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Dietary Sensitivities and ADHD Symptoms: Thirty-five Years of Research

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Abstract

Artificial food colors (AFCs) have not been established as the main cause of attention-deficit hyperactivity disorder (ADHD), but accumulated evidence suggests that a subgroup shows significant symptom improvement when consuming an AFC-free diet and reacts with ADHD-type symptoms on challenge with AFCs. Of children with suspected sensitivities, 65% to 89% reacted when challenged with at least 100 mg of AFC. Oligoantigenic diet studies suggested that some children in addition to being sensitive to AFCs are also sensitive to common nonsalicylate foods (milk, chocolate, soy, eggs, wheat, corn, legumes) as well as salicylate-containing grapes, tomatoes, and orange. Some studies found "cosensitivity" to be more the rule than the exception. Recently, 2 large studies demonstrated behavioral sensitivity to AFCs and benzoate in children both with and without ADHD. A trial elimination diet is appropriate for children who have not responded satisfactorily to conventional treatment or whose parents wish to pursue a dietary investigation.

Keywords

artificial flavors, artificial food colors, artificial food dyes, attention-deficit hyperactivity disorder, elimination diets, food sensitivities, hyperkinesis, salicylates, tartrazine

Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood, affecting roughly 7.8% of US school-aged children (4-17 years old) according to the Centers for Disease Control.[1] Children with ADHD are inattentive, impulsive, and hyperactive. Adding to their problems, children with ADHD are often diagnosed with comorbid disorders such as oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, and learning disabilities.[2] The most common treatments are psychostimulants and behavior therapy. In 2003, 2.5 million children in the US took medications for ADHD.[1] Although approximately 70% of the children improve significantly on medication, side effects are a problem for some. These include loss of appetite, decreased growth, insomnia, and headaches. In the last 10 years concerns about cardiac effects have been raised because of sudden, extremely rare deaths in children taking stimulants.[3] Given these risks of medication and the time and effort required for behavior therapy, some parents explore alternative treatments.

The causes of ADHD are unknown but are believed to be biological and multifactorial. Symptoms are associated with impaired dopaminergic and noradrenergic transmission. Both genetics and environmental factors seem to play key roles. One controversial proposed environmental factor is a hypersensitivity or intolerance to certain foods and/or food additives. The controversy began in 1973 when Benjamin Feingold, MD, Chief Emeritus of the Department of Allergy at the Kaiser Permanente Foundation Hospital and Permanente Medical Group in San Francisco, presented an invited paper at the

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Table 1. The Kaiser-Permanente Diet

- Avoid all artificial colors and flavors contained in foods, medications, and cosmetics
- Avoid preservatives BHA and BHT (butylated hydroxyanisole and butylated hydroxytoluene)[a]
- Avoid the following foods containing natural salicylates:

Almonds	Currants	Plums, prunes	Cloves
Apples	Grapes, raisins	Tangerines	Coffee
Apricots	Nectarines	Cucumber, pickles	Teas
Berries	Oranges	Green peppers	Oil of wintergreen
Cherries	Peaches	Tomatoes	

[a]TBHQ (tertiary butylhydroquinone) and sodium benzoate were later added to the list of preservatives to avoid.

annual meeting of the American Medical Association.[4] He proposed that much of the hyperactivity and learning problems seen in school-aged children was because of the ingestion of certain foods and food additives.

The Kaiser-Permanente (K-P) Diet

Feingold had observed years earlier that his atopic patients who were sensitive to aspirin were often sensitive to foods containing natural salicylates, which are similar in chemical structure to acetylsalicylic acid. Feingold devised a diet free of natural salicylates and also 7 artificial flavors that contained a salicylate radical. Feingold and other allergists had observed that many aspirin-sensitive patients also reacted to tartrazine, an artificial yellow dye, although the chemical structure is not similar to acetylsalicylic acid.[5] Feingold called his diet the "Kaiser Permanente diet" or "K-P diet"; this was free of foods containing natural salicylates and all artificial food colors (AFCs) and flavors[5,6] (see Table 1).

When treating a 40-year-old woman who presented with angioedema of the face and periorbital region Feingold prescribed the K-P diet.[6] Unbeknownst to Feingold, the woman had also been seeing the staff psychiatrist for 2 years for psychological problems with no improvements. After the K-P diet, not only did her hives disappear, but her behavioral problems also went into remission according to her psychiatrist. Feingold began to assess other patients who had psychological problems in addition to atopic disorders. He noted that children diagnosed with minimal brain dysfunction or hyperkinesis often responded dramatically to the K-P diet. He began to recruit these children and reported that they had much improved scores on behavior rating scales within 3 to 21 days. Feingold reported that of the 260 children he studied, 30% to 50% (depending on the sample and age) responded to the diet. In 1972, Feingold was invited to present his findings at the American Medical Association's annual conference.[4] By 1977, Feingold added the elimination of 2 preservatives, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), which he claimed also triggered hyperactive behavior.[7] In a speech to the American Academy of Pediatrics in 1977, Feingold stated that 60% to 70% of the children he treated improved.[8]

Feingold's presentation to the AMA sparked interest by the press, lay persons, and researchers, and the AMA scheduled a cross-country series of lectures for him to present his findings. In 1975, he published a best-selling book for parents, *Why Your Child is Hyperactive* (Random House, 1975). However, Feingold was roundly criticized by many in the medical and pharmaceutical establishments.[9,10] The food industry, represented by the National Advisory Committee of the Nutrition Foundation, declared in 1975, "No controlled studies have demonstrated that hyperkinesis is related to the ingestion of food additives."[11] Feingold was criticized for his press conference that had preceded the AMA presentation and his press conferences around the country even though they had been scheduled by the AMA. Critics argued that Feingold's book was premature and not based on sound, scientific studies; specifically, his research lacked a structured diagnosis for the subjects, control groups, and double-blind challenges and relied on parents' observations in lieu of objective data, which prevented any statistical analyses. Many nutritionists argued that the diet was nutritionally inadequate, although 2 studies disputed this.[12,13] Some of Feingold's critics attributed his findings to a large placebo effect because of extra attention children received in trying the K-P diet. However, his work was applauded by many parents who formed the Feingold Association of the United States (FAUS), which still exists today.

For the next 35 years, scientists tested and extended Feingold's hypotheses using 3 types of diets: (1) the K-P diet, (2) an elimination diet followed by challenges with AFCs, and (3) elimination of a few foods or oligoantigenic elimination diet followed by challenges with both AFCs and natural foods (Table 2).

