ORIGINAL ARTICLES

Synthetic food coloring and behavior: A dose response effect in a double-blind, placebo-controlled, repeated-measures study

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Objective: To establish whether there is an association between the ingestion of synthetic food colorings and behavioral change in children referred for assessment of "hyperactivity."

Participants: From approximately 800 children referred to the Royal Children's Hospital (Melbourne) for assessment of suspected hyperactivity, 200 were included in a 6-week open trial of a diet free of synthetic food coloring. The parents of 150 children reported behavioral improvement with the diet, and deterioration on the introduction of foods noted to contain synthetic coloring. A 30-item behavioral rating inventory was devised from an examination of the clinical histories of 50 suspected reactors. Thirty-four other children (23 suspected reactors, 11 uncertain reactors) and 20 control subjects, aged 2 to 14 years, were studied.

Design: A 21-day, double-blind, placebo-controlled, repeated-measures study used each child as his or her own control. Placebo, or one of six dose levels of tartrazine (1, 2, 5, 10, 20, 50 mg), was administered randomly each morning, and behavioral ratings were recorded by parents at the end of each 24 hours.

Results: The study identified 24 children as clear reactors (19 of 23 "suspected reactors," 3 of 11 "uncertain reactors," and 2 of 20 "control subjects"). They were irritable and restless and had sleep disturbance. Significant reactions were observed at all six dose levels. A dose response effect was obtained. With a dose increase greater than 10 mg, the duration of effect was prolonged.

Conclusion: Behavioral changes in irritability, restlessness, and sleep disturbance are associated with the ingestion of tartrazine in some children. A dose response effect was observed. (J PEDIATR 1994;125:691-8)

Since Feingold's claims that a diet free of synthetic colorings, preservatives, and naturally occurring salicylates would improve behavior in "hyperactive" children,[1-4] the

issue of whether there is a functional relationship between the ingestion of certain food additives and behavior remains

APTQ	Abbreviated Parent-Teacher Questionnaire (Conners)

unresolved and highly contentious. Initially, two types of studies were conducted to evaluate such claims. The first used Feingold's diet under double-blind conditions[5-7]; the second studied children identified by parents as favorable responders in open trials and then challenged them under
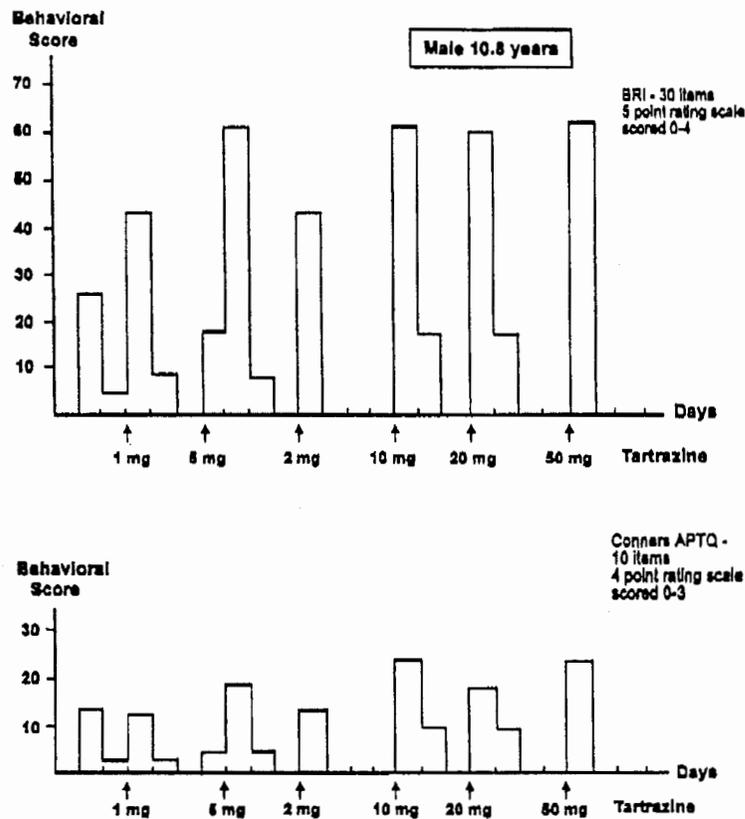
Fig. 1. Comparison between two rating scales (BRI and Conners APTQ) in a double-blind study with variable dosage of tartrazine. Boy, aged 10.8 years. *BRI*, Behavioral Rating Inventory.

