REPORT OF THE NIH EXPERT PANEL ON FOOD ALLERGY RESEARCH

March 13–14, 2006
National Institute of Allergy and Infectious Diseases
National Institutes of Health

OBJECTIVE

The Food Allergen and Consumer Protection Act of 2004 (Public Law 108-282) requires the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health (NIH), to convene an *ad hoc* panel of experts in allergy and immunology to review current basic and clinical research efforts related to food allergies, and requires that the panel make recommendations to the Secretary for enhancing and coordinating research activities concerning food allergies.

At the request of the NIH Director, the National Institute of Allergy and Infectious Diseases (NIAID) convened the NIH Expert Panel on Food Allergy Research in March 2006 as a working group of the National Advisory Allergy and Infectious Disease Council. Dr. Dean D. Metcalfe (NIAID, NIH) and Dr. Stephen J. Galli (Stanford University) co-chaired a nineteen-member panel of national and international experts. Other participants included representatives of various federal agencies, professional societies, advocacy groups and organizations, as well as interested individuals. The roster of the expert panel members and a list of panel observers are in **Appendix A**; the meeting agenda is in **Appendix B.**

The Expert Panel meeting began with a series of overview presentations, including an NIAID staff presentation reviewing the current NIAID research portfolio, followed by ten breakout sessions focused on key topics relevant to food allergy research. The presentations and breakout sessions referenced key scientific publications that are relevant to advances in food allergy research and development of research recommendations. The Panel held summary sessions to integrate and prioritize the recommendations of each breakout session.

This report summarizes the findings and recommendations of the Expert Panel.

BACKGROUND

Food allergy is an immunologic disease responsible for significant morbidity. In the United States, the prevalence of food allergy is 6–8 percent of children under four years of age, and is 3.7 percent of adults. The prevalence of food allergy appears to be increasing, with allergies to peanut increasing substantially. Food allergy is frequently accompanied by other allergic diseases including atopic dermatitis (eczema) and asthma, and asthma is an important risk factor for severe allergic reactions to food. Patients with food allergy may have mild reactions, such as hives, but are also at risk for anaphylaxis, a severe and life-threatening systemic allergic reaction characterized by hives, fall of blood pressure, upper airway obstruction, and severe wheezing. Food allergy accounts for about

35–50 percent of emergency room visits for anaphylaxis and causes about 30,000 episodes of anaphylaxis and 100–200 deaths per year in the United States. Even with assiduous avoidance of known food allergens, each year approximately one of every four food allergic individuals will have an accidental exposure that leads to a food-induced reaction. Severe, life-threatening reactions occur mostly in adolescents and young adults, and peanuts and tree nuts are the most common causes of such reactions. Currently, the only treatments for food allergy are allergen avoidance and management of reactions caused by allergen exposure. In addition to the psychological effects of the risk of death and the stigma of avoiding common foods, food allergy has nutritional impacts on the health, development, and lifestyle of children.

Hence, food allergy has emerged as an important public health problem based on its increasing prevalence, persistence throughout life for those who are sensitized to the foods most likely to cause severe reactions (peanut and tree nut), the potential for fatal reactions, and lack of preventive treatment other than food avoidance.

Physicians base the diagnosis of food allergy primarily on the clinical history. Confirmatory information can be obtained by blood tests or skin prick tests that detect allergic (IgE) antibodies to food allergens. The most definitive diagnostic test is a double-blind, placebo-controlled food challenge (DBPCFC) in which patients are fed increasing amounts of the foods in question in a carefully monitored clinical research environment. When conducted by experienced clinical investigators, the risks can be minimized, but a DBPCFC is still associated with the potential for severe allergic reactions, raising complex questions about its use in clinical research. Those issues are addressed elsewhere in this document.

OVERVIEW OF FOOD ALLERGIC REACTIONS

Food allergy is defined as an immune-mediated adverse reaction to food. In allergic individuals, certain foods trigger the immune system to produce a characteristic class of antibodies against the allergen, called immunoglobulin E (IgE). IgE binds to receptors that are present on the surfaces of two types of cells—mast cells, which are present in the tissues; and basophils, which circulate in the blood. When an individual who has been sensitized to a particular allergen is re-exposed to that allergen, the allergen binds to IgE on these cells, triggering them to release potent mediators of allergic inflammation including histamine, leukotrienes, and protein messengers known as cytokines. These mediators stimulate the accumulation of eosinophils, a type of white blood cell that is characteristic of allergic inflammation. The mediators are also responsible for the appearance of allergic symptoms. For example, histamine triggers leakage of fluid from small blood vessels into the tissues, and it causes smooth muscle to contract. In mild allergic reactions, leakage of small amounts of fluid into the skin contributes to hives, or urticaria. In severe allergic reactions, leakage of larger volumes of fluid from the circulatory system can cause the blood pressure to drop. Contraction of smooth muscles in the larynx and trachea cuts off airflow. Contraction of smooth muscles in the lung contributes to bronchoconstriction and wheezing, signs of severe asthma. Antihistamines block the effects of low and moderate concentrations of histamine and can be effective in treating mild allergic reactions, especially hives. Because severe allergic reactions

generate high concentrations of histamine and other mediators that are not blocked by antihistamines, antihistamines are far less effective in severe reactions. The most effective therapy for severe allergic reactions is epinephrine, which reverses the effects of histamine and other mediators on blood vessels and smooth muscle, and also blocks the continued release of mediators from mast cells and basophils.