K-P Diet Studies

Clearly, Feingold's theory was controversial, yet the promise of a dietary treatment for hyperactivity was attractive to parents, clinicians, and researchers. Thus, by 1983, the number of studies that had been published evaluating the effectiveness of the K-P diet was so large that a meta-analysis was possible and warranted. Kavale and Forness[14] completed the first meta-analysis of Feingold's hypotheses based on 23 studies, each of which

Table 2. Double-Blind Placebo-Controlled Studies in Children Diagnosed With Hyperactivity, ADHD, or Other Behavior Problems

	Kaiser-Permanente Diet	Artificial Food Dyes	Elimination Diets
Parental and/or teacher behavioral rating scales	Conners et al[15]; Harley et al[16]; Gross et al[17]	Goyette et al[24]; Harley et al[16]; Williams and Cram[42]; Swanson and Kinsbourne[23]; Weiss et al,[43]; Pollock and Warner[25]; Rowe and Rowe[26]	Hughes et al[35]; Egger et al[36]; Carter et al[37]; Kaplan et al[40]; Boris and Mandel[41]; Schmidt et al,[49]
Physical symptoms and sleep		Rowe[44]	Egger et al[36]; Kaplan et al[40]; Carter et al[37]
Neuropsychological tests	Fitzsimon et al[18]; Harley et al[16]	Goyette et al[24]; Harley et al[45]; Swanson and Kinsbourne[23]	Hughes et al[35]
EEG		Salamy et al,[46]	Uhlig et al[38]
Physiological measures		Salamy, 1982; Ward et al,[47]; Ward[48]	Egger et al[36]

contained a control group. They reported the average effect size (ES) for child outcomes was 0.118 (nonimportant; ES range was -1.132 to 1.285). When child outcomes were divided into several categories, only the teacher ratings of ADHD symptoms and an overall rating of hyperactivity reached the level of a small ES (0.268 and 0.293, respectively; all others were nonimportant); however, the authors reported that these small effects were driven by "reactive measures" (those that were subjective), and therefore, the relationship of the K-P diet with hyperactivity should be interpreted cautiously. In addition, the 6 studies that were not well controlled had an average ES of 0.334, whereas the 17 better-controlled studies resulted in an average ES of 0.089. The authors concluded that their analyses did not support the K-P diet as a treatment for hyperactivity. In this section, 3 studies will be highlighted that exemplify the controversy surrounding the investigations of the Feingold diet.

In 1976, Conners et al[15] conducted the first scientific study of the K-P diet with 15 hyperkinetic children using a double-blind crossover design. Children were randomly assigned to 4 weeks of the K-P diet, followed by 4 weeks of the control diet, which mirrored the K-P diet in terms of the effort to maintain the diet (eg, food preparation) and drew from similar food groupings; or they were assigned to the control diet followed by the K-P diet. Relative to a 4-week baseline period, on a standardized rating scale of ADHD symptoms, both parents and teachers rated the children as being less hyperactive on the K-P diet ($P < .05$) but not the control diet. In addition, teachers rated children as being less hyperactive on the K-P diet than on the control diet ($P < .005$). Notably, the teacher ratings, showing the most significant difference in diets, were more likely to be blind to actual diet condition. Comparisons of children's behavior on the control diet with the baseline period were nonsignificant. Although the overall results of the study were significant, only 4 to 5 children were rated as improved on both parent and teacher ratings (27%-33% response rate, similar to Feingold's earlier estimates of treatment effectiveness). In addition, relative to the children's baseline diet, the K-P diet provided less calcium, riboflavin, and vitamin C. Notably, in this study, even though parents were required to shop and prepare both diets for their children, diet infractions were rare (1.5 and 1.33 per week for the control and K-P diets, respectively). Furthermore, on a study-specific measure of diet difficulty, parents reported a similar amount of difficulty maintaining the control and K-P diets (9.53 and 8.27 out of 25, respectively); however, no normative information for this measure is included, so it is unclear whether both these scores indicate a relatively high or low degree of difficulty.

Harley et al[16] performed 2 similar double-blind, crossover studies of 36 hyperactive school-aged boys (6 to 12 years) and 10 hyperactive, preschool-aged boys (3 to 5 years). After a 2-week baseline, children were randomly assigned first to either the K-P diet or a control diet, which included AFCs. Investigators removed all previously purchased foods from each family's house and delivered the family's entire food supply weekly. Similar to the study by Conners et al,[15] dietary infractions were rare. Although the 2 diets were followed consistently, only 4 school-aged children showed significant improvement on the K-P diet as rated by both parents and teachers (11% response rate), whereas 13

mothers, 14 fathers, and 6 teachers independently rated the children as improved. Furthermore, parent ratings of improvement showed a treatment order effect: 92% of the children's mothers and 79% of the children's fathers rated their children as improved when first assigned to the control diet followed by the K-P diet. The percentages were lower for the K-P diet first followed by the control diet. All 10 mothers (and 4 out of 7 fathers) rated their preschool-aged children as improved on the K-P diet (no teacher ratings were collected for preschoolers because they participated during summer vacation); the authors proposed that younger children may be more sensitive to diet changes. Despite these positive findings, the authors concluded that based on nonsignificant results of teacher ratings, classroom observations, laboratory tasks, and other psychological tests, their results did not support Feingold's assertions.

Gross et al[17] evaluated the benefit of the K-P diet in 39 children with learning problems who were attending a summer camp; 18 had also been diagnosed with ADHD, and 17 were prescribed stimulant medications. All children followed the K-P diet for 1 week, then followed a typical American diet, with access to treats from home, for a second week. During each week, 4-minute intervals were videotaped at mealtime and rated by blinded observers for motor restlessness, disorganized behavior, and misbehavior. The authors concluded that there were no positive effects of the K-P diet, at least for children who responded to stimulant medication, and furthermore, the children intensely disliked the diet. Although the study methodology had several obvious advantages (ie, investigators had complete control of the children's diets and all children were exposed to similar environmental factors), several problems with the study methodology were also present. First, children were very aware that the first week they were eating a diet that was different from usual and were denied sweets from home during this time. In addition, and perhaps a larger caveat to the integrity of the study, the outcome measure (coding of videotapes) had not been evaluated to determine its sensitivity to changes in children's hyperactive behavior.

