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# Unusual presentations of food allergy

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**Objective:** This presentation is designed to critically review information on presentations of food hypersensitivity reactions that may be considered *unusual* regarding the source or nature of allergen, route of exposure, or clinical manifestation.

**Data Sources:** Information has been gathered primarily through a thorough search of the English literature relevant to human subjects. Some clinical cases were also included from the author's own clinical experience.

**Study Selection:** Information summarized here was critically selected on the basis of proven or acceptable scientific validity.

**Results:** The findings indicate that food allergy presentation can be unusual in three main aspects. First, the offending allergen may not be the obvious food that was ingested or be a food protein incorporated in a nonfood product. Second, systemic reactions can be provoked by very minute quantities of food allergens that may even get access through noningestant routes, eg, inhalation, odor, skin contact, or mucous membrane contact. Third, the clinical manifestations are not limited to the few gastrointestinal, cutaneous, and respiratory symptoms with which we are generally familiar.

**Conclusions:** The extent of food allergy presentation is more than has been generally realized. Our awareness of such unusual presentations adds new knowledge and should prompt our interest in carefully evaluating patients with obscure allergic reactions for possible food allergy.

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**"If we are always content with the every day things that we see and hear, then we will never arrive at true knowledge."—Plato (427–347 BC)**

## INTRODUCTION

*"It gives me a great deal of pleasure to introduce Dr. Sami Bahna. The American College of Allergy, Asthma and Immunology wisely chose Dr. Bahna this year for the recipient of the Bernard A. Berman Lectureship. Dr Bahna is a colleague who represents what Bernie stood for—a scientist, a leader, an individual of national and*

*international reputation, and one who is involved in not only research, but also understands clinical activities and brings from the clinic questions that need to be solved in the laboratory. Dr. Sami Bahna is Professor of Pediatrics and Medicine and Co-Director of the Allergy and Immunology Training Program at the University of South Florida at the All Children's Hospital in Saint Petersburg, Florida."*—Joseph A. Bellanti, MD (Georgetown University)

*"Thank you very much, Dr. Bellanti. Probably most of you know that not many situations can make me speechless. However, the most potent of them is when I am complimented or awarded undeservingly, and today's event is certainly one of them. When the program chairman, Dr. Betty Wray, informed me of my selection for this lectureship, I tried to convince her that it should be given to a more deserving person. After I failed in dissuading her, I called the College President, Dr. Ira Finegold, and*

*proposed to him some individuals for this award, but in turn, he told me that most of those persons were among the selection committee. The honor is certainly overwhelming, and I will treasure it for life. Bernie was a very dear friend to me, just as he was to many of you. I began to know him during the 1978 College annual meeting in Las Vegas—I was about to complete my allergy/immunology fellowship training at that time. I begin admiring and respecting Dr. Berman then, and I was fortunate to share with him numerous scientific and social events over the years. It is very nice to see members of his family present with us today. Dr. Berman was an exceptional person and, interestingly, my lecture's title is 'Unusual presentations of food allergy'."*

Since the term "unusual" is a relative one, perhaps some of what I will mention may be considered usual by some. In this presentation, I will address three aspects of food allergy; first, unusual or hidden allergens; second, unusual routes of exposure; and third, unusual clinical manifestations. During this presentation, the term "allergy" encompasses any hypersensitivity reaction, not necessarily mediated by IgE. Because of the time limitation, I will just mention selected examples or brief information concerning each of these aspects.

