Evaluation of Studies on Artificial Food Colors and Behavior Disorders in Children

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ADHD: Inattention, Hyperactivity, Impulsiveness

- Types of behaviors observed occasionally in most children, at some age, and under some situations

- Diagnosis of ADHD (aka hyperkinetic syndrome, hyperactivity syndrome): Spectrum of behaviors -
  - occur in developmentally and situationally inappropriate manner
  - persist over a prolonged period of time and at a high level of severity
  - may possibly be associated with learning disabilities
  - occur in multiple settings (home, school, clinic)

- Proposed factors/etiology
  - Environmental, genetic, allergic/immunologic, psychosocial, dietary, combination

Dietary

Feingold: food additives such as artificial food colors (AFC) and flavors and natural salicylates can trigger or exaggerate behavior disorders and learning disabilities (Feingold 1973,1975)

- Feingold diet: defined elimination diet
- Stimulated the field of research examining possible dietary triggers of problem behaviors in susceptible children

Review/Evaluation

Goal - Evaluation of possible role of AFC in triggering or exacerbating problem behaviors related to ADHD in susceptible children

Methods - Identified/reviewed 33 clinical trials relevant to the association between AFC and ADHD and related problem behaviors in children

- most trials focused on AFC in terms of specific elimination diets and/or color challenges
- many trials included consideration of natural salicylates, preservatives and other additives
- several trials focused on general food items which included consideration of AFC
- consideration of all data (pos., neg., and equivocal) in evaluation

Consideration of 1982 NIH Consensus statement, available meta-analyses, and animal data

Review criteria to assess reliability, relevance, and interpretability of findings

- homogeneity of sample
- randomization to treatment
- crossover designs with subjects serving as own control
- counterbalanced treatment/challenge order
- double-blind/placebo-controlled challenges
- placebo and challenge indistinguishable
- verification of effectiveness of blinding particularly for behavioral raters
- appropriate control outcome measurements
- age-appropriate outcome measures
- use validated measures (i.e. detect behavior differences/sensitive to treatment)
- confirmatory sources of outcome data (parents, teachers, testing, etc.)

Criteria compiled with consideration of Krummel et al, 1996; NIH, 1982; Schab and Trinh, 2004; Wender, 1986

Clinical Trials

Group 1: Specific focus on artificial colors and adverse behavioral effects in children to assess validity of Feingold's hypothesis (26 trials)

- *Diet crossover trials* (2)
  Random assignment to FG diet (eliminating foods with AFC, flavors and natural salicylates) or matched placebo diet for defined period, then cross over to other diet
- *Challenge trials* (24)
  Placebo controlled challenges with select AFC
- 2 diet trials / 14 challenge trials prior to 1982 NIH Consensus. 10 trials post-NIH Consensus

Group 2: Focus on assessing adverse effects of food itself in hyperactive and problem behavior children (7 trials)

- Maintain on 'oligoantigenic' or 'few foods' diet that excludes all foods, additives (including colors), and food components assumed to provoke adverse reactions in certain children, and then conduct controlled challenges with various suspected provoking food items

Group 1 Trials: Study Design

Double-blind, placebo-controlled conditions using either diet crossover or specific challenges

Diet crossover trials

- Random assignment to FG diet or matched placebo diet for defined period, then crossing over to other diet. Comparison of behavioral responses

Group 1 Trials: Study Design

Specific challenge (24 trials)

- AFC (mixtures or single colors), occasionally with food preservative, in children diagnosed ADHD, with problem behaviors, or from general population
- Maintained on a defined elimination diet (e.g., FG diet or a comparable elimination diet). Color or placebo challenge in masked delivery system
- 18 studies test populations reportedly sensitive to FG diet under non-blind conditions, i.e., marked behavioral improvements on FG diet with immediate deterioration after ingestion of prohibited food(s)
  - maximize detection of behavioral effects in challenge study

Group 1 Trials: Study Design

General Types of Outcome Measures Used Across Trials

Subjective Assessments – Various, typically standardized, behavior rating scales conducted by one or more of the following assessment sources: parents, teachers, clinicians, psychologists, trained observers, and/or other study personnel

Objective Assessments – Various neuropsychological, psychometric, clinical or laboratory behavioral tests conducted by trained study personnel

Aggregate Behavior Scores – Combined subjective and objective assessments

Of the 33 clinical trials, 22 used multiple outcome measures/sources for the behavioral assessments, while 11 used only a single outcome measure/source.