Along with investigations of Feingold's diet, some researchers have also evaluated the science behind his dietary treatment. For example, Fitzsimon et al[18] addressed Feingold's hypothesis that natural foods containing salicylates trigger behavior reactions in sensitive children. They recruited hyperkinetic children who had responded to the K-P diet, according to parental reports. In a double-blind crossover study, 12 hyperkinetic children, whose parents reported that they had responded to the K-P diet, were randomly assigned to either a 40-mg acetylsalicylic tablet or a look-a-like ascorbic acid placebo. General cognition was measured 2½ hours after ingestion of the pills and was found to be significantly impaired ($P \leq .05$) in those children who received the acetylsalicylic acid. Motor coordination and speed of movement were negatively affected ($P < .02$ and $P < .05$, respectively), and sleep disturbances were reported when children were assigned to acetylsalicylic acid. Loblay and Swain (1985) reported that 11 of 17 hyperactive children reacted to oral challenges of aspirin with increased hyperactivity, but there was no placebo challenge.[19] However, it is not known whether acetylsalicylic acid mirrors the actions of natural salicylates in foods.

Based on the results of these early investigations, there appears to be a small proportion (11%-33%) of hyperactive children who respond to the K-P diet in a way that improves their functioning both at home and at school. The percentages of responders in these studies were considerably lower than the percentages of responders Feingold initially estimated (30%-50%) and later reported (60%-70%). Somewhat surprisingly, dietary infractions were low, both in a study in which all food was provided for the family and in a study in which parents were instructed to purchase groceries and cook meals according to the K-P diet. Thus, it appears that families are able to maintain the diet, at least for short periods of time (ie, 4 weeks), although it remains unclear (1) whether families believed that the difficulty in maintaining the diet is appropriate relative to the level of improvement in their children's behavior and (2) whether families would be able to maintain strict adherence to the diet for longer time periods. Further investigations are required to evaluate whether age may moderate response to the K-P diet, whether the diet and improvements can be maintained for longer than 1 month, and whether the K-P diet consistently provides lower amounts of some nutrients (eg, calcium), which may need to be supplemented. It is recommended that future research should continue to use assessment measures that are sensitive to improvements in children's hyperactive behavior.

Artificial Food Color Studies

In addition to research regarding the Feingold diet, many investigators have narrowed the focus to evaluating the specific effects of AFCs on children's hyperactive behavior (Table 3). Schab and Trinh[20] conducted a meta-analysis of these studies (some which were previously included in the meta-analysis by Kavale and Forness[14]) to specifically evaluate the effect of AFCs on child hyperactivity. They included only double-blind, placebo-controlled trials that specifically evaluated the effects of AFCs. The authors identified 15 previous

Table 3. Double-Blind, Placebo-Controlled Studies of Artificial Food Dyes in Children With Behavior Problems

Studies	Number of Participants/ Diagnosis	Restricted Diet	Artificial Food Dyes	Vehicle	Amount of Food Dyes (mg)	Parent and Teacher Rating Scales and Other Tests	Number of Children Reacting to Food Dyes	Challenge Effect	Types of Behavior Effects
Goyette et al,[24] experiment 1	16/Hyperkinesis	Additive-free	Mix	Chocolate cookies	26	PRS, visual-motor test	3/16, 3/16	ns	
Goyette et al,[24] experiment 2	13/Hyperkinesis	Additive free	Mix	Chocolate cookies	26	PRS	2/13	$P < .025$	Disruptive behavior
Williams and Cram[42]	26/Hyperactivity	Modified K-P	Mix	Chocolate cookies	26	PRS, TRS	7/26	$P < .005$, $P < .005$	
Harley et al[16]	10/Preschool hyperactivity	K-P diet	Mix	Chocolate bars, cookies	27	PRS	10/10 Mothers, 4/7 Fathers	ns	
Harley et al,[45]	36/School aged, hyperactivity	K-P diet	Mix	Chocolate bars, cookies	27	PRS, TRS, neuropsychological tests	13/36 Mothers, 14/30 fathers, 6/36 teachers	ns, ns, ns	
Weiss et al,[43]	22/Behavior problems	K-P diet	Mix	Beverage	35.3	PRS	2/22[a]		
Swanson and Kinsbourne[23]	20/Hyperkinesis	K-P diet	Mix	Capsules	100-150	Learning task	17/20	$P < .05$	
Pollock and Warner[25]		Additive free	Mix	Capsules	125	PRS	8/19 by 25%	$P < .01$	
Rowe[44]	8/Hyperactivity	Additive free	Carmoisine or tartrazine	Capsules	50	PRS	2/8		Inattention, irritability, restlessness, sleep disturbances
Rowe and Rowe[26]	34/Hyperactivity	Additive free	Tartrazine	Capsule, Beverage	1-50	PRS	22/34	$P < .001$	Irritability, restlessness, sleep disturbances

Abbreviations: K-P, Kaiser-Permanente; PRS, Parent Rating Scale; TRS, Teacher Rating Scale.

[a]Two children reacted dramatically when challenged with dyes. Child #1 reacted with more bites, kicks, and hits compared with control days ($P < .01$). Child #2 reacted with inattention, throwing things, and whining ($P < .03$).

studies that recruited hyperactive samples and 8 previous studies that evaluated the effect of AFCs on nonhyperactive children (2 studies evaluated both samples). For studies with hyperactive samples, there was an overall ES of 0.283; however, the effect was only significant for parent ratings (ES = 0.441), not for clinician or teacher ratings. Furthermore, when the studies were divided into samples that had been previously screened for responsiveness to AFCs through either an open trial or parent report versus samples not screened for responsiveness, the previously screened samples had a significantly larger ES (0.535) than those not previously screened (0.090). The average ES for studies with nonhyperactive participants was smaller: 0.117. When studies with nonhyperactive samples were divided based on the screening of the sample population, the results were similar to the results from hyperactive samples: studies with screened samples had a much larger ES than studies of unscreened samples (ES = 0.316 and −0.112, respectively). Even with these qualifications, the authors concluded that AFCs promote hyperactivity in children with ADHD.

