Traditionally, the concept of allergy implied an abnormal response to an otherwise benign agent (eg, pollen or food), with an easily identifiable relationship between exposure and disease. However, there are syndromes in which the relationship between exposure to the relevant allergen and the "allergic" disease is not clear. In these cases the presence of specific IgE antibodies can play an important role in identifying the relevant allergen and provide a guide to therapy. Good examples include chronic asthma and exposure to perennial indoor allergens and asthma related to fungal infection. Finally, we are increasingly aware of forms of food allergy in which the relationship between exposure and the disease is delayed by 3 to 6 hours or longer. Three forms of food allergy with distinct clinical features are now well recognized. These are (1) anaphylactic sensitivity to peanut, (2) eosinophilic esophagitis related to cow’s milk, and (3) delayed anaphylaxis to red meat. In these syndromes the immunology of the response is dramatically different. Peanut and galactose α-1,3-galactose (alpha-gal) are characterized by high- or very high-titer IgE antibodies for Ara h 2 and alpha-gal, respectively. By contrast, eosinophilic esophagitis is characterized by low levels of IgE specific for milk proteins with high- or very high-titer IgE to the same proteins. The recent finding is that patients with alpha-gal syndrome do not have detectable IgG4 to the oligosaccharide. Thus the serum results not only identify relevant antigens but also provide a guide to the nature of the immune response. (J Allergy Clin Immunol 2016;137:1662-70.)

Key words: Asthma, allergen particles, IgE antibodies, eosinophilic esophagitis, alpha-gal, IgG4

The first awareness of immediate hypersensitivity came from the separate investigations of seasonal hay fever over the period 1870-1910 by Blackley, Wymann, Noon, and Von Pirquet. At that point, no evidence of an immune response to pollen could be detected in serum from these patients. However, in 1921, Prausnitz and Küstner showed that serum of allergic subjects could transfer sensitivity locally in the skin. This Prausnitz-Küstner test was used widely between 1921 and 1960 and played a major role in the discovery of IgE. Once IgE was established, it was possible to investigate many different aspects of allergic disease both in terms of diagnosis and in understanding the relevant treatment. Thus the discovery of IgE completely changed the investigation of these diseases because measurements were of a specific molecule measured in fully defined units (first in international units and then by absolute quantitation; ie, 2.4 ng/unit). The initial purification of Prausnitz-Küstner activity was primarily related to ragweed pollen. Interestingly, Ishizaka et al did not consider that the establishment of a new isotype of immunoglobulin, IgE, changed the argument about the causal role of pollen in hay fever. By contrast, measurement of IgE has now played a major role in the diagnosis of many allergic diseases other than hay fever. However, it has to be admitted that it is difficult to replicate the simple elegance of the evidence about the role of airborne pollen grains in hay fever. Early in the 20th century, Coca became Editor of the Journal of Immunology and proposed the concept of atopy or the hereditary tendency to become allergic to allergens in the environment. He included asthma, food allergy, and eczema, as well as hay fever, among the atopic diseases. Furthermore, he clearly implied that the sensitizing allergens had a causal role in these diseases. For the main forms of food allergy recognized at that time (eg, fish, nuts, egg, or milk), the rapid development of symptoms, including hives or angioedema, after exposure left little doubt about causality. By contrast, for chronic asthma in patients sensitized to 1 or more of the perennial allergens, the evidence of a relationship between allergens and disease is more difficult to establish. This is particularly true for allergens, such as dust mite or cockroach, where the allergens only become airborne during disturbance. We would like to focus on the evidence for causality and the role of IgE in relation to 3 conditions:

1. chronic asthma in patients who are sensitized to 1 or more perennial allergens;
2. allergic symptoms in patients who are colonized with fungi in their lungs, sinuses, or nails; and
3. the different forms of food allergy, including those newly recognized syndromes in which the relationship between exposure and response is not “immediate.”