double-blind conditions.[8-12] However, the findings from both types of studies have been equivocal because of logistic and methodologic problems.[13-15] These problems have included the identification of responding children from heterogeneous populations; dietary compliance; placebo effects; the possible lack of inertness of the control substance[15]; varying and imprecise diagnostic criteria for "hyperactivity"[16-24]; doubts about the validity and reliability of behavioral outcome measures[25] (particularly those appropriate to the assessment of dye challenge effects); and the detection of treatment effects when only a small number of children respond.[26-30]

There has also been considerable confusion about suitable dosage levels of coloring for use in challenge trials.[13] Studies conducted in North America have used a standard mixture consisting of nine colors, varying in dose from 27 mg,[8, 9] to 36 mg,[31] to 150 mg,[32] whereas others used tartrazine alone in doses varying from 1.2 mg[33] to 250 mg.[34] None of these studies incorporated different dosages into the design.

Since the National Advisory Committee on Hyperkine-

sis and Food Additives (NACHFA) report in 1980,[13] there have been few controlled clinical studies examining the effects of ingested synthetic food coloring on behavior.[30, 31-33, 35] Nevertheless, despite the inconclusiveness of the evidence, some parents remain adamant that their children react adversely to the ingestion of synthetic colorings, both in foods and in medications.

As a consequence of the publicity that Feingold's hypothesis received in Australia, many inquiries were received at the Royal Children's Hospital, Melbourne, regarding assessment of children with suspected hyperactivity. A preliminary study attempted to evaluate the claimed utility of the Feingold-KP diet[3] in affecting behavioral change. From 55 children who participated in a 6-week open trial of the Feingold diet, 8 of 14 suspected reactors to food coloring were involved in a double-blind, placebo-controlled, repeated-measures study in which 50 mg doses of two implicated colors, tartrazine and carmoisine (azo dyes), were used.[30] For two children, there was a clear association between the ingestion of both dyes and behavioral symptoms of irritability, restlessness, and sleep disturbance. Similar behav-

Table I. Age and sex of identified reactors in each category ("likely" or "uncertain" reactors) as classified by parents before the double-blind study

Age (yr)	Likely reactors				Uncertain reactors				Control subjects			
	Male		Female		Male		Female		Male		Female	
	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
2-6	8	1	3	0	0	1	0	0	0	6	0	4
7-14	7	2	1	1	2	6	1	1	2	3	0	5
Reactors	15/18		4/5		2/9		1/2		2/11		0/9	

R, Reactors; *NR*, nonreactors.

ioral responses were reported by Mattes and Gittleman-Klein.[11]

These findings raised the issue of whether the strict criteria for inclusion in studies concerned with hyperactivity based on attention deficit may miss some children who react to the ingestion of food colorings, and may account for the inconclusive results obtained in those studies using the Conners Abbreviated Parent-Teacher Questionnaire,[36] particularly because the scale places little emphasis on irritability and contains no measure of sleep disturbance.[37] These and related limitations of the APTQ[11, 15] motivated an attempt to identify the specific behaviors associated with the ingestion of a synthetic food coloring, by using each child as his or her own control; to develop a behavioral rating scale validated for dye challenge; and to examine the validity of the clinical impression that some children who appear to react to the ingestion of coloring may not necessarily be considered hyperactive in terms of attention deficit—as indicated by the *Diagnostic and Statistical Manual of Mental Disorders*, second edition,[22] and specified by the third edition[23] and by the third edition, revised.[24]

The purpose of this study was to identify whether there was an association between the ingestion of tartrazine and behavioral change in children referred for assessment of hyperactivity.

