John A. Anderson, MD
Head, Division of Allergy and Clinical Immunology
Department of Medicine
Henry Ford Hospital
Detroit, Michigan

Kathleen C. Barnes, BS, MA
Doctoral Student
Department of Anthropology
University of Florida
Gainesville, Florida

Paul L. Doering, MS
Professor of Pharmacy Practice
College of Pharmacy
University of Florida
Gainesville, Florida

Leslie Sue Lieberman, PhD
Associate Professor of Anthropology and Pediatrics
Departments of Anthropology and Pediatrics
University of Florida
Gainesville, Florida

Victoria Olejer, MS, RD
Nutritionist
Asthma Allergy Clinic
Shreveport, Louisiana

Judy E. Perkin, DrPH, RD
Program Director and Associate Professor
Clinical & Community Dietetics
College of Health Related Professions
University of Florida
Gainesville, Florida

Steve L. Taylor, PhD
Professor and Head
Department of Food Science and Technology
University of Nebraska
Food Processing Center
Lincoln, Nebraska

Food Allergies and Adverse Reactions

Judy E. Perkin, DrPH, RD
Program Director of Clinical and Community Dietetics
University of Florida
Gainesville, Florida

AN ASPEN PUBLICATION®
Aspen Publishers, Inc.
Gaithersburg, Maryland
1990

bent and Sampson[5] studied 69 legume-sensitive patients and found only 2 with sensitivity to more than one legume.

Crustacea have been extensively studied in terms of their cross-reactive potential. Significant cross-reactivity has been demonstrated for crawfish, lobster, and shrimp.[3] Because of the severe nature of the allergic manifestations related to crustacean consumption, Sachs and O'Connell[3] feel open challenges to confirm cross-reactivity potential are unwarranted and cross-reactivity to various crustacea can be presumed.

Clinical manifestations of food allergy are reviewed in Chapter 1, and specific manifestations associated with major food allergens will be discussed in this chapter. It is important to remember that although seemingly rare, food-induced anaphylaxis resulting in death can occur. Yunginger et al[6] identified 7 such deaths within 16 months. (Peanut was involved in four of these deaths; the others were related to pecan, crab, or fish consumption.) Such deaths emphasize the importance of avoidance because fatal anaphylaxis in the case of true food allergy may be initiated upon consumption of very small amounts of the offending food. Patients with food allergies must also be able to self-administer epinephrine when needed.

MAJOR FOOD ALLERGENS

Cow's Milk

Cow's milk contains approximately 30-35 grams of protein per liter,[1] and over 25 protein fractions have been identified in cow's milk that have the capability to induce an allergic response.[7] Most clinical cow's milk allergy, however, is believed to be related to the allergenicity of three fractions: (1) ß-lactoglobulin (a whey protein), (2) α-lactalbumin (another whey protein), and (3) casein.[1,7,8] Bovine serum albumin and globulin may be allergenic but are considered to be less so than the above three protein types.[2,7] (The effects of processing on allergenicity of cow's milk protein are discussed in Chapter 9.)

Proteins of goat's milk, which serve as antigens, are closely related to cow's milk protein fractions. This means that persons having a cow's milk allergy will frequently be allergic to goat's milk as well.[7,9] Cow's milk protein hydrolysates commonly do not elicit an antibody response; therefore, they are used in products serving as cow's milk or cow's milk-formula substitutes. Businco et al,[10] however, have reported that Alpha-Ré®, a cow's milk whey protein hydrolysate formula product of the Nestle Corporation, did evoke anaphylactic reaction in five infants with cow's milk allergy. (Residual casein epitopes in the formula were believed to be responsible.) Chapter 2, Part II, includes a discussion of whey versus casein hydrolysate formulas.

Components in cow's milk other than its natural protein constituents may also be responsible for an allergic reaction. Examples of such substances include penicillin and proteins of ragweed, linseed, peanut, and/or wheat.[11] The US Food and Drug Administration does have regulations aimed at prevention of penicillin contamination of milk products.[7]

It has been noted that individuals with cow's milk allergy may react to other food allergens. It has been estimated that 10 to 30% of persons who are sensitive to cow's milk will also be sensitive to soy.[12]

Allergy to cow's milk is considered by some to be the most common food allergy in the United States.[9] The prevalence in infants and children is estimated to be between 1 and 3%.[2,13] Some evidence suggests that cow's milk allergy is seen in up to 30% of children with allergies.[14] Olejer in Chapter 2, Part II, provides data that suggest even higher levels of prevalence in both the total and allergic populations.

