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Neurological Manifestations of Adverse Food Reactions

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INTRODUCTION

The notion that food causes neurological illness or behavioral change is distinguished by the amount of passion this concept evokes. No other set of disorders involving adverse reactions to foods or additives is characterized by so many devoted believers and dedicated nonbelievers.

There are understandable reasons for these positions. Neurological disorders, of themselves, are extremely complex, being perturbations of complex systems. The tools to measure objective neurological change are not easily accessible or familiar to allergy specialists. Often the neurology specialist is unfamiliar with the clinical pathophysiological features of hypersensitivity disorders. Many times, the end point of a challenge relies on the subjective response and cooperation of the patient. For example, investigators must depend on the subject to tell them whether a headache occurs and how great is the pain.

Other barriers interfere with clear evaluation. These include the incomplete

understanding of the epithelial blood–brain barrier in humans and which factors lead to its disruption [1–3]. There is also variability in the nervous system's generation of neurotransmitter, which can be influenced by diet, immune responses, and psychological factors [4]. Recent demonstrations of cytokine generation in the nervous system and cytokine receptors on neural cells are adding another set of factors to consider [5,6].

Nevertheless, there are sufficient observations in the medical literature to allow the reader to form an opinion about the relevancy and importance of food triggered disorders of the nervous system. Some of the works cited are from the earlier literature, which emphasize description rather than the testing of hypotheses and have no *P* values. These studies remain as valuable clinical insights. Time has proved them to be correct, even if the initial methods are not up to the standards of the recent modern medical literature.

PATHOPHYSIOLOGY OF FOOD DERIVED NEUROLOGIC DISORDERS

Mechanism of the Reactions

Toxic Reactions

Foods may contain substances that are directly toxic to the nervous system. These are a natural component of the food or a result of microbial or human contamination. Members of the mushroom family contain powerful muscarinic agents. Fortunately, with commercial mushroom farming, toxic reactions from mushroom are uncommon. Contamination of food with *C. botulina* toxin causes an often fatal neurological disease. A product of a wheat smut is a recognized source of the hallucinogen lysergic acid diethylamide (LSD), which causes serious disorganization of cerebral nervous system function.

Intolerant Reactions

Foods can contain substances with desirable pharmacological activities. Chocolate is capable of uplifting moods, containing phenylethylamine, caffeine, and theobromine. Alcoholic beverages in moderate amounts have pleasant effects for humans. For people who have diminished activity of the respective catabolic enzymes, chocolate can cause excessive stimulation and modest amounts of alcohol cause inebriation and "hangover." Caffeine in a cup of coffee has a mild stimulant effect for most people, but others experience anxiety or insomnia with this same drink. Red wine–induced headaches occur in people who are deficient in the enzyme phenylsulfone transferase or monamine oxidase.

Food Hypersensitivity

An immune-mediated reaction implies a specific sensitization to a food antigen and similar cross-reacting antigens. Perturbation of the nervous system results from the activity of biological modifiers generated by the immune response. Both the more classic mediators and more recently described cytokines can influence nervous system function [7,8]. There is evidence that a nearby local allergic response can alter function of the peripheral nerves [8a].

Food Idiosyncracy

Food idiosyncracy is a proposed mechanism for the role of dyes and preservatives in attention deficit hyperreactivity disorder. It may explain the Chinese restaurant syndrome associated with monosodium glutamate. Headaches have been described on challenge of patients with these sensitivities. It has been suggested that the reactions may be mediated through NO, increasingly recognized as an important inflammatory mediator [9].

ACTIONS OF ALLERGY-RELATED MEDIATORS IN THE NERVOUS SYSTEM

Most of the information about the actions of neurotransmitters in the nervous system is based on studies in animals or in human brain slices. Interpretations of the results and their meaning for human illness must consider this. The animal species used for models do not always share similar patterns of nervous system reactions with humans. For example, a neurotransmitter may be stimulatory in one species and inhibitory in another. Interpreting results of studies in isolated human brain slices also must be cautious. With these caveats, the results to be described do give us a conceptual basis to explain how allergic reactions could affect the nervous system.

Histamine

Histamine serves a critical role in activation and regulation of the central and peripheral nervous systems. Three differing pharmacological receptors for histamine, H_1, H_2, H_3, have been described, with the use of different antagonists [10]. Central nervous system histamine is synthesized from histidine by neurons in the hypothalamus. Pyridoxal phosphate is a key cofactor in histamine synthesis. The brain contains two systems for degrading histamine, the enzymes diamine oxidase and imidazole *N*-methyl transferase. Under normal circumstances, peripheral histamine appears not to cross the blood–brain barrier [11]. However, during food triggered allergic reactions, plasma histamine levels can increase more than 10-fold to 100-fold. These levels may overcome the capacity of the blood–brain

barrier. Higher concentrations of peripheral histamine break down the endothelial blood–brain barrier [12]. Release from perivascular mast cells found in the brain may contribute to histamine levels, after an antigen–antibody reaction.

Histamine, acting through its H_1 receptor, increases reuptake of norepinephrine (noradrenalin) and serotonin in brain slice experiments [13]. Histamine stimulates alertness in rodents, cats, and probably in humans by the H_1 receptor [14]. This may explain the sedating effect of the classic H_1 antagonists. The H_2 and H_3 receptors are important in the autoregulation of histamine synthesis [15]. All three histamine receptors are found on cerebral blood vessels. Blocking H_1 and H_2 receptors has not proved to be clinically effective in migraine therapy or prophylaxis. Animal studies suggest blockade of the H_3 receptor may have potential value in preventing vascular headaches [16]. Histamine applied to the brain causes electroencephalographic (EEG) abnormalities, increasing the frequency of electrical spikes [17].