METHODS

Stage 1: open trial. During a 6-year period, more than 800 children were referred to the Royal Children's Hospital, Melbourne, for assessment of suspected hyperactivity. Two hundred children, whose parents claimed to have noted variability in their child's behaviors in association with diet, were included in a 6-week open trial of a diet free of synthetic colorings. The parents of 150 children reported initial improvement with the diet during the trial period, but deterioration in behavior with the introduction of foods containing synthetic coloring. Again, there were consistent observations by parents of behaviors related to irritability, restlessness, and sleep disturbance, which supported findings from the initial study.[30]

From an examination of the clinical histories of 50 suspected reactors, a content analysis was made of parental descriptions of observed behavioral changes. On the basis of a frequency count of the behavioral descriptions, and with related behaviors grouped together in proportion to their mentioned occurrence, we devised a preliminary 30-item inventory containing five clusters of related behaviors: (1) *irritability/control,* 11 items, (2) *sleep disturbance,* 9 items, (3) *restlessness,* 4 items, (4) *aggression,* 3 items, and (5) *attention span,* 3 items. Responses to items were required on five-category Likert scales: "Not at all," "Mild," "Moderate," "Very," and "Extremely" (scored 0 to 4, respectively). A 21-day double-blind pilot study of the inventory, with eight suspected reactors who had sociodemographic characteristics similar to those of the participants in the open trial, indicated that the items did discriminate between ingestions of dye and placebo. Moreover, the item nomenclature and their associated rating scales were clearly understood by parents.

Stage 2: double-blind study. Parents of 34 children who differed from those used to develop the inventory, and the parents of 20 children who did not have behavioral concerns, agreed to their child's participation in a double-blind, placebo-controlled, repeated-measures study (16 girls, 38 boys; age range: 2 to 14 years, mean = 7.1 years, SD = 3.5). Before the double-blind study, parents categorized their children as likely reactors[23] or uncertain reactors.[11] The control children had 6 weeks on the diet; the remainder had been maintained on a diet free of synthetic food coloring for a minimum of 3 months (average 6 months) before participation in the study. The parents in the "likely reactor" group were confident that they could identify the behavioral changes associated with the ingestion of synthetic colors. The children were maintained on a coloring-free diet and were given one colorless capsule each morning for 21 days. The capsules (placed in a dated envelope) contained either placebo (lactose) or tartrazine (FD&C yellow No. 5, E102) buried in an inner capsule surrounded by lactose. Children <6 years of age (n = 25) were given packaged orange juice (250 ml, also dated),
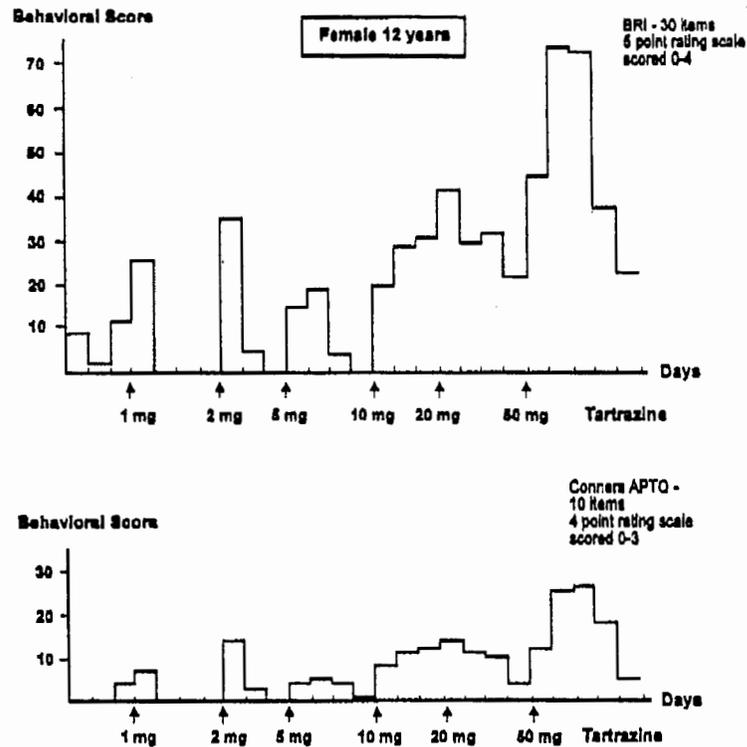
Fig. 2. Comparison between two rating scales (BRI and Conners APTQ) in double-blind study with variable dose of tartrazine. Girl, aged 12 years. *BRI*, Behavioral Rating Inventory.