Cow's milk allergy seen in infants and children may be related not only to the allergenicity of protein fractions, but may also be related to the large amounts of cow's milk consumed relative to body weight. Also, the relative immaturity of the gastrointestinal tract may allow greater antigen uptake.[2] Roberton et al[15] found higher serum ß-lactoglobulins in preterm, as contrasted to term, neonates.

The phenomena of cow's milk allergy, although most prevalent in the pediatric age group, can occur at any age.[16] Olalde et al[17] recently presented an interesting case history of a 29-year-old patient with cow's milk allergy. The allergic manifestations in this patient were bronchospasm and urticaria.

Several immune response mechanisms may be involved in cow's milk allergy. Bahna and Heiner[13] have indicated potential involvements of type I, type III, and type IV reactions. Children who never manifest symptoms of cow's milk allergy may still demonstrate high levels of antibodies to cow's milk protein.[18]

Anderson et al[19] have identified several factors that may impact on the development of cow's milk allergy in the infant. These include diet history (ie, formula versus breastfeeding), health status (ie, the presence of gastrointestinal disease), and familial history of atopic disease. Gerrard and Shenassa[20] have postulated different types of cow's milk allergy linked to breastfeeding versus formula feeding. These researchers feel an IgE-mediated mechanism is probably associated with cow's milk allergy seen in the breastfed infant. At any rate, the prognosis for cow's milk allergy in early life is generally good with disappearance of clinical problems by age 2 years.[14]

The clinical presentation of cow's milk allergy can be extremely varied. Gastrointestinal problems are considered to be the most common clinical manifestations.[13,14] Intestinal changes may range from minor inflammation of the lamina propria to villus flattening with inflammation.[21] Specific gastroin-

testinal problems seen in conjunction with cow's milk allergy may include diarrhea, vomiting, steatorrhea, abdominal or stomach pain, malabsorption (particularly of zinc and calcium), colonic inflammation, protein-losing enteropathy, and bleeding (either overt or occult).[7,13,14] Occult blood loss is considered to be a common problem and an area of concern because it can be a cause of iron deficiency anemia.[14] Blood loss in the occult form may be as high as 10 ml per day and small losses (less than 5 ml/dl of stool) may go undetected using a guaiac test.[7] Wilson et al [22] report that in their pediatric practice experience, occult bleeding related to cow's milk ingestion is seen in about half the children with diagnosed iron deficiency who reportedly consume large quantities of milk per day (one quart or more).

Two forms of gastroenteropathy associated with milk ingestion have been outlined by Katz et al.[23] Milk-sensitive enteropathy, a type not associated with IgE abnormalities, is reported to appear most commonly in the first year of life. This type of enteropathy is often said to resolve with cow's milk elimination. The other outlined chronic gastroenteropathy type, labeled as eosinophilic, is associated with IgE-mediated food allergies. This latter type responds well to corticosteroid treatment.

Respiratory problems are another potential manifestation of cow's milk allergy. Respiratory symptoms may include wheezing, coughing, and nasal congestion or draining. Cow's milk has not been shown to either produce mucus or affect mucus viscosity.[14,24] Heiner's syndrome is a specifically defined respiratory disorder associated with cow's milk allergy.[7,14] Heiner's syndrome is characterized by lung infiltrates, elevated levels of eosinophils, and high levels of serum precipitins to cow's milk. Patients may have respiratory and/or gastrointestinal problems, anemia, or fail to thrive.[7,14] The development of Heiner's syndrome is believed to involve either type III or type IV immune reaction.[7]

Some patients with cow's milk allergy may have skin manifestations such as hives, angioedema, or eczema. Some patients may react to skin contact with dermatitis. Anaphylactic reaction as a clinical manifestation is rare but can occur.[14]

Sleeping problems in infants may, in some instances, be related to adverse reaction to cow's milk, and this is an area of current investigation.[25,26] Researchers in this field support the exploration of behavioral therapies for infant sleep disorders prior to experimental dietary manipulation involving cow's milk elimination. Although some have linked use of cow's milk formula to colic,[27] a definitive association has yet to be established.[26,28]

Treatment of cow's milk allergy involves elimination of the offending source from the diet.[29] This means avoidance of cow's milk, its products, and beverages and foods containing cow's milk, cow's milk products, or cow's milk protein as an ingredient. Management of cow's milk allergy in infants and toddlers is discussed in Chapters 2 and 6. General guidelines for a diet eliminating cow's milk protein are shown in Appendix A. Label reading is an important skill because milk protein content may be indicated using terms such as whey, curds, or sodium caseinate.[8] A diet that eliminates cow's milk protein sources may result in inadequate calcium, vitamin D, riboflavin, and/or vitamin A intake.[29] Supplementation as appropriate to meet individual needs may be warranted. Consumption of alternative bioavailable calcium sources can be encouraged.