Adding histidine the precursor to histamine to the diet increases the histamine concentration in the central nervous system of rats and in peripheral basophils. Pyridoxine added to the diet also raises the central nervous system (CNS) histamine content. The combination increases CNS histamine levels more than either agent alone [18].

Serotonin

Only 2% of the body's serotonin is found in the central nervous system, 8% is bound to platelets, and 90% is in the enterochromafin cells of the intestine [19]. Serotonin is synthesized by cells in the hypothalamus. Increases in dietary tryptophan and vitamin B_6 will increase the concentration of serotonin in the brain [18]. It is possible that the massive release of serotonin from platelets during a migraine attack may transiently increase brain serotonin level. Serotonin is important in regulating mood, appetite, and sleep [20]. It is a spasmogenic mediator, constricting the external carotid system arteries. Serotonin release in migraine may represent an attempt to reverse the vasodilatation of a migraine. If serotonin is depleted, then migraine frequency and intensity increase [21].

Prostaglandins and Leukotrienes

Prostaglandin D perturbs the effectiveness of the epithelial blood–brain barrier, with resultant increased permeability and acute cerebral edema in animals [22]. Cerebral edema has been described in immune complex–mediated serum sickness affecting the central nervous system [23].

Prostaglandin E2 causes hypalgesia and is an antagonist of natural and synthetic opioids [24]. When injected peripherally, prostaglandin E2 causes a short-lived migraine attack [25].

Leukotrienes also can cause cerebral edema, by perturbing the blood–brain

barrier They also cause recruitment of inflammatory cells into the brain [26]. Leukotrienes and prostaglandins are synthesized by a number of different cell types in the nervous system, including the microglial cells, epithelial cells, and astrocytes.

Bradykinin

When it is injected subcutaneously, bradykinin causes pain and erythema. If it is applied to the central nervous system, bradykinin excites the sensory neurons mediating the pain response. The application leads to peripheral hypalgesia [27]. Intracerebral bradykinin also magnifies the inflammatory reaction of carrageenan-induced paw edema in rats [28]. Bradykinin is yet another mediator capable of disrupting the integrity of the endothelial blood–brain barrier, allowing for passage of other molecules and cerebral edema [29].

Platelet Activating Factor

The mediator platelet activating factor (PAF) has a number of actions, many of which are associated with the late-phase allergic response. PAF has dramatic effects in the nervous system. It causes increased vascular permeability and breakdown of the blood–brain barrier [30]. In disorders such as migraine, there is evidence of increased platelet activation. The platelets of migraine patients demonstrate decreased responses when treated with exogenous PAF, suggesting they are already in an up-regulated state [31].

Neuropeptides

Neuropeptides are a group of peptide hormone–like molecules, which include substance P (SP), neuropeptide Y (NP-Y), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP). Neurokinin is a presumed cause of the pain of migraine. Neuropeptides have a wide range of activities. They are released during peripheral allergic reactions and can affect the nervous system through this mechanism. SP, VIP, and CGRP are potent vasodilators. NPY is a vasoconstrictor found in a network of sympathetic fibers in arteries, arterioles, and veins [32]. Neuropeptides can be responsible for some of the pain described in certain allergic reactions. They also cause vasospasm of the cranial vessels. Levels of VIP and CGRP are elevated in cluster headaches, but only CGRP level is elevated during a migraine Neuropeptides are important neuroregulators [33].

Complement

Various components of the complement cascade are synthesized by astrocytes, ependymal cells, microglia, and neurons. These cells also express receptors for complement fractions. The synthesis of complement and its

receptors on membranes is regulated by both proinflammatory and antiinflammatory cytokines. Complement components participate in immune reactions of antigen and antibody in the nervous system. It has been suggested that complement may have additional nonimmune functions in the central nervous system [34].

Cytokines

There is strong evidence that cytokines act as bidirectional messengers between the immune system and nervous system [35]. The ever increasing number of recognized cytokines indicates that it may be some time before the exact pathways and interactions will be understood. Interleukin 1 (IL-1) generated from peripheral immune reactions stimulates release of corticotropin releasing factor in the brain. IL-1 also increases the levels of norepinephrine in the central nervous system [36]. Nerve growth factor (NGF) synthesis is increased by tumor necrosis factor α (TNF-α) and IL-1. NGF is synthesized peripherally and will pass into the brain only when there is an inflammatory process that perturbs the blood–brain barrier [37]. Patients with common migraine demonstrate the spontaneous release of TNF-α from mononuclear cells at a rate greater than that of nonmigrainous control subjects [38]. Cytokines found in the nervous system result from local production but also are derived from peripheral cell synthesis. This allows peripheral immune responses to influence the activities of the nervous system [39].

ALLERGY IN THE NERVOUS SYSTEM

Do significant allergic responses occur in the nervous system, or are the reported clinical allergic disorders of the nervous system the result of peripheral mediator overflow into the nervous system? There is insufficient evidence to answer this question in humans; animal models may be unsuited to answer it. Large macromolecules are normally able to penetrate the brain of the rat [40]. In humans, such permeability has been reported only in autoimmune disease, such as CNS lupus erythematosus [41]. Animal experiments show breakdown of the epithelial blood–brain barrier by the common allergic mediators. It is unknown whether these effects occur in humans, but it appears reasonable to consider this disturbance of the blood–brain barrier in humans probable.

Although there is a relative paucity of perivascular mast cells in the CNS, an attenuated immunoglobulin E (IgE) antigen-mediated response can likely occur. Circulating basophils also move through the CNS with the potential for further interaction and mediator release. How much these components can contribute to central nervous system derangement is unclear. At present it appears both local and peripheral sensitivity reactions are involved in human disorders.