Production of IgE antibodies is a complex process involving sequential cellular interactions involving several types of cells of the immune system including antigen-presenting cells, which engulf the allergens and present them to the immune system, and T and B lymphocytes. In allergic individuals, a subset of T lymphocytes produces certain cytokines that induce B lymphocytes to produce IgE in addition to other classes of antibodies. Other cytokines are potent inhibitors of IgE synthesis. The balance of these T cell-derived cytokines in a given individual contributes to the likelihood of becoming sensitized and having allergic symptoms.

CURRENT STATUS AND RECENT ADVANCES IN FOOD ALLERGY RESEARCH

OVERVIEW OF NIH-SPONSORED FOOD ALLERGY RESEARCH

NIH is the major source of federal funding for basic, translational, and clinical research on food allergy. Within NIH, NIAID is the designated lead institute, although other NIH Institutes (e.g., the National Institute of Diabetes and Digestive and Kidney Diseases) support basic research relevant to food allergy research, such as immunology of the gastrointestinal tract. NIAID convened expert panels to review food allergy research in 1996 and 2003, and the current panel in 2006.

The NIAID food allergy research portfolio has expanded substantially since the last expert panel review. This portfolio includes several single investigator-directed projects; a multi-investigator program project grant on milk allergy; and a consortium of food allergy researchers (CoFAR) that conducts pre-clinical research and clinical trials. In addition to these projects, the NIAID-sponsored Inner-City Asthma Consortium (ICAC) is conducting an observational study of children, enrolled at birth, who are at high risk for development of allergic diseases. NIAID also supports a wide range of basic research projects on fundamental immunology, allergic mechanisms, and mucosal immunology that will undoubtedly facilitate progress in food allergy research.

In FY 2006, NIAID will open two clinical trials to prevent food allergy and other allergic diseases through another clinical research program, the Immune Tolerance Network (ITN). The clinical trials conducted by CoFAR, ICAC, and the ITN are outlined later in this report in the section on clinical research. Recent and future year planned initiatives focusing on food allergy research are briefly outlined in the following paragraphs.

- In FY 2005, NIAID initiated CoFAR with planned support for five years, plus additional support dedicated to a CoFAR statistical and clinical coordinating center. This initiative addresses recommendations of the 2003 NIH Expert Panel on Food Allergy Research and will support: 1) preclinical research; 2)

observational studies and immune-based interventions for treatment or prevention; and 3) the development, implementation, and dissemination of educational programs for children, their parents, and pediatric healthcare workers.

- In FY 2007, NIAID will initiate a program called "The Allergen and T Cell Reagent Resources for the Study of Allergic Diseases," which will provide new understanding of allergen structure and make novel reagents available to the research community. NIAID anticipates that some of the funded studies will be directly relevant to food allergens.

- In 2004 and 2005, NIAID and the Food Allergy and Anaphylaxis Network cosponsored a series of conferences on the definition and management of anaphylaxis. The conference reports were published in leading journals and provided opinions of international experts on the definition and management of anaphylaxis and an outline of a proposed research agenda.

The Panel discussed a number of challenges that NIH faces in expanding support for food allergy research. Chief among them is the small cadre of academic investigators working in this arena. Any sustained expansion of the research effort will require bringing new investigators into the field, a challenging prospect in an era of tight fiscal constraints. Furthermore, the recent growth in food allergy research has been highly leveraged through solicited research programs, as opposed to intrinsic growth in the number of investigator-initiated research project grants. In this regard, only 15 percent of the current NIAID support for food allergy research is through investigator-initiated awards, compared to approximately 60 percent of investigator-initiated awards for the full spectrum of NIAID-supported research on immunology and immune-mediated diseases. The solicited research programs in food allergy include CoFAR and a multi-investigator program project grant on milk allergy. Young investigators typically regard a robust portfolio of investigator-initiated research as a sign that a field will enjoy continued NIH support and, understandably, consider the level of that support in choosing career directions. Other challenges include the relatively narrow interests of the biotechnology and pharmaceutical industries in food allergy research compared to other immune-mediated diseases. For example, a survey of the federal clinical trials database (www.clinicaltrials.gov) revealed only six therapeutic intervention trials, two of which are sponsored by industry. Fortunately, recent advances may make the field more attractive to academic investigators and industry. These include the development of new and improved animal models and an evolving understanding of the molecular mechanisms involved in food allergy and anaphylaxis. These advances should enable the identification of new therapeutic targets and their preclinical evaluation.

