*Special Article*

# Artificial food dyes and attention deficit hyperactivity disorder

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*Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children. Symptoms of ADHD include hyperactivity, low frustration tolerance, impulsivity, and inattention. While the biological pathways leading to ADHD are not clearly delineated, a number of genetic and environmental risk factors for the disorder are recognized. In the early 1970s, research conducted by Dr. Benjamin Feingold found that when hyperactive children were given a diet free of artificial food additives and dyes, symptoms of hyperactivity were reduced. While some clinical studies supported these findings, more rigorous empirical studies conducted over the next 20 years were less positive. As a result, research on the role of food additives in contributing to ADHD waned. In recent years, however, interest in this area has revived. In response to more recent research and public petitions, in December 2009 the British government requested that food manufacturers remove most artificial food dyes from their products. While these strictures could have positive effects on behavior, the removal of food dyes is not a panacea for ADHD, which is a multifaceted disorder with both biological and environmental underpinnings.*





## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children, affecting 3–7% of school-aged children.[1] As defined by the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, the essential features of ADHD include a pervasive pattern of hyperactivity-impulsivity and/or inattention, which is observed before the age of 7 years and occurs for a minimum of 6 months.[2] Hyperactivity and/or inattention must occur in two or more settings (e.g., school and home), and there must be evidence of developmentally inappropriate social, academic, or occupational functioning. In day-to-day life, these features translate into children who have difficulties focusing on a task, sitting still, listening to and following instructions, organizing tasks, and processing information as quickly and accurately as others. Children with ADHD may also be impatient, often interrupting others' conversations, blurting out inappropriate comments, and displaying their emotions without restraint.[1–6]

Although most commonly observed in children, symptoms of ADHD can extend into adolescence and adulthood. Adolescents with ADHD suffer from poor peer relationships; academic problems; conflicts with parents, teachers and other authority figures; a heightened risk of drug abuse and delinquency; and low-self esteem. Symptoms of hyperactivity and impulsivity tend to decrease with age but in adults with ADHD, an inability to pay attention can lead to problems in the workplace and in social environments.[3,7,8]

## ETIOLOGICAL FACTORS IN ADHD

ADHD is a multifactorial disorder resulting from the confluence of a number of risk factors including genetics,

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brain injuries, environmental variables, and nutrition.[1,3,5,9] Adoption studies, demonstrating that the biological relatives of children with ADHD are more likely than adoptive relatives to be diagnosed with the disorder, and twin studies showing that the concordance rate for ADHD is substantially greater in identical twins than in fraternal twins indicate that ADHD is highly heritable.[10–13] Moreover, recent work has identified "candidate" genes that could affect susceptibility to the disorder. In particular, associations have been found between ADHD and genes that are involved in neurotransmission in the dopaminergic, noradrenergic, and serotoninergic systems.[3,10–13] It is hypothesized that these genes moderate activity in catecholaminergic systems in areas of the brain that are important for executive functioning, attention, and motor behavior, including the prefrontal cortex, cerebellum, and subcortical structures.[3,14–16]

Environmental factors also contribute to the development of ADHD.[17] Of particular importance are complications associated with pregnancy and delivery. Children who are born prematurely, who suffer from hypoxia at birth, or who experience fetal distress, as well as children whose mothers smoke or abuse alcohol during pregnancy have an increased risk of developing ADHD.[1,3,18] Exposure to environmental toxins, including lead, mercury, organophosphates, and polychlorinated biphenyls during development may also lead to hyperactivity and inattention in children.[17,19]

A negative family environment can also predispose a child to ADHD. Chronic family conflict, parental psychopathology, and poor family cohesion are observed more frequently in the families of children with ADHD than in the families of children without the disorder. Additionally, low maternal education, having a single parent, and low socioeconomic status increase a child's susceptibility for developing ADHD.[20]

## TREATMENT OF ADHD

Stimulant drugs, such as methylphenidate and dextroamphetamine, comprise the most common treatment for ADHD.[4,6,21] These drugs enhance the activity of the neurotransmitters dopamine and norepinephrine. Approximately 70–90% of children with ADHD respond positively to these drugs with reduced impulsivity and hyperactivity, and improved ability to pay attention. Although these drugs have a high degree of efficacy, they often are accompanied by undesirable side effects including appetite suppression, weight loss, decreased growth rates, stomachaches, headaches, sleep problems, and mild increases in blood pressure.[4,6,21,22] Additionally, most commonly used stimulant medications have the potential for abuse. Other drugs have been used in the treatment of ADHD. However, like stimulant drugs, these drugs have side effects that make both children and parents sometimes unwilling to use them.[21,22]