**CHRONIC ASTHMA IN PATIENTS WITH SENSITIZATION TO 1 OR MORE PERENNIAL ALLERGENS**

The opinion about the relevance of perennial allergen exposure to chronic asthma has differed from enthusiastic acceptance to denial or, worst of all, complete indifference.8,9 In part, this reflects the failure of some important avoidance studies and the relentless pressure for treatment with pharmaceutical products. A more important cause is that the relationship between exposure and symptoms is not simple. Indeed, for mite, cockroach, “domestic” mice, and Alternaria species, patients often have very little sense that they are allergic and do not understand the role these allergens play in their asthma.10 For cat and dog, it is not unusual for the allergic patients to report that they have acute symptoms on entering a house with a relevant animal. However, in many communities the majority of patients with cat allergy do not live in a house with a cat, and nonetheless, sensitization is strongly associated with asthma.11,12 In some studies there is clear evidence that children raised in a house with a cat are less likely to be sensitized.13 However, for cat, the levels of this allergen in schools and homes without a cat increases with the prevalence of domestic cats in the community.13 Statements of this kind are possible because the source of these allergens can be identified (ie, 4-legged animals) and because of the availability of sensitive assays for relevant allergens in dust or airborne allergens.14 For cat and dog, it is very little sense that they are allergic and do not understand the role these allergens play in their asthma.10 For cockroaches and mice, visual identification is possible but less reliable than measurement of specific allergens. For dust mites, there is no way of evaluating their presence or concentration in a house without microscopy or the use of an immunoassay.5,15

There are several major variables that have been used to understand the relationship of allergen exposure to IgE antibodies and asthma:

1. Many studies have been carried out in areas where dust mites flourish in all homes (eg, the United Kingdom, New Zealand, Australia, Costa Rica, and the Southeast or Northwest of the United States).16-19
2. Studies have been conducted in areas where, because of cold temperatures and low humidity, dust mites, cockroaches, and Alternaria species are either absent or at very low levels in homes.12,20,21
3. There are groups within the United States with dramatically different attitudes to animals, such that a large section of the population have much lower exposure and sensitization.19,22
4. Pollens and fungal spores, such as Alternaria species, have major seasonal and geographic differences in their outdoor particle counts. Since the 1950s, overall exposure to pollen allergens, particularly ragweed, has decreased considerably because of widespread use of home air conditioning, which started during the 1960s.

**DIAGNOSTIC RELEVANCE OF IgE ANTIBODIES TO ASTHMA**

In almost all clinical studies, IgE antibodies or skin tests are carried out with extracts derived from the relevant allergens, and these include multiple proteins. The relevance of the results can be assessed based on the prevalence of positive test results, the titer of IgE antibody, or the size of wheals or, alternatively, by tests using specific proteins.13,23 Tests for sensitization to proteins can use purified or recombinant allergens, but these tests are carried out almost exclusively with *in vitro* assays.

There are many situations in which the significance of sensitization to certain specific proteins is different from that for the whole extract. A simple example is the tropomyosin Der p 10, which cross-reacts with both cockroach and shrimp and might not be a relevant inhalant allergen.23 A more complex situation has developed with cat extracts. The major inhalant allergen was purified by Ohman et al24 in 1974 as Cat 1, which subsequently became Fel d 1. More recently, Fel d 4 has been recognized as a second major inhalant allergen.25 However, cat extracts can produce positive skin test or IgE assay results because of IgE to 2 allergens that are not relevant to inhalant allergy. The first of these is Fel d 2 (or cat albumin), which cross-reacts with pork albumin, giving rise to the pork-cat syndrome.26,27 The second is galactose α-1,3-galactose (alpha-gal), which has emerged as a major allergen related to red meat and is the main epitope on cat IgA.28-30 A major cause of confusion comes from the difference between pelt extracts, which contain cat albumin and many proteins carrying alpha-gal, and dander extracts, which may only contain significant quantities of Fel d 1.

**UNDERSTANDING THE ROLE OF ALLERGENS IN ASTHMATIC PATIENTS AND THE RELEVANCE OF IgE ANTIBODIES**

We would like to focus on 3 observations about chronic allergic asthma: (1) the strongest association is with sensitization to common perennial inhalant allergens, which is true in particular for high-titer IgE antibodies to allergens that are prevalent in the patient’s community; (2) the relevant allergens, such as dust mite, cat, dog, or cockroach, have been shown to become airborne on particles of 5 to 35 μm in diameter (Fig 1 and Table 1); and (3) many or most acute episodes of wheezing cannot be related to increased or even high-level exposure to allergens. The implication of this last observation is that exacerbations are most likely occurring as a result of viral or other triggers in the context of underlying inflammation of the lungs and the associated bronchial hyperreactivity.18,31,32