## UNUSUAL OR HIDDEN ALLERGENS (Table 1)

### *Psyllium in Cereals*

The husk of psyllium (*Plantago ovata*), also known as ispaghul, is widely used in bulk-forming laxatives.<sup>1</sup> Lantner et al<sup>2</sup> reported the case of a 60-year-old woman who had anaphylaxis after eating a psyllium-containing cereal for the first time. Her previous exposure to psyllium was only through dispensing, as a nurse, a psyllium-containing laxative until 4 years earlier, without any symptoms. She showed a positive skin prick test

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Table 1. Unusual Presentations of Food Allergy

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|-------------------------------------------------------------------------------------------|
| Unusual or hidden allergen                                                                |
| Food protein                                                                              |
| Nonfood protein                                                                           |
| Protein hydrolysate formulas                                                              |
| Transgenic food                                                                           |
| Food additives (preservatives, acidifiers, dyes, flavorings)                              |
| Unusual routes of exposure                                                                |
| Inhalation                                                                                |
| Skin contact                                                                              |
| Nonoral mucous membrane contact                                                           |
| Combination of food and other factors (exercise, hormone, infection, GI disorder, stress) |
| Unusual clinical manifestations                                                           |
| Chronic serous otitis media                                                               |
| Chronic pulmonary disease (Heiner syndrome)                                               |
| Hypersensitivity pneumonitis                                                              |
| Constipation                                                                              |
| Gastroesophageal reflux                                                                   |
| Vasculitis                                                                                |
| Fixed skin eruption                                                                       |
| Irritability/sleeplessness in infants                                                     |
| Arthropathy                                                                               |
| Nephropathy                                                                               |
| Thrombocytopenia                                                                          |

(SPT) with a psyllium-containing laxative (Metamucil, Procter & Gamble, Cincinnati, OH) and her basophils showed an in vitro histamine release on exposure to psyllium, which was much reduced after the cells were desensitized with anti-IgE. James et al<sup>3</sup> described a wide variety of symptoms reported by 20 patients after eating psyllium-containing cereals.

#### *α-Amylase in Bread*

Kanny and Moneret-Vautrin<sup>4</sup> reported the case of a woman who had asthma for 20 years that got worse while working in a bakery and she did not improve after she quit that job. SPTs with inhalants and foods showed a positive reaction only to *Aspergillus oryzae* α-amylase, which was in the bread she had been consuming. SPT with α-amylase from another source (*Bacillus subtilis*) was negative. A double-blind placebo-controlled food challenge (DBPCFC) caused a systemic reaction 30 minutes after she ingested 5 mg of uncooked α-amylase and within 15 minutes of in-

gesting 10 mg of a cooked preparation. Eating 50 g of bread caused wheezing and urticaria within 2 hours. Avoidance of all products that contain α-amylase resulted in complete remission of her asthma. α-Amylase is present in many baked foods and may be in starch, fruits, vegetables, beverages, sugar, honey, and diet foods.

#### *Milk in Dairy-Free Sorbet*

Jones et al<sup>5</sup> reported the case of a child with systemic anaphylaxis to cow's milk (CM). While he was on a strict milk-free diet, he developed anaphylaxis within minutes of ingesting < 1 tablespoonful of raspberry sorbet. The results of SPT with raspberry was only slightly positive. Analysis of that sorbet revealed a milk allergen equivalent to 11% of that in nonfat dry milk. The manufacturer admitted that that particular batch of sorbet was packaged by equipment that was used to package ice cream. Of special interest in this case is that the product was labeled "Kosher-pareve, dairy-free."

The magnitude (quantity and frequency) of hidden food allergens in commercially prepared foods is greater than we realize, even with proper labeling. In recent years, the food industry has been better educated regarding the potential impact of this problem and has made some improvement in labeling and quality control. Whenever an error is discovered, the manufacturer usually issues a public warning and often withdraws the product. The Food Allergy Network, Fairfax, VA plays an active role in rapidly disseminating such information to its members and to the allergists.

#### *Parasite in Fish and Seafood*

Alonso et al<sup>6</sup> described five patients who had allergy symptoms after eating raw or undercooked seafood. Skin prick tests and RASTs were negative to fish and seafood but positive to *Anisakis simplex*, a nematode that infests fish and seafood, with a high prevalence in Japan and Spain. *A. simplex* larvae are susceptible to heat (greater than 60° C for 10 min) or freezing (–20° C for 48 hours). Those patients

continued to eat deep-frozen fish and seafood without any symptoms.