Behavioral treatments can reduce symptoms of ADHD. These treatments typically employ contingency management techniques in which positive behaviors are rewarded. Behavioral strategies have been successfully used in home, school, and recreational settings, and can provide an important adjunct to pharmacological treatment.[23]

## NUTRITION AND ADHD

The currently incomplete understanding of the etiology of ADHD, coupled with the problems associated with drug treatments, has led researchers and parents to search for definitive causes and alternative treatments of the disorder. Results of these searches indicate that dietary variables may contribute to the development of ADHD.[24–26] For example, hyperactivity and inattention are common symptoms associated with marginal zinc, iron, and magnesium deficiencies,[27–30] and significant negative correlations have been observed between both serum ferritin and zinc levels and parental reports of hyperactive behaviors.[31] Moreover, in some children, intake of supplements containing these micronutrients can reduce hyperactive behavior.[27–31] Additionally, recent work suggests that diets containing low levels of omega-3 polyunsaturated fatty acids can predispose children to ADHD, and that the use of supplements containing omega-3-polyunsaturated acids can ameliorate symptoms of hyperactivity in some children.[32–35]

For the past 40 years, however, the most enduring and controversial issue with respect to diet and ADHD is the possible role of food additives/dyes in the development of the disorder.

### Early work on food additives/dyes and ADHD

For thousands of years, people have used herbs and spices to enhance the flavor of foods, salt to preserve meats, sugar to preserve fruits and vegetables, and natural pigments to provide attractive coloring to foods. However, as humans have transitioned from a primarily locally grown food supply to the easy availability of foods from around the world, the use of food additives has increased dramatically. It is estimated that between 2,500 and 3,000 different agents are presently used as food additives.[36]

Many additives serve important roles in the food supply, such as maintaining consistency, freshness, and safety; improving nutritional value; and enhancing taste.[36,37] However, some types of additives are used for cosmetic purposes rather than maintenance of a healthy food supply.

Coloring agents are added to foods for a variety of reasons including the following: enhance natural colors; decrease color loss due to exposure to air, light, moisture, and extreme temperatures; correct natural variations in color; make food more attractive to the consumer; and provide color to colorless and "fun" foods.[36] Both natural and synthetic products are used as food colors. Natural colors are derived from grapes, saffron, paprika, grapes, carrots, beets, and algae, and are used to color a variety of foods.[36] However, synthetic dyes are largely preferred by the food industry because they provide superior intensity and uniformity of color, are less expensive, more stable, and blend more easily with foods to produce an array of colors.[38] At present, nine synthetic food dyes are approved by the U.S. Food and Drug Administration. Over the past 50 years, daily per capita intake of these dyes has increased fivefold[38,39] in parallel with the rise in intake of processed foods including baked goods, breakfast cereals, snack foods, and soft drinks,

Concerns about the negative behavioral effects of artificial food additives and dyes were first expressed in the early 1970s by Dr Benjamin Feingold, a pediatric allergist. He hypothesized that the reported increase in prevalence of ADHD was related to the increased use of artificial flavors and colors in the American diet.[40,41] To test his hypothesis, Feingold treated hyperactive children with a diet that eliminated artificial food additives and dyes. Also, as some children who had an allergic reaction to yellow food dye reacted negatively to acetylsalicylic acid (aspirin), fruits and vegetables containing natural salicylates (e.g., apples, apricots, raisin, cucumbers, green peppers, and tomatoes) were also removed from the diet. Feingold reported that over 50% of children responded positively to his elimination diet. Feingold stressed the importance of the following for ensuring the best results: 1) adherence to the diet is obligatory, 2) successful treatment requires that the subject's entire family participate in the diet, and 3) an individual sensitive to food additives must avoid them for life.[40,41]

The results of Feingold's work were broadly publicized and rapidly gained popularity among the lay public. Families of children with ADHD joined together to form Feingold Associations, which advocated the Feingold diet as a primary treatment for the disorder. During the subsequent 40 years, the original Feingold diet has been modified in recognition of the fact that the majority of the fruits and vegetables excluded on the original diet contained only minimal amounts of salicylates. More recent versions of the diet eliminate only artificial food additives and/or dyes.

