Report of the Expert Panel on Food Allergy Research
June 30 and July 1, 2003
National Institute of Allergy and Infectious Disease
National Institutes of Health

OBJECTIVE

In June 2003, the National Institute of Allergy and Infectious Diseases (NIAID) convened an expert panel of internationally recognized scientists to evaluate the current state of IgE-mediated food allergy and anaphylaxis research and to make recommendations for targeted basic science and clinical research that would support the development of new strategies for treatment and prevention.

BACKGROUND

Food allergy is an immunologic disease responsible for substantial morbidity and mortality in the U.S. population. Food allergy occurs in 6 – 8% of children and 2% of adults. Six foods (milk, egg, peanuts, tree nuts, fish, shellfish) cause 90% of all allergic reactions to foods; approximately 30,000 anaphylactic episodes and 150 deaths per year are due to food allergy. Diagnosis of food allergy is based primarily on clinical history and confirmed, only in a minority of patients, by the double-blind, placebo-controlled food challenge. The most effective strategy to prevent an allergic episode is strict food avoidance. Recent advances in this field suggest that new, focused research directions will advance understanding of the pathophysiology of food allergy and may provide new options for identification and treatment of susceptible individuals.

SPECIFIC AREAS OF REVIEW

- **NATURE AND SCOPE OF THE PROBLEM**
    - Published reports document the increasing prevalence of food allergy and food-induced anaphylaxis; reasons for these increases are poorly understood.
    - Food allergy reactions include gastrointestinal, cutaneous, respiratory and other systemic symptoms.
    - Severe food allergy may progress to anaphylaxis and death.
    - Food allergen immune responses encompass IgE-mediated hypersensitivity (oral allergy syndrome, anaphylaxis), cell-mediated hypersensitivity (food protein-induced enterocolitis) and combined IgE- and cell-mediated immunity (eosiniophilic gastroenteritis, atopic dermatitis).
    - Strict food avoidance is very difficult for allergic individuals and their families.
    - Limitations of, and lack of consensus on, methods for diagnosis and management of food allergy hinder development of best clinical practices.

- **RISK FACTORS ASSOCIATED WITH FOOD ALLERGY AND ANAPHYLAXIS**

Markers of predisposition to food allergy and anaphylaxis may improve prevention strategies.

- **Risk factors linked with food allergy:**
  - family history of allergy and asthma
  - genetic predisposition to allergic disease
  - age (< 3 years old)
  - elevated allergen-specific serum IgE concentration
- **Risk factors associated with fatal or near-fatal anaphylaxis:**
  - a history of food allergy, especially if severe
  - allergy to peanuts or tree nuts
  - asthma, typically mild asthma
  - adolescence/young adulthood
  - delay in appropriate treatment

- **GASTROINTESTINAL MUCOSAL IMMUNITY AND ORAL TOLERANCE**

The gastrointestinal (GI) immune response is uniquely immunosuppressive and contributes to the development of oral tolerance. For example, the mucosal barrier and tight junctions between intestinal epithelial cells reduce antigen uptake, regulatory T cells secrete the immunosuppressive cytokines TGFβ and IL-10, and sIgA antibodies agglutinate antigens and prevent viral and bacterial attachment to intestinal epithelial cells. Intestinal flora contribute to development and maintenance of oral tolerance. It is notable that, of the enormous number of food proteins and potential allergens consumed, very few induce food allergy.

GI tract and immune system immaturity in early childhood contribute to high prevalence of food allergies before age 3. Childhood allergy to several foods, such as cow's milk and eggs, may be transient, with oral tolerance emerging often by age 5. Tolerance to peanuts, tree nuts, fish, and shrimp is less likely to develop.

Adult-onset food allergy represents breakdown in previously established tolerance and is generally persistent.

- **SENSITIZATION TO FOOD ALLERGENS**

Food allergy is an antigen-specific reaction. Foods prominent in childhood allergies are cow's milk, egg, peanut, soy, wheat and fish; adults are sensitized most often to peanut, tree nut, fish and shell fish.

The type of food and chemical structure of the allergen bias allergenic potential and antigen presentation through MHC Class I or Class II pathways. For example, dry roasted peanuts, boiled peanuts and soybeans contain many similar proteins, yet dry roasted peanuts are associated with a higher risk of sensitization than boiled peanuts

and soybeans. IgE antibodies directed against sequential, not conformational, casein epitopes are associated with persistent cow's milk allergy.