Many investigations of the effects of AFCs on hyperactive behavior in children and adolescents have followed a logical methodological pattern: a baseline diet free of AFCs, followed by a double-blind, placebo-controlled crossover challenge of AFCs. However, studies have varied widely in terms of study length, sample size, methodological rigor, and AFC challenges, which varied in amounts and selected dyes. Often different AFCs were mixed together as the challenge. Allura red, erythrosine, brilliant blue, indogotine, tartrazine, and sunset yellow were usually included. The total amounts of these mixed dyes varied from 26 mg to 150 mg. (See Table 3). The Nutrition Foundation estimated per capita intake in the US as 27 mg/d.[52] However, in 1976, in a memorandum from the Food and Drug Administration, However, in 1979, in a report to the Food & Drug Administration, the National Research Council of the National Academy of Sciences stated that the average dye intake was 82 mg while the average of the top 10% was 166 mg.[21]

Swanson and Kinsbourne[22,23] conducted 2 short-term AFC challenge studies. In the first study, 8 patients with clinically significant hyperactivity were placed on the K-P diet for 5 days—2 days of baseline and 3 days of challenge with 26 and 100 mg of AFCs. It is unclear if the diet had an effect on the children's behavior. Relative to placebo, children made more errors on a laboratory learning task when challenged with 100 mg AFCs ($P < .001$); however, there was no treatment effect for 26 mg of AFCs. These authors then completed a similar trial with 20 hyperactive children and 20 nonhyperactive comparison children in a hospital setting. All children were placed on a diet free of food dyes, artificial flavors, preservatives (BHT and BHA), and salicylates for 5 days—3 days of baseline and 2 days of placebo-controlled challenge of 100 to 150 mg of AFCs. The performance of the hyperactive children on learning tasks was significantly impaired ($P < .05$) after the AFC challenge but not after the placebo challenge, whereas the comparison children's performance was not affected by challenge with AFCs. In addition to the significant Challenge (placebo vs AFC) × Subject interaction, there was a significant Time × Challenge interaction: specifically, hyperactive children's performance impairment in response to AFCs occurred about half an hour after ingestion, peaked at about 1½ hours, and lasted at least 3½ hours (last assessment point; $P < .05$). This timing would explain why some children in other studies who were rated beyond 3½ hours might not show behavior changes.

Additional investigations of the effect of AFCs on hyperactivity have used the same general methodology as the previous 2 articles, but most used a longer AFC and placebo challenge period (total time 1 to 8 weeks). Goyette et al[24] reported 2 AFC challenge studies with hyperkinetic, diet-responsive children. In the initial study, investigators recruited 16 children (ages 4-11), who were placed on an elimination diet; authors reported that parents and teachers reported children's behavior problems were reduced by 57% and 34%, respectively, while on the diet. After the elimination diet, children participated in an 8-week double-blind placebo-controlled challenge; in alternating 2-week intervals, children were challenged with dye-free chocolate cookies or with chocolate cookies containing artificial colors. There were no significant differences in parent or teacher ratings of hyperactive behavior during the active and placebo conditions; behavior problems remained low throughout the 8-week challenge. Children's performance on a visual motor tracking task performed 1 to 2 hours after the challenge showed a trend toward deficits after the dyes but not the placebo. The authors concluded that behavioral impairment as a result of AFCs may occur relatively quickly, and rating scales scored over a longer period (48-72 hours) might miss reactions. Thus, they designed a subsequent crossover experiment of 13 hyperkinetic children who had an average 45% reduction in behavior problems with the elimination diet. Results indicated that more behavioral problems were reported immediately following an AFC challenge than following a placebo challenge ($P < .025$); it is unclear whether similar laboratory test findings were present in this sample. The researchers concluded, "Artificial colors do indeed act to impair and disrupt the behavior of children." (P. 40)

Pollock and Warner[25] completed a 7-week double-blind AFC crossover challenge with 39 children (19 completers; only completer data reported) whose parents

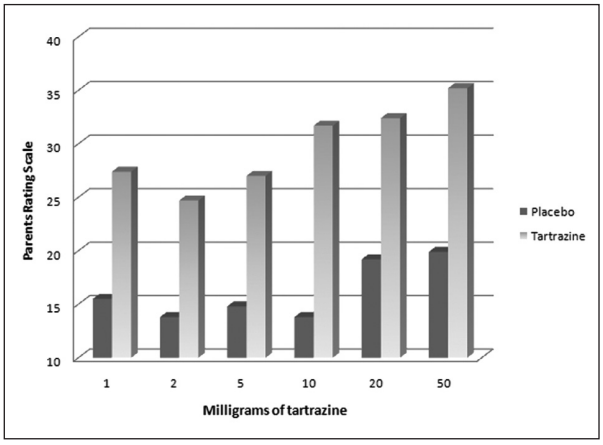

Figure 1. Dose–response effect of tartrazine on parent rating scales (adapted from Rowe and Rowe[26])

reported that their children were sensitive to AFCs. All children were maintained on their current AFC-free diet; the variance in each child's diet was unclear. For 2 of the 7 weeks, children were challenged daily with 125 mg of mixed food dyes, and for 5 weeks, children were challenged with placebo capsules; 3 weeks of placebo preceded every AFC challenge. Parents completed daily questionnaires about their children's behavior and somatic symptoms; they reported significantly more behavioral problems after consumption of AFCs as compared with the placebo ($P < .01$); however, there was no difference in parents' ratings of somatic symptoms between challenge conditions. Although this study provided support for the relationships between AFCs and hyperactive behavior, only 2 of the 19 children were rated as exhibiting a clinical level of behavioral problems following AFC challenge.

Although many of the studies evaluated reactions to a combination of different AFCs, Rowe and Rowe[26] evaluated the effect of 6 doses of tartrazine in diet-responsive children (Figure 1). A total of 200 children who were referred for an assessment for hyperactivity and whose parents reported behavioral sensitivity to dietary changes were included in a 6-week open trial of an AFC-free diet. Parents of 150 children reported improved behavior on the diet and worse behavior when the dyes were added back, although no data supporting this finding were included. Based on a review of the clinical history of 50 suspected AFC reactors, the authors developed a 30-item behavior inventory, including 5 clusters of related behaviors: (1) irritability/control, (2) sleep disturbances, (3) restlessness, (4) aggression, and (5) attention span. Next, 34 different hyperactive children, who had responded to the AFC diet, and 20 nonhyperactive comparison children completed a double-blind, placebo-controlled challenge trial. For 21 days, the children were either challenged with placebo or 1 of 6 doses of tartrazine (range 1-50 mg). In all, 24 children (22 hyperactive and 2 comparison children) had significant and consistent responses to tartrazine challenge, whereas the other 30 children were considered nonreactors because of inconsistent response. For the reactors, parents rated significantly more behavioral problems after the tartrazine challenge than placebo for each dosage of tartrazine. In addition, reactors exhibited significantly more behavioral problems (according to parent ratings) after tartrazine challenge relative to nonreactors at all dosages of tartrazine. Both younger (ages 2 to 6) and older (ages 7 to 14) children who reacted to the tartrazine challenge exhibited increased irritability and restless/overactive behaviors. In addition, severe sleep disturbances commonly occurred in the younger children, whereas older children exhibited impulsivity, whining, and negative mood. Thus, it appears that AFCs even at small doses noticeably affect children's behavior (for children who are sensitive to AFCs), behavioral problems other than hyperactivity are provoked by AFCs, and preschool- and school-aged children may respond differently to an AFC challenge.