CLINICAL NERVOUS SYSTEM DISORDERS ASSOCIATED WITH ADVERSE FOOD REACTIONS

Migraine

Food induced or dietary migraine has been extensively studied. The association between migraine and diet is better established than any other aspect of food related neurological disease. More recent studies, utilizing double-blind placebo-controlled studies, have demonstrated that food or additives can trigger migraine. Some of these studies also have provided evidence for the involvement of mast cells and basophils (see below, Refs. 64–66).

There are several references in the Talmud that describe a hemicranial throbbing headache associated with eating certain foods. In the nineteenth century, migraine was considered one of the atopic disorders, along with eczema, rhinitis, and asthma. At the beginning of the twentieth century, pioneers in allergy research, including Richet, classified migraine as an anaphylactic disorder [42].

Surprisingly, after all this time, the exact relationship between migraine and the atopic disorders is not resolved. This difficulty may be overcome, at some future date, as the important mechanistic differences between classic and common migraine are considered in the analysis. Food- and foodstuff-provoked head aches are typically common migraines without any aura. In some patients, a throbbing unilateral or bilateral headache without the characteristic nausea and vomiting occurs. These are simple vascular headaches. In both cases food related headaches seem to arise from disturbance in vessels predominantly of the external carotid system. In classic migraine with aura, there are defects in intracerebral electrical activity or blood flow [43].

Older Clinical Reports

Brunton in 1883 reported that milk and eggs caused migraine attacks in his patients. Brown almost 40 years later found that food hypersensitivity was one of the four commonly recognized precipitants of migraine attacks [44].

Vaughan, in one of the most insightful early reports, described his experience with food related migraines. His study involved 33 patients, 12 of whom had relief of migraines using dietary avoidance He noted that the foods triggering migraine caused a late-phase response when he performed allergy skin testing [45].

De Gowin reported that 78% of migraine patients could obtain complete or partial relief from dietary manipulations based on history and intradermal food skin tests [46]. Eyermann evaluated 63 patients with allergic headaches, which were characterized as unilateral and throbbing. Often the headache was preceded by unilateral nasal congestion, clear nasal discharge, abdominal discomfort, and nausea. Over a third of the patients improved with elimination diets [47].

Nonallergic Mechanisms

Besides allergic mechanisms, other dietary factors provoking migraine have been reported. These include a number of monamines (tyramine, phenylethylamine), which are vasoactive and can enter the central nervous system. Other food additives or chemical components of foods can trigger migraine, including sodium metabisulfite, monosodium glutamate, sodium nitrite, sodium nitrate, and histamine. [48,49]. Many patients with migraine experience a typical attack or an unusual bitemporal pulsatile headache after eating smoked meats, sausages, and flavored cheeses. Nitrates and nitrites are potent vasodilators, and the amount tolerable to the general population, which is estimated and approved as up to 500 μg/g, has deleterious effects in migrainers. This is an example of the nonspecific vascular hyperreactivity in migraine analogous to the bronchial hyperreactivity of asthma. Migraine patients demonstrate a shift to the left in the dose–response curve to the nonspecific cerebral vasodilatation caused by carbon dioxide or histamine [50].

Alcoholic beverages, particularly red wines, are common precipitants of migraine. Red wine contains alcohol, histamine, and many phenylsulfones, all of which individually can trigger migraine attacks. Ethanol is a peripheral vasodilator, does not affect intracerebral blood vessels. It can, however, affect branches of the external carotid. In a very interesting study, the ability of equivalent amounts of ethanol provided as vodka or red wine to provoke a migraine in patients was tested. The amount of ethanol in the volume of red wine that triggered a migraine was dispensed in the form of vodka and did not cause a migraine. The conclusion was that the phenolic monamines in the wine were the significant precipitants [51].

Reports of challenge provocation of migraine headaches by aspartame, monosodium glutamate, and metabisulfite have appeared in the medical literature [52]. On the other hand, studies attempting to define the value of routine avoidance of these food components have shown disappointing clinical results. There was little change in migraine frequency or intensity. This is particularly true of diets avoiding the monamines such as tyramine, in spite of the fact that tyramine appeared capable of altering EEG patterns of migraine patients [53].

Later Clinical Reports

Unger and Unger described an extensive experience in the diagnosis and treatment of migraine. They reported achieving good clinical results using a combination of therapies including elimination diets. Thirty-five of 55 patients had complete relief of migraines, and another 9 had a 75% improvement. They observed that foods seem to trigger attacks directly or can serve as facilitators of migraines triggered by other factors such as fatigue, stress, or hormonal events [54]. This aspect of food induced disease, that is, facilitation, has been more recently reported and con-

firmed by blind challenges in disorders such as food related exercise induced anaphylaxis and delayed pressure urticaria. There is a need for a careful study evaluating the same relationship of two stimuli in triggering migraines.

With the advent of radioallergo sorbent test (RAST) technology, Monro asked whether this new tool could help predict an successful avoidance diet for migraine patients. Twenty-three of 36 subjects with migraine who were placed on an extensive elimination diet trial with reintroduction had decreased migraine attacks. Unblinded rechallenges triggered attacks. Monro discovered that a performing a panel of 25 in vitro RAST food tests for specific IgE predicted the foods that were the triggers of migraine in the patients who obtained relief. In general the RAST values at foods provoking migraine were highly positive [55].

In an earlier report, Grant, a neurologist, used a lengthy strict elimination diet beginning with lamb and pear and then single food introductions after 5 days, to evaluate the role of diet in migraine subjects. With this meticulous and laborious approach, of 60 patients, 51 became migraine-free, and 9 improved. From 1 to 30 foods appeared to provoke attacks of migraine (average number was 10 foods). No double-blind challenges were performed. Grant used a pulse test to determine whether the subject was sensitive to a food. This test is generally considered invalid. Some of the remarkable results may have been placebo effects [56].