Legumes

Several legumes have been cited as food allergens. These include soybeans, peanut, green peas, taugeh (a variety of sprouted green bean used in egg rolls), garbanzo, and lima beans.[1,3,5,30] Of these, the soybean and peanut have been most extensively studied.

The allergenic protein fractions of soybeans have yet to be fully characterized. The globulin 2S component is considered by some to be the most allergenic fraction with 7S and 11S globulins and hemagglutinin (soybean trypsin inhibitor) also believed to be allergenic.[1,2] Burks et al[31] reported they could find no one soy fraction to be more allergenic than any other.

Manifestations of soybean allergy include gastroenteropathy,[32] asthma,[33] urticaria,[34] eczema, and anaphylaxis.[35] Exposure to soybeans may come from bean consumption, consumption of products containing soy (eg, tofu, miso, soy sauce, textured vegetable protein), occupational exposure to soy flour, or use of a soy-based formula.[33,36]

Because many infants with cow's milk allergy are allergic to soy, soy formulas are no longer recommended by many practitioners as a hypoallergenic alternative.[37] Some practitioners, however, continue to switch a cow's milk-sensitive infant to a soy formula and believe that such a switch is an appropriate therapy strategy. (Olejer in Chapter 2, Part II, discusses use of soy formulas for infants allergic to cow's milk.) Burks et al[38] studied the allergenicity of two types of soy-based infant formulas, liquid versus powder. *In vitro* testing in this study indicated the liquid form may be more allergenic. Donovan and Torres-Pinedo[39] report that some infants who do poorly on soy formulas seem to react adversely to the sugar components, sucrose or dextrimaltose, rather than the soy proteins. They report these infants can be helped by use of a soy-lactose formula.

The ability of soybean oils to cause allergic symptoms has been a subject of investigation. An article written by Swedish researchers indicated that soy proteins could be present in some fat products (margarines and oils).[40] After

Chapter 7

Adverse Reactions to Food Additives and Other Food Constituents

Judy E. Perkin

INTRODUCTION

In some instances individuals appear to be sensitive to food or beverage additives through mechanisms not, for the most part, classified as immunologically mediated.[1] This chapter includes a review of substances most commonly associated with these adverse reactions. This chapter also reviews selected natural food constituents for which adverse reactions have been described. The majority of the adverse reactions discussed in this chapter seem to be food intolerances. (See Chapter 1.)

ASPARTAME

In 1985, the Food and Drug Administration (FDA) established the Adverse Reaction Monitoring System (ARMS). Aspartame has headed the list in terms of the ingredient most complained about (80% of ARMS complaints as of November 1988).[2] Soft drinks have been cited most as the aspartame-containing food culprit, and headaches are the most common adverse reaction reported.[2]

Aspartame is a nutritive artificial sweetener. Although it is caloric (4 Kcal/g), its sweetness relative to sucrose (180-200 times sweeter) makes it an attractive very low calorie sweetener.[3-5]

Aspartame chemically is L-aspartyl–L-phenylalanine methyl ester. The components of aspartame are two amino acids, phenylalanine and aspartic acid and an alcohol methanol.[6] When consumed by humans, aspartame may be absorbed and metabolized via two different pathways.[7] Both pathways ultimately result in the appearance of aspartate, phenylalanine, and methanol in the portal blood. Pathway number one involves hydrolysis to the three

the residues of the allergenic proteins during typical processing. Also, with certain products such as the edible oils, there is some concern about recontamination of the products in home or food service settings. Similar concerns exist for celiac patients and foods prepared from wheat, rye, barley, and oats. Again, only foods with detectable residues of the protein fractions of these grains will be hazardous in all likelihood. However, the presence or absence of proteins in various ingredients and products made from these grains such as malt extract, wheat starch, or rye alcohol has not been carefully established. Therefore, the most prudent advice is to avoid all exposures to any products made from these grains.[65] Such concerns are not as important in the cases of metabolic food disorders or idiosyncratic reactions. Because some tolerance exists for the offending substance, the avoidance of all foods containing the offending material may not be necessary.