A predominantly Th2 immune response (IL-4, IL-5, IL-13) supports development of food allergy, whereas a predominantly Th1 response (IFN-γ) may be protective. Children who outgrow peanut allergy display a shift from Th2 to Th1 as tolerance to peanuts develops.

Other factors contribute to development of food sensitization, including route of exposure, dose and presence of adjuvant.

- **IMMUNOTHERAPY**

The single effective strategy to prevent food allergic reactions is strict food avoidance; however, increased use of prepackaged and processed foods limits the utility of this approach. Conventional immunotherapy with food allergens is associated with an unacceptably high rate of systemic reactions. New therapeutic strategies are being evaluated:

- **IgE receptor blockade**. Anti-IgE antibodies bind serum IgE, prevent IgE binding to the high affinity IgE receptor, and reduce expression of the high affinity IgE receptor on mast cells and basophils, thus blocking IgE-mediated activation of these cells. Anti-IgE antibody is licensed in the United States for treatment of adult and adolescent moderate to severe asthma, but not for food allergy. Research studies have shown some benefit from anti-IgE in severe IgE mediated food allergy but major issues of dosing and efficacy remain to be resolved.
- **Immune modulation via immunostimulatory DNA.** Immunostimulatory sequences, or unmethylated CpG oligonucleotides, covalently linked to allergens are associated with reduced ability to bind IgE antibodies *in vitro* and to activate IgE-mediated allergic responses *in vivo*. These DNA-allergen constructs display an improved safety profile, compared to native allergen, in phase I and II ragweed allergic rhinitis immunotherapy trials. Immunostimulatory constructs of food allergens have not been synthesized.
- **Peptide immunotherapy.** Subcutaneously-administered, allergen epitope-specific peptides reduce early and late phase T cell skin reactions to cat dander, however temporary exacerbation of the allergy occurred in a subset of volunteers. The diminished allergen-specific skin response persisted 3 - 9 months following peptide therapy. No food allergy trials have been performed.
- **Receptor cross-linking.** Engagement of IgG receptors mitigates IgE receptor activation signals and blocks mast cell and basophil activation. Bi-functional fusion proteins that crosslink the IgE and IgG receptors also inhibit mast cell and basophil activation. The Gamma-Epsilon fusion protein crosslinks the receptors directly, and the Gamma-Allergen fusion protein binds the IgG receptor directly and IgE receptor indirectly through

the covalently-attached allergen. Several *in vivo* and *in vitro* human studies tested successfully a cat allergen-IgG construct. Preparation of Gamma-food allergen fusion proteins is planned.

- **Immunotherapy with genetically modified allergens**. An "engineered" recombinant Ara h1-3 peptide that differs from the naturally occurring IgE epitope by a single amino acid, co-administered with heat-killed E.coli, reduces the magnitude of the murine allergic reaction to peanut by markedly reducing peptide-IgE binding and increasing the Th1 response. Clinical trials are in the planning stage.

- **ANIMAL MODELS**

Although animal models provide powerful tools for dissection of pathogenic mechanisms of human disease and for testing new therapies, the route of antigen exposure, dose, and response characteristics may mimic only partially the human disease. Several new animal models overcome these limitations and may provide valuable insights into the mechanisms of oral tolerance, and into the treatment and prevention of food allergy and anaphylaxis:

- an intestinal loop mouse model for study of oral tolerance
- a peanut allergy and anaphylaxis mouse model
- a transgenic mouse engineered to produce human, monoclonal IgE antibodies
- an ovalbumin allergic skin mouse model
- a rhesus monkey allergy model

Several studies have shown that adjuvants, such as cholera toxin, endotoxin and alum, activate innate immunity and may be necessary to induce food allergy in mice. A recent study links exposure to high concentrations of endotoxin with development of Th1 responses and low concentrations with Th2 responses.

- **EOSINOPHILIC GASTROINTESTINAL INFLAMMATORY DISEASE**

Eosinophilic gastrointestinal inflammatory disease (EGID) is characterized, in part, by peripheral blood and localized GI tract eosinophilia, gastric dysmobility and weight loss. Immunologic parameters shared by EGID and food allergy include antigen-specific IgE and IgG1 and a GI Th2 microenvironment containing IL-4, IL-5 and IL-13. Eighty percent of individuals with EGID are food allergen skin test positive; mechanistic links between the two diseases are unknown.