Double-Blind Placebo-Controlled Studies of Food Related Migraine

A series of double-blind placebo-controlled studies have been performed in the last two decade (Table 1). These studies have provided double-blind placebo controlled evidence that ingesting certain foods would reproducibly provoke a migraine. In general, the rate of migraine during placebo challenges was less than 15%. Active foods suspected of causing migraine administered in a double-blind fashion triggered migraine in 70% of the challenges.

Egger et al. reported on 99 migrainous children, who were placed on an oligoantigenic diet consisting of one meat (chicken or lamb), one starch (rice or potato), one fruit (apple or banana), one vegetable (brassica), water, and vitamin supplements. Children who improved then had foods reintroduced to determine which may have precipitated migraine. Eighty-eight children completed the diet trial. Seventy-eight children became free of migraine, 4 improved, and 6 showed no benefit. Upon reintroduction of foods, 74 children had one or more foods that seemed to trigger migraines.

Forty children underwent double-blind placebo-controlled challenges, using masked whole foods. Migraine responses occurred in 6 of 40 placebo challenges (15%) and in 26 of 40 active challenges (65%). If allergy skin testing had been used to plan the diet, only 3 children would have had all the dietary precipitants of migraine eliminated [57].

TABLE 1 Double-Blind Placebo-Controlled Challenges in Migraine[a]

Author [Ref.]	Number subjects	Placebo positive	Placebo negative	Active positive	Active negative	Mediator changes
Egger [57]	40	6	34	30	10	No
Mansfield [58]	10	0	10	8	2	Histamine
Vaughan [59]	23	3	20	16	7	No
Olsen [60]	5	0	5	5	0	Histamine PGD_2
Steinberg [61]	1	0	1	1	0	Histamine PGF_2
Total	79	9 (11.4%)	70 (88.6%)	60 (75.9%)	19 (24.1%)	

[a] See text for references; in all cases in which mediators were measured, they increased during a migraine-producing challenge. PG = prostaglandin.

Mansfield, Vaughn, and colleagues studied 43 adults with at least four common migraine episodes per month. The subjects were diagnosed and referred from the neurology service. The patients were placed on an elimination diet trial, based on the patient's history and food allergy skin testing. If there were no positive skin test, results, then the subjects were placed on a milk, egg, wheat, corn-free diet.

Thirteen of the 43 subjects had a 66% or greater reduction in migraine attacks during the diet trial. Double-blind placebo-controlled challenges were performed in seven subjects with opaque capsules containing 8 g of freeze dried foods or the equivalent number of placebo capsules. No placebo responses occurred, whereas five of seven active challenges led to migraines. In 3 subjects who agreed to another blind challenge, plasma histamine levels rose during the active food challenge, that induced migraine, while staying unchanged in the placebo challenges (Fig. 1). The plasma histamine level peaked just before or at the onset of the migraine. Overall dramatic improvement occurred in 30% of the study subjects, with a confirmation rate of 70% by double-blind placebo-controlled challenges. This study also provided the first demonstration of mediator elevations during a blind food challenge triggering migraine.

In accord with Egger's findings, prick skin testing read at 15 minutes was not useful to determine the foods involved in provoking migraine. However, patients with any allergic sensitization were more likely to have food triggered migraines than nonallergic subjects [58].

Vaughn, in a follow-up study, reported a series of 104 subjects with at least three migraines per month. They were all placed on a milk; egg; wheat; corn-free