Group 1: Results

Pre-NIH Statement (1981 and earlier)

- Equivocal findings of improved behavior on Feingold's diet or adverse reaction to color challenge in only small subsets of children with problem behaviors and presumed sensitivity to AFC

	Group 1 Pre-NIH	Group 1 Post-NIH	Group 2
Positive	**2**	**3**	4
Negative	**6**	**4**	0
Equivocal	**8**	**3**	3

Post-NIH Statement (1982 to present)

- Some responses to color additive challenge typically in subsets of children
- Reponses (irritability, fidgetiness, and sleep problems) in hyperactive and non-hyperactive children not typically representative of a hyperactivity syndrome
  - Similar reported behavioral responses assessed only in problem behavior children (Mattes and Gittelman, 1978) and children with ADHD (Carter *et al.*, 1993)

Group 1: Collection of Caveats and Limitations Occurring Across Trials

Pre-NIH Statement (1981 and earlier)

- Equivocal findings
- Small percentage of responders under controlled conditions
- Inconsistent reports of treatment effects between different sources of behavior assessment
- Inexplicable treatment order effect
- Questionable effectiveness of blinding conditions

Post-NIH Statement (1982 to present)

- Use of unstructured non-validated rating systems
- Non-blinded study personnel responsible for behavior ratings or effectiveness of blinding not verified or questionable
- Use of single source for behavioral outcome measures not confirmed by other sources of measurement
- No randomized assignment to treatment
- No statistical analysis or incomplete presentation of data

Group 1: Conclusions

1982 NIH Consensus:

- Limited positive association between 'the defined diets' and a decrease in hyperactivity
- Involved only a small proportion of patients
- Decreases in hyperactivity not observed consistently
- Small group of hyperactive children on defined diet experienced an increase in hyperactivity when given moderate doses of AFC
- Increase was not consistently reported by teachers, parents, and other observers

Meta-analysis (Kavale and Forness, 1983)

- Meta-analysis provided no support for the FG hypothesis
- Treatment was of questionable effectiveness
- Produced only slight improvements in behavior of hyperactive children

FDA Findings

- Suggestive of limited beneficial effects of FG diet in hyperactive children
- Limited association between AFC and behavioral changes in a small subgroup of children with hyperactivity or other problem behaviors

Group 1: Conclusions (post-1982 NIH Consensus)

Meta-analysis (Schab and Trinh, 2004)

- Primary analysis: Suggestive of a limited association between AFC and hyperactivity behaviors
- Secondary analysis: suggestive of provoking general behavioral disturbances rather than hyperactive symptomatology
- Sensitivity to AFC may not be limited to only hyperactive children

FDA Findings

- Suggestive of possible intolerance to AFC in certain susceptible subgroups of problem behavior children with and without ADHD and, possibly, certain susceptible children from the general population without particular behavioral problems
- Typically small to moderate behavioral changes which may not necessarily be characteristic of the ADHD syndrome

Group 1: Overall Conclusion

Certain subgroups of children with problem behaviors that may or may not be related to ADHD and, possibly, certain children from the general population without particular behavioral problems, may exhibit a unique intolerance to AFC resulting in typically small to moderate behavioral changes which may not necessarily be characteristic of an ADHD syndrome.

Group 2 Trials: Study Design

Focus

- Assessing the effects of food itself in hyperactive and problem behavior children. Use of ‘oligoantigenic’ or ‘few foods’ diet.

Double-blind, placebo-controlled conditions

Diet crossover trials (2 trials)

- Random assignment to elimination diet (all foods, additives, including AFC, and food components assumed to provoke adverse behavioral reactions in hyperactive and problem behavior children) or matched placebo diet for defined period, then crossing over to other diet. Comparison of behavioral responses.