Hidden sources of the offending food or food ingredient can exist. Some examples have already been provided, such as the presence of milk proteins in lactose[87] and the presence of soy proteins in lecithin.[80] The inadvertent or intentional contamination of one food with residues of another is also a major concern. Many of the most serious allergic reactions to foods occur following the inadvertent consumption of the offending food, often from hidden sources.[74] While caution is advised, a listing of all possible hidden sources of food allergens would be impossible to compile. In the formulation of food products, care must be taken to avoid the presence of hazardous allergenic residues or to acknowledge the presence of such foods on the label of the food product.[21] Also, care should be exercised in the formation of new food products to avoid especially potent allergenic materials where alternatives exist. Obviously, many products would not be the same without the presence of peanuts, but their presence should be noted on the label. In a recent incident with a new potentially allergenic material (cottonseed protein), use of this material in a food product resulted in adverse reactions and cottonseed allergy.[88]

Cross-reactions can also occur between closely related foods, although no general statements can be made on this topic. Tremendous individual differences occur with respect to cross-reactions. In a few cases, cross-reactions are rather commonly encountered among individuals with a particular type of food allergy. Examples would include cross-reactions between different species of avian eggs[89] and between cow's milk and goat's milk.[90] As noted earlier, cross-reactions are also very common in celiac disease among wheat, rye, barley, and oats. However, with other IgE-mediated food allergies, cross-reactions are somewhat less common. With respect to crustacea, many individuals with crustacean allergy will be sensitive to all species, including shrimp, crab, lobster, and crayfish, but some individuals will be sensitive to only one or a few of the species.[91] In the case of seafood allergies, individuals

are often counseled to avoid all seafood species even though cross-reactions between finfish, crustacea, and mollusks have not been reported.[76] This advice is probably unnecessary, although cross-reactions within the crustacean and finfish categories have been documented. With respect to finfish, many fish species contain parvalbumins with structural similarities to allergen M, which may explain the existence of frequent cross-reactions between species.[92,93] However, cross-reactions do not always occur among all finfish.[94] With some types of IgE-mediated food allergies, cross-reactions with closely related foods are rather uncommon. The best example would be with legumes. On a comparative basis, many more individuals have peanut allergy than have soybean allergy. Only a few patients with peanut allergy are also sensitive to soybeans or other legumes,[95] although numerous peanut-allergic subjects will have positive skin tests to other legumes.[95,96] Cross-reactions can also occur between environmental and food allergens. The best examples are between birch pollen and various fruits, vegetables, and tree nuts including hazelnut, carrot, and apple,[23,31,97] between mugwort pollen and celery,[98] and between watermelon and ragweed.[99] The phenomenon of cross-reactivity is complex and poorly understood. Consequently, generalized advice is difficult to provide.

CONCLUSION

Specific avoidance diets are the best method available presently for the treatment of food allergies and sensitivities. However, these diets should be formulated so the patients can experience the widest possible array of foods within the necessary limits. Often, specific avoidance diets are too strict. However, with the present state of information, it is often not possible to provide individual patients with specific answers to many of their questions. The improved formulation of avoidance diets will require improved diagnosis of food allergies and sensitivities, additional research on critical questions such as the inactivation of allergens or the existence of cross-reactivity, and trained dietitians to assist patients with the formulation of safe and effective avoidance diets. In cases where incomplete information exists, the best advice is often conservative advice, especially for patients with histories of life-threatening or severe reactions.

REFERENCES

1. Taylor SL, Nordlee JA, Rupnow JH. Food allergies and sensitivities. In: Taylor SL, Scanlan RA, eds. *Food Toxicology: Perspectives on the Relative Risks.* New York: Marcel Dekker, Inc; 1989:255–295.

Waring et al[60] suggest there may be two types of mechanisms by which individuals experience adverse reactions to shrimp. One mechanism would be IgE mediated, and the other would be reaction through another immune or nonimmune mechanism.