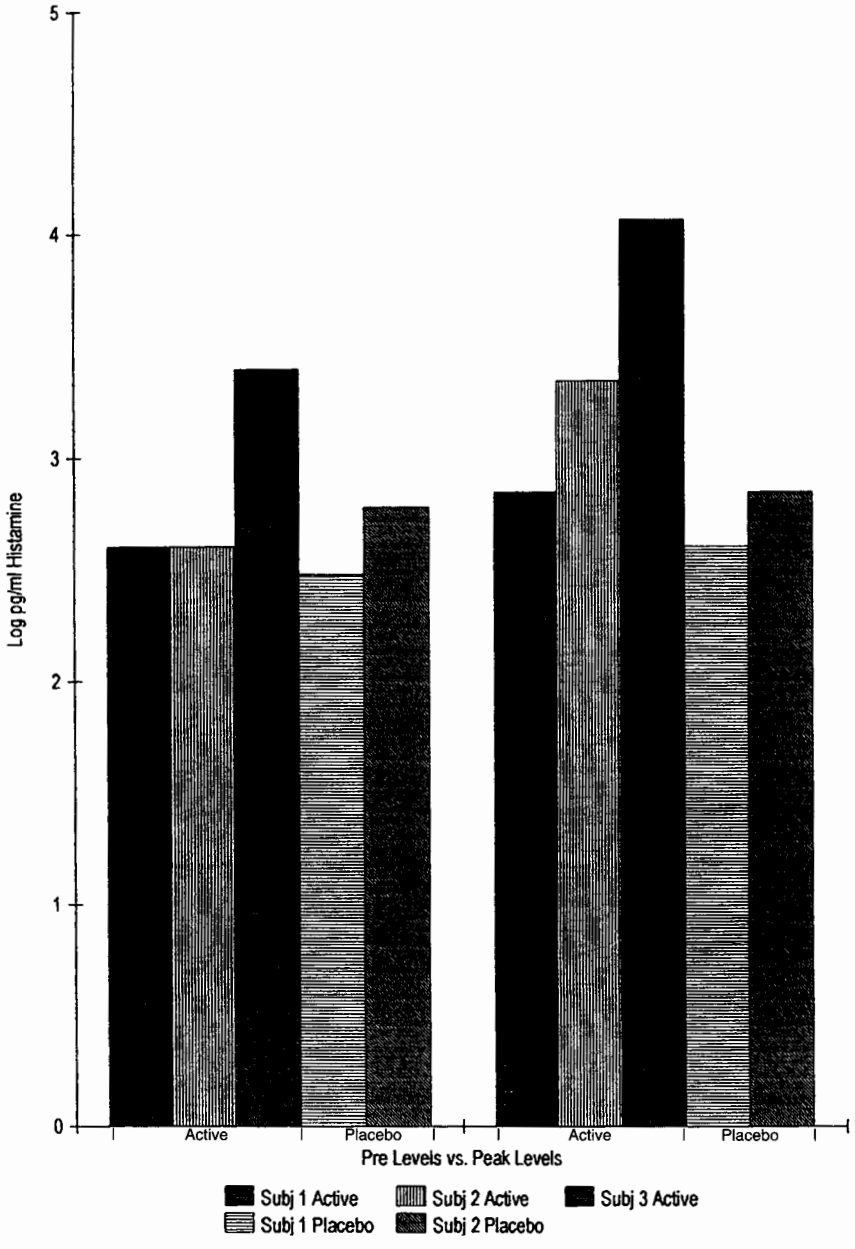

FIGURE 1 Challenge pre and peak Histamine. Active-migraine-caused placebo. No migraine occurred.

diet along with avoidance of foods suggested by history, or skin test–positive foods. Forty of the 104 subjects had at least a 50% reduction in migraines during the diet trial. Eight became headache-free.

Subsequently, 27 of 36 subjects who underwent open food reintroduction could identify one to four foods that precipitated migraine. Twenty-three patients underwent a double-blind challenge phase that consisted of 2 days of placebo capsules alternating with 2 days of active food capsules. A positive response was a migraine on either the first or second active challenge day without a headache on the placebo days.

In 3 of the subjects, migraine occurred during the placebo days; active challenge triggered migraines in 15 subjects, with 4 subjects not having migraines on either day. In this study, there did not appear any benefit of immediate allergy food skin tests in identifying migraine provoking foods [59].

Olsen studied five subjects from the study group with repeat double-blind placebo-controlled challenges. He measured changes in plasma histamine and prostaglandin D_2 (PGD_2) levels. The placebo challenges did not trigger migraines or changes in the levels of the mediators. Histamine levels increased markedly during the food provoked migraine just before or at the time of migraine. PGD_2 level increased at the same time as histamine level, and also 4 to 6 hours after challenge. Histamine did not increase at the later time. The investigators suggested that lack of elevated histamine level made the role of the basophil less important in the pathogenesis of the migraine attack [60]. This finding if confirmed would greatly alter the concepts of basophil dynamics in migraine. In contrast, in a single case example, a woman with beef induced migraines showed elevations of histamine and PGF_{2a} levels during active challenge but not during placebo challenge [61].

Guarisco and colleagues studied 22 adolescents with at least two migraines per month. Twenty one teenagers with migraine served as controls. The study group ate an oligoantigenic diet while the controls ate their usual diets. If a study subject improved, then foods were introduced in a open fashion. Foods thought to cause migraine were retested with a modified blind challenge. Twelve patients completed the oligoantigenic diet phase. Six became migraine free, five improved. There were no changes in the control diet group [62].

Marteletti discovered that cytokines in plasma were altered during a food challenge–induced migraine. The levels of Il-4 and Il-6 decreased after a positive challenge result, whereas levels of IFN-γ and granulocyte macrophage colary stimulating factor (GM-CSF) increased [63]. This suggests possibly important interactions between the nervous system and the immune system in dietary migraine at a level distinct from hypotheses offered prior to the recognition of the cytokines.

The foods that have been commonly associated with migraine and for which there is double-blind confirmation are shown in Table 2.

TABLE 2 Foods and Additives Commonly Reported to Cause Migraine or Headaches Confirmed by Blinded Challenges[a]

Possible enzyme deficiency
Red wine
Monosodium glutamate
Sodium metabisulfite
Aged cheeses
Aspartame sweetened foods
Vasoactive agents
Alcoholic beverages—ethanol, aromatic compounds
Chocolate—phenylethylamine, theobromine
Coffee—caffeine
Coca-Cola
Allergic mechanisms
Cow's Milk
Wheat
Corn
Legumes—peas, beans. peanuts
Cinnamon
Pork
Eggs
Coffee
Shrimp

[a] Any food appears capable of causing allergic migraine. In general allergy is a response to foods commonly eaten and unrecognized.

Laboratory Evidence of the Relationship Between Allergy Food and Migraine

There are a number of abnormalities described in migraine patients that are shared with other recognized food allergic subjects. The serum or plasma histamine level at baseline is generally higher in migraine patients than normal individuals [64]. Spontaneous release of histamine from basophils is increased in migraine [65]. Basophil degranulation occurs during migraine attacks including release of heparin [66].

Platelets in migraine are activated and demonstrate increased aggregation in nonstimulated and epinephrine stimulated studies [67]. Releasable platelet serotonin level decreases during a migraine attack, whereas serum levels of serotonin and its metabolites increase [68].

Recently, it was reported that release of TNF_{α} was higher from cells of migraine patients than normal individuals [38].

Common migraine subjects have evidence of nonspecific vascular hyperactivity, which may even be unilateral on the side where headaches most often occur. Migraine patients have a lower threshold to the vasodilating effects of carbon dioxide and histamine [69]. Intravenous histamine given to normal individuals causes a bilateral throbbing headache, with the same response occurring in migraine patients at lower concentrations. Interestingly, the side where the patient usually suffered the migraine attack often demonstrated a response at an even lower histamine dose. The contralateral side did not start pulsating until a higher histamine or carbon dioxide concentration was used [70]. These results are analagous to the nonspecific hyperactivity that occurs in the nose of rhinitics and the lungs of asthmatics.

