibodies. Also, the use of nonimmunoglobulin mediators of intestinal viral replication such as protease inhibitors²⁸ and glycoproteins²⁹ should be the subject of continued investigation. The development of practical and economically sound methods for the prevention and treatment of gastrointestinal infections would represent a major accomplishment in terms of the health of children and adults living in all parts of the world.

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