In a simplistic view the fact that bronchial provocation of an allergic patient with nebulized allergen extract can induce both a decrease in FEV₁ and eosinophil-rich inflammation of the lungs could be taken as evidence that allergen exposure is causally related to asthma. However, the contrast between natural exposure of the lungs to particles, such as mite feces, and a bronchial challenge with nebulized allergen could hardly be more extreme (Fig 2).33,34 Exposure to dust mite allergen is thought to consist of 5 to 100 fecal particles entering the lungs per day. Nebulized allergen is estimated to be 10 million droplets inhaled over 2 to 5 minutes, where each droplet is approximately 2 μm in diameter. Mite feces have been estimated to contain 0.2 ng of Der p 1, whereas the comparable figure for nebulized droplets is less than 10⁻⁷ ng (Table 1). We assume that deposition of a particle on the bronchial wall represents sufficient local allergen not only to activate mast cells but also to recruit eosinophils, basophils, and lymphocytes. What is not clear is how long such an inflammatory focus would last. Our view is that some consequences of local inflammation could...
persist for months or longer. These include persistence of changes in the vasculature that encourage local arrival of cells and persistence of allergen-specific T cells. It seems likely that allergen-specific T cells, as well as mast cells, could contribute to the long-term persistence of bronchial hyperreactivity. Taken together, the results could explain how IgE antibodies are relevant to the process and that locally accumulating T cells could be a target for peptide immunotherapy.35

SENSITIZATION TO FUNGI COLONIZING THE SKIN, NAILS, OR LUNGS AS A RISK FACTOR FOR ALLERGIC DISEASE

There are literally hundreds of pollinating plants or fungi that produce spores, which can act as a source of inhalant allergens. By contrast, there are only a limited number of fungi that induce the production of specific IgE by growing on patients. Fungi can be found growing on the skin, on mucosal surfaces, in the sinuses, or in the lungs. In many cases these fungi have specific properties that facilitate their growth. Thus dermatophytes have a specific ability to grow on keratinized surfaces (ie, skin and nails). By contrast, Aspergillus species are able to grow both at the temperature of the soil and also at 37°C in the lungs or sinuses. Although the significance of fungal sensitization was recognized in the 1930s, acceptance of their clinical importance fluctuated until allergic bronchopulmonary aspergillosis (ABPA) was established by Hinson; Pepys; and Patterson.36,37 With the discovery of IgE, it became possible to define the diseases better and to show that many of these patients had IgE antibodies specific for fungal allergens. Although the primary focus of studies on fungal sensitization related to the lungs, it was recognized years ago that sensitization to both dermatophytes and Candida species can also be a cause of urticaria and angioedema.38 Diagnostic criteria have been suggested for some fungal diseases; however, even with ABPA, a large proportion of patients who are growing either Aspergillus species or other fungi in their lungs do not fulfill the criteria for ABPA or allergic bronchopulmonary mycosis. These patients can be described as having forme fruste allergic bronchopulmonary mycosis.

There is an important distinction between patients in whom the fungus is growing at the site of the inflammatory reaction, such as Aspergillus species or other fungi growing in the lungs or sinuses, and patients in whom fungi growing on the feet appear to be the cause of an inflammatory response elsewhere in the body.39-41 The latter form can be described as an “ID” reaction (ie, comparable with those skin lesions associated with
pulmonary tuberculosis but did not contain organisms that could infect a guinea pig). Historically, Candida and Trichophyton species were well recognized by dermatologists as causes of ID reactions in the hands or skin.38,42 In Box 1 we present 3 cases that illustrate these differences.

Over the last 30 years, the field of fungal sensitivity has changed progressively because of the availability and widespread use of new oral antifungal drugs. In the early 1980s, the only oral drugs that were available were griseofulvin and ketoconazole; both of these drugs had severe side effects. The first new drug to arrive was fluconazole, and then came itraconazole, terbinafine, and voriconazole.43-45 This means that there are not only better drugs that can be used to treat fungal infections associated with allergic disease but also there might be fewer cases of severe onychomycosis because of successful treatment in primary care. On the other hand, the use of antibiotics and steroids encourages growth of fungi, particularly yeasts. It is well recognized that many women need to take 2 or 3 doses of fluconazole when they are treated with antibiotics. It is a different question whether high-dose inhaled steroids can enhance yeast growth in the lungs. Our view is that all patients with severe asthma who produce sputum should be monitored for growth of aspergillus, yeasts, or other fungi in the lungs (see case I in Box 1).46