#### *Alcohol in Melon*

Mallon and Katalaris<sup>7</sup> reported the case of a woman who had multiple episodes of systemic anaphylaxis after ingesting alcoholic beverages. She had an episode after eating overripe rock melon that had a pungent odor. Skin testing with common foods was negative, as were oral challenges with several additives and preservatives. An oral challenge was positive to 50 mL of 2% ethanol but negative to fresh rock melon. She refused challenge with overripe rock melon.

#### *Latex in Sandwich*

Schwartz<sup>8</sup> described allergic reactions in two patients after they had eaten food prepared by persons who wore latex gloves. Skin testing results were negative to foods, whereas RAST was positive to latex.

#### *Dust Mites in Flour*

Erben et al<sup>9</sup> reported the case of a man in Michigan who arrived at the emergency department with anaphylaxis. His symptoms occurred 15 minutes after eating beignets made of a powder mixture purchased 4 weeks earlier from a shop in New Orleans, where he had eaten beignets without any reaction. That man was known to have asthma and sensitivity to house dust mites. Microscopic examination of the remainder of the beignet mixture revealed mite infestation, whereas a new box of the same product obtained from the same shop contained no mites. The SPT results with aeroallergens and foods, including every ingredient of the beignet mixture, were positive only to house dust mites. The SPT and RAST results were positive to the infested mixture but not to the new one. Inhibition assays of RAST and ELISA using the infested mixture showed curves similar to those by using *Dermatophagoides farinae*. A few years later, more cases were reported from Spain<sup>10</sup> and Venezuela.<sup>11</sup> In Caracas, Venezuela, mites were found in 37% of flour purchased from 25 stores but not in fresh flour from the factory. These re-

ports demonstrate that an allergen that is primarily an inhalant and causes respiratory allergy can cause a systemic reaction if ingested in large quantity.<sup>11</sup>

#### *Protein Hydrolysate Formulas*

Extensively hydrolyzed protein formulas are widely accepted as hypoallergenic and yet may cause reactions in exquisitely allergic subjects. We<sup>12</sup> reported the case of a milk-sensitive child who had explosive systemic anaphylaxis to one sip of 1:4 diluted extensively hydrolyzed casein formula. Ragno et al<sup>13</sup> evaluated the allergenicity of three hydrolysate formulas in milk-sensitive children. They documented positive challenges to an extensively hydrolyzed casein formula in 2 of 20, to an extensively hydrolyzed whey formula in 2 of 15, and to a partially hydrolyzed whey formula in 9 of 20.

#### *Transgenic Food*

Nordlee et al<sup>14</sup> demonstrated the transfer of Brazil nut allergen to transgenic soybean that was genetically engineered by Brazil nut gene to increase its methionine content. Such a finding halted several major agricultural projects because of the potential consequences to allergic consumers.

#### *Food Additives*

Food additives include preservatives, acidifiers, dyes, and flavorings. Their number is estimated to exceed 20,000.<sup>15</sup> In the United States, there are 2,922 additives, of which 1,755 are regulated by the Food and Drug Administration.<sup>16</sup> Investigation of reactions to food additives can be a very tedious, time-consuming process and with minimal yield. At present, there is no reliable skin test or in vitro test for sensitivity to food additives. When a few particular additives are strongly suspected by history, the culprit might be identified by conducting multiple DBPCFCs.<sup>17,18</sup> The reports in the literature are not many, and some lack convincing documentation.<sup>17-23</sup>

Desmond and Trautlein<sup>24</sup> described the case of probable anaphylaxis to the azo dye tartrazine in an asthmatic medical student who was hospitalized with severe anaphylaxis after the ingestion

of orange juice and three yellow jelly beans. A recurrence occurred while he was still in the hospital and was receiving a yellow liquid theophylline preparation. Beaudouin et al<sup>25</sup> reported a case of systemic reaction (generalized urticaria, angioedema, bronchospasm) after the ingestion of colored yogurt that contained approximately 1.3 mg of the natural dye carmine.