with each sealed opening for the straw having been punctured and resealed, regardless of whether or not it contained dye. The tartrazine was administered randomly in 1, 2, 5, 10, 20, and 50 mg doses for each child. To avoid the potential problem of carryover effects, however, we had the 20 mg and 50 mg doses administered toward the end of the study period. The design, in which each child was his or her own control subject,[38] allowed for a placebo lead-in period of 3 days and placebo washout periods of at least 2 days between each dose of coloring. Dietary infractions were recorded, including quantity and proprietary name.

To ensure that the sleep period was included, we required parents to complete two rating scales at the end of each 24-hour period: (1) the devised 30-item behavioral inventory, which we referred to as the Behavioral Rating Inventory (available on request from the authors), and (2) the Conners 10-item APTQ,[36] for comparative purposes. Additional sociodemographic data, atopic history, and skin-prick testing for eight common allergens and tartrazine (0.1 mg/ml) were also obtained. Results were deemed to be positive when the wheal exceeded the control solution (0.9% saline solution) by 3 mm. Informed consent was obtained from all parents and the older children, and approval for the study was granted by the Royal Children's Hospital Ethics Committee.

Statistical analyses. For analytic purposes, the raw data obtained for each child were ordered so that, after the placebo lead-in period, the data for dye challenge days were placed in increasing dose levels, separated by their respective placebo days. Conventional methods were used for the computation of means and standard deviations, and analyses were computed by standard parametric and nonparametric techniques, the details of which are given below. Distributions of categorical data were compared by means of a chi-square test of independence, with the Yates correction for continuity. Group differences on continuous variables were determined by t tests and regression effects by F tests. Confidence intervals and power-based assessments of statistical tests were computed with the use of the DE-SIGN-POWER software.[39] For all tests, the conventional $\alpha < 0.05$ level of probability (p value) was chosen as the level of rejection for each of the associated null hypotheses, and tabulated results indicated statistical significance at or beyond this level only.
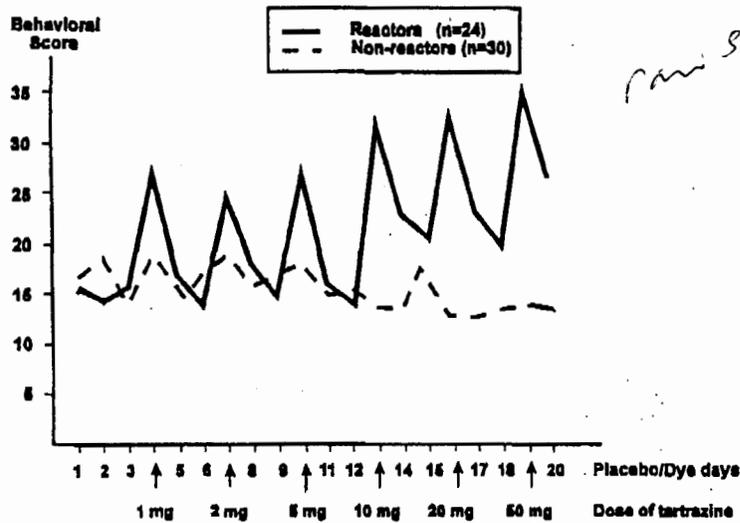
Fig. 3. Mean placebo and dye challenge scores for reactor and nonreactor groups.

RESULTS

Using data obtained from our 30-item Behavior Rating Inventory, we computed a daily total behavioral response score for each child and plotted the data for each day. Examples of individual responses are presented in Figs. 1 and 2. The data identified consistent variations in behavior for at least five of the six dose challenges in 24 of the 54 participating subjects. Moreover, the amplitude and duration of effect increased with increasing dosage levels. All children were within the normal range for behavior when not exposed to the synthetic coloring.