Food allergy research has also benefited from the generous support of philanthropic organizations and advocacy groups. This support has been instrumental in establishing a number of university-based food allergy research programs and greatly enhanced the capabilities of the academic research community to conduct research sponsored, in part, by NIH.

BASIC AND PRECLINICAL RESEARCH

Food allergens and their interactions with the immune system. The majority of well-characterized inhalant and food allergens are water-soluble proteins. However, recent studies indicate that lipids and lipid-carbohydrate complexes (e.g., glycolipids extracted from cypress pollens) can trigger immune and allergic responses. While lipid food allergens have not yet been identified, new studies have revealed the molecular pathways by which lipid and glycolipids can activate the immune system.

Cells that express the surface marker CD4 constitute a common subset of the T lymphocytes, known as T helper cells, that circulate in the blood. Recent observations suggest that approximately 60 percent of the lung CD4+ cells in patients with moderate-to-severe persistent asthma may be not conventional CD4+ T helper cells, but a special type of lymphocyte, called a natural killer T (NKT) cell.[1] NKT cells are involved in the immune response to infectious agents and have been shown in mouse models to be involved in the development of asthma. NKT cells constitute a very rare population of circulating T cells and are activated by a special set of proteins (CD1d) on the surface of the antigen-presenting cells that display lipids and glycolipids to the immune system. These observations, plus the association of food allergy and asthma, suggest that glycolipid allergens and NKT cells may be involved in other allergic diseases, including food allergy.

Recent advances have also strengthened our understanding of the structure of protein allergens and how they interact with IgE antibodies. Protein structures can now be widely studied through advanced technologies, such as X-ray crystallography and nuclear magnetic resonance, which are capable of revealing three-dimensional structures and protein-protein interactions at the atomic level. Structural information can then be exploited to identify therapeutic targets and design novel drugs. Such structure-based insights may also be important for understanding the interactions between food allergens and the IgE antibodies to food. These antibodies recognize structures, called epitopes, within food allergens that can be of two different types: linear epitopes and conformational epitopes. How the immune system perceives these distinct epitopes appears to be important in food allergy. Individuals with persistent allergy to milk, egg, and peanut have IgE antibodies that recognize mainly linear epitopes, whereas those with transient allergy recognize a higher proportion of conformational epitopes. Analysis of epitope selection may eventually allow useful predictions about the future course of food allergy in individual subjects and provide the insights for novel therapeutic approaches.

Other studies indicate that subjects with a history of severe peanut allergy have IgE antibodies that recognize a broader range and larger number of distinct epitopes than those with less severe reactions. This greater IgE diversity correlates with higher levels of

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[1] After the Food Allergy Expert Panel report was completed, further data were published indicating that NKT cells are not increased in asthma and that these cells represent less than 1% of the lung CD4+ cells. Other published studies demonstrated significant increases in NKT cells in subjects with moderate to severe asthma, but the total number of NKT cells was less than 1% of the lung CD4+ cells. Despite these differing observations, the role of NKT cells in allergic diseases, including food allergy, merits further investigation.

peanut allergen-triggered release of inflammatory mediators from basophils, a type of white blood cell involved in allergic inflammation.

Animal models of food allergy and gastrointestinal immunity. In the past, there were few mouse models of food allergy because it is difficult to induce IgE antibody by oral administration of allergen. Within the last several years, NIAID-supported investigators have developed and characterized mouse models of human food allergy and related syndromes, such as eosinophilic gastroenteritis. Although rodent models of food allergy do not mimic all the features of human food allergy, some of the newer models display important characteristics of the human disease. As such, they should be useful for preclinical evaluation of new treatment and prevention strategies, and to define molecular and cellular mechanisms that may lead to new directions in food allergy research.

Studies of gastrointestinal immunity have demonstrated that the normal response to foods is oral tolerance, a state of immunological unresponsiveness that is established and maintained by a complex relationship between microbial flora in the gut and the immune cells of the gut mucosa. An emerging concept is that gut microbes and their products activate cells of the innate immune system, generating signals that strongly inhibit the development of allergic responses to foods. These inhibitory signals serve to maintain oral tolerance.

The availability of more informative animal models will undoubtedly facilitate high quality research that cannot be performed in humans; this research includes studies of exposure routes, mechanisms of the gut immune response, and the role of the mucosal barrier in the induction, maintenance, and loss of oral tolerance.