Group 2 Trials: Study Design

Specific challenge (5 trials)

- Suspected provoking food items, including AFC, in children diagnosed with ADHD or problem behaviors
  - Phase I – Identify children who reportedly show improved behavior on open (non-blind) food elimination diet
  - Phase II – Re-introduce foods/components (non-blinded) to tentatively identify specific provoking food items for individual subjects
  - Phase III – Double blind, placebo controlled challenge testing with one or more suspect provoking food items to verify and assess behavioral effects

Group 2 Trials: Study Design

General Types of Outcome Measures Used Across Trials

Subjective Assessments - Various, typically standardized, behavior rating scales conducted by one or more of the following assessment sources: parents, teachers, clinicians, psychologists, trained observers, and/or other study personnel

Objective Assessments - Various neuropsychological, psychometric, clinical, or laboratory behavioral tests conducted by trained study personnel. Skin prick test for allergy and serum IgE levels.

Group 2: Results

- Some responses of intolerance to suspected provoking foods in ADHD or problem behavior children

	Group 1 Pre-NIH	Group 1 Post-NIH	**Group 2**
Positive	2	3	**4**
Negative	6	4	**0**
Equivocal	8	3	**3**

- Some evidence of small increase in hyperactive behaviors and other behaviors (irritability, fidgetiness, and sleep problems)
- Equivocal findings regarding atopy, although desensitization results suggest non-IgE response

Group 2: Collection of Caveats and Limitations Occurring Across Trials

- Use of unstructured non-validated rating systems
- Non-blinded study personnel responsible for behavior ratings or effectiveness of blinding not verified or questionable
- Use of single source for behavioral outcome measures not confirmed by other sources of measurement
- All/part of data not statistically analyzed or incomplete presentation of data

Group 2: Conclusions

- Children with ADHD or other problem behaviors may exhibit a unique intolerance to a variety of foods and food components, including but not limited to AFC.
- Exposure of this group to various individual provoking food items may result in behavioral changes associated more with irritability, fidgetiness, and sleep problems, rather than attention deficit and learning deficiency or a hyperactivity syndrome.
- This food intolerance may involve some type of immunologic process possibly involving a non-IgE cellular response to antigen rather than an antibody mediated immunization.

Conclusions

Group I trials (color): Certain subgroups of children with problem behaviors that may or may not be related to ADHD and, possibly, certain children from the general population without particular behavioral problems may exhibit a unique intolerance to AFC resulting in typically small to moderate behavioral changes which may not necessarily be characteristic of the ADHD syndrome.

Group II trials (foods): Certain children with ADHD and/or other behavior problems when exposed to various provoking food items, including AFC, may result in behavioral changes associated more with irritability, fidgetiness, and sleep problems rather than attention deficit and learning deficiency or a hyperactivity syndrome.

Possible biological mechanisms

- Are these effects possibly due to some (neuro)toxic, physiologic, allergic, or other immunologic process?

- Are the potential behavioral effects caused by one particular color or food item, by the combined action of multiple food items, or by some interaction, perhaps synergistic, with other component(s) in the food?

- Are these potential effects associated with some factor(s) that predispose children to ADHD or other types of behavioral pathology, or could the effects be associated with some predisposing factor(s) not necessarily related to behavioral disorders?

Neurotoxicity/Animal Studies

- *In vitro* erythrosine (Red No. 3) inhibited uptake of neurotransmitters, specifically dopamine (Lafferman and Silbergeld, 1979; Logan and Swanson, 1979). Due to nonspecific interactions with biological membranes rather than specific neuronal effect (Mailman and Lewis, 1983).
- Variable results in early behavioral experiments with erythrosine: no effects (Goldenring *et al.*, 1981; Mailman *et al.*, 1980), positive effects with no clear dose response or at high dose levels (see review by Silbergeld and Anderson, 1982)
- Erythrosine does not appreciably penetrate the blood brain barrier (Levitan *et al.*, 1985); activity unaffected in adult mice (Galloway *et al.*, 1986); no neurobehavioral toxicity in developing rats with dietary exposure (Vorhees *et al.*, 1983); few minor behavioral milestone changes in male mice at the highest dietary level of 0.045% erythrosine (Tanaka, 2001).
- Similar results of no effects to minimal and variable behavioral or developmental effects at high doses with other tested color additives (artificial and natural): Red 40 (allura red AC), amaranth (Red No. 2), carmoisine, tartrazine (Yellow 5), sulfanilic acid (metabolite of azo dyes such as Yellow 5 and 6), *lac* dye.

