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Food Allergies and Adverse Reactions

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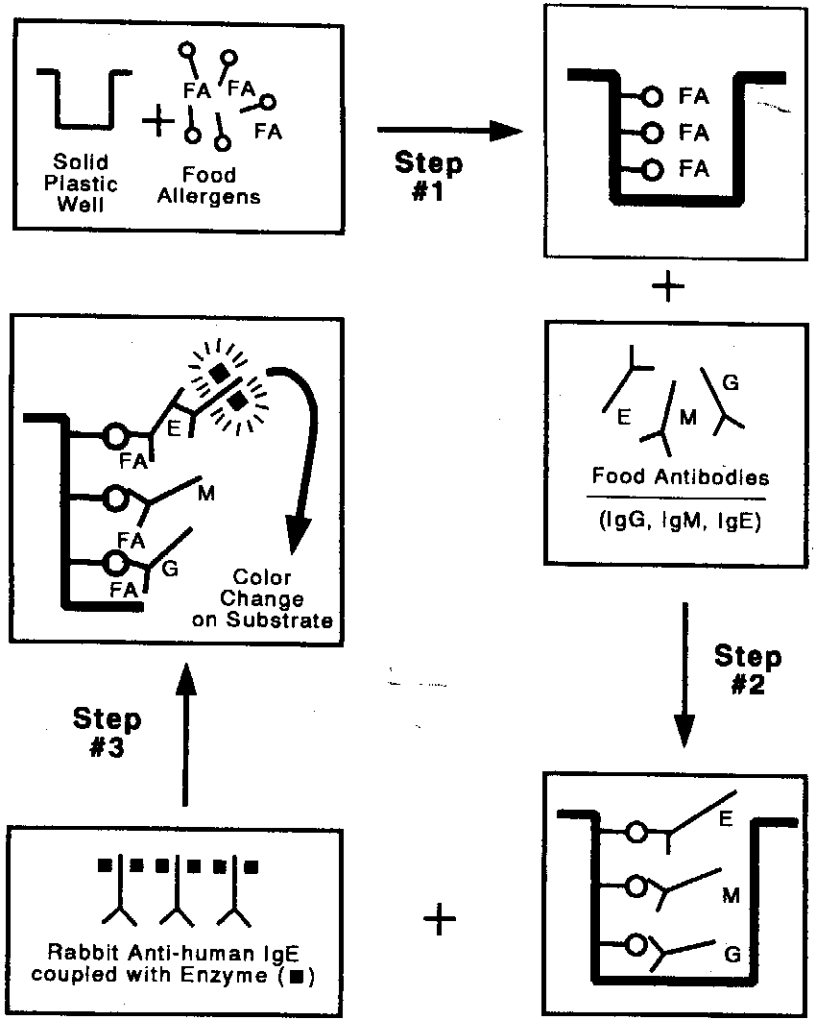

Figure 2-2 Enzyme-Linked Immunosorbent Assay (ELISA)

conditions. Therefore, it is not valuable to do both tests under these circumstances. The reverse, however, is not true. If the *in vitro* test is negative, the epicutaneous skin test may be positive. The *in vitro* test system is preferred in the following situations: (1) systemic anaphylaxis, (2) extensive dermatitis on the patient, (3) dermographism in the patient, and (4) antihistamine use by the patient which can block the skin test reaction.

OTHER IMMUNOLOGIC TESTS OF VALUE IN THE DIAGNOSIS OF FOOD ALLERGY

Most of the conditions in which non-IgE food-related immune reactions have been considered seem to fall into the general category of delayed (in timing) reactions.[12,13] If immune mechanisms are involved, they are usually classified as Gell and Coombs type III—immune complex reactions—or type IV cell-mediated reactions (see Chapter 1, Table 1-3 and text). The only recognized proven IgE type III immune food reaction is cow's milk-induced syndrome with pulmonary disease (Heiner's syndrome). In this condition, serum cow's milk precipitants are associated with the signs and symptoms of the disease. The milk-precipitant test, which measures high levels of IgG-milk antibody, is performed by a gel diffusion technique in which the cow's milk antigen allergens are placed in one well of Ochterlony agar gel plate and the patient's serum in another well. After an overnight incubation at room temperature, precipitant bands are seen in the gel between the wells as the milk allergen and milk antibody diffuse from each of the plate wells.