The results of Schab and Trinh's[20] meta-analysis indicated that in nonhyperactive samples, the relationship between hyperactivity and AFCs was present but smaller than in hyperactive samples. Around the same time as their meta-analysis, Bateman et al[27] completed a large-scale study that evaluated the effect of AFCs on a general population of 277 3-year-old children unselected for ADHD. Children were divided into 4 groups based on the presence or absence of atopy and/or hyperactivity: (1) 36 with hyperactivity and atopy, (2) 79 without hyperactivity but with atopy, (3) 75 with hyperactivity but not atopy, and (4) 87 with neither hyperactivity nor atopy. All children were maintained on an AFC-free diet while they participated in a double-blind, placebo-controlled challenge of a mixture of 20 mg of AFCs (sunset yellow, tartrazine, carmoisine, ponceau 4R) and 45 mg of sodium benzoate. Parent ratings of hyperactive behavior, but not clinic-based tests of ADHD symptoms, were sensitive to the AFC challenge; parents rated a greater increase in hyperactivity during the active AFC challenge than the placebo challenge ($P < .02$). The authors concluded that the effects of food additives on behavior occurred independently of preexisting hyperactivity or atopy and suggested that the reactions were pharmacological, not allergic.

McCann et al[28] sought to replicate the findings by Bateman et al[27] and extend the investigation to a general population of school-aged children. They conducted a double-blind placebo controlled crossover trial with 2 groups of children: 137 preschoolers (age 3) and 130 school-aged children (ages 8 and 9). Each group of

children was challenged with a combination of sodium benzoate plus 2 different dye mixes—A and B—or a placebo. Mix A was similar to the AFC challenge in the Bateman et al study and contained either 20 mg (for preschool-aged children) or 24.98 mg (for school-aged children) of AFCs (sunset yellow, carmoisine, tartrazine, ponceau 4R) and 45 mg of sodium benzoate. Mix B contained either 30 mg (for preschool-aged children) or 62.4 mg (for school-aged children) of AFCs (sunset yellow, carmosine, quinoline yellow, allura red) and 45 mg of sodium benzoate. Both age groups had significantly increased Global Hyperactivity Aggregate scores when challenged with one or both of the dye mixtures compared with placebo. The younger children significantly reacted to mix A ($P = .044$) but not mix B. The older children reacted significantly to both mix A ($P = .023$) and mix B ($P < .001$) compared with placebo. The editor of *American Academy of Pediatrics Grand Rounds* commented about this study, "The overall findings of the study are clear and require that even we skeptics, who have long doubted parental claims of the effects of various foods on the behavior of their children, admit we might have been wrong."[29] (p. 17)

In response to these studies, the government in the United Kingdom is encouraging and pressuring food manufacturers to avoid these additives in favor of natural food colors and flavors. Starting in July 2010, Regulation No 1333/2008 of the European Parliament and Council, the European Union required manufacturers to eliminate these AFCs from foods and beverages: sunset yellow, quinoline yellow, tartrazine, carmoisine, allura red, and ponceau red or list the following warning on the label: "[this dye] may have an adverse effect on activity and attention in children."[30] In 2008, the Center for Science in the Public Interest, with support from 2 dozen physicians and researchers, formally petitioned the FDA to ban the use of food dyes in the United States. They pointed out that the use of food dyes certified in the United States has increased 5 times since 1955: 12 mg per capita/d were certified by the FDA in 1955, 32 mg in 1975, 47 mg in 1998, and 59 mg in 2007.[31] This increase could be important if there is a dosage effect.

Animal studies seemed to support the hypothesis that food dyes can cause changes in behavior. Shaywitz et al[32] studied the effects of chronic administration of AFCs on rats. A mixture of AFCs—brilliant blue, indigotine, fast green, erythrosine, tartrazine, sunset yellow, and orange B—was administered orally in normally developing rat pups beginning at 5 days of age and continued until 1 month of age. (Another group of rats was treated with 6-hydroxydopamine, a positive placebo, which is known to produce hyperactivity and learning deficits with many similarities to ADHD in children.) Each day, the pups received either the food coloring mixture or water. Activity and cognitive performance in a T-maze were measured at different points for 21 days. General motor activity increased in all the groups as the animals matured. As expected, rats receiving the 6-hydroxydopamine solution were significantly more active than those receiving only water. Administration of food dyes also significantly increased motor activity ($P < .001$). There was no significant dose–response effect, but the highest dose of food dye produced the nominally greatest activity. The largest dose (2.0 mg/kg) of the mixed AFC was also associated with a significant reduction of activity habituation ($P < .001$). A low dose of AFCs at 21 days also influenced avoidance learning in a T-maze ($P < .001$), although higher doses were not significantly different. The authors concluded that food dyes significantly affected both activity and avoidance performance in rat pups. However, they urged caution in generalizing these findings to children with ADHD.

Goldenring et al[33] studied the effects of sulfanilic acid (p-amino-benzoic acid) in developing rats. Sulfanilic acid is a major metabolite of azo food dyes (allura red, tartrazine, and sunset yellow) in rat intestines. Rats received either sulfanilic acid or saline intraperitoneally daily. Similarly, 2 more groups of rats received 6-hydroxydopamine or placebo (saline + ascorbic acid) injected daily. Blinded measurements of activity, shock escape, and shock avoidance were reported from 12 days of age to 26 days. As in the previous study, 1 group of rats was given 6-hydroxydopamine and was significantly more active than those treated with saline. Activity also increased significantly ($P < .005$) in sulfanilic acid–treated rats. At 21 days of age, pups receiving sulfanilic acid took 227% more time to escape the shock compared with those receiving saline ($P < .005$). Although reduced concentrations of brain catecholamines are thought to be involved in ADHD in children, brain concentrations of dopamine and norepinephrine were not significantly affected by administration of food dyes or sulfanilic acid. However, they were significantly lower in the rats treated with 6-hydroxydopamine. Therefore, the authors questioned the relevance of their study to ADHD in children.