A Wilcoxon matched-pairs signed-ranks test[40] was computed on the set of scores for the 6 dye challenge days for each child, paired with a set of corresponding scores for the 6 placebo days immediately before each dye challenge day. These analyses confirmed 24 children who had significant behavioral responses to dye challenge (Table I). Of 23 children initially classified by parents as a likely reactors, four did not have significant responses, but 3 of 11 uncertain reactors and 2 of 20 control subjects were identified as reactors. On the basis of the six paired observations for each child, power assessments $(1 - \beta)$ at the $p < 0.05$ α level on the Wilcoxon tests (one tailed) yielded averaged indexes of 0.95 (reactors) and 0.93 (nonreactors), respectively. Individual children had a marked dose response effect when scored by their parent (usually mother) under double-blind conditions.

The data from those children identified as reactors from individual profiles were compared with data from those who had random fluctuations in behavior unrelated to dye challenge. For each of the two age groupings (2 to 6 years and 7 to 14 years), there was no difference in the distribution of boys and girls for either the reactor or the nonreactor group. A chi-square test of independence, with Yates correction, was not significant for the reactor group (chi-square value = 0.54; $df = 1$; $p = 0.464$) or for the nonreactor group (chi-square value = 0.67; $df = 1$; $p = 0.411$). Total scores for reactor boys and for reactor girls on dye days (two-tailed t tests) were not significantly different ($t = 1.69$; $df = 22$; $p = 0.124$). A similar analysis for testing the score differences between the two major age categories in the reactor group was likewise not significant ($t = 0.12$; $df = 22$; $p = 0.817$).

The mean behavioral response score profiles for the reactor and the nonreactor groups, with the score of the placebo day before challenge and the score for the challenge day, indicated a significant response for the reactor group at dosage levels greater than 2 mg; the nonreactor group profile showed nonsignificant random fluctuations in behavior (Fig. 3).

The line of best fit for the relation between the behavioral score and the dosage for the reactor group (i.e., the peaks in Fig. 3) is given by the third-order polynomial: $y = 24.849 + 0.779x - 0.025x^2 + 0.001x^3$ ($R^2 = 0.89$), where x = dosage in milligrams and y = behavioral score.

The difference between the mean behavioral scores on dye challenge days for the reactors (30.9) and the nonreactors (14.4) was 16.5, with a 95% confidence interval from 8.4 to 24.6 ($t = 3.56$; $df = 52$; $p < 0.001$) (Table II). The results of between- and within-groups univariate analyses at

Table II. Paired mean placebo and dye challenge behavioral scores for reactor and nonreactor groups, with 95% confidence intervals and between-groups and within-group *t* values and degrees of freedom

Dosage levels	Reactors		Nonreactors		95% CI of mean differences	Between groups *t* values (*df* = 52)	Within-group *t* values	
	Mean	SD	Mean	SD			Reactors (*df* = 23)	Nonreactors (*df* = 29)
Level 1							−2.70*	−1.56(NS)
Placebo	15.5	15.4	14.1	16.9	−7.2 to 10.0	0.29 (NS)		
Dye (1 mg)	27.4	21.3	19.1	19.6	−2.7 to 19.3	1.47 (NS)		
Level 2							−2.81*	0.61
Placebo 2	13.8	12.2	17.0	18.9	−5.1 to 11.5	−0.69 (NS)		
Dye 2 (2 mg)	24.7	21.3	19.1	19.6	−1.1 to 20.9	1.76†		
Level 3							−3.29*	1.05(NS)
Placebo 3	14.8	18.3	19.2	17.1	−5.1 to 13.9	−0.90 (NS)		
Dye 3 (5 mg)	27.0	18.5	15.4	18.4	1.7 to 21.5	2.29†		
Level 4							−4.41*	0.72(NS)
Placebo 4	13.8	12.4	15.6	16.1	−5.8 to 9.4	−0.45 (NS)		
Dye 4 (10 mg)	31.7	20.6	13.7	12.3	8.7 to 27.3	3.89†		
Level 5							−2.94*	2.30
Placebo 5	19.2	16.0	17.8	21.3	−8.6 to 11.4	0.26 (NS)		
Dye 5 (20 mg)	32.4	23.6	12.8	16.7	8.4 to 30.8	3.54†		
Level 6							−4.00*	0.19(NS)
Placebo 6	19.9	19.2	13.4	17.9	−3.5 to 16.5	1.26 (NS)		
Dye 6 (50 mg)	35.2	21.2	13.0	13.4	12.7 to 31.9	4.49†		