Tests of cell-mediated immunity (Gell and Coombs type IV) reactions have been used in an attempt to identify an immune reaction in patients with late-onset reactions due to food (delayed clinical reactions).[27] These tests, which include lymphocyte transformation and the measurement of lymphokines, are usually research tools.[13]

UNPROVEN AND UNAPPROVED "ALLERGY" TESTS USED IN THE DIAGNOSIS OF SUSPECTED FOOD ALLERGY

Historically, the term "allergy" refers to an altered response. In this sense then almost any reaction might be identified as an allergy, even if those reactions bear little or no resemblance to an immune response or a type I IgE-mediated allergic reaction[1,6] (see Chapter 1, Table 1-1 and text). Because eating foods is a daily event, it should not seem unusual that common medical complaints patients might have could be attributed to food and diet, not just those complaints having a recognized etiology. Some of these complaints share common characteristics.

1. They involve a large portion of the population.
2. They are symptoms, not diseases.
3. They have many trigger factors.
4. They have no one proven pathogenesis.
5. Rarely is there one single standardized test to objectively and conveniently prove (or disprove) the existence of the condition.

Symptoms or conditions such as headache, myalgia, hyperactivity, fatigue, behavioral abnormalities, learning disorders, mental fuzziness, depression, restlessness, confusion, colic, and enuresis fall into this category.

Occasionally, these complaints are attributed to food allergy in its broadest historical sense, an altered response. In an attempt to prove an altered response or allergy to either a diet or specific food, several tests have evolved through the years and have been promoted as valuable by a few physicians who believe food and diet can cause these conditions or complaints, many times through a dysfunction of the immune system.[6,8,28] Unfortunately, the tests are called allergy tests but fortunately no immune abnormality is likely to be proven by these tests.

All of these so-called allergy tests can be classified as unproven and unapproved.[29] None of them has satisfied a proper evaluation trial to be acceptable as safe and efficacious. The tests that have been falsely promoted as helpful in the diagnosis of food allergy include the following:

1. *The Leukocytoxic Food Test:* The leukopenic index was introduced in 1934. In this clinical test, the total white cell count (WBC) was believed to fall following oral challenge with a specific food in the patient. Black introduced the leukocytoxic *in vitro* test in 1956, and it was refined by Bryan and Bryan in 1960 (and now frequently bears their names). The technique is based on the theory that the addition of a specific food allergen to a microscopic slide on which there is a drop of fresh WBC and fresh plasma from the patient will result in the alteration or destruction of the WBCs. Results of many controlled studies have failed to show that this type of testing is efficacious.[6,7,28,29] In 1985, the US Food and Drug Administration (FDA) ruled this test as unproven and further ruled against marketing cytoxic testing kits.[30]
2. *Intracutaneous and Subcutaneous Food Provocation and Neutralization Testing:* This type of clinical testing was first introduced by Lee in 1961 and refined by Rinkel in 1964. In one variety of the technique, successive five-fold dilutions of food extract are injected intradermally in minute doses (usually 0.01 cc) to an endpoint (the dose which produces a wheal 2 mm in diameter or produces subjective symptoms). When using the subcutaneous technique, serial doses of 0.05 cc are injected subcutaneously. In the case of both techniques, attempts are made first to neutralize the provoked subjective symptom by further injections (intracutaneously or subcutaneously) of weaker dilutions of the same food allergen. If this is unsuccessful, then stronger dilutions are injected in order to attempt to neutralize the reaction. If the neutralizing weaker dose worsens the symptoms, still weaker doses are used.[28,29]

   Currently there is no immunologic rationale for this procedure. Most controlled trials (all involving food allergens) have failed to show any correlation between clinical symptoms and allergen injections.[7] In spite of these facts, this type of testing is still practiced today.
3. *Sublingual Provocation and Neutralization:* In 1941 Hansel described a method for coseasonal treatment of hay fever, involving drops of ragweed extract under the tongue. In 1964, Dickey and Pfeiffer expanded on this concept to the diagnosis and treatment of food allergy. According to the technique usually used, diluted food extracts are administered by dropper (eg, three drops of 1:10 weight by volume) sublingually. If the symptoms appear within 20 minutes, a diagnosis of food allergy is established. Once this has occurred, a more dilute solution of food extract is applied under the tongue in order to neutralize these subjective symptoms. If this is successful, this latter dose can be used routinely by the patients who cannot (or do not wish to) avoid the offensive food. The proponents of the use of this test theorized that the sublingual administration of the allergen allows for unaltered and direct absorption. Supposedly, this type of absorption leads to a desensitization process for that specific food allergen.