Fish

A major fish allergen that has been extensively studied and described is allergen M from codfish. Allergen M is a parvalbumin type of protein of the sarcoplasm.[1,62] Protamine sulfate may also serve as a fish allergen in some instances. Other allergens are believed to be present in fish, but to date have not been identified or described.[1] Fish allergens are considered to be heat stable.[2]

Fish may cause an allergic reaction through ingestion, inhalation, or contact.[2,34,63] Aas[63] even reported that some individuals will react to steam produced during the cooking of fish. Contact dermatitis has been reported via water in which codfish had been washed.[34] Dust from a household where fish has been cooked also may serve as another allergen exposure source. Allergy to one type of fish may or may not be associated with cross-reactivity.[62]

Clinical manifestations of fish allergy may include asthma, urticaria, nasal problems, nausea, vomiting, pruritus, angioedema, diarrhea, and headache.[2,62] Clinical manifestations may appear very quickly after ingestion.[2] Testing is recommended to correctly identify the species of fish to be avoided.[62] Once this is accomplished, dietary counseling can be initiated.

Fruits (Noncitrus) and Vegetables

Several fruits and vegetables have been cited as foods causing allergic reaction. Allergen types in most fruits and vegetables have to be identified but glycoproteins with allergenic potential have been extracted from the tomato.[1] Fruit and vegetable allergies seem to be associated with hay fever and allergies to certain pollens. Ortolani et al[64] describe associations between allergy to cherry, apple, carrot, or pear to birch and allergy to watermelon and tomato to grass. Associations were also found between birch and fennel and walnut allergies and mugwort and allergies to watermelon, celery, and apple.

Ortolani et al[64] also describe a constellation of clinical symptoms known as oral allergy syndrome, which may be seen in conjunction with fruit and vegetable allergy, particularly celery allergy. The initial symptom of oral allergy syndrome consists of swelling and irritation of the mouth and lips occurring a few minutes following consumption. This initial stage may be followed by other symptoms such as urticaria, angioedema of the pharynx,

rhinoconjunctivitis, asthma, or anaphylactic shock. Pauli et al[65] also describe symptoms of urticaria, rhinitis, asthma, pruritus, conjunctivitis, and anaphylaxis with celery allergy. Of the 20 patients studied by this group, 16 of the celery-allergic subjects were also sensitive to pollen. Vallier et al[66] recently published evidence that the cross-reacting components among celery, mugwort, and birch pollen may be carbohydrates.

Egg

Hen's eggs contain many potential allergens. The allergens with primary allergenicity are contained in the egg white.[2] At least one report has cited 13 potentially allergenic components in egg white.[67] The principal allergens in the egg white are ovalbumin, ovotransferrin (conalbumin), and ovomucoid.[1,67] Egg yolk proteins may also be allergenic. Specifically cited in this regard have been the yolk proteins apovitellenin I and VI.[68] Research to date also suggests allergic cross-reactivity may exist between some egg proteins in the white and yolk.[69]

IgE antibodies to egg white have been detected in cord blood, and egg allergy is considered to be relatively common during infancy. The incidence of egg allergy appears to decline with age.[70]

Egg allergy may result not only from exposure through ingestion, but inhalation as well.[71–74] Edwards et al[71] concluded that inhalation did not significantly impact on skin-test reactivity to eggs in adults, but Kemp et al[72] reported cases of anaphylaxis in children exposed by the inhalation route to pavlova mix that was being prepared by parents (1 case) and a nurse (1 case). Hoffman and Guenther[73] describe the case of an adult patient who raised birds as a profession and subsequently developed allergy to ingested egg yolk. Allergy to egg yolk subsequent to acquisition of a parrot has also been described.[74]

Symptoms of egg allergy may include pruritus, atopic dermatitis, asthma, vomiting, hives, angioedema, diarrhea, and anaphylaxis.[70,75] Egg allergens may cause adverse reaction through both intestinal allergy and contact dermatitis.[70] Iyngkaran et al[76] present a case study of an infant in whom egg allergy appeared to elicit intestinal abnormalities. These abnormalities included villous atrophy, impaired xylose absorption, and marked decreases in lactase, maltase, and sucrase activities. Rossi et al[77] suggest that in some instances egg allergy may be linked to immune dysfunction, specifically hyperimmunoglobulinemia E in conjunction with defects in polymorphonucleocyte and T-lymphocyte function. Ford and Taylor[78] suggest that egg allergy may be more long-lived in patients who exhibit a variety of clinical symptoms.