I evaluated a 13-year-old girl who was very distressed with recurrent generalized urticaria. Some of her episodes occurred after eating ice cream or other foods. Findings from SPTs with a large number of foods were negative. A supervised aspirin challenge resulted in severe generalized urticaria and facial angioedema. She denied taking any medications. I discovered that acetylsalicylic acid is frequently used as an acidifier in several commercially prepared foods, including ice cream.

Another 6-year-old child suffered a few episodes of generalized urticaria within a few minutes of eating ice cream to which a certain chocolate syrup was added. The same ice cream was eaten alone without any reaction. The RAST to cocoa was negative, as was an oral challenge with chocolate. Another brand of chocolate syrup was well tolerated. The label of the offending chocolate syrup was not helpful in ruling out one particular ingredient.

### **UNUSUAL ROUTES OF EXPOSURE**

Reactions to foods through inhalation or skin contact have been well recognized in numerous occupational settings.<sup>26</sup> In contrast, sporadic food reactions through noningestant routes are usually more difficult to recognize.

#### *Peanut Inhalation*

Carlston<sup>27</sup> reported the case of a peanut-sensitive asthmatic woman who had acute bronchospasm on a flight when peanuts were being served to other passengers. Among the exquisitely food-sensitive series we recently reported<sup>28</sup> was the case of a school-aged child with severe peanut allergy who wheezed after a teacher, who had

just eaten peanuts, entered the child's classroom.

Recent surveys identified some individuals who experienced various allergic reactions to the odor of peanuts in schools<sup>29</sup> or on commercial flights.<sup>30</sup> Such incidents generated much debate in the national press for some time. Some outspoken patients' advocates hoped to ban peanut products in schools and on commercial airlines. Such a regulation would not only be infeasible but also would have substantial undesirable ramifications.<sup>31</sup>

#### *Vegetable Inhalation*

Castells et al<sup>32</sup> reported the case of a child with severe potato allergy by ingestion, skin contact, and inhalation. The odor or fumes of cooking potatoes caused systemic anaphylaxis and walking in potato fields during the pollen season caused wheezing. Igea et al<sup>33</sup> reported the case of a woman who experienced rhinoconjunctivitis, asthma, and urticaria when she touched fresh green beans or inhaled its vapor while boiling. She had no symptoms when touching or eating cooked green beans.

#### *Milk Protein Inhalation*

Rossi et al<sup>34</sup> reported a case of allergic rhinoconjunctivitis and asthma caused by inhaling caseinate in a man working as a kneader mixing minced meat with caseinate powder. Also, a milk-sensitive Italian woman had a fatal anaphylaxis to vapors of boiling CM.<sup>35</sup>

#### *Egg Protein Inhalation*

Edwards et al<sup>36</sup> documented bronchospasm to aerosolized egg protein in some bakery workers. Some of those patients did not show a positive SPT or RAST to eggs. It is conceivable that the specific IgE antibodies are primarily at the shock organ—the bronchial tree.

One of my highly allergic pediatric patients<sup>37</sup> had a history of anaphylaxis to eating eggs, fish, or seafood or even inhaling the fumes of cooking fish. He repeatedly had urticaria when he touched egg or shrimp. On one occasion, urticaria appeared while he was in the vicinity of the kitchen where his mother was cooking with eggs, although he was not aware of what she was doing. Another

episode occurred during fishing as soon as a fish was caught.

#### *Fish Inhalation*

Crespo et al<sup>38</sup> reported that, of 197 children allergic to fish by ingestion, 20 (10%) showed symptoms when exposed to fish odor or fumes. The symptoms were respiratory (mostly wheezing) in nine, cutaneous (mostly urticaria) in nine, and combined in three. The age of onset by inhalation was later than that by ingestion. Airborne exposure was while fish was being fried in 14, boiled in 6, and served to others in the vicinity in 5.