   In spite of these theories, the immunologic basis for this technique has never been proven. No studies involving food allergen have proven its efficacy in controlled trials.[31] One study, however, involving allergic rhinitis patients, has shown that house dust mite extracts administered sublingually at the neutralizing dose over a 2-week period relieved nasal symptoms.[32] At this stage, this diagnostic (and treatment) technique should be considered experimental and not be routinely administered as a clinical test (or treatment).
4. *Food-Specific IgG Antibodies and Immune Complex In Vitro Assays:* In an effort to explain immune changes in patients with apparent delayed (in timing) onset food reactions, investigators have turned to assays involving the measurement of IgG antibodies and IgG-immune complexes to specific foods.[28] These tests have become more popular in recent years, as support for the leukocytoxic food test has waned. In spite of this popularity, there is little or no justification for the use of such tests in the diagnosis of suspected food allergy.[33] IgG antibodies to food (eg, bovine gammaglobulin) can be detected in 70% of normal individuals. IgG-immune complexes can be routinely found in normal individuals, and many studies have shown no differences in the type or amount of food-immune complexes generated between healthy and sick patients, even with delayed clinical reactions.[28]
5. *Tests of Immune Functions To Support a Clinical Ecology Diagnosis:* In 1950, Randolph and Rollins first reported on patients allergic to foods (beet sugar—sucrose) and food chemical additives (monosodium glutamate of beet origin) that resulted in multiple symptoms, atypical of the

usual allergic reaction.[34] Later Randolph developed a new concept: clinical ecology, in which patients who suffered from multiple typical complaints reacted to things in their environment such as foods, food chemical additives, and chemicals in the atmosphere.[35] The claims of factors in the environment that can affect the patients adversely has recently been extended to a common fungus (*Candida albicans*) hypersensitivity by Crook, as popularized in his book "The Yeast Connection."[36] Some of these patients have become psychologically incapacitated because of the belief they were allergic to everything—the so-called 20th century syndrome.[37] One of the major explanations for this reaction is that patients with this condition develop an abnormal immune response, so-called immune dysfunction.

Practitioners who believe in clinical ecology theories routinely use the unapproved and unproven diagnostic test techniques such as the leukocytoxic testing, provocation and neutralization procedures, and IgG-immune complex assays. They also use a number of routine immune function tests, such as lymphocyte counts, assays of T and B cells, measures of T suppressor cells, immunoglobulin determination, and autoimmune tests.

An extensive analysis of 50 consecutive patients with a clinical ecology diagnosis supposedly caused by environmental chemicals and/or foods, who had been worked up by practitioners of the clinical ecology beliefs, demonstrated that no evidence of abnormal immune response could be found in any of the patients. All immune tests fell within the range of normal patients.[35] The clinical ecology concepts, advanced first by Randolph in the 1950s and 1960s, are still promoted by some physicians 30 and 40 years later, in spite of the fact that the theories have never been adequately validated.[7,28,31,35]

Part II: The Dietitian's Perspective

Victoria Olejer

INTRODUCTION

Due to the enormity of the task, little is known of the overall incidence of adverse food reactions in the general population. Food intolerance is believed to far outnumber true allergic reactions, but the affirmation of this belief awaits confirmation. Instead, attention has focused on the prevalence of food allergy in the general pediatric population with particular emphasis placed on the incidence of cow's milk allergy (CMA). Based on studies in the

United States, Canada, Great Britain, and the Scandinavian countries, estimates of CMA vary but are thought to fall in the range of 0.3-7.5%, with the incidence decreasing with increasing age.[38-44] Not surprisingly, the incidence for CMA is much higher in allergic children, approaching, for example, 30-59% in children with atopic dermatitis referred to tertiary health care centers.[45-47] Allergy to hen's eggs is estimated to occur in approximately 0.5% of the general pediatric population, increasing to approximately 5% in atopic children.[48]

In an impressive effort to examine the incidence of adverse food reactions in a normal pediatric population, 480 previously unselected, consecutively born infants were followed prospectively from birth to 3 years of age.[49] Of the 133/480 (28%) children suspected by either parents or physicians of experiencing adverse food reactions, only 8% could be confirmed by elimination and oral provocative food challenge, pointing to the relatively high frequency with which foods are thought to result in symptoms in this age group. More conservative estimates place the incidence of adverse food reactions between 4-6% in infants and between 1-2% in children.[50]

While experts disagree concerning the exact incidence of food allergy, few contest the difficulty involved in diagnosing and managing this malady. Until accurate laboratory tests possessing reliable clinical correlations are developed, clinicians must continue to rely on repeated trials of elimination and challenge, with the obvious exception of systemic anaphylaxis, to substantiate the removal of individual foods from the diet.