At present, the bulk of migraine therapy is either symptomatic relief or prophylaxis based on neurovascular mechanisms. The approach is similar to using bronchodilators to treat asthma. The finding of nonspecific hyperreactivity and the clinical benefit of corticosteroids in migraine suggest that attention to inflammatory mechanisms would be worthwhile for migraine. One might expect a increase in histamine and carbon dioxide tolerance after a period of successful allergen avoidance. Presumably these changes would be associated with clinical improvement. Recently developed oral agents that affect the arachidonic acid, lipoxygenase pathways, or agents such as azelastine may also benefit such patients.

Cluster Headaches

Cluster headache shares many metabolic and pathological abnormalities with migraine; however, it clearly has a number of important differences. Except for dietary agents that are vasodilators, there is no evidence to support an important role for food and foodstuff in the provocation of the clusters. The headaches are usually unlateral, described as boring or piercing, and can be accompanied by ipsilateral nasal symptoms and Horner's syndrome. They occur in groups or clusters of headache and relief and headache and relief, with several or groups during any given day. Elevations of plasma histamine level during the clusters are much greater than those found in common migraine during an attack. Elevations of levels of urinary serotonin metabolites are also found in cluster headache attacks, suggesting release and physiological activity as seen in migraine. The cluster headaches respond to corticosteroids, sumatriptan, calcium channel blockers, oxygen, and intranasal lidocaine. There is a beneficial response to the combination of H_1 and H_2 antagonists, not reported in migraine. This may reflect a difference in pathogenesis. Platelet abnormalities are found in cluster headaches comparable to those of migraine headaches. Serotonin is released during clusters comparable to those of migraine. Similar but not exact perturbations of neuropeptides and cytokines have been found in cluster headache patients and in migraine patients [71,72].

Epilepsy

A link between migraine and epilepsy has been suggested by many authors [73,74]. Epileptics were reported to have the same spasmogenic substance in their blood as asthmatics, migrainer patients, and atopic eczema patients [75]. Pioneer neurologists such as Foster Kennedy described convulsions presumed caused by food allergy [76]. Dr. Kennedy personally observed acute transient edema of the optic nerve and retina caused by food allergy.

Ward and Patterson evaluated 1000 epileptics in two long-term residential facilities. They used 100 normal individuals and 100 mentally retarded patients as their control population. They tested all subjects with 64 to 72 scratch food skin tests. The incidence of at least one positive test result was 57% in the epileptics, 38% percent in the mentally retarded controls, and 8% in the normal patients [78].

Wallis et al. reported 38% of epileptic subjects reacted to one or more food allergens with only 4% of the control population reacting [79]. These pioneer investigators thought that allergy sensitization provoked some seizures and that allergic management could decrease seizure frequency and severity.

Dr. Susan Dees tested this hypothesis by treating 22 epileptic patients with a combination of desensitization, avoidance measures, and antiallergic medications. Epileptic problems decreased in 18 of 22 epileptic children. Nine of the 20 treated patients taking anticonvulsants were able to stop the medications. In a control group of 15 nonallergic epileptic children, only 1 of 15 was able to discontinue anticonvulsant drug therapy during the study. There were only minimal changes in the comparison patients' clinical status [80].

Egger more recently reported that an oligoantigenic diet decreased seizures in 63 epileptic children. Forty-five of the epileptic children also suffered from migraine or hyperactivity. Epilepsy by itself occurred in only 18 children. Twenty-five subjects became seizure-free, and 11 others improved. All of the subjects who improved had epilepsy plus migraine or hyperactivity. The 18 patients who had epilepsy as a single problem did not improve on the diet [81].

The diet was followed by a reintroduction phase, with certain foods being associated with the return of seizures. On the basis of the responses during the reintroduction phase, 16 subjects underwent placebo-controlled blinded food challenges. Eight children out of 16 had seizures with one or more food challenges. No seizures occurred during the placebo challenges [81].

Attention Deficit Disorder Hyperactivity Syndrome

In 1922 Shannon reported that food sensitivity affected learning ability and activity. [82] Differing food allergy problems have been suggested as triggers of attention deficit disorder hyperactivity (ADHD) syndrome. These include sucrose

and preservatives, pharmacologically active foods (caffeine), and immunological food reactions.

Sugar (Sucrose) Sensitivity

There is a popular idea that sucrose is an important cause of behavior problems. Studies of sucrose's effects on behavior and attention have shown that even relatively large amounts of sucrose did not adversely affect behavior, except perhaps in some preschool children [83–90]. There may be local cerebral dysfunction in glucose metabolism among adults who had been hyperactive in childhood [91].

Dyes and Preservatives

Dr. Ben Feingold wrote a book to the lay community proposing that dyes, preservatives, and salicylates from the diet caused attention deficit hyperreactivity disorder [92]. The hypothesis was not tested in scientific study before being proclaimed to the public. Testimonials to the diet's effectiveness abounded.

After an enthusiastic public response, investigators evaluated the hypothesis that dye, preservative, and salicylate caused ADHD with blinded placebo-controlled methods. In no study did the diet control symptoms better rhan stimulants In fact, only one subgroup of patients appeared to benefit from the diet. This was the group of younger preschool children [93]. Table 3 summarizes some of these studies [94–99].

It soon became apparent that the Feingold diet did not remove salicylates and these components now appear of less concern.

Blind Controlled Studies

Besides the study by Egger, other investigators have reported experience with food related ADHD. In a recent study by Carter with a double-blind placebo-controlled challenge phase with 16 children with ADHD, the children were more symptomatic on food dye and preservative challenge days, compared to placebo days. They were less symptomatic on the days off dyes and preservatives [100].