#### *By Inhalation and Not by Ingestion!*

In baker's asthma, bronchospasm occurs when wheat flour is inhaled, whereas eating wheat bread is generally well tolerated.<sup>39</sup>

#### *Skin Contact with Fish*

Dominguez et al<sup>40</sup> reported that, of 197 children allergic to fish by ingestion, 29 (15%) showed symptoms upon skin contact with fish. The reactions were mostly urticaria/angioedema, but one patient wheezed as well. The age of onset by contact was later than by ingestion. More than one-half of patients had atopic dermatitis diagnosed before the onset of fish allergy by contact. In 17 (59%), the reactions occurred even after indirect contact, such as fish-contaminated napkins, eating utensils, or fingers of another person. Reactions by indirect skin contact with CM or peanuts have been reported through kissing or touching contaminated clothes.<sup>28</sup>

#### *By Touching and Not by Ingestion!*

Nagano et al<sup>41</sup> reported three cases of local contact urticaria to raw crustacea. In one patient, the reaction occurred on contact with the shell but not with the meat.

#### *Milk in Ointment*

Jarmoc and Primack<sup>42</sup> reported the case of an infant who was receiving a strict milk-free diet because of severe CM allergy. Nevertheless, he experienced two episodes of anaphylaxis after the application of a particular ointment to the diaper area. Among its many ingredients, that ointment contained calcium caseinate (in a 5%

quantity) that was listed on the label of the outer box but not on the label of the ointment tube itself.

#### *Carrageenan in Barium Enema*

Tarlo et al<sup>43</sup> reported a case of a woman with chronic gastrointestinal (GI) symptoms, mild asthma, and local pruritus to latex gloves. She experienced anaphylaxis during a barium enema, without using any latex products. SPT results were negative to latex but positive to the barium enema solution. SPT results with each of the 15 components of the barium enema solution were positive to only one—sodium carrageenan, which constituted 0.4% (wt/vol). Her serum was positive for carrageenan-specific IgE antibodies. Her chronic GI symptoms disappeared after avoidance of carrageenan-containing foods and pharmaceuticals.<sup>43</sup>

#### *Bovine Serum Albumin through Artificial Insemination*

Wuthrich et al<sup>44</sup> reported the case of a woman who had severe anaphylaxis during artificial intrauterine insemination with her husband's sperm. The SPT and RAST findings were positive to the medium for the sperm and bovine serum albumin (a component of that medium) but negative to latex and the antibiotics in the medium.

#### *Food in Combination*

Whenever a patient reports an adverse food reaction at times but not at others, the involvement of an additional factor should be considered. Such factors may be physical exercise, hormonal change, infection, GI disease, or emotional stress. This aspect of food allergy has not been adequately investigated. The best recognized combination is the food-dependent exercise-induced anaphylaxis, in which the two factors should occur within a short time (usually less than 2 hours) from each other. In some patients, the symptoms may be limited to urticaria or bronchospasm. The implicated food can be a specific one or any meal.<sup>45</sup> Dohi et al<sup>46</sup> noted that the offending food was specific in 7 of 11 patients, and the reaction in two patients was limited to the time of menstruation, ie, a combination of three factors. Our incomplete under-

standing of the role of such combinations is probably responsible for the very low discovery rate of this entity.

### **UNUSUAL CLINICAL MANIFESTATIONS**

Generally speaking, the common or familiar manifestations of food hypersensitivity are vomiting, diarrhea, abdominal pain, oropharyngeal itching, occult intestinal bleeding in infants, urticaria, angioedema, eczema, rhinitis, cough, wheezing, and systemic anaphylaxis. In contrast, listed in Table 1 are other manifestations that may arbitrarily be considered unusual or unfamiliar. This list is not complete by any means and some of these manifestations may, understandably, be referred to as controversial.