Preclinical studies in animal models. One immunotherapy approach being studied in mouse and larger animal models is to use a chimeric fusion protein, composed of part of another class of human antibody, IgG, fused to the major cat allergen, Fel d1. This and related constructs were developed based on recent insights regarding signaling pathways that down-regulate IgE-mediated responses. This approach was effective in blocking skin and systemic reactivity to Fel d1 when administered to humanized mice.

Another approach in a mouse model is to use bacteria engineered to produce recombinant and modified peanut proteins. The peanut proteins are modified so that they are less likely to induce allergic reactions. These bacteria are then heat-killed, after which they are administered rectally to mice. This experimental treatment modified the mouse immune response and protected peanut allergic mice from allergic reactions to peanut.

EPIDEMIOLOGY AND GENETICS OF FOOD ALLERGY AND ANAPHYLAXIS

Epidemiology of food allergy and asthma. Asthma is a risk factor for severe allergic reactions to foods, but only limited epidemiologic data address the relationship between asthma and food allergy. Similarly, we have few insights regarding the prevalence and incidence of food allergy in genetically or demographically defined population groups. One intriguing observation concerns children living in our nation's urban areas—a group known to have a high prevalence of asthma and high morbidity from asthma, but widely thought to have a relatively low incidence of certain immunologic diseases, including food allergy. However, a recent retrospective analysis, which was made possible through access to clinical samples obtained in the 1990s as a part of the NIAID-sponsored National Cooperative Inner-City Asthma Study, is shedding new light on this question. This analysis suggests that food allergy may, in fact, be a major co-morbid condition among inner-city children with asthma, in that about half of such subjects had detectable IgE antibodies to foods. Thus, food allergen sensitization is prevalent in inner-city children with asthma and appears to be associated with both increased hospitalization and a requirement for steroid treatment.

Epidemiology of systemic food allergic reactions: mild and moderate vs. severe reactions. Few studies have addressed predictive factors for severe reactions, but some limited clinical data are available. Individuals who require only a low dose of food to trigger food allergic responses (i.e., a low threshold) have an increased risk of severe systemic reactions to that food. However, the precise biological responses that determine these thresholds are not yet known. While higher levels of IgE antibodies to food predict the likelihood of an allergic reaction upon exposure to that food, the IgE antibody levels do not predict reaction severity.

A number of recent studies are providing intriguing insights into correlates of clinical severity that, if confirmed, may eventually serve as clinically useful biomarkers, or indicators, of food allergy severity. As previously mentioned, the number of allergen epitopes recognized by an individual may predict the severity of food-allergic reactions. Another recent study suggests that blood levels of an enzyme called platelet activating factor acetylhydrolase (PAF-AH) may be reduced in subjects with anaphylactic reactions to peanut as compared to healthy subjects and to children with non-fatal severe reactions to peanut. Further studies will be needed to determine the reproducibility of this finding and to discover whether comparable defects also increase the risk of anaphylaxis.

Genetics of food allergy. Recent advances, including the completion of the Human Genome Project (http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml) and the HapMap project (http://www.hapmap.org/), a multi-country effort to identify and catalog genetic similarities and differences in human beings, are creating opportunities to define the genetics of human food allergy. A recent example of a link between genetic variability and allergic disorders concerns filaggrin, a protein that maintains skin and mucosal barrier function. Atopic dermatitis and asthma are strongly associated with a loss of function in the filaggrin gene. Currently, the relationship of filaggrin to food allergy, if any, is unknown. In other studies, a subset of children of Japanese descent diagnosed with atopic dermatitis and food allergy was shown to have a variant of the gene that

codes for the serine protease inhibitor Krazal type 5 (SPINK5). Similar to the situation with filaggrin, SPINK5 contributes to the maintenance of the skin barrier.

Epidemiology of eosinophilic esophagitis. Eosinophilic esophagitis is an emerging disease, with an incidence of about one in 10,000 children per year. It has a high rate of association with atopic diseases (70 percent), including food allergy (46 percent). Genomic analysis from esophageal biopsies demonstrates markedly increased expression of a set of genes involved in eosinophil biology, especially the gene for eotaxin-3, a molecule that attracts eosinophils to sites of inflammation. Not only is there striking expression of eotaxin, but also a possible genetic link to disease susceptibility associated with a single nucleotide polymorphism (SNP) in the eotaxin gene.

CLINICAL TRIALS TO PREVENT AND TREAT FOOD ALLERGY

Prevention studies. Recent observations support the conclusion that a number of novel approaches could be explored in food allergy prevention studies. A European study suggests that, in children with allergic rhinitis, immunotherapy with airborne allergens can prevent or delay the onset of asthma, but comparable studies have not been conducted in the area of food allergy. Another study showed that high levels of exposure to dog and cat allergens in early childhood reduces the development of allergy. This effect may be mediated by the dog and cat allergens themselves, or by microbial products, such as endotoxins, which are carried by pets and farm animals. Endotoxins are potent activators of innate immune responses that can skew immune responses away from the development of allergies. Thus, according to an emerging concept called the hygiene hypothesis, high levels of exposure to pets and farm animals results in exposure to microbial products, including endotoxins, and may condition the developing immune system toward a non-allergic state.