Boris and Mandel reported a similar study confirming a benefit of removing dyes and preservatives from the diet of ADHD children. Sixteen of 26 children showed lessened symptoms on the dye- and preservative-free diet. Complete symptom relief was not obtained [101].

Egger, using the same type of oligoantigenic diet described, noted improved behavior in 62 of the 76 children with ADHD he studied. Many children appeared to be adversely affected by benzoic acid and tartrazine. However, there were no children identified as solely reactive to one or the other or both of these agents. Forty-six different food sources provoked hyperactivity. During the oligoantigenic diet trial, 21 children's behavior became completely normal. Dur-

TABLE 3 Trials of Feingold Hypothesis in Attention Deficit Hyperactivity Disorder

First author	[Reference] year	Subjects, Number	Blinded	Results	Raters	Comments
Cook	[94] 1976	15	No	Improved on diet	P	Order effect
Conners	[95] 1976	15	Yes	Improved on diet	P and T	Younger better
Harley	[96] 1978	36 nine challenges	Yes	Diet was Superior Challenges 1/9 worse	P and T	Younger children
Goyotte	[97] 1978	16 >= 6Yr 13<= 5yr	Yes	Challenges d> 6 yr no effect <5 yr worsen	Authors	All had responded to diet
Williams	[98] 1978	26	Yes	8 improve on diet	P and T	Modest effect Medication superior
Egger	[99] 1985	76	Part I = no Part 2 = yes	Improved = 62 Normal = 21 28 have rechallenge return to hyperactive	P and N and Psy	No effect on psychological testing

P, parents; T, teachers; N, neurologists; Psy, psychologists.

ing the double-blind challenge diets, suspected foods more often were associated with behavioral changes than were the placebos [99].

Kittler and Baldwin reported normalization of EEG result abnormalities in 9 of 20 children with behavior disorders while they were on an elimination diet. No blinded challenges were performed. No performance changes occurred in tests of intellectual function, even when the EEG result improved [102].

Diet may stimulate hyperactive behavior as a result of pharmacological activity such as that of caffeine in cola drinks or coffe, and phenylethylamine in chocolate. There is marked variation in the catabolism of these agents.

Insomnia and increased activity, with a letdown and lethargic phase, can occur. Aspartame and monosodium glutamate can show an excitogenic effect on EEG of animal models. In larger doses, they also lower the seizure potential of the animals [103,104].

Food or foodstuffs presumably acting on an allergic basis may aggravate attention deficit syndrome. The group most likely to benefit from diet control are preschool children. Studies have tested the hypothesis that food or food additives affect behavior and learning in children. There is an effect of diet on affected children. Children with the milder behavioral changes appear to benefit from diet changes alone, making this approach sufficient for their care. Severely affected children still require the other recognized means of treatment. However, we believe dietary factors should be explored in these patients also.

Tension Fatigue Syndrome: Allergic Toxemia

In 1930, Rowe described a syndrome of "allergic toxemia" caused by food allergy [105]. The symptoms of this syndrome were (a) drowsiness; (b) mental confusion, (c) lack of initiative, (d) slowness of thought, (e) fatigue, (f) weakness, (g) bodily aches, (h) irritability; (i) and a feeling of being poisoned. The patients often had gastrointestinal complaints. The average age of these patients was 45 years. They were most often female. These types of patients are presently diagnosed as having chronic fatigue syndrome. Rowe reported great benefit with diets. There were no double-blind challenges or controls in his studies.

The symptom complex was renamed the *allergic tension–fatigue syndrome* by Speer [106], who added the important concept of fatigue, which was not relieved by rest. He stressed the occurrence of insomnia in some patients and an uncomfortable, nonphysiological fatigue. He and others, such as Crook, believed that food allergy was an important provoker of this symptom [106]. Recent work suggests that allergic reactions of the tension–fatigue syndrome may be mediated through cell sensitization [107].

One controlled study of patients confirming that food allergy provocation of the syndrome occurs has been performed [108]. This study is only partially accepted by the general medical community. The described symptoms are common to patients seen by physicians in all specialties.

A recent study of patients who described food related fatigue symptoms discovered a large percentage with depressive disorders [109].

At present there is a clear need for additional studies of food and foodstuff in the diverse group of patients who present the symptoms of chronic fatigue. At present there is no clear support for a prominent role of food allergy in the pathogenesis of chronic fatigue syndrome.

Meniere's Syndrome, Vertigo, and Fluctuating Hearing Loss

Duke placed five patients with Meniere's syndrome on elimination diets that allowed long-term relief [110]. That food allergies trigger vertigo, along with more classic Meniere's syndrome symptoms, is a well accepted idea among otolaryngological allergists [111,112].

Some infants and young children suffer from benign paroxysmal vertigo with fluctuating hearing loss. They improve on an avoidance diet. Challenges with cow's milk provoke the symptoms. This is the best demonstration that foods can affect the vestibular and auditory organs [113].

Paralytic Syndromes

Stafferi reported that hemiplegia and allergic symptoms routinely followed ingestion of certain foods in a patient [114]. Although the authors stated similar cases had ben described, they cited no references, so that this statement is not verifiable. At this present time, there is no support for this association.

Insomnia

Kahn observed infants who were fitful sleepers or insomniacs in a pediatric sleep laboratory. When the infants drank cow's milk or cow's milk–derived formulas, the symptoms were present. If cow's milk or cow's milk formula was replaced in the diet, the infants slept normally. Upon reintroduction of cow's milk, the sleep disturbance returned. The infants did not demonstrate specific anti–cow's milk immmunoglobulin E (IgE) antibodies [115].