Tanaka et al[34] reported the effects of varying large amounts (686-2557 mg/kg/d) of tartrazine on exploratory behavior in 3 generations of mice starting at 5 weeks of age in the F_0 generation to 9 weeks in the F_2 generation. Several behavioral developmental tests using swimming direction (a measure of coordinated movement), olfactory orientation (a measure of olfactory development sense), and surface righting showed acceleration of development in the F_2 generation treated with tartrazine compared with controls.

Movement activity of exploratory behavior at 3 weeks of age in the F_2 group measured in total distance ($P < .05$), average distance ($P < .05$), and average speed ($P < .01$) were significantly decreased in male offspring. It is not clear how these outcomes might relate to children with ADHD-type symptoms. It was interesting to note that there were fewer adverse effects on female offspring. The researchers commented that the high doses used in the study were not comparable with smaller amounts found in foods consumed by humans.

Most of these studies, both human and animal, suggest that challenges of AFCs, whether mixed or with just tartrazine, compared with placebo may result in significant changes in behavior, at least in subpopulations of those with ADHD, perhaps in the general pediatric population as well, and in laboratory animals.

Elimination Diet Studies

Using elimination diets, researchers began to investigate whether common, natural foods could also trigger behavior problems in some children (Table 4). These elimination diet studies generally mirror the methods used by the AFC challenge studies described above: (1) open diet phase (some reported response to diet) and (2) double-blind crossover challenge with offending foods versus placebo. Some studies also completed open challenges with likely offending foods to individualize the challenge phase for each child. As elimination diets vary widely in their level of restrictiveness, in this section, diets will be discussed in order from the most restrictive diet to the least restrictive.

In an open trial, Hughes et al[35] reported that 10 children with severe ADHD were prescribed a chemically defined diet (CDD), which provided all nutritional needs (1800 kcal/d). On an empirically validated rating scale of ADHD symptoms, parents and teachers reported significant improvement when children were on the diet compared with pretreatment ($P < .001$). Of 3 neurological tests of brain stem, central auditory processes, and corpus callosum activity, only the test of transmission of signals through the corpus callosum was significantly improved after the CDD ($P < .05$). After the week-long diet, the authors reported that parents "attempted to execute food management"; however, the authors did not describe these dietary changes nor how participating in the CDD affected later food management. At a 1-year follow-up, 3 distinct groups emerged: (1) 4 children who responded well to CDD and maintained improvement with dietary management, (2) 4 children who had partially responded to the CDD but 3 of whom required medication at follow-up to maintain improvement, and (3) 2 children who did not respond well to the CDD (symptoms were still clinically significant) and whose symptoms returned to pretreatment level at follow-up, even with medication management. Thus, the CDD diet appeared to be at least somewhat beneficial for 80% of this small sample, and 63% of these children were able to be maintained using dietary management (without medication) following the CDD diet. The CDD appears to be somewhat useful as an indicator of the child's potential response to dietary management, although it is unclear whether it is necessary to use such a drastic procedure to determine potential food sensitivity.

Three studies investigated the "few foods" or "oligoantigenic" diet.[36-38] Initial sample sizes ranged from 45 to 78 unmedicated children with hyperactivity. All participants participated in an open trial of the oligoantigenic diet for 3 to 4 weeks. For example, 2 meats (lamb and chicken), 2 carbohydrate sources (potatoes and rice), 2 fruits (bananas and apples), vegetables, and water (with calcium and vitamin supplementation) were allowed in the Egger et al[36] study. Positive response rates to the diet were fairly consistent (71%-82%); however, only the Uhlig et al[38] study identified a specific criterion for treatment response. After the open diet trial, potentially offending foods were reintroduced into the children's diets; if the food was tolerated, it was integrated into the child's diet, and if the child reacted, the food was removed again. Artificial colors and preservatives were the most common culprits, causing reactions in 70% to 79% of the children, but no child reacted only to these. Common foods that triggered behavior reactions included milk, chocolate, soy, egg, wheat, corn, and legumes. A small proportion of the initial samples (24%-37%) completed a double-blind crossover challenge of offending foods or placebo. In all 3 studies, parents reported significantly higher levels of hyperactive behavior when their children had received an active challenge (offending food or AFC) than placebo. Carter et al[37] also reported that when children were challenged with provoking foods, they had worse latency and made more errors on a matching figures test ($P < .01$) and were rated more hyperactive by blinded psychologists ($P < .01$). In addition, Uhlig et al[38] reported that children's electroencephalographic β activity was significantly increased when challenged with provoking foods, relative to placebo. Clarke et al[39] found that approximately 15% of children with ADHD-combined type had significantly elevated β (2 standard deviations above the mean of comparison children) and that these children were significantly more likely to have mood/temper problems than children with ADHD without excess β (76.5% vs 23.5%, respectively).[39] Because irritability is one of the common symptoms associated with sensitivity to AFCs, future research studies of AFCs and hyperactivity should evaluate the co-occurrence of neurological and mood changes in response to AFC challenges.

Table 4. Studies Using Elimination Diets to Identify Hypersensitivities to Common Foods and Artificial Food Dyes in Children With ADHD or Other Behavior Problems

Studies	Number of Participants, Diagnosis	Age (years)	Foods Eliminated	Number Responding to Elimination Diet	Double-Blind Challenges	Number Reacting to Common Foods	Number Reacting to Artificial Food Dyes	Rating Scales and Other Tests	Challenge Effects
Hughes et al[35]	10, Severe ADHD	6-13	All foods except chemical defined diet (Vivonex)	3/10 partial improvement,[a] and 7/10 primary improvement[a]	—	—	—	PRS, neurological tests	
Egger et al[36]	76, Severe overactivity	2-15	Few foods diet[b]	62/76	Foods, artificial colors, preservatives	Milk, 35/55; soy, 27/34; chocolate, 20/34	27/34		
Carter et al[37]	78, ADHD	3-12	Few foods diet[c]	59/78	Foods, artificial colors, preservatives	Milk, 26/45; chocolate, 28/37; orange, 20/35	22/32	PRS, blinded psychologist	$P < .05$; $P < .01$
Schmidt et al,[49]	49, Hyperactivity and disruptive behavior	6-12	Few foods diet[d]	Learning test 22/49, play 21/49	—	—	—	Learning test, play classroom	$P = .0002$; $P = .0006$; $P = .31$
Kaplan et al[40]	24, Hyperactivity, sleep problems	Preschool	No artificial colors, flavors, preservatives, MSG, caffeine, chocolate[e]	10/42 improved by ≥25%	—	—	—	PRS	$P < .0001$
Boris and Mandel[41]	26, ADHD	Average age 7.5 years	No artificial colors, preservatives, dairy, wheat, corn, yeast, soy, citrus, egg, chocolate, peanuts	19/26	Foods, mix artificial colors (100 mg)	—	—	PRS	$P = .003$
Pelsser et al[50]	15 ADHD	Average age 6.2 years	Few foods diet[f]	11/15	—	—	—	PRS, TRS	$P < .001$; $P < .01$