Other epidemiologic studies have reported that early life exposure to peanut is associated with remarkably low rates of peanut allergy. For example, more than 90 percent of Israeli children eat a popular peanut snack beginning in the first year of life. In contrast, young children in the United States, Europe, and Australia generally avoid peanuts or consume relatively small amounts. The prevalence of peanut allergy in Israel is 0.04 percent, roughly 10–20 fold lower than is observed in the United States, Europe, and Australia. Independent observations suggest that the immunological and clinical response to peanut allergens may also depend on cooking and preparation methods; roasting peanuts at high temperatures appears to alter the structure of allergens, possibly making them more allergenic.

Taken together, these findings suggest that early-life, high-dose allergen exposure might prevent the development of IgE antibody to that allergen. These possibilities are further borne out by experiments in rodents showing that oral or other mucosal exposure to allergen stimulates oral tolerance, particularly in neonatal rodents.

Currently, NIAID supports two clinical trials and associated mechanistic studies of early-life allergen exposure and its effects on the development of allergic diseases, including food allergy. In the first trial, which is focused specifically on a food allergen,

peanut avoidance will be compared to daily oral peanut consumption, including the peanut snack popular with Israeli children. The study will determine whether this treatment prevents the development of peanut allergy in children from four to ten months of age. In the second trial, daily oral mucosal immunotherapy with grass, cat and house dust mite allergens will be provided for one year to children aged 18–30 months. These children will be assessed for the development of allergy to the test allergens, to other allergens including food allergens, and to the development of seasonal and perennial rhinitis and asthma.

Treatment studies. Several clinical studies have demonstrated the feasibility of immune-based approaches to treat food allergy, and further studies are in early planning stages. One approach has been to lower IgE antibody levels and the number of their receptors on mast cells and basophils through the use of monoclonal antibodies that bind to human IgE (anti-IgE antibodies). One such monoclonal antibody, omalizumab, was recently licensed by the U.S. Food and Drug Administration (FDA) for treatment of asthma. In one study, patients with peanut allergy were grouped according to their sensitivity to oral food challenge with peanut and then randomly assigned to either receive a placebo or graded doses of a monoclonal anti-IgE antibody that is believed to be similar to the FDA-approved drug. High doses of the monoclonal antibody raised the threshold for an allergic reaction to oral peanut challenge from about one half of a peanut to nine peanuts, a change generally believed to be clinically relevant. These results represent the clearest evidence that immune-based approaches have potential value in the management of severe food allergy, even if only to reduce the severity of reactions to an accidental exposure. However, additional evaluation of this therapy will be needed, as a subset of the subjects did not increase their threshold in response to treatment with anti-IgE antibodies.

In contrast to subcutaneous immunotherapy with airborne and insect venom allergens, subcutaneous injection of food allergens is associated with unacceptably high rates of severe allergic reactions. Hence, additional approaches are being devised to allow food allergen immunotherapy trials to proceed. These include allergen administration via the mucosal, rather than the subcutaneous, route; chemical modification or recombinant genetic engineering to modify allergen structures; use of peptide fragments rather than the intact protein allergen; and conduct of allergen immunotherapy studies under a protective umbrella provided by anti-IgE monoclonal antibody. In support of the latter approach, a recent study sponsored by NIAID and an industry partner showed that pre-treating adults with ragweed allergic rhinitis with the FDA-approved monoclonal anti-IgE antibody allowed them to undergo rush immunotherapy (a type of immunotherapy that involves a rapid increase in the dose of ragweed over a period of hours) with a five-fold lower risk of anaphylaxis to the ragweed allergen injections.

In another NIAID/industry partnership, ragweed allergen was chemically coupled to small immunostimulatory pieces of bacterial DNA that activate a component of the innate immune system. This conjugate was given subcutaneously to adults with ragweed allergies prior to the onset of ragweed season. In comparison to the placebo group, conjugate-treated subjects showed markedly reduced symptoms, an improvement that persisted through the following ragweed season, one year after therapy was discontinued.

If its safety and efficacy can be confirmed, such an approach could be adapted to food allergens.

As noted, one promising approach is to administer allergens by the mucosal route because mucosal delivery of allergens apparently induces a protective immune response with a markedly reduced risk of systemic allergic reactions. Tests of the mucosal route include the rectal administration, in mice, of the mutated peanut proteins mentioned above. To date, human trials have used oral therapy or sublingual immunotherapy (SLIT). SLIT in humans is associated with a substantially reduced risk of provoking serious adverse events after allergen administration. SLIT reduces symptoms of allergic rhinitis and, apparently, asthma. The mechanisms by which SLIT reduces allergic symptoms are unknown, but this approach has been used successfully in Europe and is undergoing trials in the United States. One trial has demonstrated that SLIT can be safe and effective in treating patients with hazelnut allergy.