Currently, available information does not establish a link specifically between color additives and hyperactivity.

Neurochemical

Dopamine

- Altered dopaminergic neurotransmission may be involved in the pathophysiology of ADHD (Brookes *et al*., 2006; Sonuga-Barke, 2003)
- Therapeutic dopaminergic treatments for ADHD (Banerjee *et al*., 2007) suggest potential target of other treatments (e.g., colors).
- Gene variants associated with susceptibility to ADHD including dopamine receptor and dopamine transporter genes (Banerjee *et al*., 2007; Farone *et al*., 2001; Farone *et al*., 2005).

Neurochemical

Histamine

- Release increased by environmental factors, e.g., infections, food items, certain AFC
- Possible mechanistic basis for gene-food interactions: histamine (H3) receptors present in the brain and genetic polymorphisms involving histamine genes can impair histamine clearance
- Genetic variants related to histamine and possible modulation of behavioral responses to AFC in some children suggested by Stevenson *et al.* (2007, 2011)

Genetic

- Genetic component for ADHD (Banerjee *et al.*, 2007; Goodman and Stevenson, 1989; Stevenson, 2006)
- Food may be a risk factor to elicit or exaggerate, but not cause, hyperactive behaviors in some children (Cruz and Bahna, 2006; Mattes, 1983; NIH, 1982; Schab and Trinh, 2004; Wender, 1986)
- More hyperactive children reacted to color challenge than normal children (Rowe and Rowe, 1994): possible genetic predisposition for hyperactivity and sensitivity to food colors
  - Behaviors reported by Rowe and Rowe (1994) differ from the behaviors associated with ADHD
  - Similar incongruity for food intolerance; reported to elicit behaviors not characteristic of ADHD (Carter *et al.*, 1993)

Food Intolerance/Allergy/Immunologic

- Color additive reaction likely not an atopic (IgE mediated) response (Bateman *et al.*, 2004; MacGibbon, 1983; Pollock and Warner, 1990). Possibly non-IgE dependent histamine release (Bateman *et al.*, 2004).
- Children with reported improvement on the FG diet did not respond to color additives (Bishop, 1983; Stare *et al.*, 1980). Other factors in the diet may be responsible.
- Studies expanded into any food items suspected of causing an adverse reaction. Multiple food items may provoke adverse behavioral reactions (Kaplan *et al.*, 1989; Schmidt *et al.*, 1997).
- Some children with ADHD may have intolerance to a variety of food items. Children with ADHD were desensitized to food items that previously provoked adverse behavioral reactions (Eggers *et al.*, 1992).
- Suggestive of certain children having a predisposition leading to a food or color sensitivity rather than direct neurotoxicity.

Overall Conclusions

Exposure to food and food components, including AFC and preservatives, may be associated with behavioral changes, not necessarily related to hyperactivity, in certain susceptible children with ADHD and other problem behaviors, and possibly in susceptible children from the general population.

Findings suggest that this food related triggering of behavioral changes is not due to an inherent neurotoxic property of the food or food components, including AFC and preservatives, but appears to result from a unique intolerance exhibited by certain predisposed children to a variety of food items and color additives. The etiology of this type of unique intolerance is unclear but may involve genetic, endocrine, or immunologic pathways.

Summary

- Data suggestive of predisposition for food intolerance or hypersensitivity in certain children.
- Triggering food or food component different for each child.
- Behavioral responses to a food, food component, additive, flavor, or AFC appear to depend upon the individual and not on the class of provoking item.
- Suggests that these food components in the diet are not inherently neurotoxic, but that the response to the provoking item will depend upon the individual person.
- Current FDA regulatory labeling requirements mandate listing certified color additives by name on food label, thus providing information to identify ingredients and enable personal avoidance.