Table 7-3 Guidelines for Dietary Mold Avoidance

1. Eat canned foods immediately
2. Eat fresh fruits soon after preparation
3. Do not eat leftover foods
4. Do not consume meats or fish that have been stored for over 24 hours
5. Exclude the following foods:
   - —Beer
   - —Breads, soured or made with large quantities of yeast
   - —Buttermilk
   - —Cider
   - —Cheeses (all types)
   - —Dried fruit
   - —Mushrooms
   - —Sauerkraut
   - —Sour cream
   - —Soured milk
   - —Vinegar and foods that contain vinegar
   - —Wine and other alcoholic beverages

Histamine

Histamine occurs in some foods naturally[162–164] and may be present in wines, particularly red wines.[165,166] Examples of foods with a high histamine content include Parmesan, blue, Roquefort, and Monterey Jack cheeses; spinach; eggplant; tomatoes; and chicken livers. Examples of wines which may have high levels of histamine are Chianti and burgundy.[164] Most individuals do not have adverse reactions to dietary components that contain histamine because the histamine is metabolized through methylation by n-methyltransferase or oxidized by histaminase.[167] The drug isoniazid, however, is a strong histaminase inhibitor, and Uragoda[167] reports histamine poisoning in two tuberculosis patients associated with food consumption. The patients had consumed tuna fish that contained histamine. Symptoms included headache and reddening of the eyes, face, and palms. Enzyme insufficiency (histaminase) may therefore relate to symptoms. Other problems that may predispose to problems with ingested histamine or other biogenic amines may include abnormal intestinal permeability and portacaval shunt.[163] Malone and Metcalfe[164] have reported that clinical signs of histamine toxicity may occur in some individuals when 32 to 250 mg of histamine are consumed. Certain foods are also known as histamine releasers. These include alcohol, chocolate, egg whites, fish and shellfish, pineapple, strawberries, and tomatoes.[162] Intake of high amounts of starch has also been related to histamine production by gut bacteria.[162,163]

Scombroid fish poisoning is a type of foodborne illness that involves conversion of histidine to histamine and is characterized as histamine poisoning. Fishes involved commonly include mackerel, bonito, and tuna but sardines, bluefish, and mahimahi have been implicated as well.[168] The histidine to histamine conversion occurs when the fish are not properly cooled and are kept at high temperatures. Symptoms of scombroid poisoning include headache, flushing, and throbbing pain in the neck. Symptoms generally appear within minutes or up to 3 hours after ingestion.[162,168,169] Chin[144] has postulated a link between high histamine consumption and Chinese restaurant syndrome symptoms. (See previous discussion under monosodium glutamate.)

Certain factors may favor nonspecific histamine release. These include (1) lectins (discussed later in this chapter), (2) bacterial endotoxins, and (3) enzyme and mineral deficiencies.[163] Japanese individuals may experience facial flushing, tachycardia, and muscle weakness after alcohol ingestion. These symptoms have been linked to a deficiency of alcohol dehydrogenase and histamine liberation.[163,170] Magnesium deficiency in rats has been associated with increased histamine release and sensitivity.[171] Humans who exhibit allergic symptoms, but fail to be diagnosed as truly allergic, have also been noted by some to have decreased levels of cellular magnesium.[163]

Tyramine and Phenylethylamine

Tyramine is a vasoactive biogenic amine found in foods such as cheeses (cheddar, Gruyere, Brie, Camembert, Roquefort), wine (especially red wines), herring, and baker's yeast.[163] Tyramine has been implicated in the etiology of migraines and urticaria.[163] Patients taking monoamine oxidase inhibitors are advised to avoid foods or beverages that are high in tyramine as intake by such patients is associated with adverse reactions such as headache, hypertension, flushing, and death.[163]

Phenylethylamine is a vasoactive amine found in chocolate and some fermented cheeses.[163] Phenylethylamine ingestion has been implicated in dietary-related migraine.[172]

Octopamine and Phenylephrine

Octopamine and phenylephrine are vasoactive amines present in citrus fruits. They may be associated with adverse reactions particularly headache.[162]

Table 8-2 Mechanisms Theorized by Which Diet May Influence Arthritis or Other Joint Disease

- Food allergy
- Food intolerance
- Changes in intestinal absorption
- Alterations of immune system functioning
- Alterations of prostaglandin and leukotriene synthesis
- Changes in body weight

provement in rheumatoid arthritis related to the diet was not demonstrated by this study. Improvement was similar in treatment and placebo groups.[24]

Denman et al,[2] also in 1983, published the results of a study designed to test the efficacy of selected dietary restrictions on clinical manifestations of rheumatoid arthritis. No rationale in the research report was provided for choice of foods excluded. Foods eliminated were red meats, eggs, dairy products, food colorings and preservatives, chocolate, and selected baked goods. A major problem of this study was the inability to elicit compliance with the restricted diet for a sufficient period. Of the 18 subjects enrolled in the study, 13 (72%) did not follow the diet for more than 2 months. Tests to measure disease status showed no difference pre- and post-treatment for the five subjects who did follow the diet for more than five months.