Other studies are exploring allergen non-specific therapies, namely probiotics and Chinese herbal medicines. Probiotics are live microorganisms, such as *Lactobacillus* species, that may beneficially affect the host by improving the balance of intestinal microbes. Probiotics are present in fermented foods such as yogurt. Limited experimental data suggest that probiotics administered early in life to infants at high risk of developing allergic diseases may prevent or delay the onset of atopic dermatitis. In mouse models, probiotics may dampen certain immune-mediated inflammatory diseases, including experimental colitis. The underlying mechanisms are unclear, but may involve direct stimulation of the innate immune response and/or suppression of an adaptive allergic immune response. In mouse models, Chinese herbal medicines block peanut-induced anaphylaxis, even several weeks after therapy is discontinued. The mechanisms by which this occurs are not fully understood. Neither probiotics nor Chinese herbal medicines have been tested in human trials to prevent or treat food allergy.

Impediments to clinical trials. The Panel identified several current impediments to the conduct of clinical trials for food allergy. These include: 1) safety concerns related to the potential for severe adverse reactions associated with therapies that contain food allergens; 2) the need to study pediatric populations, as the allergens of interest, the immunologic mechanisms underlying disease, and severity of disease may differ in children and adults; 3) the need to study infants and young children in food allergy prevention trials; and 4) a lack of regulatory guidance on acceptable study designs.

Concerning the last point, the panel discussed two proposed general study designs and outcome measures.

In the first type of study, researchers would evaluate safety and efficacy of candidate drugs in the setting of double-blind, placebo-controlled food challenge (DBPCFC), the only method which allows assessment of the safety of a patient consuming a particular food under conditions where risks can be minimized. This study design includes observation under carefully monitored conditions and medical supervision, but involves risks associated with the food challenges. Even at experienced food allergy research centers, approximately 25 percent of DBPCFCs are associated with moderately severe

reactions. Because of the risks inherent in DBPCFCs, the procedure is performed only by experienced investigators, who monitor subjects carefully during and after the food challenge and undertake early, definitive treatment of allergic reactions. These measures limit the severity of the reactions. Under these controlled conditions, epinephrine is used in approximately 10 percent of subjects with allergic reactions; there have been no fatal reactions in more than 5,000 oral food challenges performed by the experienced investigators in the NIAID Consortium of Food Allergy Research.

The second study design would assess safety and efficacy of drug vs. placebo in decreasing the frequency and severity of adverse reactions to accidental food allergen exposure. The latter study design eliminates the risks of DBPCFC, but requires large numbers of subjects to be followed for relatively long times. This study design also introduces confounding factors related to the lack of a controlled or documented exposure history and management of adverse events by physicians and emergency medical technicians not directly involved in the study. It is possible that each study design may have an appropriate role at different stages of drug development and licensure.

RECOMMENDATIONS

The Expert Panel organized its recommendations into five areas: 1) Clinical Trials Design; 2) Clinical Trials to Prevent and Treat Food Allergy; 3) Epidemiology and Genetics of Food Allergy; 4) Basic and Pre-Clinical Research Studies; and 5) Research Resources. These are addressed in the following sections, giving priority to those areas believed to be most essential to future progress.

CLINICAL TRIALS DESIGN

The Panel recommends that the Secretary of Health and Human Services direct the NIH and the FDA to resolve impediments to the design and conduct of clinical trials for the prevention and treatment of food allergy. The Panel recommends that the agencies establish regular meetings as a mechanism to identify the critical issues and develop solutions, and submit a written update to the agency heads on progress at the end of one year. The Panel identified the following issues that need formal or informal FDA guidance in order to facilitate the design of food allergy clinical trials, accelerate progress in this area, and encourage additional research sponsors:

- Inclusion of pediatric subjects in clinical trials of food allergy treatment and prevention strategies
- Inclusion of subjects with history of anaphylaxis to food
- Use of DBPCFC in clinical research and clinical trials, including acceptable safety and efficacy endpoints for phase 2 and 3 DBPCFC trials; strengths and limitations of this approach; and appropriate allergen doses and dose escalations in DBPCFC studies
- Use of outcome of natural (accidental) exposure to food allergens as an efficacy endpoint for licensure studies; consideration of alternative study designs that can be conducted in a more controlled environment, such as DBPCFC
- Use of available biomarkers as risk stratification tools

- Identification of the regulatory requirements, if any, for studies that use foods or food components as therapeutic agents

CLINICAL TRIALS TO PREVENT AND TREAT FOOD ALLERGY

The Expert Panel recommends that the Secretary of Health and Human Services direct the NIH to evaluate promising new approaches in the prevention and treatment of food allergies in clinical studies and clinical trials. Promising approaches may include, but not be limited to:

Prevention
- Treatment of high-risk, young children with high dose allergen by mucosal routes to prevent the development of food allergy
- Evaluation of the results of these trials to consider changing current guidelines on allergen avoidance in early childhood
- Assessment of probiotics as prevention measures

Treatment
- Treatment with allergens in combination with agents that improve the safety of allergen immunotherapy
- Treatment with allergens modified to maintain immune responses but improve safety
- Treatment with allergens by routes of delivery different from subcutaneous (e.g., oral, nasal, sublingual, rectal)
- Treatment with a combination of approaches
- Assessment of non-allergen specific approaches

Prevention and Treatment of Severe Food Allergic Reactions or Food-Induced Anaphylaxis
- Refinement of existing treatment protocols of severe reactions (e.g., intramuscular vs. subcutaneous epinephrine, early treatment with beta-adrenergic agonists, steroids, use of non-sedating antihistamines in infants)
- Use of pharmacological and immunological approaches to develop new therapies to prevent or more effectively treat severe reactions

Interventions to Treat Eosinophil-Associated Mucosal Syndromes
- Development of therapies for this spectrum of diseases
- Definition of its relationship to food allergy

EPIDEMIOLOGY AND GENETICS OF FOOD ALLERGY

The Expert Panel recommends that the Secretary of Health and Human Services direct the NIH to investigate epidemiological, genetic, developmental, environmental and pathogenetic relationships between:

- Mild to moderately severe food-induced allergic reactions and severe, life-threatening reactions

- Reactions occurring only at high threshold doses of food exposure and those occurring at low threshold doses
- Atopic dermatitis and food allergy
- Asthma and food allergy
- Food allergy and eosinophilic gastrointestinal disorders

Epidemiologic and genetics studies may include, but not be limited to:
- Investigation of biomarkers of severe food allergy, foods associated with reaction severity, and genetic components of reaction severity
- Evaluation of the genetic basis of food allergy and whether it is distinct from genetic susceptibility to atopic dermatitis, asthma and allergic rhinitis
- Investigation of the relationship between mutations in the filaggrin gene and other candidate genes known to be associated with atopic dermatitis, and cutaneous sensitization to food allergens
- Investigation of the role of NKT cells, proposed as a marker of asthma, in food allergy

BASIC AND PRE-CLINICAL RESEARCH STUDIES

The Expert Panel recommends that the Secretary of Health and Human Services direct the NIH to facilitate and promote investigator-initiated and solicited research on:

Allergen Structure
- Evaluation of epitopes and their diversity in subsets of food allergic subjects
- Identification of new food allergens, especially non-aqueous allergens and post-translationally modified proteins

Animal Models
- Expansion of studies of genetic, environmental (e.g., microbial flora), and developmental factors that modulate sensitization vs. tolerance to food.
- Evaluation of mechanisms (immunological, mucosal barrier function, leukocyte trafficking) that mediate local immune responses
- Evaluation of biomarkers in animals that may be useful in assessing the occurrence, severity and resolution of severe responses/anaphylaxis to food in humans

RESEARCH RESOURCES

The Expert Panel recommends that the Secretary of Health and Human Services direct the NIH to determine the feasibility and utility of a national and international registry of food-induced allergic reactions, including the use of existing datasets; expansion of asthma studies to include these data; and opportunity costs.

- Development of a national/international database of food-induced allergic reactions, both after accidental exposure and in association with oral food challenges, and promotion of its use in epidemiologic and genetic studies and to facilitate clinical study design.

APPENDIX A

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*Deceased

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APPENDIX B (Agenda)

Bethesda North Marriott Hotel
5701 Marinelli Road
Rockville, Maryland 20852

MONDAY, MARCH 13, 2006

7:30 a.m. **Arrival/Sign In**
Continental Breakfast

8:00 a.m. **Welcome, Purpose of this Meeting**
Daniel Rotrosen, M.D., Director, Division of Allergy, Immunology and
Transplantation, NIAID, NIH

8:10 a.m. **Introduction: Nature and Scope of the Problem**
Discussion Leaders: Stephen Galli, M.D., Stanford and Dean Metcalfe, M.D.,
NIAID

8:30 a.m. **Review of NIH Food Allergy Portfolio**
Richard Sawyer, Ph.D., NIAID and Marshall Plaut, M.D., NIAID

9:00 a.m. **Consortium of Food Allergy Research**
Hugh Sampson, M.D., Mount Sinai*****

9:30 a.m. **Break**

9:45 a.m. **Allergen Structure and Its Implications for Bioengineered Foods**
Rudolf Valenta, M.D., University of Vienna******

10:30 a.m. **Pathogenesis and Thresholds**
Susan Hefle, Ph.D., University of Nebraska Lincoln