Despite the lack of standardization of commercially available food extracts, skin testing remains the most accessible diagnostic tool for evaluating the presence of food-specific IgE. The popularity and utility behind the use of skin testing as an aid in identifying potentially sensitizing foods rest largely in the strength of its negative predictive indices.[4,23,51] Nonetheless, negative skin test results do not rule out the presence of an IgE-mediated food response.[52] Likewise, positive skin test results do not confirm the presence of a clinically relevant allergic response to the food in question,[52] but provide a basis for additional investigation. Intradermal skin testing, as compared to prick-puncture skin testing, does not improve on the sensitivity of the test procedure, results in a higher frequency of false-positives, and risks the occurrence of systemic anaphylaxis in exquisitely sensitive individuals.[51] Radioallergosorbent tests (RAST) using a patient's serum also do not add to the predictive accuracy of the test, contribute substantially to the cost, and are best reserved for the occasional patient with pronounced dermatographism, extensive eczematous or urticarial skin lesions, or a history of suspected or confirmed anaphylaxis to foods.[50]

The diagnostic process in food allergy, regardless of the age of the patient, always begins with a careful medical history and physical examination aimed

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.

been reported: kiwi fruit, papaya, mango, pomegranate, sea urchin, turtle, and sunflower seed. Fallier[53] also reports that allergic reactions to teas such as chamomile and linden have been observed.

Bee Pollen

Patients may develop allergies to products sold as nutritional supplements. Bee pollen is a classic example. The *FDA Consumer*[86] cites a case of a person with seasonal allergy who developed anaphylactic shock subsequent to bee pollen consumption.

Parenteral Nutrition

Allergic reactions to ingredients in parenteral nutrition solutions seem to be rare, but dietitians need to be aware such reactions can occur and have been reported. There was a 1987 report of a child receiving peripheral parenteral nutrition who developed anaphylaxis that appeared to be the result of an allergy to components of an amino acid solution and a multivitamin-infusion product.[87] In 1990, a case report linked another pediatric vitamin product in a parenteral solution to the development of hives.[88] Other components of parenteral nutrition that have been cited as being potentially allergenic include iron, dextran and lipid emulsions.[89,90]

PRINCIPLES OF DIETARY MANAGEMENT

Dietary management of food allergy involves avoidance of the offending allergen or allergens.[91] Dietitians can help patients with the processes of label reading, recipe modification, and special product purchase. It is also the dietitian's responsibility to ensure the diet is nutritionally adequate and provide advice on supplementation when appropriate. Dietitians need to perform nutritional assessments at appropriate intervals. Patient needs may vary in time related to allergy persistence and other concomitant medical problems. As always, dietitians also need to provide encouragement and support, especially to those who are attempting major dietary changes. Specific guidelines for counseling with regard to selected allergies are given in Appendixes A through E. Recipe sources for allergy diets are found in Appendix F.

Elemental diets may be necessary in some instances as a therapeutic modality, but are more commonly used in diagnosis.[92] Elemental diets due to

flavor, social, and economic considerations are rarely accepted on a long-term basis. Every effort should be made to reserve these products for short-term therapeutic use only.

Nutritional problems have been documented in relationship to dietary manipulations used to treat food allergies. Lloyd-Still,[93] in 1979, reported on the inappropriate prescription of elimination diets for children that resulted in low calorie intakes and failure to thrive. He also speculated that the use of wheat elimination to treat chronic diarrhea may in some instances lead to a failure to correctly diagnose gluten intolerance (celiac sprue). Sinatra and Merritt[94] describe the development of kwashiorkor in four patients who were placed on a nondairy creamer low in protein. This product had been recommended for treatment of suspected milk allergy. David et al[95] compared diets of children with multiple allergy restrictions to controls and found calcium intake to be a problem for those children following the restricted diet. These researchers urge dietetic involvement in continued assessment and treatment.

Reintroduction of foods to the diet may be associated with problems. Anaphylaxis with reintroduction of corn, chicken, soy, and cow's milk has been reported.[96] Reintroduction of foods should be accomplished only under physician directive.

SUMMARY

Major and some minor food allergens have been described. Although some knowledge exists regarding specific allergen components in food, much work needs to be done in this area of identification. Avoidance of allergens while maintaining appropriate nutritional intake is the goal of dietary therapy.

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sumption may be linked to increases in serum tyrosine that is a norepinephrine precursor.[24] (It should be noted, however, that some researchers link phenylalanine to decreased rather than potentially increased catecholamine synthesis. These individuals say phenylalanine in aspartame does not have the same effects on brain as phenylalanine consumed in a protein source and in humans aspartame consumption most likely reduces tyrosine uptake by the brain.[25,26])

Schiffman et al,[24] in 1987, published the results of a double-blind crossover trial in 40 subjects who had attributed headaches to aspartame. Aspartame challenges in this study were given at the level of 30 mg/kg of body weight over a 4-hour period. The headache incidence after aspartame was not significantly different from placebo and was in actual numbers less, 35% incidence after aspartame compared to 45% incidence after placebo. This study also failed to support a potential norepinephrine-headache link. Despite preceding treatment (aspartame or placebo), subjects who developed headaches exhibited lowered plasma concentrations of both epinephrine and norepinephrine preceding headaches. Steinmetzer and Kunkel[27] have questioned the Schiffman study findings for a variety of reasons. Most importantly was the evaluation time used. Steinmetzer and Kunkel[27] suggest reactions may occur up to 72 hours after intake, and the Schiffman study allowed only 48 hours between challenges. They also question the value of a single challenge and the composition of the diet during trials (eg, was intake of other potentially vasoactive substances controlled?).