*$p < 0.05$ (two-tailed test).
†$p < 0.05$ (one-tailed test).
CI, Confidence interval; *NS*, not significant.

each paired placebo/dye dosage level showed, that, for the reactor group, the mean score differences between placebo and dye challenge ratings were significant at all six paired levels, and that the mean score differences between the reactor and the nonreactor groups were significant at and beyond the 2 mg dosage level of dye challenge. There was no significant difference between the mean paired placebo days for both groups.

To examine the group regression effects on the behavioral outcome variables across dye challenge occasions, we computed a repeated-measures analysis of variance on the six dye challenge scores, with reactors and nonreactors as the two-level between-groups factor.[41] The results yielded a significant between-groups main effect ($F = 12.7$; $df = 1$, 52; $p < 0.001$; $1 − \beta = 0.90$), but averaged across dye challenge occasions the within-groups effect was not significant ($p = 0.74$; $1 − \beta = 0.29$). The two-way interaction effect of groups by dye challenge occasions was likewise not significant ($p = 0.11$; $1 − \beta = 0.53$).

All reactors were atopic (history of asthma, eczema, or allergic rhinitis, and positive skin test reactions to one or more of eight common allergens). None reacted to tartrazine. All but two reactors (one was adopted) had a family history of migraine in at least one first-degree relative.

All reactor children have been followed for a further 3 to 5 years and have voluntarily adhered to a coloring-free diet,

with the exception of several adolescents who have tested their need to remain on the diet. Fifty percent of the children from the open trial did not consider that they were on a "diet" at follow-up, but on further questioning from the dietitian it was revealed that they were avoiding synthetic coloring as part of their food choice. One child (a girl, 12 years of age) who participated in the initial study[30] remained a clear reactor in this study after 5 years.

There were, however, notable differences in the clinical features of the children aged 2 to 6 years, compared with those aged 7 to 14 years. The younger children had constant crying, tantrums, irritability, restlessness, and severe sleep disturbance, and were described as "disruptive," "easily distracted and excited," "high as a kite," and "out of control." Their parents were exhausted through lack of sleep and the constant demands of their children, who were unable to be comforted or controlled. The older children were described as "irritable," "aimlessly active," "lacking self-control," "whiney and unhappy," and "like a bear with a sore head"; sleep difficulties were less likely to disturb the entire family. The sample size, compared with the number of items, precluded meaningful analysis of the behavioral differences between reactors in the two age groups in this study. Many parents claimed that it had taken upwards of 2 years after their child commenced the diet before they "actually liked him [her] again."

DISCUSSION

This study demonstrated a functional relation between the ingestion of a synthetic food color (tartrazine) and behavioral change in 24 atopic children, aged 2 to 14 years, with marked reactions being observed at all six dosage levels of dye challenge. Even though tartrazine has been implicated as a precipitating agent in asthma, eczema, urticaria, angioedema, and migraine,[42, 43] the behavioral changes observed in this study were independent of such manifestations. Beyond 10 mg there was a ceiling effect; higher doses increased the duration of effect beyond 24 hours, suggesting a dose-related response. Although the children were initially referred for suspected hyperactivity, only two reactors scored >15 on the Conners APTQ.[36] Moreover, the main behavioral features described and subsequently rated by parents were irritability, restlessness, and sleep disturbance, which were constant across age and sex.

Contrary to prevailing wisdom,[24, 44, 45] parents were found to be reliable observers and raters of their children's behaviors (see also Rowe and Rowe[46, 47]), and sensitive to variable dosages of synthetic coloring in the context of the double-blind, placebo-controlled design. Similarly, in the single case study by Mattes and Gittleman-Klein,[11] the mother was able to identify the active challenge correctly in 8 of 10 instances. In our study the average duration of 6 months on a coloring-free diet for subjects before the study may well have facilitated the observations because of the prolonged period of stable, improved behavior. Dietary infractions were also infrequent because family eating patterns had stabilized. Parents in our study were also reliable predictors of dye challenge response during the open trial stage (19 of 23 "likely reactors"). An unexpected finding was the identification of 2 of the original 20 control subjects as reactors. Each of these children scored less than 15 on the Conners APTQ and was not considered to have behavioral problems by his or her parents, but an examination of dietary histories revealed that each child had a well-balanced, nutritious diet and rarely ingested foods or beverages containing synthetic coloring. These children were also atopic; the significance of the atopic features in all reactors and the associated family history of migraine require further investigation. Because of the small sample size, no conclusion could be drawn about the prevalence of reactors in the population.