[a]Based on 3 neurological tests and behavior rating scales.
[b]Allowed 2 meats (lamb, chicken), 2 carbohydrates (potato, rice), 2 fruits (banana, apple), vegetables.
[c]Allowed 2 meats (lamb, turkey), 2 carbohydrates (potato, rice), 2 fruits (banana, pear), root and green vegetables.
[d]Allowed 2 meats (lamb, turkey), 2 carbohydrates (potato, rice), 2 vegetables (cabbage, carrots), 2 fruits (apple, banana).
[e]In all, 15 children avoided dairy because their parents thought they were milk sensitive.
[f]Allowed rice, turkey, lamb, vegetables, fruits, margarine, vegetable oil, tea, and pear juice.

The oligoantigenic diet described above requires fairly significant restrictions in the child's food intake. Other less-restricted elimination diet studies have been reported to be effective in reducing hyperactivity. Kaplan et al[40] evaluated the effectiveness of a diet free of artificial colors and flavors, chocolate, monosodium glutamate (MSG), preservatives, caffeine, and any other food a particular family suspected (eg, milk) on the hyperactive behavior of 24 preschool children diagnosed with ADHD. Families participated in the study for 10 weeks, including a 1-week baseline period in which children ate their typical diet and parents recorded their child's food intake. During the remaining 7 weeks, investigators provided children and their families with either the experimental diet (4 weeks) or a control diet designed to mirror the child's baseline diet (3 weeks). Based on parents ratings of ADHD symptoms, 10 children were responders (more than 25% improvement), and 4 children were classified as mild responders (average 12% improvement); however, there was no treatment effect on ratings by daycare staff. Parents also reported less sleep latency and fewer night wakenings when children were on the elimination diet. This study was one of the few dietary investigations that evaluated the nutritional content of their diet treatment; the experimental diet contained significantly fewer calories, carbohydrates, simple sugars, and vitamin C and significantly more vitamins A, B6, B12, and D; thiamine; niacin; folate; and biotin.

Boris and Mandel[41] reported similar results using an elimination diet that excluded dairy products, wheat, corn, yeast, soy, citrus, egg, chocolate, peanuts, artificial colors, and preservatives. First, 26 children aged 3 to 11 years old who met the criteria for ADHD participated in a 2-week open trial of the elimination diet. In all, 73% of the children improved ($P < .001$) on the elimination diet based on a Parent Rating Scale of ADHD symptoms relative to pretreatment scores. Participants then completed a period of open challenge, in which parents introduced a potentially offending food every 2 days and noted the child's reaction. A total of 16 of the original 26 participants completed a 1-week, double-blind, placebo-controlled challenge; suspected foods (ie, 5 g of powdered food or 100 mg of AFCs) were disguised in other foods, and parents monitored their child's behavior. Parents' ratings of hyperactivity were significantly higher on days on which the child ingested the active challenge relative to placebo. Notably, parents' ratings of hyperactivity during challenge days were still significantly lower ($P < .001$) than their ratings of their children's behavior at baseline, when presumably the child was eating a diet containing provoking foods and AFCs. In addition, authors reported that a higher percentage of diet responders (79%) were atopic than were nonresponders (28%). This finding is in contrast to the findings by Bateman et al[27] who found that AFC affected child behavior independent of atopic status. Perhaps atopic children are more sensitive to provoking natural foods, which was not evaluated in the Bateman et al study. Evaluation of the effect of atopic status on response to dietary interview and challenge with AFCs and natural foods in a larger sample is recommended before firm conclusions are drawn.

All these studies reported high response rates to the various elimination diets (>70%); however, it is again unclear whether diets without offending foods can be maintained to support long-term improvement. All studies containing a double-blind challenge phase found that parents reported more hyperactivity when children were challenged with offending foods and/or AFCs than placebo. Children's performance on learning tasks and blinded psychologists' ratings of children's hyperactivity were consistent with parent ratings, although daycare staff did not report a difference in children's behavior between active and placebo challenges. Artificial colors and preservatives were the most likely challenges to cause reactions; however, no child responded only to AFCs. Most provoking foods did not contain salicylates and would not have been removed following the K-P diet guidelines. Thus, removing all AFCs from the diet may not be a complete treatment protocol for some children. It is recommended that future investigations continue to evaluate the nutritional composition of elimination and comparison diets to determine whether the improved nutrition that can occur with an elimination diet (documented by Kaplan et al[40]) contributes to the child's improvement.

Summary of Research Results

In the 1970s, Benjamin Feingold published his controversial hypothesis that artificial colors, artificial flavors, and natural foods containing salicylates adversely affected the behavior of 30% to 50% of the children he had studied. Parts of his hypothesis have been validated by careful scientific studies. The research reviewed in this article suggests some points that are described below. (1) There is a subpopulation of children with ADHD who improve significantly on an AFC-free diet and react with ADHD-type symptoms on challenge with AFCs. (2) The size of this subpopulation is not known. In the cited studies it has varied from 65% to 89% of the children tested when at least 100 mg of dye was used for the challenge, so the proportion of the whole ADHD population is undoubtedly smaller.

However, the children in these studies were often selected because they were suspected of sensitivities to AFCs, so the proportion of the whole ADHD population is undoubtedly smaller. (3) A search of the literature did not find any challenge studies of the specific effects of artificial flavors or natural salicylates alone. (4) Instead, oligoantigenic studies have indicated that some children with ADHD, in addition to being sensitive to artificial food dyes, are also sensitive to common, nonsalicylate containing foods (milk, chocolate, soy, eggs, wheat, corn, legumes) and to grapes, tomatoes, and orange, which do contain salicylates. This may explain why some studies that used challenge cookies made of chocolate and wheat with and without AFCs did not show more of an effect. (5) According to the Egger and Carter studies, no child reacted to just the dyes alone; all with sensitivity were sensitive to at least 2 foods. The Bateman et al[27] and McCann et al[28] studies suggest that sensitivity to AFCs and benzoate is not confined to the ADHD population but is instead a general public health problem and probably accounts for a small proportion of ADHD symptoms.