#### *Chronic Serous Otitis Media*

The role of food allergy in causing serous (or secretory) otitis media is difficult to evaluate. The relationship has been reported to be common by some authors<sup>47</sup> but not by others.<sup>48</sup> There is evidence that the primary shock organ for the allergic reaction can be the Eustachian tube or the middle ear itself.<sup>49</sup>

#### *Chronic Pulmonary Disease (Heiner Syndrome)*

A syndrome of chronic pulmonary disease in infants has been attributed to CM hypersensitivity.<sup>50</sup> It seems to be rare but probably underdiagnosed. In addition to chronic cough or recurrent wheezing, there may be upper respiratory symptoms, GI symptoms, failure to thrive, eosinophilia, and anemia. The latter can be secondary to occult intestinal bleeding and occasionally to alveolar bleeding. Radiologically, the pulmonary lesion is usually in the form of patchy infiltrates. The serum contains high titers of precipitating antibodies to multiple bovine milk protein fractions. Immune complex deposits in the alveolar vasculature cause an Arthus-type reaction and perivascular inflammation. In some patients, the vasculitis may be severe enough to cause alveolar bleeding and pulmonary hemosiderosis. The latter can be verified by the demonstration of

iron-laden macrophages in tracheal aspirate or by lung biopsy.

#### *Hypersensitivity Pneumonitis*

Zubeldia et al<sup>51</sup> described the case of a woman who had chronic respiratory symptoms with multiple severe exacerbations that required hospitalization and extensive evaluation. The findings from her lung biopsy were typical of hypersensitivity pneumonitis, but her serum did not contain specific antibodies to avian droppings, fungi, or animal dander. The patient was working in veterinarian diet research that involves soybean. Delayed hypersensitivity skin testing and serum precipitins to soybean were positive. Her symptoms completely resolved after she avoided exposure to soybean powder. Acute exacerbation was induced 6 hours after bronchial inhalation challenge with 1 ng of soybean but not with placebo.

#### *Constipation*

Hypersensitivity reactions are generally expected to cause hyperreactivity. However, food, particularly milk, as a cause of constipation in infants, has been often suspected by parents but usually dismissed by physicians. Iacono et al<sup>52</sup> evaluated 27 infants receiving CM formula and chronic "idiopathic" constipation and found that the problem was milk related in 21.

#### *Gastroesophageal Reflux*

Kelly et al<sup>53</sup> examined 10 children who had gastroesophageal reflux and eosinophilic esophagitis and showed poor response to antireflux therapy, including fundoplication in six. Restricting the diet to an elemental formula resulted in remarkable improvement within 2 to 6 weeks in all 10 children. Oral challenge with selected foods resulted in recurrence of symptoms. Cow's milk and soy formula were the most common offenders. Cow's milk was also implicated in another series of infants with gastroesophageal reflux.<sup>54</sup>

#### *Vasculitis*

Allergic vasculitis, particularly food induced, constitutes a small group of the vasculitic disorders. Only a few reports implicated certain foods or azo

dyes.<sup>55</sup> Lunardi et al<sup>56</sup> described five patients (13 to 45 years old) with allergy and cutaneous vasculitis for 1 to 13 years. Evaluation did not reveal infections, autoimmune disease, or neoplasms. After 3 weeks of following a hypoallergenic diet, the vasculitis disappeared in four and markedly improved in one. Oral challenges, at 5-day intervals, with 14 foods and 9 food additives confirmed the offending substance to be a food in two patients, an additive in another two, and both food and an additive in the fifth patient. Avoidance of the offending substance resulted in no recurrence of vasculitis during a 2- to 4-year followup. Wuthrich<sup>57</sup> described a case of disulfite-induced urticarial vasculitis and a case of anaphylactoid purpura to tartrazine and benzoate.

I encountered the case of a child who had multiple hospitalizations for acute episodes of severe cutaneous and mucous membrane vasculitis.<sup>58</sup> The mother noticed that the episodes appeared after the child ate chocolate. Avoidance of the latter resulted in remission, except for a few mild episodes after accidental eating of cocoa-containing food.