The number of reactors in this study contrasts markedly with those of previous studies, which may have been due to the method used to select subjects for the study. That is, the children were drawn from a general pediatric population with a range of behavioral problems under the guise of hyperactivity, but also included some children whose parents suspected a relation between food coloring and behavioral change. We did not employ the strict criteria of attention deficit disorder,[23, 24] or a score >15 on the Conners APTQ, before including subjects in the study; this allowed for the inclusion of suspected reactors who were described by parents as having irritability, restlessness, and sleep disturbance. By using each child as his or her own control subject and plotting the daily behavioral scores, we were able to identify reactors. Idiosyncratic reactions to a substance may not be noted if responses are treated as group effects, and the number identified may be even smaller if the selection criteria for the group to be studied are exclusive and the outcome measures do not ask the appropriate questions.

REFERENCES

1. Feingold BF. Food additives and child development [Editorial]. Hosp Pract 1973;8(Oct):11.
2. Feingold BF. Hyperkinesis and learning difficulties (H-LD) linked to the ingestion of artificial food colors and flavors. Paper presented at the annual meetings of the American Medical Association, Section on Allergy, Chicago, June 24, 1974.
3. Feingold BF. Why your child is hyperactive. New York: Random House, 1975.
4. Feingold BF. Hyperkinesis and learning disabilities linked to artificial food flavors and colors. Am J Nurs 1975;75:797-803.
5. Conners CK, Goyette CH, Southwick DA, et al. Food additives and hyperkinesis: a controlled double-blind experiment. Pediatrics 1976;58:154-66.
6. Harley JP, Ray RS, Tomasi L, et al. Hyperkinesis and food additives: testing the Feingold hypothesis. Pediatrics 1978;61:818-28.
7. Williams JI, Cram DM, Tausig FT, Webster E. Relative effects of drugs and diet on hyperactive behaviors: an experimental study. Pediatrics 1978;61:811-7.
8. Harley JP, Matthews CG, Eichman PL. Synthetic food colors and hyperactivity in children: a double-blind challenge experiment. Pediatrics 1978;62:975-83.
9. Goyette CH, Conners CK, Petti TA, et al. Effects of artificial colors on hyperkinetic children: a double-blind challenge study. Psychopharmacol Bull 1978;14:39-40.
10. Weiss B, Williams JH, Margen S, et al. Behavioral response to artificial food colors. Science 1980;297:1487-8.
11. Mattes J, Gittelman-Klein RA. A crossover study of artificial food colorings in a hyperkinetic child. Am J Psychiatry 1978;135:987-8.
12. Levy F, Dumbrell S, Hobbes G, Ryan M, Wilton N, Woodhill JM. Hyperkinesis and diet: a double-blind crossover trial with a tartrazine challenge. Med J Aust 1978;1:61-4.
13. The National Advisory Committee on Hyperkinesis and Food Additives. Final Report to the Nutrition Foundation. New York: The Nutrition Foundation, Inc., 1980.
14. Conners CK. Food additives and hyperactive children. New York: Plenum Press, 1980.
15. Rippere V. Food additives and hyperactive children: a critique of Conners. Br J Clin Psychol 1983;22:19-32.

16. Hinshaw SP. On the distinction between attentional deficits/hyperactivity and conduct/aggression in childhood psychopathology. Psychol Bull 1987;101:443-63.

17. Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. Am J Psychiatry 1991;148:564-77.

18. Shaywitz BA, Shaywitz SE. Comorbidity: a critical issue in attention deficit disorder. J Child Neurol 1991;6(suppl):S13-22.

