AMP and cyclic GMP during phagocytosis implies a difference in mechanism of action for these nucleotides. Since cyclic GMP is consistently found within the granular cytoplasmic region of the cell, it is likely, as others have suggested (*8, 13, 21*), that cyclic GMP plays a role in the functional process of secretion.

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Food Dyes and Impairment of Performance in Hyperactive Children

We discuss here a number of issues which were not directly addressed by Swanson and Kinsbourne (*1*) but which are essential to proper interpretation of their results.

The first issue relates to criteria for diagnosing hyperactivity. Although there is continuing debate regarding the propriety or utility of using the diagnostic label "hyperactivity" (hyperkinetic syndrome, minimal brain dysfunction), the label remains widely applied. The descriptors of and criteria for the syndrome are undergoing change (*2*), but as far as we are aware, Swanson and Kinsbourne (*3*) are the only advocates of using drug response as a confirmatory criterion for a diagnosis of hyperactivity. Thus, it is possible that many of their so-called "nonhyperactives" would indeed be considered hyperactive by most researchers in this area. The general position of professionals is perhaps most clearly represented by the continuing efforts to predict *which* hyperactive children will respond favorably to stimulant medication (*4*). Moreover, recent data indicating that the cognitive and behavioral responses of hyperactive and normal children are qualitatively similar (*5*) appear to invalidate unequivocally any further use of drug response as a diagnostic criterion in hyperactivity.

The second point concerns the between-group focus taken by Swanson and Kinsbourne (*1*) which overlooks an important aspect of the data. Interpreting the three-way interaction by analyzing the simple interaction effects of challenge and test time, they concluded that the dye challenge affects performance of hyperactives but not of "nonhyperactives." However, even a cursory examination of their figure 1 (*1*) reveals that the performance of the two groups was similar under dye challenge but differed on placebo. Thus the interesting between-group difference, and the cause of the significant three-way interaction, is the contrasting placebo functions. While we do not dispute the correctness of their analysis, concurrent examination of the effects of test time within group X challenge conditions is essential to a complete understanding of the results. Comparison of group means derived from their figure 1 suggests significant and similar deteriorations in performance over time in all conditions except the hyperactives after placebo challenge. Thus the data do not permit the conclusion that "the performance of the nonhyperactive group was not affected by the challenge with the food dye blend." Under placebo conditions baseline data reflected the expected superiority of the "nonhyperactive" group, but by the final test session their performance had fallen to a level similar to the hyperactive group which showed no change. Why did the "nonhyperactives" manifest the observed deterioration in performance under the placebo condition? This question must be answered before the findings of the challenge study can be interpreted unambiguously.

Finally, the children in the study (*1*) were involved in a "controlled implementation of the Feingold diet" although no assessment of the diet treatment itself is presented. It should be emphasized that the clinical significance of any "challenge effect" will not be established until it is demonstrated that the same children (or some subset) giving a challenge response aiso show a good diet response in controlled study. Only then could we attribute the day-to-day behav-

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ior and learning problems of specific hyperactive children to the same pharmacological or toxic mechanism demonstrated in the challenge situation.

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Ferguson *et al.* (*1*) object to our subtyping of hyperactive children on the basis of their responses to stimulant drugs (*2*). We do not agree with Ferguson *et al.*, and even if we did, our basic conclusion about the adverse effect of food dyes on hyperactive children would not change. If we follow their suggestion and consider all 40 patients as one group, a significant interaction between challenge and test time [$F(3, 108) = 2.73$, $P < .05$] remains in our data (*2*, p. 1486). This provides statistical support for our conclusion that a large dose of a blend of food dyes impaired performance on the learning test, even for the combined heterogeneous group of hyperactive children in our study. We have never claimed that this subtle "challenge effect" had clinical significance or that food dye affected social behavior (*2*, p. 1486).

Ferguson *et al.* (*1*) point out that there are group differences in performance with the placebo condition. This has also been pointed out by others (*3*-*5*), and discussed by us elsewhere (*5*). To clarify this issue further, we have performed additional analyses as suggested by Ferguson *et al.* (*1*). A between-subject analysis of the placebo data reveals that indeed the two subgroups differ statistically in the placebo condition, but that the difference is due entirely to the test given at 9:30 a.m. before the children were challenged with the food dye blend [see (*2*), figure 1]. On the three tests given after the placebo challenge, the two subgroups are matched on both number of errors and patterns of performance. An analysis variance of the placebo and dye challenge data for these three tests still yields a significant main effect of challenge [$F(1, 127) = 6.78$, $P < .02$], and a significant two-way interaction between subtype and challenge [$F(1, 91) = 4.84$, $P < .04$]. Thus, the between-group differences are not solely due to the between-group differences in the placebo condition, as claimed by Ferguson *et al.* (*1*), since a statistically significant difference remains when placebo performance is matched for the groups.

We do not agree with Ferguson *et al.* (*1*) that a single study reported in various places (*6*-*8*) showing a similarity of response to stimulant drugs by 15 hyperactive and 14 normal children should "invalidate unequivocally any further use of drug response as a diagnostic criterion in hyperactivity." The results of the NIMH study (*6*-*8*) should be qualified by the principle of task specificity of response to stimulant drugs (*9*): stimulant drugs may improve performance of normal adults only on low-level intellectual tasks but not on high-level tasks, except when abnormal conditions exist (for example, sleep deprivation or extreme boredom).

Weingartner *et al.* (*7*, p. 34) and Rapoport *et al.* (*8*, p. 941) have challenged the usual interpretation of task specificity of response to stimulants on the basis of free and cued recall data from a memory task in which subjects were presented with material once for a few seconds and were then distracted by another task to prevent rehearsal. We (*10*), too, have used this type of test. We agree that "performance of normal men and hyperactive and normal boys improved on this task" (*8*, p. 941) and that drug response on this test does not have diagnostic significance. But the results from other tests may be different. On a paired-associate or serial learning test requiring rehearsal and repetition of the same material for 20 to 30 minutes, the performance of normal adults is not enhanced and may even be significantly impaired by stimulants (*11*, *12*). Furthermore, on a memory scanning task requiring rehearsal, doses of methylphenidate equivalent to or lower than 0.5 mg of *d*-amphetamine per kilogram of body weight produce "behavior toxicity" in hyperactive children (*13*, *14*) and may even reduce performance below the level on placebo in other clinical groups of children (*15*).

We recognize the importance of the NIMH study (*6*-*8*) and that it partially addressed the issue of task specificity by using a variety of tasks, but our evaluation of the literature leads us to conclude that a study that unequivocally supports or dismisses the diagnostic significance of favorable (and adverse) responses to stimulant medication in the laboratory has not yet been done (*16*).

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