#### *Fixed Skin Eruption*

Apparently foods can cause a fixed eruption, as do certain drugs. Kelso<sup>59</sup> reported the case of a woman in whom a recurrent erythematous itchy patch on a particular area of her left buttock developed within 1 to 2 days of eating strawberries. Yanguas et al<sup>60</sup> reported a case of recurrent erythema with burning sensation on wrists, hands, and lips caused by eating lentils. The lesions were reproduced within 15 minutes after eating 25 g of cooked lentils.

#### *Irritability/Sleeplessness in Infants*

Parents often report irritability and sleeplessness in their infants even after feeding them, usually a conventional milk formula. In some such infants, the condition is believed to be due to milk-induced colic and usually disappears after feeding a hypoallergenic formula.<sup>61</sup> In other infants, the condition is believed to arise from central nervous system stimulation. Kahn et al<sup>62</sup> examined some

infants in the sleep laboratories and noted that substituting the conventional milk formula with an extensively hydrolyzed one resulted in more than doubling the average sleeping time and in almost no awakening at night.

#### *Arthropathy*

Several reports suggested relationships between food intake and systemic rheumatic disease in selected patients.<sup>55</sup> Parke and Hughes<sup>63</sup> reported the case of a 38-year-old woman who had progressive rheumatoid arthritis for 11 years, with negative rheumatoid factor and poor response to medications. She was consuming up to 1 lb of cheese daily for the past 18 years. Her arthritis remarkably improved within 3 weeks of changing to a milk-free diet. Ten months later, a milk challenge in the hospital caused remarkable deterioration within 24 hours. Panush<sup>64</sup> evaluated the cases of 16 patients with arthritis and negative rheumatoid factor, who claimed food-related joint symptoms. While receiving an elemental diet, double-blind food challenges confirmed the relationship in three patients, two to foods and one to nitrate. Golding<sup>65</sup> described three patients with recurrent synovitis related to food. Within a few hours of milk challenge in one, knee swelling developed and 30 mL of fluid was aspirated. Van de Larr and van der Korst<sup>66</sup> evaluated the cases of six adults with rheumatoid arthritis highly suspected to be food-related. Partial to total remission occurred within 4 weeks of a diet limited to an elemental formula. Use of DBPCFC confirmed a relationship to specific foods in four of the six patients. However, long-term benefit from dietary avoidance was noted in only two patients.

#### *Nephropathy*

Food-induced proteinuria has been suggested in a few reports.<sup>67,68</sup> Sieniawska et al<sup>69</sup> evaluated 17 children with steroid-resistant nephrotic syndrome. All had normal creatinine clearance and BUN levels. A 14-day trial of milk-free diet resulted in the disappearance of proteinuria in six patients. Milk challenge caused recurrence of proteinuria in three

of the six patients. After 1 year of milk avoidance, one patient was not seen again, two tolerated milk without recurrence of proteinuria, one became steroid-responsive, and two were still intolerant to milk.

### Thrombocytopenia

Whitfield and Barr<sup>70</sup> noted some correlation between CM intake and thrombocytopenia in children with the thrombocytopenia and absent radius syndrome. Jones<sup>71</sup> reported the case of a newborn with severe thrombocytopenia that disappeared when milk was avoided and recurred when challenged with milk.

### SUMMARY

The understanding of food allergy, once an unrecognized entity, has come a long way. As curious clinicians listen to their patients and explore appropriate possibilities, new knowledge is attained that, in turn, helps us in our ever-continuing race after disease. The information provided in this article was critically selected from the literature and indicates that adverse reactions to food are not limited to the usual, at least in three aspects. First, the offending allergen may not be the main food that was ingested. Second, the immune system may react systemically to minute quantities of food allergens that may even get access through noningestant routes. Third, the clinical manifestations of food allergy are not limited to the few GI, cutaneous, and respiratory illnesses with which we have been familiar. Let us always remember that the book was written according to the patient and that the patient does not get sick according to the book!

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