were prospectively followed to 4 years of age. CMH status was assessed annually by CM challenges, initially with double-blind placebo-controlled food challenges and subsequently with open food challenges.

**Results.** By the ages of 2, 3, and 4 years, children with delayed reactions developed tolerance to CM faster than those with immediate reactions (64%, 92%, and 96% vs 31%, 53%, and 63%, respectively). A wheal size of <5 mm in SPTs correctly identified 83% of 124 infants who developed tolerance to CM by the age of 4 years, and a wheal size of ≥5 mm in SPTs correctly identified 71% of 39 infants with persistent CMH. Milk-specific IgE of <2 kU/L correctly identified 82% of infants who developed tolerance to CM, and milk-specific IgE of ≥2 kU/L correctly identified 71% of infants with persistent CMH.

**Conclusion.** SPTs and milk-specific IgE in the serum are useful prognostic indicators of the development of tolerance to CM in infants with CMH.

**Reviewer’s Comments.** Previous investigations have reported certain SPT wheal sizes and milk-specific IgE levels that predict a high likelihood of tolerance developing in infants and children with IgE-mediated CM allergy. The Vanto et al article addresses this very important clinical issue. In general, the study design is well done, but it would have been preferable for the investigators to have been consistent throughout the investigation and performed double-blind placebo-controlled food challenges instead of using open food challenges at the assigned follow-up evaluations. In addition, there was a mixture of patients in this investigation with 1 group encompassing classic IgE-mediated CMH and the other group representing children with non–IgE-mediated and delayed hypersensitivity reactions to CM. Despite this, the investigation does demonstrate that SPT wheal size of <5 mm and milk-specific IgE of <2 kU/L are useful prognostic indicators for the development of tolerance in children with CMH. It does not come as any real surprise that the infants with the IgE-mediated form of CMH were more likely to have a more persistent involvement than those with the non–IgE-mediated (often delayed and isolated to gastrointestinal symptoms) form of CMH and who almost always become tolerant by the age of 4 years. These data should provide useful and practical information to the clinician who manages infants and children with CMH.

**Results.** Twenty-eight of the 66 egg-allergic and 16 of the 33 milk-allergic patients lost their allergy over time. The decrease in egg sIgE levels ($P = .0014$) was significantly related to the probability of developing clinical tolerance, with the duration between challenges having an influence ($P = .06$). For milk, there was also a significant relationship between the decrease in sIgE levels ($P = .0175$) and the probability of developing tolerance, but there was no significant contribution with regard to time. Stratification into those <4 years of age and those ≥4 years of age at time of first challenge revealed that the younger age group was more likely to develop clinical tolerance in relation to the rate of decrease in sIgE. The median food sIgE level at diagnosis was significantly lower for the group developing “tolerance” to egg ($P < .001$), and a similar trend was seen for milk allergy ($P = .06$). Using these results, a model for predicting the likelihood of developing tolerance in milk and egg allergy based on the decrease in food sIgE over time was constructed.

**Conclusions.** The rate of decrease in food sIgE levels over time was predictive for the likelihood of developing tolerance in milk and egg allergy. Using the likelihood estimates from this study could aid clinicians in providing prognostic information and in the timing of subsequent food challenges, thereby decreasing the number of premature and unnecessary double-blind placebo-controlled food challenges.

**Reviewer’s Comments.** The majority of children with milk and egg allergy eventually develop clinical tolerance; however, there are no reliable tools to predict when and in which patients this may occur. The authors demonstrated a relationship between the degree of decrease in food-specific IgE concentrations over time and the likelihood of developing tolerance. This may be a useful model, allowing clinicians to time food challenges appropriately and provide more prognostic information to patients.

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**DETERMINATION OF FOOD SPECIFIC IgE LEVELS OVER TIME CAN PREDICT THE DEVELOPMENT OF TOLERANCE IN COW’S MILK AND HEN’S EGG ALLERGY**


**Purpose of the Study.** To determine if monitoring food-specific IgE levels over time could be used as a predictor for determining when patients develop clinical tolerance.