19. Halperin JM, Matier K, Bedi G, Sharma V, Newcorn JH. Specificity of inattention, impulsivity, and hyperactivity to the diagnosis of attention deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1992;31(2):190-6.

20. Pliszka SR. Comorbidity of attention deficit hyperactivity disorder and overanxious disorder. J Am Acad Child Adolesc Psychiatry 1992;31(2):197-203.

21. World Health Organization. International classification of diseases. 9th ed. Geneva: World Health Organization, 1978.

22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 2nd ed. Washington, D.C.: American Psychiatric Association, 1968.

23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed., revised. Washington, D.C.: American Psychiatric Association, 1987.

25. Rowe KJ, Rowe KS. The relationship between inattentiveness in the classroom and reading achievement. Part A: Methodological issues. J Am Acad Child Adolesc Psychiatry 1992; 31:349-56.

26. Dews PB. Comments on some major methodologic issues affecting analysis of the behavioral effects of foods and nutrients. J Psychiatr Res 1982/1983;17:223.

27. Schwab EK, Conners CK. Nutrient-behavior research with children: methods, considerations, and evaluation. J Am Diet Assoc 1986;86:319-24.

28. Harley JP. Methodological issues in behavioral nutrition research. In: Miller SA, ed. Nutrition and behavior. Philadelphia: Franklin Press Institute, 1981:277-83.

29. Cox C. Detection of treatment effects when only a portion of subjects respond. In: Miller SA, ed. Nutrition and behaviour. Philadelphia: Franklin Press Institute, 1981:285-9.

30. Rowe KS. Synthetic food colourings and "hyperactivity": a double-blind crossover study. Aust Paediatr J 1988;24:143-7.

31. Mattes JA, Gittelman R. Effects of artificial food colouring in children with hyperactive symptoms: a critical review and results of a controlled study. Arch Gen Psychiatry 1981;38:714-8.

32. Swanson JM, Kinsbourne M. Food dyes impair performance of hyperactive children on a laboratory learning test. Science 1980;207:1485-6.

33. Rose TL. The functional relationship between artificial food colors and hyperactivity. J Appl Behav Anal 1978;11:439-46.

34. David TJ. Reactions to dietary tartrazine. Arch Dis Child 1987;62:119-22.

35. Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF. Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. Lancet 1985;1:540-5.

36. Conners CK. Rating scales for use in drug studies with children. Psychopharmacol Bull [Special Issue on Children] 1973:24-84.

37. Busby K, Firestone P, Pivik RT. Sleep patterns in hyperkinetic and normal children. Sleep 1981;4:366-83.

38. Barlow DH, Hersen M. Single case experimental designs: strategies for studying behavior change. 2nd ed. New York: Pergamon Press, 1984.

39. Bavry JL. DESIGN-POWER: statistical design analysis system. Mooresville, Indiana: Scientific Software, 1987.

40. Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bull 1945;1:80-3.

41. Winer BJ. Statistical principles in experimental design. 2nd ed. London: McGraw-Hill, 1971.

42. Juhlin L. Intolerance to food colorants. In: Chandra RK, ed. Food intolerance. Oxford: Elsevier, 1984.

43. Stevenson DD, Simon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. J Allergy Clin Immunol 1986; 78:182-91.

44. Conners CK. A teacher rating scale for use in drug studies with children. Am J Psychiatry 1969;126:884-8.

45. Brown RT. Teacher ratings and the assessment of attention deficit disordered children. Journal of Learning Disabilities 1986;19:95-100.

46. Rowe KJ, Rowe KS. Assessing student behaviour: the utility and measurement properties of a simple parent- and teacher-administered behaviour instrument for use in educational and epidemiological research. Paper presented at the 1993 annual conference of the Australian Association for Research in Education, Fremantle, Western Australia, Nov. 22-25, 1993.

47. Rowe KS, Rowe KJ. The RBRI user's manual: Parent- and teacher-administered inventories for the assessment of child externalizing behaviors, for use in educational and epidemiological research. Melbourne: Department of Pediatrics, University of Melbourne, Royal Children's Hospital, and Centre for Applied Educational Research, University of Melbourne, 1994.