With all these fungal diseases, it is an open question whether it is necessary to obtain cultures before treatment. There is good evidence that patients with ABPA who are colonized with an Aspergillus species sensitive to itraconazole respond better to treatment with that drug.44 The in vitro tests of sensitivity of cultured fungi to antifungals are improving and have become more readily available. We would argue that identifying the species improves the understanding of the condition and can contribute to the success of treatment. On the other hand, Denning et al45 demonstrated that itraconazole could improve the outcome for patients with asthma who have skin sensitization to fungi without establishing the presence of a colonizing organism.46

**ROLE OF IgE ASSAYS IN THE DIAGNOSIS OF DIFFERENT FORMS OF FOOD ALLERGY: PEANUT ANAPHYLAXIS, EOSINOPHILIC ESOPHAGITIS (EoE), AND DELAYED ANAPHYLAXIS TO RED MEAT (THE ALPHA-GAL SYNDROME)**

Over the last 20 years, both the scientific investigation of allergic disease and the practice of allergy have moved progressively toward food allergy. In our practice in central Virginia, this has included major increases in 3 different forms of allergic

**TABLE I. Sizes of particles carrying some airborne allergens associated with asthma**

<table>
<thead>
<tr>
<th>Diameter (µm)*</th>
<th>Allergen concentration</th>
<th>To deliver 20 ng</th>
<th>Entering the lung</th>
<th>Allergen per particle or droplet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen grains</td>
<td>~20</td>
<td>~20 mg/mL†</td>
<td>~100</td>
<td>~5-100/d</td>
</tr>
<tr>
<td>Mite fecal pellets</td>
<td>15-35</td>
<td>~20 mg/mL</td>
<td>~100</td>
<td>~5-100/d</td>
</tr>
<tr>
<td><em>Alternaria</em> species spores</td>
<td>14 × 10</td>
<td>Unknown</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rat allergen</td>
<td>7</td>
<td>1 mg/mL‡</td>
<td>~27,000</td>
<td>~10,000/h</td>
</tr>
<tr>
<td>Nebulized allergen</td>
<td>2</td>
<td>1 µg/mL‡</td>
<td>&gt;10⁶</td>
<td>~10⁷ min</td>
</tr>
</tbody>
</table>

*Sizes were determined from (1) direct microscopy, (2) distribution on a Cascade impactor, and (3) the theoretic behavior of a Wright nebulizer.
†Concentration of allergen in mite feces was calculated from quantity and diameter. Concentration of rat allergen was measured in whole rat urine.
‡Concentration of mite antigen P₃ or ragweed antigen E, which are commonly used for bronchial provocation.

![FIG 2. Contrast between natural exposure to airborne allergen (A) and bronchial provocation with nebulized extract (B). Natural exposure is to relatively large particles, which contain a wide range of allergens and adjuvants.](image-url)
Box 1. Three cases with severe allergic disease, documented fungal infection, sensitization, and response to antifungal treatment

- Case I: 43-year-old woman; repeated severe attacks of asthma; Candida species colonization of sinuses and lungs and full response to fluconazole; IgE to Candida albicans was 13.3 IU/mL.
- Case II: 62-year-old man; judge with almost continuous facial angioedema, taking 50 mg of prednisone per day; severe fungal infection of feet for “many years”; skin test Trichophyton + + IgE antibody of 5.0 IU/mL; Trichophyton species grown from nail scrapings; no response to 3 months of fluconazole; full response to itraconazole over 1 year.
- Case III: 56-year-old man; diving instructor; increasingly severe late-onset asthma; continuous obstruction with FEV1 of 45% of predicted value despite 40 mg of prednisone per day; culture of bronchoalveolar lavage fluid grew Aspergillus and Nocardia species; successful treatment with voriconazole and Augmentin for 1 year.