Metabolic Psychiatrict Disease

Dohan, a psychiatrist, noted that the incidence of schizophrenia was decreased among the populations of the Nazi occupied countries during World War II. The populations had a restricted diet. Normal dietary items such as wheat were expropriated for use by the German army and civilians. He subsequently theorized that gluten was a factor in the pathogenesis of schizophrenia. In a series of articles, Dohan reported resolution of schizophrenic episodes was more rapid on a wheat-free diet and specified the medication requirements for successful treatment [116]. There is a blind challenge study that supports Dohan's conclusions [117].

A rather interesting case report described a nurse who repeatedly suffered depressive symptoms after blinded challenges with cow's milk but not placebo [118]. Investigators in Norway provided evidence that autisitic children fare bet-

ter on a milk-free and gluten-free diet. The excretion of abnormal urinary peptides by autistic patients was decreased. The change in peptide excretion was associated with improved autistic symptoms [119].

Special Considerations in the Evaluation of Food Triggered Neurological Disorders

Details of the general approach to the evaluation of food related illness are discussed in other chapters. As stated in the Introduction to this chapter, there remains a great deal of controversy about neurological, neuromuscular, emotional or psychiatric disease that is caused by dietary factors [120] (in spite of the well recognized effects of things humans eat and drink on their physical health, performance, and mood.)

It is important to understanding the role of unique hypersensitivy to dietary factors as a possible cause of neurological disease for the evaluating physician to think about other recently described mediators such as the cytokines that change during immune hypersensitivy responses. There is evidence for the activation of sensitized mononuclear cells which can participate in these reactions. The modification by peripheral immune responses in nervous system function has been described [8]. The metabolic disturbances demonstrated in serum during certain illnesses such as migraine suggest that we need to reexamine concepts about mediator exclusion from the central nervous system by the blood–brain barrier. The previously described evidence from animal models suggests high concentrations of these mediators will disrupt the epithelial blood–brain barrier.

There are some special issues relating to neurological disease possibly caused by food or foodstuff. The first step is taking a detailed history of the problem from the patient or parent. The second step is providing for a period of symptom diet diary recording by the patient. It is important to be candid with the patient about the present state of knowledge and disagreement. However, for each patient a careful evaluation can lead to an accurate evaluation of dietary effects on the medical condition of concern.

1. The evaluation may take place over a long period of observation, sometimes involving months, with careful well planned recording of food symptom diaries. The patient should be aware of the importance of this recording during a baseline period, during the elimination diet trial, and during a reintroduction phase. Figure 2 is a modified milk, egg-, corn-, and wheat-free diet that we have found useful to begin the evaluation.

2. Foods or foodstuffs that seem to be incriminated during the open trial should be confirmed by blind challenges if at all possible. This may not al-

Please Note :

1. For this diet, all fruit and vegetables except for lettuce and melons must be cooked.
2. All foods should be either fresh or frozen
3. Avoid foods containing preservatives or colorants, dry cereals, dried fruits
4. Avoid smoked meats or cheeses, hot dogs, sausages, ham, bacon
5. It is best to avoid alcohol or keep intake to a minimum (less good), you must avoid red or rose wines
6. Try to limit the use of cokes, coffee, tea, chocolate. Use decaffeinated drinks whenever possible.
7. Avoid chewing gums, thickened salad dressings
8. Avoid any foods which you have found cause headaches

FOODS YOU MAY EAT

Tapioca	Beef	Asparagus
White Potato	Chicken	Spinach
Rice	Pork (Not ham or smoked)	Carrots
Sweet Potato	Squash	Cranberries
Lettuce	Chard	Apricots
Maple Syrup	Peaches	Pears
Beets	Gelatin (plain)	Pineapple
Artichoke	Apples	Grapes
Avocado	Melons	Sorghum
Water	Club Soda	Coffee
Tea	Vegetable Oil	Vegetable (100%) Shortening
Vinegar	Salt, Pepper, Garlic, Onion	

FIGURE 2 Migraine diet: a modified milk-, egg-, wheat-, and corn-free diet.

ways be possible in today's medical environment. However, if the food or foodstuff is very difficult to avoid or a major diet constituent, approval can be usually obtained.

3. An analog scale can be helpful to determine degrees of pain or increases in subjective discomfort. Figure 3 is an example of a recording device for migraine. This device can be used during the trial as well as the challenges.

4. With respect to laboratory testing, skin tests, that allow for evaluation of late-phase responses as well as early responses may be of greater utility than simple immediate skin tests. However, this area needs further study before it will be clear how much additional benefit late-phase testing will offer.

Radioallergosorbent testing (RAST), perhaps because it is less sensitive than usual skin testing, may actually be superior in diagnosing IgE-mediated food reactions affecting the nervous system. Additional studies like Monro's are required to confirm whether this is true [55].

Please complete this record as soon as you can. Accurate information will help us better understand how to help relieve your migraines.

Migraine Headache Record **Patient Name**
Date

What time did the attack start ?: am/pm date
What time did it stop?: am/pm date
Did you have any sensations before this attack? yes no
If yes, what were they?:

Where was the headache? Right Side Left Side Both Sides
What was the pain like?: Constant Throbbing Pulsating Sharp Pressure
How much did it hurt at the peak of the pain ?:

a little	mild	moderate	severe	very severe	excruciating
(1)	(2)	(3)	(4)	(5)	(6)

Place a mark on the line which best describes your pain.
Did you also have?: Nausea Vomiting Abdominal Pain Light Sensitivity
Did you take any medications? Yes No
What medicines in what doses and when did you take them?

medication name	dose used	time taken
1		
2		
3		
4		
5		
6		

Comments

FIGURE 3 Example of a recording device for a migraine.

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