Ratner et al[26] studied the effect of eliminating dairy products and beef on the course of rheumatoid arthritis and psoriatic arthritis in 15 women and 8 men. This research group reported that 7 women (6 with seronegative rheumatoid arthritis and 1 with seronegative psoriatic arthritis) ceased to be symptomatic within 3 to 4 weeks after initiation of the test diet. Provocation with dairy foods elicited recurrence of symptoms. (Testing was not conducted in a blind fashion.) All of the women responding positively to the diet were determined to be lactase deficient. Antibody testing results were described as not being definitive. The authors speculated that arthritis may be seen as one manifestation of allergy to cow's milk protein. They further speculated that lactase deficiency may potentiate arthritis by affecting permeability of the intestine.

Panush et al[13] published results of an inpatient clinical research center study of a female patient who demonstrated signs and symptoms compatible with the diagnosis of rheumatoid arthritis. The prospective partially blind study contrasted symptomatology experienced while on the patient's customary diet versus trials of fasting, elemental diet, and elemental diet plus capsules of placebo (D-xylose) or lyophilized foods (lettuce, carrot, chicken, beef, rice, and milk). Both the elemental diet only and fasting trials were accompanied by improvement in symptoms. For example, on the patient's

customary diet, she experienced about 30 minutes of stiffness each morning. During the 3-day fast and 2-day elemental diet only, the patient experienced no morning stiffness. Challenge with milk evoked clinical symptoms similar to those observed on the customary diet. Measurement of joint tenderness index and grip strength was significantly affected in a deleterious manner in association with the milk challenge. Measurements of serum IgE did not vary significantly during study phases. Slight increases in IgG antimilk were noted, as were sporadic elevations in circulating immune complexes. The patient also had abnormally high mononuclear cellular reactivity to milk. Skin tests demonstrated mild reaction to milk. The authors concluded milk played a role in the arthritic symptoms of this patient. They felt either the patient suffered from milk allergy with arthritis as a manifestation or the patient had rheumatoid arthritis exacerbated by milk protein.

A single-blind outpatient study of 53 subjects (10 male and 43 female) conducted by Darlington et al[12] correlated clinical improvement in symptoms of rheumatoid arthritis with dietary therapy. Specifics of the tested dietary regimen were not given in the research report, but therapy appeared to have consisted of withdrawal of potentially offending foods with reintroduction of foods by families at greater than 4-day intervals. Subjects were randomly divided into two groups after a 2-week washout period. One group was placed on 6 weeks of the diet therapy, and the other group received placebo therapy for 6 weeks followed by 6 weeks of diet therapy. Both groups exhibited improvement in parameters such as pain and erythrocyte sedimentation rate. Although weight loss occurred during this study, weight loss was not necessarily related to positive clinical response. The research group concluded dietary restrictions may benefit some patients.

Inglis,[27] in 1987, proposed that contamination of milk with bacterial lipopolysaccharide may induce arthritis. He further speculated that milk fat may enhance absorption of this lipopolysaccharide. These speculations have yet to be confirmed.

Carini et al[28] were able to induce joint symptoms by food challenge in 10 patients. Symptoms appeared 12 to 48 hours after challenge. When examining total IgE levels on an individual level, however, there was no association with joint symptoms. A subgroup of six patients was assessed for the presence of IgG anti-IgE autoantibodies. Three patients exhibited autoantibodies that peaked 24 hours after food challenge. Although the authors admit the biological relevance of IgG anti-IgE autoantibodies to allergic disease is at present unknown, they postulate that IgG anti-IgE autoantibody may first bind to IgE and subsequently bind to mast cells with resultant release of inflammatory substances.

Panush[20] reported in 1988 that his research group had studied a total of 15 patients who had participated in double-blind food challenges. Three were