Table II. Clinical and immunologic differences among 3 common forms of allergic disease

<table>
<thead>
<tr>
<th>Relevant allergens</th>
<th>Peanut-induced anaphylaxis</th>
<th>EoE</th>
<th>Delayed anaphylaxis to mammalian meat (alpha-gal syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE antibody</td>
<td>High-titer IgE to peanut proteins (5-500 IU/mL)</td>
<td>Low-titer or negative IgE to cow’s milk proteins† (&lt;0.1-2 IU/mL)</td>
<td>High-titer IgE to alpha-gal (often 10% to 30% of total IgE)</td>
</tr>
<tr>
<td>Prevention</td>
<td>Prevent eczema</td>
<td>Feed peanut from 3 mo</td>
<td>Not known</td>
</tr>
<tr>
<td>Timing of reaction to foods</td>
<td>15-60 min to local and generalized swelling§</td>
<td>12-24 h</td>
<td>3-6 h after eating red meat</td>
</tr>
</tbody>
</table>

*Chung et al.28 and Commins et al.29
†Erwin et al.47
‡Erwin et al.29
§Du Toit et al.48

Reactions to food. The thing that is truly interesting about this is that these 3 forms of “allergy” appear to be distinct both in their clinical presentation and in their underlying immune response (Table II).28,29,47,48 Peanut allergy is taken as the model for immediate and often anaphylactic reactions to food in children. This condition has been well recognized for many years but has increased rapidly during the period 1990-2010.49 Initially, it was possible to argue that there was increased awareness of the disease, but the prevalence of high-titer IgE antibody in random samples of children has increased rapidly during the period 1990-2010.49 Initially, it was possible to argue that there was increased awareness of the disease, but the prevalence of high-titer IgE antibody in random cohorts of children has increased.

The second form of food allergy is EoE, which was hardly recognized at all before 1990 and has become progressively more common over the last 20 years so that today most academic centers in the United States have an EoE clinic. The disease is characterized by chronic inflammation of the esophagus, which gets better with a diet including avoidance of cow’s milk.51-53 Although many of the children have detectable IgE antibodies to cow’s milk, wheat, egg, or soy proteins, the titers are consistently low (Fig 3).47 Recent studies have shown that almost all children with EoE have high- or very high-titer IgG4 antibodies to cow’s milk proteins.54,55 Clinically, patients with EoE continue eating cow’s milk proteins because they are not aware of being allergic. Thus EoE does not have the features of an IgE-mediated disease and also does not improve during treatment with omalizumab. If EoE is a T cell–mediated disease, we should be able to focus on T cells that can recruit eosinophils, give rise to low levels of IgE, and strongly enhance IgG4. In addition, these findings have major implications for the correct treatment.

The third group of patients present with anaphylaxis or urticaria to red meat, which is most common in adults. Indeed, the typical case is a man older than 50 years with episodes of hives, angioedema, or anaphylaxis that start several hours after a meal including red meat. On skin testing, they have negative or weakly positive skin prick test responses to a commercial beef extract but strongly positive IgE assay results for the oligosaccharide alpha-gal.28,29,57,58 Similar syndromes have now been described in many countries, including Australia, Sweden, France, Germany, and Japan.57,59-62 In each of these countries, the reported reactions to meat have been delayed for several hours after eating, IgE antibody is directed at the same oligosaccharide, and there is reasonable or good evidence that tick bites are the primary cause of the sensitization.59,61,62 In our practice the presence of alpha-gal–specific IgE that represents more than 1% of total IgE, a convincing report of bites from ticks (or chiggers), and a history of urticaria or anaphylaxis starting 2 to 6 hours after consuming red meat provide a high level of diagnostic certainty.

Evidence about these 3 forms of food allergy has provided a stronger basis for evaluating reactions to food in general, and several other syndromes have become much clearer. A simple example is the pork-cat syndrome, which was first recognized in
In evaluating cases of reactions attributed to red meat, we found patients with negative results to alpha-gal but positive results to pork, and weak results to beef. In these cases the pork response was explained by IgE specific for pork albumin. Absorption studies provided evidence that cat albumin was responsible for the initial sensitization and that food reactions were due to cross-reactivity. Patients with IgE to alpha-gal can have delayed reactions to foods containing gelatin, such as marshmallows or jelly babies. This occurs because gelatin made from mammals can carry alpha-gal; however, in addition, there are patients who are allergic to the protein epitopes on gelatin. The gelatins cross-react extensively, and this has given rise to anaphylactic reactions to vaccines containing gelatin. Most recently, we have seen a case reporting delayed reactions to mammalian products, including cow’s milk and beef, who was negative to alpha-gal. In this case the dominant assay result was to milk, and the specific protein was BSA. What matters here is that testing IgE to specific proteins and/or to the oligosaccharide alpha-gal makes it possible to identify the relevant allergens in many cases.