In 1988, Koehler and Glaros[28] published the results of a community-based double-blind crossover trial comparing headache incidence after consumption of 300 mg of aspartame and placebo. (Dosage was not given on a kilogram of body weight basis.) In this study, five subjects experienced no increase in headache following aspartame ingestion and six did. These researchers postulate individual threshold differences may be involved.

Other clinical reports[29–31] support the view that aspartame may trigger headache in susceptible individuals. Ferguson,[29] in 1985, described an eating disorder in which aspartame consumption (10 packets of sweetener per day), spitting up of carbohydrate, and concomitant tranylcypromine use were associated with headache. The patient's headaches ceased when saccharin, as opposed to aspartame, was used as the artificial sweetener. Johns,[30] in 1986, described a patient in whom migraines were associated with aspartame consumption of approximately 1,000 to 1,500 mg/day. [The patient reported consuming on some days 6 to 8 cans (12 oz each) of diet soda and 15 aspartame tablets.] Challenge with a 500-mg aspartame solution in a clinical setting also provoked headaches in this patient. Finally, Lipton et al[31] report aspartame as a dietary factor potentially involved in headaches of 8.2% of 171 patients evaluated at the Montefiore Headache Unit.

Another concern with regard to adverse reaction to aspartame relates to increases in seizure susceptibility for certain individuals. Maher[9] states that the phenylalanine component of aspartame may lower thresholds for seizure occurrence. He bases this statement on what he cites as phenylalanine's ability to inhibit catecholamine synthesis and a demonstration of lowering of seizure thresholds in mice.[26]

Wurtman,[32] in 1985, reported cases of three individuals experiencing grand mal seizures at times of varying levels of aspartame consumption. One individual was cited as consuming four quarts of diet soda containing aspartame and also about four quarts of aspartame-sweetened lemonade daily. One individual reportedly drank four to five glasses of aspartame-sweetened lemonade, and the third individual was cited as consuming at least 900 ml of iced tea containing aspartame as a sweetener. Wurtman's letter postulates, but does not prove, a role for aspartame. Walton,[33] in 1986, also published an individual case report of grand mal seizure, which he postulated could be associated with consumption of aspartame-sweetened ice tea (about 1 gal/day). The Epilepsy Institute, however, has stated the position that it does not believe aspartame is unsafe for persons with epilepsy.[34]

Aspartame may also affect appetite. A 1986 letter[35] reporting on the effects of appetite control in 95 subjects stated that in some subjects aspartame may stimulate appetite. Ryan-Harshman et al,[36] however, failed to demonstrate such effects in two subsequent studies with male volunteers. Because aspartame is used as a part of diets aimed at weight control, further research in this area should prove interesting.

Allergy-like symptoms reportedly associated with aspartame consumption are probably of most interest to dietitians and other health professionals reading this volume. Bradstock et al[23] (in their 1986 Centers for Disease Control-based analysis) reported receipt of 23 such complaints from consumers (with rash being the most common symptom). In 1985, there was a report of a confirmed case (by challenge) of a patient with granulomatous panniculitis manifested by leg nodules associated with aspartame ingestion.[37] (This patient was consuming 36 to 44 oz/day of aspartame-sweetened soft drink.) Kulczycki,[38] in 1986, reported a case of urticaria confirmed by double-blind challenge to be induced by aspartame. Symptoms in this patient occurred 1 to 2 hours after ingestion of relatively small quantities of aspartame-containing substances (for example, diet soda). Kulczycki[38] postulates that formation of amide bonds between endogenous proteins and aspartame or the aspartame decomposition product, diketopiperazine, might be responsible for the allergic reaction. Studies to date do not indicate that aspartame degranulates either mast cells or basophils.[34]

The clinician concerned with adverse reaction to aspartame may be dealing with individuals sensitive to smaller amounts than defined standards for

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]

potential for multiple daily intake.[184] This fact, coupled with the different forms of salicylate in aspirin and food, leaves it unclear if food salicylates are involved in adverse reactions.