**Study Population.** Eighty-eight patients with hen’s egg allergy and 49 patients with cow’s milk allergy who underwent repeated double-blind placebo-controlled food challenges were included in the study.

**Methods.** Using the Pharmacia CAP System FEIA, specific IgE (sIgE) levels to cow’s milk and hen’s egg were determined retrospectively from stored serum samples obtained at the time of the food challenges. Logistic regression was used to evaluate the relationship between tolerance development and the decrease in sIgE levels over a specific time period between the 2 challenges.

**Results.** Twenty-eight of the 66 egg-allergic and 16 of the 33 milk-allergic patients lost their allergy over time. The decrease in egg sIgE levels ($P = .0014$) was significantly related to the probability of developing clinical tolerance, with the duration between challenges having an influence ($P = .06$). For milk, there was also a significant relationship between the decrease in sIgE levels ($P = .0175$) and the probability of developing tolerance, but there was no significant contribution with regard to time. Stratification into those <4 years of age and those ≥4 years of age at time of first challenge revealed that the younger age group was more likely to develop clinical tolerance in relation to the rate of decrease in sIgE. The median food sIgE level at diagnosis was significantly lower for the group developing “tolerance” to egg ($P < .001$), and a similar trend was seen for milk allergy ($P = .06$). Using these results, a model for predicting the likelihood of developing tolerance in milk and egg allergy based on the decrease in food sIgE over time was constructed.

**Conclusions.** The rate of decrease in food sIgE levels over time was predictive for the likelihood of developing tolerance in milk and egg allergy. Using the likelihood estimates from this study could aid clinicians in providing prognostic information and in the timing of subsequent food challenges, thereby decreasing the number of premature and unnecessary double-blind placebo-controlled food challenges.

**Reviewer’s Comments.** The majority of children with milk and egg allergy eventually develop clinical tolerance; however, there are no reliable tools to predict when and in which patients this may occur. The authors demonstrated a relationship between the degree of decrease in food-specific IgE concentrations over time and the likelihood of developing tolerance. This may be a useful model, allowing clinicians to time food challenges appropriately and provide more prognostic information to patients.


**Purpose of the Study.** To develop a peptide microarray-based immunoassay to map IgE-binding segments (epitopes) of peanut allergens by using microliter quantities of serum.

**Study Population.** Sera from 77 peanut-allergic patients and 15 non–peanut-allergic control patients were analyzed.

**Methods.** A set of 213 overlapping 20-residue peptides was synthesized corresponding to the primary sequences of the major peanut allergens, Ara h1, Ara h2, and Ara h3. These were arrayed in triplicate along with the corresponding recombinant proteins onto glass slides and used for immunolabeling.

**Results.** The majority of patients (97%) had specific IgE to at least 1 of the recombinant allergens, and 87% had detectable IgE to sequential epitopes. Microarray mapping correlated well with previous studies. However, the analysis of individual patients revealed remarkable heterogeneity in the number and patterns of epitope recognition. High epitope diversity was found in patients with a history of more severe allergic reactions. Also, sensitization of
effect cell with more diverse IgE antibodies conferred greater reactivity to specific allergens.

**Conclusions.** The protein microarray immunoblot confirmed that Ara h1, Ara h2, and Ara h3 are major peanut allergens and allows for parallel epitope analysis. This has led to the discovery of an additional important epitope of Ara h1 and the recognition of a high degree of patient heterogeneity. This qualitative difference in epitope diversity might provide prognostic information about the patient.

**Reviewers' Comments.** Current techniques for mapping large numbers of epitopes by using individual patient sera are relatively time consuming, labor intensive, expensive, and prone to error. However, such studies have been useful, because identification of certain IgE-binding segments correlates with clinical outcomes such as likelihood for an allergy to resolve. Peptide microarray technology is a novel assay that allows characterization of large numbers of individual patient samples simultaneously with minimal amounts of blood. Microarray technology may be a useful diagnostic tool to assess differences in epitope recognition among patients and may provide more prognostic information regarding patients' peanut allergies. In addition, these assessments of allergens may speed the production of allergy vaccines engineered in the future.