**RELEVANCE OF THE ROUTE OF SENSITIZATION TO THE SPECIFICITY AND TITER OF IgE ANTIBODY RESPONSES**

For many years, there have been questions about whether sensitization to allergens could occur through routes other than the inhaled or oral routes. The obvious example was atopic dermatitis, in which the skin is already damaged and IgE antibodies to inhalant allergens can reach high levels. Furthermore, patients with severe atopic dermatitis often have IgE specific for foods, bacterial antigens, and also fungi, particularly yeasts, such as Pityrosporum ovale. During the last 15 years, the evidence for sensitization through the skin has become much clearer. In relation to peanut allergy, it is well established that sensitization correlates with eczema and that use of topical treatments that incorporate peanut proteins increases the risk of sensitization. The success of early introduction of oral peanut in decreasing sensitization has added further evidence. Perhaps equally striking is the outbreak of wheat sensitization among women in Japan who use a mildly abrasive face preparation that contains wheat proteins.

Given that the oral route can be tolerogenic and that there are obvious advantages to not becoming allergic to food, the question arises whether the skin route can break tolerance induced through the oral route. This question became more complicated with the discovery that sensitization to alpha-gal was common in large areas of the United States. It is now clear that tick bites are the dominant cause of this novel form of allergy in the United States and that this syndrome provides another example of high-titer IgE production in which the skin is the route of sensitization.

Because we all make IgM and IgG2 specific to alpha-gal as part of an innate response to gut bacteria, it could be argued that the IgE response to alpha-gal must have broken tolerance. However, we have remarkably little understanding of either the immunology of IgE responses to oligosaccharides or the relevance of T cells in the response to tick bites. Initial studies in collaboration with Dr Rispens in Amsterdam suggested that the response to
alpha-gal does not include IgG4. Recently, we have extended those observations to confirm that neither the natural responses to this oligosaccharide nor the IgE-dominated response include IgG4. There is excellent evidence that oral desensitization of children with immediate hypersensitivity to milk or peanut can increase or induce IgG4 antibodies. Our current view is that the skin is an excellent route for inducing IgE to, for example, schistosomes, ticks, and peanut but in general is a poor route for inducing or boosting IgG4 antibodies. The exception might be multiple bee stings. The early data on IgG4 argued that this response required prolonged exposure. We would add that the oral route might be the best route for boosting high levels of IgG4 in an already sensitized subject and that the esophagus might be an important route for this response (Fig 4).

### CONCLUSIONS

The 3 areas on which we have focused here were chosen because they illustrate the difficulty of understanding the role of allergens in diseases in which the relationship between exposure and the disease is not obvious to the patient. In these studies the ability to measure IgE levels to allergen extracts, purified proteins, and novel allergens has been central to understanding the nature of the condition. Our first experience with this process came from investigating the epidemic of asthma in children in the United Kingdom at a time when it was already clear that many of these children were allergic to dust mites. The proof that Der p 1 was a major target for IgE was an essential part of the definition of this protein as a major mite allergen. Although sensitization to yeasts and dermatophytes was well known before the discovery of IgE, the level of scientific or clinical acceptance was “meager.” Purification of *Aspergillus* species allergens allowed measurements of IgG and IgE antibodies. Sensitization to *Trichophyton* species provides another example of the overall problem because very few of the patients have considered the possible relevance of the fungal infection.
on their feet to their disease. Purification of the relevant proteins was an important part of understanding the immune response that starts in the skin. Clinically, the availability of the newer anti-fungals has completely changed the equation. We would stress that these cases continue to appear and that without considering fungal sensitization and using oral antifungal treatment, they will continue to be treated with high doses of steroids.

The 2 new syndromes of food allergy illustrate well the problems with diagnosis and treatment of allergic diseases in which allergen exposure does not give rise to immediate symptoms. With EoE, the closest guide to the relevance of foods comes from the response to diet and particularly from the exacerbations that can occur after reintroduction of specific foods. However, the esophageal symptoms do not reappear for 24 hours or more. Skin tests are generally not convincing in defining the important sensitivity. By using serum IgE assays, the presence of IgE to cow’s milk proteins is clear. Nonetheless, it seems unlikely that IgE antibodies play a direct role in the disease. The most recent obvious, and that the ability to measure IgE and IgG4 antibody responses, that a large proportion of allergic disease involves clear that sensitization was occurring through the skin. For an oligosaccharide provided a further enigma until it became establishing that the IgE binding to meat extracts was IgE specific VOLUME 137, NUMBER 6

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