Exorphins (Opioid Peptides)

Opioid peptides are food peptides that have actions similar to morphine.[185,186] The major sources of exorphins are wheat (glutenin and gliadin), milk (for example, cow's milk and human milk), and meat. Table 7-4 summarizes major exorphin types identified to date.

The most discussed, potentially adverse reaction to exorphins involves schizophrenia. In 1966, Dohan[187] proposed that cereals (such as wheat) with what he termed as a "pathogenicity factor" could interact with a genotype for schizophrenia to produce clinical mental disease. Zioudrou et al[185] in 1978 reported finding opioid peptides in wheat gluten and α-casein and indicated this finding provided potential biochemical evidence for Dohan's hypothesis.

Studies subsequent to Dohan's hypothesis have not provided definitive support for Dohan's views.[188] Dohan and associates[189,190] did publish two dietary trial studies supporting their view, and Singh and Kay[191] also published data in 1976 that supported Dohan. The Singh and Kay[191] study, however, has been questioned. Levy and Weinreb[192] state that the Singh and Kay data show decreasing, rather than increasing, mental pathology with gluten challenge, and Smith[193] has criticized the statistical methodology of the Singh and Kay study. Studies that have found no support for Dohan's hypothesis are those of Potkin et al[194] and Osborne et al.[195] Potkin et al[194] tested eight chronic schizophrenic patients on a milk-, cereal grain-, and gluten-free diet with gluten and placebo challenges. These researchers could find no deterioration of clinical mental status with gluten challenge. They also could detect no intestinal inflammatory responses. The Osborne[195] study

Table 7-4 Major Exorphin Types

Milk	α-casein exorphin
	ß-casomorphin
Beef	Cytochrophin
	Hemorphin
Wheat	Gluten exorphin

tested the effect of a gluten-free diet in five patients with diagnosis of schizophrenia. (The theory being tested by the Osborne group was that gluten absence might enhance absorption of the neuroleptic drug butaperazine.) The Osborne group could not demonstrate the efficacy of eliminating gluten in schizophrenia.

More research on this topic is needed related to Dohan's hypothesis. Future studies need to be double-blind and use objective criteria for improvement. Length of diet may be an important factor. Dohan and Grasberger[189] have suggested a gluten-free, cereal-free, and milk-free diet may need to be followed for 6 to 12 months before improvement can be noted. Potkin et al[194] have suggested if patients are going to do so, they will in one month. It may be, also, that only a subpopulation of schizophrenics experiences adverse reactions to the opiate peptides.[195] Singh[196] has put forth the hypothesis that paranoid schizophrenics and those with schizoaffective disorders are more likely to benefit from dietary restrictions involving the opioid peptides.

Opioid peptides (exorphins) may elicit allergy-like adverse reactions. This is postulated because some opioids stimulate degranulation of mastocytes and produce cutaneous wheal and flare.[186] Paroli[186] has suggested that the β-casomorphins particularly may induce an adverse reaction of this type.

Gliadin and Other Prolamins

Prolamins are alcohol-soluble fractions of gluten. Some prolamins have been associated with adverse reactions (specifically celiac sprue and dermatitis herpetiformis). Prolamins in cereal grains that have been associated with adverse reactions include gliadin (wheat), secalin (rye), and hordein (barley).[197]

Gliadin is one of the most extensively studied prolamins, and it is currently believed that four gliadin fractions have the potential to be toxic to intestinal mucosa.[197,198] Secalin (rye) and hordein (barley) are closely related to wheat gliadin. The prolamins in oats (avenin) and corn (zein) do not appear to be closely related, and thus seem to have less potential for adverse reaction.[197] More details on food products and potential problems are discussed in the latter part of this section dealing with current dietary guidance principles.

Celiac sprue (or celiac disease) is a prolamin-associated adverse reaction characterized by atrophy of the gut villi.[199] Genetic factors appear to be associated with celiac disease. A high level (70%) concordance has been found in monozygotic twins, and association of certain genetic markers with celiac disease has also been demonstrated.[200] Theories related to timing of wheat introduction in population groups are discussed in Chapter 10. Environmental factors have also been studied in regard to celiac sprue expression.

achieve best results depends on prolamin content of foods and beverages and individual differences in levels of tolerance.[197]