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**Scott H. Sicherer, MD**
**New York, NY**

**THE EFFECTS OF A DOUBLE BLIND, PLACEBO CONTROLLED, ARTIFICIAL FOOD COLOURINGS AND BENZOATE PRESERVATIVE CHALLENGE ON HYPERACTIVITY IN A GENERAL POPULATION OF PRESCHOOL CHILDREN**


**Purpose of the Study.** To test whether food additives, specifically a limited number of food dyes and a preservative, have a pharmacologic effect on behavior irrespective of other characteristics of the child.

**Study Population.** This study started with 2878 children who were resident and registered with a general practitioner on the Isle of Wight, United Kingdom, on their third birthday. The dates of birth were between September 1994 and August 1996. After screening and the signing of consent forms, the eventual study population was 397, of which 277 completed most aspects of the study.

**Methods.** There were 2 scales used to assess hyperactivity: the Emotionality, Activity, and Sociability Hyperactivity Scale and the Weiss-Werry-Peters Activity Scale. Atopic status was determined by skin-test reactivity to house dust mites, grass pollen, cat, milk, egg, or peanut. The children were divided into 4 groups and entered into a randomized, placebo-controlled, double-blind, crossover challenge study. The groups were hyperactive and atopic, nonhyperactive but atopic, and maternal age at leaving full-time education. There was no difference in the activity scores measured in the clinic during any time period of the study. However, parental ratings of behavior showed a reduction in hyperactive behavior when the food additives were removed from the diet. There was a significantly greater increase in hyperactive behavior reported by the parents during the active versus placebo phase of the challenge. These effects were not influenced by the presence or absence of hyperactivity in the child nor by the presence or absence of atopy.

**Conclusions.** There is an effect of artificial food coloring and benzoate preservative on the activity of 3-year-old children that is detectable by the parent but not at all detectable by an assessment of activity in the clinic. Subgroups are not made more vulnerable to this effect by prior level or history of hyperactivity or by atopy.

**Reviewers' Comments.** This was a very different article to review. The authors have taken the gold-standard model of “testing” and applied it with behavior as the outcome. A potential problem is the fact that this was done at home and over an extended period of challenge and was not done solely in the clinic. Also, there is precious little “allergy” in the article notwithstanding the use of limited skin testing, the mention of IgE, and histamine. What is of note here is a very common issue for pediatricians. Not too infrequently do parents seek allergy referral for behavior issues. This is a vexing problem, and rarely is the issue an IgE-mediated condition. Also of note is that the dyes and preservatives are not available for skin testing. The take-home message that may be of help to a primary care provider includes the fact that being allergic to inhalants did not predispose the child to react to the additives. Another message in this study is that the tools and the situation that is offered in the study do not match the parental observations.

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**ANAPHYLAXIS AND INSECT ALLERGY**

**A POPULATION-BASED STUDY OF THE INCIDENCE, CAUSE, AND SEVERITY OF ANAPHYLAXIS IN THE UNITED KINGDOM**


**Purpose of the Study.** To determine the incidence, severity, and causes of anaphylaxis in the United Kingdom.

**Study Population.** United Kingdom residents born between 1912 and 1999 who were registered in the General Practice Research Database between 1994 and 1999.

**Methods.** The General Practice Research Database includes demographic and clinical data provided by general practitioners in the United Kingdom. Inclusion criteria for this study were an age of <80 years and having at least 6 months of recorded data in the database. After all cases were identified, 70 cases were selected randomly to undergo a more detailed evaluation that included contacting the general practitioner involved in the case. The investigators defined anaphylaxis as an acute allergic reaction characterized by generalized urticaria, often accompanied...
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Julie Wang and Scott H. Sicherer

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