The potential importance of Feingold's claims was not lost on the scientific community. During the 1970s and 1980s, a number of studies were conducted to test his hypothesis. Initial clinical trials, in which children simply consumed the Feingold diet, supported Feingold's original findings. However, in these clinical trials, parents, teachers, and researchers were aware of the change in the children's diet. Thus, expectations could have contributed to positive outcomes.[42–44]

To eliminate the influence of expectations in studies of the Feingold diet, and to examine the effects of the diet on ADHD in a more controlled manner, dietary replacement studies in which the behavioral effects of two diets, one containing and the other not containing food additives and/or dyes, were undertaken. The two diets were constructed to be as similar as possible. Results of dietary-replacement studies were mixed.[42–52] Early studies did report that some children with ADHD displayed less hyperactive behavior when consuming a diet free of food additives and dyes than when consuming a diet containing these ingredients.[42,51] However, in subsequent studies, the findings were less dramatic. Children only responded positively when the additive-free diet was given after the control diet. Additionally, improvements in behavior were noted by parents but not by teachers or objective observers.[47]

One problem with dietary replacement studies is that although the two diets tested are constructed to be as similar as possible, they often differ, not only with respect to the presence of artificial food additives, but also with respect to nutritional content (e.g., vitamin and mineral levels). Thus, it is difficult to determine from dietary replacement studies if the behavioral differences observed in children consuming the two diets are due to food additives or other dietary variables.

Other studies examining the effects of food additives on behavior have used a dietary challenge paradigm in which children were fed their standard diet or a diet that eliminated food additives. The children's behavior was evaluated 1–3 hours after they had been challenged with either food additives or a placebo.[37] One advantage of dietary challenge studies is that double-blind procedures can be implemented. The food additives and placebo can be packaged (e.g., in a cookie or pill) in such a way that none of the food-challenge administrators, children, parents, and teachers can detect what is being consumed. Additionally, to control for possible order effects, a cross-over design can be used such that half of the children receive the artificial food additives on the first day of testing and placebo on the next day, while the remaining children receive the placebo first and the food additives second. Although they are performed infrequently, dietary challenge studies also allow for testing of more than a single dose of food additives.

As with the dietary replacement studies, results of dietary challenge studies were not consistent. In some studies, food additives and/or dyes did lead to increased hyperactivity in a small portion of children,[42,45,48,49] but in other studies these ingredients had no such detrimental effects.[42,46,50,53]

The disparate findings on the effects of artificial food additives on behavior can be explained, at least in part, by inconsistencies in research protocols. For example, some studies used preschoolers while others used young adolescents. Comparison of these studies suggests that younger children are more sensitive to the deleterious effects of food additives than older children. Also, some studies tested children with confirmed diagnoses of ADHD, while others looked at children who were free of the disorder. With respect to behavioral measures, studies in which subjective ratings of parents and/or teachers were used as the dependent variable more often reported negative effects of food additives than studies using objective behavioral rating scales completed by individuals blind to the nutritional conditions. Another serious difficulty in determining the possible effects of food additives on hyperactive behavior is that there is little consistency among studies with respect to the nature and/or doses of the food additives tested. In some studies, the effects of only artificial food additives on behavior were tested, while in others, foods containing natural salicylates were also removed from the diet.

With the caveat that comparisons among studies are difficult, what can be gleaned from this initial research? 1) While Feingold's original claims were overstated, a small proportion of children with ADHD may be adversely affected by artificial food flavorings and dyes. 2) Preschool aged children may be more sensitive to food additives than older children. 3) There may be a dose-response curve for artificial food additives, such as there is for any toxic substance, but the exact nature of this response remains to be determined.

## Recent research on synthetic food dyes and ADHD

During the 1990s, parents continued to be concerned about the relationship between food additives/colors and ADHD. Scientific investigations in the area, however, waned as a result of the difficulties in conducting well-controlled empirical research and the failure of some studies to find effects of food additives on behavior. During the past several years, scientific interest in the role of synthetic food dyes in ADHD has been revived by a meta-analysis of previous studies[54] and the results of three new studies on the effects of food dyes, specifically, on behavior.[55–57]

In 2004, Schab and Trinh[54] reviewed 15 double-blind, placebo-controlled studies involving children diagnosed with ADHD and eight studies that met their experimental criteria but used either non-hyperactive children or heterogeneous groups of children. No differences in teachers' or health professionals' ratings were found as a function of dietary manipulations in any of the studies. However, parental ratings did indicate a small, but significantly negative effect of food dyes on behavior. While acknowledging the need for additional research, on the basis of their analysis, Schab and Trinh concluded that intake of artificial food dyes may be associated with ADHD in some children.[54]