- **BIOENGINEERED FOODS**

Genetically-modified foods have sparked much public debate. Risk assessment paradigms to evaluate genetically-modified foods predict allergenic potential based on allergenicity of the parent protein, sequence homologies of modified proteins to known allergens, sensitivity to enzymatic digestion and denaturation, and allergenicity in animal models. To date, serious adverse events have not been attributed to consumption of genetically-modified food.

PANEL RECOMMENDATIONS

- **NATURAL HISTORY OF FOOD ALLERGY**

The panel recommended targeted research to define the natural history of childhood and adult-onset food allergy. The panel emphasized the importance of understanding spontaneous reassertion of tolerance following development of allergy. Peanut allergic individuals who become tolerant to this generally persistent allergen provide a unique study population in which to evaluate these phenomenon.

Clear, well-accepted definitions of clinical reactivity will be necessary for systematic study of predictors of allergy, transience or persistence of allergy, response severity and anaphylaxis.

- **IMMUNOPATHOLOGY OF FOOD ALLERGY**

The panel recognized the importance of GI-specific physiology and immunology to development of oral tolerance and food allergy. Suggested areas of research include:

- **Cellular mechanisms of food allergen sensitization**
  - lumenal uptake and processing of food proteins
  - activation parameters for intestinal dendritic cells and lymphocytes
  - role of adjuvants and endotoxin in immune activation
  - interplay of Th2 and Th1 microenvironments in the development and resolution of allergy
  - contribution of intestinal flora to GI barrier properties and immunity
  - mechanistic overlap between food allergy and eosinophilic gastrointestinal disease
- **Oral tolerance**
  - role of regulatory T cells in the maintenance and loss of oral tolerance
  - the relationship of GI maturity to development of oral tolerance
  - emergence of tolerance in food allergic children
  - loss of oral tolerance in adult-onset food allergies
- **Genes and exposure**
  - contribution of genetic predisposition to food allergy
  - interaction between route of allergen exposure and development of food allergy

- **PATHOPHYSIOLOGY OF ANAPHYLAXIS**

The panel emphasized study of pathophysiologic mechanisms of food allergen-induced anaphylaxis and the mechanism of action for epinephrine, the primary treatment of anaphylaxis.

- **CHARACTERIZATION OF ALLERGENIC PEPTIDES**

The panel recognized the importance of research targeting:

- molecular characteristics of the six most common food allergens
- relationship between the linear and conformational epitopes and allergenicity

- relationship between the linear / conformational epitopes and transience or persistence of food allergy in children
- changes in the allergenic potential of food proteins or the quantity of allergenic peptides in raw vs cooked/processed food

- **PRE-CLINICAL AND CLINICAL STUDIES**

Diagnosis of food allergy is based most often on clinical symptoms, the allergen skin prick test and, infrequently, the double-blind, placebo-controlled food challenge. The panel called for new measurements of allergenicity, expanded clinical criteria and biomarkers of allergic reaction (severity of response, persistence vs transience) to support the diagnosis and treatment of food allergy.

Primary treatment of food allergy is strict food avoidance. The panel recommended development of new immune-based therapies that block allergic reactions or promote tolerance.

Epidemiologic analysis of familial clustering of food allergic populations, prevalence in special populations, such as inner city children and minority populations, and impact of food allergy on family life will support development of improved clinical management programs.

- **DEVELOPMENT OF RESOURCES**

Noting the importance of shared resources, the panel recommended development of:

- a patient registry and sample repository housing both clinical information and serum and cell samples
- validated animal models of oral sensitization
- standardized research materials, including:
  - antigens (whole food preparations, peptides, and recombinant peptides)
  - relevant cell lines (mast cells, T cells, intestinal dendritic cells)
- standardized assays of allergen cell activation

CONCLUSIONS

The Expert Panel on Food Allergy concluded that food allergy research is poised to make significant advances in the prevention and treatment of food allergies and anaphylaxis. New initiatives will eliminate critical gaps in understanding GI physiology and immunology and the mechanism of oral tolerance; the pathophysiology of food allergy and anaphylaxis and the molecular characteristics of food allergens. These studies will provide the scientific basis for expanded diagnostic criteria and continued development of novel treatment and prevention strategies, clinical management and education programs.

"The Food Allergy Consortium Concept approved at the September 2003 Council is available at: http://www.niaid.nih.gov/ncn/budget/concepts/c-ait0903.htm. Council approval does **not** guarantee that a concept will become a program announcement, request for applications, or request for proposals. NIAID bases this determination on scientific and programmatic priorities balanced with the amount of funds available."