It is generally recognized that wheat flours (whole wheat, white, and graham) and products containing wheat flours (breads, cakes, and cookies) should be avoided. Wheat flours contain the starch endosperm portion of the wheat grain where gliadin is present.[197] Wheat bran theoretically should not contain gliadin, but because it may be contaminated with gliadin, many times it is placed on the list of foods that celiac disease and dermatitis herpetiformis patients are advised to avoid.[197] Rye and barley, as mentioned previously, contain prolamins that are similar to gliadin. Triticale is a cross between wheat and rye and is recommended to be excluded. The evidence linking the prolamin-hordein in barley to celiac disease is not clear; however, due to the antigenic similarities between hordein and gliadin, most authorities do recommend elimination (Malt made from sprouted barley) is to be excluded. Malt extract, a different product, does not need to be excluded.[197]

Oats, which contain the prolamin avenin, remain controversial in terms of avoidance or nonavoidance in the gluten-free diet.[197] It may be that a subgroup of individuals experiences problems with oats and should avoid them. Prolamins of millet, corn, and rice do not appear to cause adverse reaction and can be used by individuals with celiac sprue or dermatitis herpetiformis.[197]

A low-gluten diet (as opposed to a gluten-free diet) has been suggested by some as a viable alternative for celiac disease treatment. In 1985, Kumar et al[212] assessed 85 patients and concluded that many were tolerating small amounts of gluten. These same researchers also formally placed 8 patients on a 2.5-g gluten diet and indicated that 6 patients did well. Montgomery et al[213] compared 12 patients on a low-gluten diet (2.5-5 g/day) with 13 patients on the more conventional gluten-free diet. No significant differences were found in terms of antigluten antibody titers (IgG, IgM, and IgA) or villous height or depth of intestinal crypts. These researchers did report that the low-gluten diet was associated with some infiltration of jejunal mucosa by lymphocytes.

More research is needed to clarify the efficacy of the low-gluten diet. The use of such a diet could aid in achieving patient compliance. Additional research is also needed with regard to nutritional adequacy of gluten-avoidance diets as practiced.[197]

Lactose

Lactose is a water-soluble disaccharide composed of glucose and galactose.[214,215] It is found primarily in the whey portion of dairy foods.[215] Appendix K provides an overview of the lactose contents of some commonly consumed foods and beverages.

Adverse reaction to lactose is primarily related to absence or loss of intestinal lactase activity. Lactase enzyme in the intestinal brush border breaks down lactose into its monosaccharide components in order for absorption to occur.[216] When lactase is absent or deficient, lactose cannot be fully digested or absorbed. Undigested lactose reaching the colon is acted on by colonic bacteria to form short-chain fatty acids, hydrogen gas, and lactic acid. It is believed that if the capacity of colonic bacteria to achieve the above breakdown is exceeded, diarrhea, and pain and abdominal bloating may become manifest due to the presence of a carbohydrate (lactose) osmotic load.[215,217,218] Individual reaction to the point of clinical manifestation of symptoms is variable and depends on many factors such as degree of lactase deficiency, lactose dosage, and concomitant foods or ingredients consumed.[215,218]

Because lactose is found in milk or dairy products, adverse reaction to lactose may be confused with cow's milk allergy. Table 7-5 contrasts causes, clinical manifestation, and treatment of these two problems.[218] Cow's milk allergy is discussed extensively in Chapter 2, 3, and 6.

Table 7-5 Comparison of Milk Allergy and Primary Lactose Intolerance

	Milk Allergy	*Lactose Intolerance*
Age	Early infancy	After age 2 y
Cause	Milk protein (lactalbumin)	Milk sugar (lactose)
Inherited		
Symptoms	Variable	Yes
Diarrhea	Yes	Yes
Vomiting	Yes	Uncommon
Abdominal pain	Yes	Yes
Abdominal bloating	Yes	Yes
Dermatitis	Yes	No
Rhinitis	Yes	No
Asthma	Yes	No
Urticaria	Yes	No
Anaphylaxis	Yes	No
Duration	Usually declines rapidly after first year	Indefinite after onset
Milk protein contraindicated	Yes	No
Milk consumption contraindicated	Yes	Not if amount is moderate

Source: Reprinted from "The Acceptability of Milk and Milk Products in Populations with a High Prevalence of Lactose Intolerance" by N. Scrimshaw and E. Murray, 1988, *American Journal of Clinical Nutrition*, Suppl. 48 (4), p. 1084, © *Am J Clin Nutr*, American Society for Clinical Nutrition.