Further support for a role for artificial food dyes in the etiology of ADHD was provided by two studies performed in the United Kingdom, which investigated the effects of a diet that eliminated artificial dyes and benzoate preservatives on hyperactivity in a community-based setting.[55,56] In the first study,[55] preschool-aged children were fed a diet eliminating artificial food dyes and benzoate preservatives for 4 weeks. Using a double-blind crossover design, children were then challenged with a drink containing 20 mg artificial dyes and 45 mg benzoate preservatives or a placebo drink. The amount of food dyes and preservatives in the drink was similar to what would be consumed by a preschooler in a day. Behavior was assessed preceding the study, then daily by parents at home and at weekly intervals by research psychologists in a laboratory setting. The psychologists' ratings did not differ as a function of dietary conditions; however, parents reported significant reductions in hyperactive behavior when children were placed on the elimination diet, and significantly greater increases in hyperactive behavior when children were challenged with the drink containing the artificial dyes and preservatives than when challenged with the placebo. No differences were observed between children with and without a diagnosis of ADHD.

The second study, conducted by the same group of researchers, aimed to determine if 1) the results of the first study could be replicated using a wider range of measures of hyperactivity, and 2) if similar negative effects of synthetic food colors on behavior would be observed in older children.[56] As in the previous study, children were placed on an elimination diet and then tested using double-blind techniques for their responses to a challenge drink containing artificial food colors and preservatives. Intake of synthetic food colors increased a measure of global hyperactivity which combined parents' and teachers' ratings of behavior with direct observations by clinically trained observers, and the results of a computerized test of attention.

The results of these two studies suggest that synthetic food dyes can contribute to hyperactive behavior in some children. However, it is important to note that while intake of synthetic dyes and preservatives statistically increased hyperactivity, the investigators also reported substantial individual differences in the responses of children to the food challenges. Thus, while intake of food dyes had negative effects in some children, in others, they had no effects. A second issue with these studies is that the majority of the children were not suffering from ADHD, and there were no major differences in the effects of food dyes and preservatives as a function of whether the children were or were not diagnosed with the disorder.

As noted above, one of the major concerns in studies examining the role of food dyes in ADHD has been the substantial degree of individual differences in response to food dyes both between studies and within studies. Results of one recent study suggest that genetic factors may be contributing to the observed differences in response to artificial food dyes. Using genotyping information from the children in the two previously described studies from the United Kingdom, researchers found that the adverse effects of food dyes on symptoms of ADHD were moderated, at least in part, by histamine degradation gene (HNMT) polymorphisms.[57] Further indirect support of this as a plausible idea comes from research demonstrating that 1) there are histamine receptors in the brain; 2) food additives can trigger histamine release; and 3) HNMT polymorphisms can impair histamine clearance. Additionally, drugs used in the treatment of ADHD, such as methylphenidate and atomoxetine, affect the histamine system.[58]

## POLICY IMPLICATIONS

The results of these recent studies have prompted public policy groups to petition government agencies and food manufacturers both in the United States and abroad to reduce or ban the use of synthetic food dyes,[38,39] or at a minimum to place a warning label on foods stating that intake of synthetic food dyes may be associated with hyperactivity in some children. In response to these petitions, in December 2009, the British government mandated that food manufacturers remove most of the artificial food colors from their products. In July 2010, the European Food Safety Authority began requiring that foods containing artificial dyes carry warning labels stating "may have an adverse effect on activity and attention in children" (http://www.efsa.europa.eu/en/news.htm). While international food manufacturers are complying with the British and European regulations in those markets, artificial food colors continue to be used in products sold in the United States, where similar regulations are not currently in place.[38]

## CONCLUSION

For clinicians treating pediatric patients with ADHD, determining how to counsel parents with respect to artificial food colors and hyperactivity remains a major concern. First, it should be recognized that eliminating artificial food dyes is not simply a nutritional manipulation and that maintenance of a strict elimination diet in today's society, where meals are often eaten away from home, can be challenging. As noted by Feingold, an elimination diet is most successful when followed by the entire family,[40,41] which suggests that social factors may contribute to dietary adherence and consequent beneficial effects. Providing children and adolescents with a diet different from that of their peers can influence their behavior, making strict adherence to the diet difficult to achieve.

Parents of children with ADHD should be counseled to make careful food selections, choosing natural foods with no or limited amounts of synthetic food dyes, if they suspect or have concerns about a food-based association. However, it should be recognized that eliminating artificial food dyes from children's diets is not a panacea for the treatment of ADHD. As recognized by Feingold in his original reports[40,41] and in all subsequent investigations, even in the best-case scenarios, only a portion of children respond positively to the removal of synthetic food dyes from the diet. ADHD is a multifaceted disorder, and one treatment will not work for all.

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