Clinical Suggestions

Diagnosing hypersensitivities to AFCs and common foods is not an easy task for physicians and families. Parents should be informed by their doctors that research shows that some children react adversely with ADHD-type symptoms to common foods and food additives but that these have not been established as the main cause of ADHD. Furthermore, delay of conventional treatment to try alternatives carries the risk of leaving the problem untreated for a while if the alternative does not work. The studies reported here suggest that the following groups of children may be more likely to respond to dietary changes than other children: (1) younger children, (2) children with IgE-mediated allergies, and (3) children with irritability and sleep problems. Parents who are interested in nonpharmacological interventions for ADHD or whose children do not respond to standard treatment should be encouraged to examine their children's diets. When there is an interest, there is no reason that children on medications cannot also be tested for food and additive hypersensitivities. Families who wish to try an elimination diet will require appropriate information and support from their doctors. They may also need the services of a dietician to help them choose alternative foods and to determine if the final diet meets the child's nutrient requirements.

A proper search for food and AFC hypersensitivities may take several weeks. Parents could follow the procedures used by Boris and Mandel[41] in their study of foods and additives in children with ADHD.[26] For 2 weeks, the child should follow a careful elimination that excludes dairy, wheat, corn, yeast, soy, citrus, egg, chocolate, and peanuts (Table 6) or perhaps use the few-foods diet described earlier. They should avoid all AFCs, artificial flavors, and preservatives. Avoiding AFCs is not easy and requires careful label reading at home and at the grocery. In foods and beverages, AFCs are listed as "US certified dyes," and dyes are indicated by a number, such as yellow dye #5, or by a name such as tartrazine (see Table 5). Artificial flavors including vanillin (an artificial form of vanilla) or preservatives such as BHA, BHT, TBHQ, and sodium benzoate should also be avoided. Parents will find that many common foods are artificially colored and/or flavored, including most bakery items, cookies, cakes, icings (even white frosting), most candy, most soft drinks, fruit punches, sports drinks, gelatin, pudding, barbecue sauce, pickles, snack foods, soup, salad dressings, and so on. Alternative brands may be available that are made without AFC dyes and artificial flavors. Medications (both prescription and over-the-counter drugs) and personal care products are often dyed with AFCs. If the child is to remain on medication for ADHD during the elimination diet, there are white tablets available at certain dosages for these drugs: Ritalin SR (20 mg), methylphenidate (10 and 20 mg), Concerta (36 mg), Adderall (5 mg), and Strattera (10 mg).

Using the SNAP, Conner's Hyperactivity Index, or some other simple appropriate assessment measure before and after the elimination diet may help quantify any improvement. To test the artificial colors, parents should purchase little bottles of food dyes at the grocery store. On a weekend, when the parent is home, he/she should ask the child to print/or write his name, read aloud from an age-appropriate book, and solve some math problems. Then, the parent should put a few drops of each color into water or pure fruit juice and ask the child to drink it. At 30 minutes, the parent should repeat the baseline tests of handwriting, reading, and math and again at 90 minutes and 3 hours. They should also look for changes in irritability and sleep problems that night. If no reaction occurs, they should repeat these steps after doubling the amount of food dyes. In the same way, 1 restricted food should be reintroduced into the diet every 2 days. Those that cause a problem should be put on the elimination list; those that are well tolerated can be resumed. For example, corn can be tested by giving the child salted plain air-popped or microwave-popped corn. If dairy

Table 5. Artificial Food Colors Allowed in the US and Canadian Diets by the Food and Drug Administration and Health Canada[a]

FD & C Number	Common Name	Type of Chemical	Shade	Foods Containing Colors
Blue #1[b]	Brilliant blue	Triphenylmethane	Blue	Beverages, candy, baked goods, ice cream, cereals
Blue #2	Indigotine	Sulfonated indigo	Dark blue	Beverages, candy
Green #3	Fast green	Triphenylmethane	Blue-green	Beverages, candy, gelatin, jellies
Yellow #5[b]	Tartrazine	Azo dye	Yellow	Gelatin, candy, chips, ice cream, cereals, baked goods, pickles
Yellow #6[b]	Sunset yellow	Azo	Orange	Beverages, jam, sausages, baked goods, candy, gelatin
Citrus Red #2	Citrus red	Azo	Orange	May only be used on skins of some Florida oranges
Red #3	Erythrosine	Xanthene dye	Pink	Candy, baked goods, popsicles, cereals
Red #40[b]	Allura red	Azo	Red	Candy, beverages, gelatin, pastries, sausages, cereals
Orange B[c]		Azo		Hot dog and sausage casings only

[a]Other dyes are allowed in drugs and cosmetics.
[b]Voluntary phase-out by 2009 in the United Kingdom.
[c]Not allowed in Canada.

Table 6. Foods Child Should Avoid and Foods Child May Eat on Elimination Diet[a]

	Avoid	Serve
Additives	All artificial colors, flavors, all preservatives	
Milk	Dairy: cows' milk, cheese, yogurt, ice cream	Rice milk[b]
Chocolate	Chocolate	
Grains	Wheat, rye, barley	Oats, rice, rice cakes, rice crackers, rice noodles
Meats, poultry, fish, eggs	Eggs, processed meats	Unprocessed meats, poultry, fish
Fruits	Citrus	All others[c]
Vegetables	Legumes (peanuts, beans, peas, etc), soy, peanut oils, corn, corn oil, or corn syrup	All others
Nuts	Peanuts	Walnuts, pecans, almonds, and so on[d]

[a]Do not extend elimination diet past 2 weeks.
[b]Child may need an age-appropriate calcium supplement.
[c]To get enough vitamin C, include these vitamin C–rich fruits: strawberries, blueberries, raspberries, cantaloupe, watermelon, papaya, mango, and kiwi. Other sources include broccoli, tomatoes, and peppers.
[d]Do not buy nuts that are processed with peanut or soy oil.

products are a problem, the child will need calcium supplements appropriate for his/her age. The elimination diet should not be continued permanently: if there is no benefit within 2 weeks, the elimination diet should be stopped, and if there is benefit, the parent should start adding foods back to test for sensitivity. A careful search for offending foods and food additives may be time-consuming and frustrating, but what is not looked for will probably not be found.

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