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

clinical ecologists (as outlined by Barrett) include total allergy syndrome, cerebral allergy, environmental illness, and 20th century disease.[3]

Clinical ecologists believe environmental sensitivity symptoms may occur in all parts of the body.[6] Clinical manifestations are reported to include altered intellectual functioning, asthma, bloating, constipation, cramps, diarrhea, drowsiness, eczema, fatigue, memory loss, irritability, headache, pain in the muscles and joints, mood alterations, nasal problems (congestion and running), frequent urination, itching of the nose and eyes, sneezing, swelling, tingling in the arms and legs, dark eye circles, and schizophrenia.[3,6] The major diagnostic test used by clinical ecologists is provocation and neutralization, a technique not considered standard by the medical community as a whole.[3]

Alteration of the diet is usually a component of clinical ecology therapy. The Executive Committee of the American Academy of Allergy and Immunology[7] has described dietary plans as being very limited in terms of food types allowed in many instances. Rotation of foods at 3- to 5-day intervals may be advocated, and avoidance of synthetic food chemicals may be attempted through avoidance of foods with artificial additives, such as flavorings or colorings.[7,8] Mold or yeast avoidance may also be suggested.[8] Food antigens in low doses may be given as part of neutralization treatment.[7,8] Vitamin and mineral supplementation may or may not be used.[8] The potentially restrictive nature of the diets that may be prescribed for patients by some clinical ecologists should be of concern to dietitians.

Terr,[8] in 1986, reviewed the cases of 50 patients who had been diagnosed by clinical ecologists as having environmental illness. Eight of the 50 were said to have no ascertainable clinical symptoms. Among the 50, no common pattern of laboratory or physical findings could be noted. Symptoms also did not appear to be related to duration of exposure. Terr[8] concluded his review of patients did not support the validity of clinical ecology and cautioned that use of this model could be associated with production of unreasonable patient fear and induce changes in living patterns that are unnecessarily restrictive.

Brodsky[9] conducted psychiatric evaluations of eight patients treated by clinical ecologists. Patients had diagnoses related to environmental illness or some form of chemical hypersensitivity. Common elements could be identified for these patients. Examples of these elements included gradual onset of symptoms, a history of unsubstantiated physical problems, a history of extensive searches for a physician who would provide a diagnosis of physical illness, and avoidances (as a part of treatment) that were life-changing. Brodsky[9] concluded that use of a clinical ecology practitioner would seem to appeal to individuals with chronic problems of a psychiatric nature. Stewart and Raskin,[10] after studying 18 patients, also concluded that patients with the clinical ecology diagnosis of 20th century disease were likely in actuality to have psychiatric problems.

Until more information is available, the clinical ecology approach remains unproven. Some patients who are following these treatments may be at risk both medically and nutritionally. Patients treated in this mode are best informed of its experimental nature.[7]

CANDIDIASIS HYPERSENSITIVITY

Candida albicans (commonly known as "yeast") is a fungus that normally resides in the human body, particularly the vagina, mouth, and gastrointestinal tract.[3] The *Candida* fungus can be infective in certain conditions. Some also believe it can be allergenic.[11–15] The Executive Committee of the American Academy of Allergy and Immunology[11] has stated that evidence supporting the existence of the candidiasis hypersensitivity syndrome leaves the diagnosis as yet unproven. The committee considers the diagnosis and treatment of candidiasis hypersensitivity to be experimental.

The idea that *Candida* can be an allergen is not new. Liebeskind[12] described 25 cases given this diagnosis in a 1962 report. Recent advocates of the idea that *Candida* hypersensitivity can exist have been Truss and Crook. Crook's book entitled *The Yeast Connection* has presented the concept to the public.[14]

Symptoms of candidiasis sensitivity are said to be multiple and may include constipation, diarrhea, bloating, fatigue, irritability, pain in the musculoskeletal system, skin problems (urticaria, psoriasis), mental problems (anxiety, depression), weight gain, impotence, infertility, and cystitis.[13] Kroker[15] has stated each *Candida* strain may contain 30 to 35 antigens, with polysaccharides on the cell surface being the major antigens present.

Dietary restrictions and nutritional supplements may be prescribed as part of the treatment for candidiasis hypersensitivity, and Kroker[15] has stated that dietary alteration is the major component of therapy. The diet prescribed is generally low in carbohydrate with variance in levels established for individual patients. Some patients are advised to avoid refined sugars, syrups, fruit juices, and milk. Others may be limited to a daily intake of 60 to 80 g of carbohydrate. Children may not be placed on carbohydrate restrictions. Kroker[15] has indicated carbohydrate cravings are characteristic of candidiasis hypersensitivity patients. The rationale for dietary restriction is that carbohydrates are considered the major nutrient source for the organism.

Yeast may or may not be restricted in the diets of those said to suffer from this malady. A diet incorporating both carbohydrate and yeast restriction may, however, be prescribed.[15]

The popularity of candidiasis hypersensitivity as a diagnosis has spawned the marketing of special products in health and natural foods stores. These include Cantrol, Candida Cleanse, Yeast Fighters, and Yeast Guard.[3] Barrett has asked the Food and Drug Administration (FDA) and the Federal Trade