11:15 a.m. **Genetics of Food Allergy**
Carole Ober, Ph.D., University of Chicago

12:00 p.m. **New Therapeutic Approaches to Food Allergy**
Donald Leung, M.D., Ph.D., National Jewish Medical and Research Center

12:45 p.m. **Working Lunch, discussion of breakout sessions**
Stephen Galli, M.D., Stanford and Dean Metcalfe, M.D., NIAID

1:30 p.m.   **Breakout Sessions I**

        Severe Reactions and Anaphylaxis
        Gideon Lack, M.D., St. Mary's Hospital, chair; Stephen Galli, M.D.,
        Stanford, co-chair; Lloyd Mayer, M.D., Mt. Sinai; Dean Metcalfe, M.D.,
        NIAID.

        Antigen Structure
        Rob Aalberse, Ph.D., Sanquin Research, chair; Rudolf Valenta, M.D.**,
        University of Vienna, co-chair; Jean-Pierre Kinet, M.D., Beth Israel
        Hospital; Cathryn Nagler-Anderson, Ph.D., Massachusetts General
        Hospital.

        Atopic Dermatitis
        Raif Geha, M.D., Ph.D., Children's Hospital Boston, chair; Donald Leung,
        M.D., Ph.D., National Jewish, co-chair; Hugh Sampson, M.D.*, Mt. Sinai;
        Mark Larche, Ph.D., Imperial College London.

        Genetics of Food Allergy
        Kathleen Barnes, Ph.D., Johns Hopkins University, chair; Carole Ober,
        Ph.D., University of Chicago co-chair; Marc Rothenberg, M.D., Ph.D.,
        University of Cincinnati; Gary Van Nest, Ph.D., Dynavax.

        Thresholds
        Scott Sicherer, M.D., Mount Sinai chair; Susan Hefle, Ph.D., University of
        Nebraska Lincoln co-chair; Patrick Holt, Ph.D., University of Western
        Australia; Marc Jenkins, Ph.D., University of Minnesota.

3:00 p.m.   **Break**

3:45 p.m.   **Review of Breakout Sessions I and Recommendations**
        Discussion Leaders: Stephen Galli, M.D., Stanford and Dean Metcalfe, M.D.,
        NIAID, NIH.

5:15 p.m.   **Adjourn**

6:30 p.m.   **Dinner**
        Tragara (Restaurant)
        4935 Cordell Avenue
        Bethesda, MD 20814

TUESDAY, MARCH 14, 2006

7:30 a.m.   **Arrival/Sign In**
        Continental Breakfast

8:00 a.m.   **Breakout Sessions II**

Animal Models of Food Allergy
Cathryn Nagler-Anderson, PhD. Mass General, chair; Raif Geha, M.D., Children's Hospital, co-chair; Stephen Galli, M.D., Stanford; Susan Hefle, Ph.D., University of Nebraska.

Eosinophils and Mucosal Syndromes
Marc Rothenberg, M.D., Ph.D., Children's Hospital, Cincinnati, chair; Lloyd Mayer, M.D., Mount Sinai, co-chair; Rob Aalberse, Ph.D., Sanquin Research; Dean Metcalfe, M.D., NIAID.

Novel Therapeutic Approaches
Jean-Pierre Kinet, M.D., Beth Israel Boston, chair; Gary Van Nest, Ph.D., Dynavax, Co-chair; Donald Leung, M.D., Ph.D., National Jewish; Carole Ober, Ph.D., University of Chicago.

Respiratory Allergy and Food Allergy
Mark Larche, Ph.D., Imperial College London, chair; Hugh Sampson, M.D., Mount Sinai, co-chair; Kathleen Barnes, Ph.D., Johns Hopkins University; Scott Sicherer, M.D.; Mount Sinai.

Tolerance and Food Allergy
Patrick Holt, Ph.D., University of Western Australia, chair; Marc Jenkins, Ph.D., University of Minnesota, co-chair; Gideon Lack, M.D., St. Mary's Hospital; Rudolf Valenta, M.D.******, University of Vienna.

9:30 a.m.   **Break**

9:45 a.m.   **Comments from the Audience**

10:30 p.m.   **Review of Breakout Session II and Recommendations**
Discussion Leaders: Stephen Galli, M.D., Stanford and Dean Metcalfe, M.D., NIAID

12:45 p.m.   **Working Lunch, final summary discussion**

1:15 p.m.   **Adjourn**

*Hugh Sampson, M.D., Mount Sinai, was unable to attend the Panel meeting on the first day. His presentation, "Consortium of Food Allergy Research," was made by Dr Scott Sicherer, Mount Sinai.

** Rudolf Valenta, M.D., University of Vienna was unable to attend the Panel meeting. His presentation, "Allergen Structure and Its Implications for Bioengineered Foods," was made by Dr. Dean Metcalfe, NIAID, NIH.