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 (§ 13, 21), that cyclic GMP plays a role in the functional process of secretion.

KATHERINE B. PRYZWANSKY
Department of Bacteriology and Immunology,
University of North Carolina,
Chapel Hill 27514

ALTON L. STEINER
Department of Medicine and Pharmacology,
University of North Carolina

JOHN K. SPITZNAEGEL†
Department of Bacteriology and Immunology,
University of North Carolina

CHIRANJIV L. KAPOOR
Department of Medicine and Pharmacology,
University of North Carolina

References and Notes
7. Cells were fixed in 1 percent paraformaldehyde in 0.075M cacodylate buffer containing 0.72 percent sucrose, pH 7.5, at 4°C for 30 minutes. Fixation in FMA was as follows: 3.7 percent formaldehyde in phosphate-buffered saline (PBS), pH 7, at room temperature for 10 minutes; at 20°C in methanol for 4 minutes, and at 20°C in propylene oxide. Cells were washed in PBS after 3.7 percent formaldehyde and after acetone. To preserve the ultrastructure, cells were stained directly in the resin. We believe we are staining receptor-bound nucleotides, since soluble nucleotides would be removed by PBS washing.
14. Staining intensity of cyclic nucleotides was dramatically increased if cells were incubated with 10-8 M cyclic AMP to saturate receptor sites.
21. We thank M. H. Cooney for excellent technical assistance. Supported by NIH grants AM17438 and 03-040-22. This work was presented at a meeting of the American Society for Cell Biology in November 1979.
22. Present address: Department of Medicine, Division of Endocrinology, University of Texas Medical School, Houston 77025.
23. Present address: Department of Microbiology, Emory University School of Medicine, Atlanta, Ga. 30322.
24. April 1980; revised 4 August 1980

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 (5) 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 also show a good diet response in controlled study. Only then could we attribute the day-to-day behav-

410 0036-0875(81)0123-041050.00 Copyright © 1981 AAAS

SCIENCE, VOL. 211, 21 JANUARY 1981

Downloaded from http://science.sciencemag.org on January 1, 2018
ior and learning problems of specific hyperactive children to the same pharmacological or toxic mechanism demonstrated in the challenge situation.

H. BRUCE FERGUSON*
Laboratory of Psychology and Psychopathology, National Institute of Mental Health, Bethesda, Maryland 20205

JUDITH L. RAPOPORT
Unit on Childhood Mental Illness,
National Institute of Mental Health

HERBERT WEINGARTNER
Laboratory of Psychology and Psychopathology,
National Institute of Mental Health

References and Notes
5. Present address: Department of Psychology, Carleton University, Ottawa, Ontario, Canada K1S 5B6.
6. 14 April 1980; revised 8 August 1980

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 of 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” (9, 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).

JAMES M. SWANSON
Fairview State Hospital,
Costa Mesa, California 92626, and
Hospital for Sick Children,
Toronto, Ontario, Canada M5S 1A8

MARCEL KINSBOURNE
Eunice Kennedy Shriver Center for
Mental Retardation,
Waltham, Massachusetts 02254

References and Notes
4. T. J. Sobotta, Status of hyperactivity/diet question” (Food and Drug Administration, Memorandum HFF-162, Washington, D.C., April 1980).
16. We (J. M. Swanson and M. Kinsbourne, Mod. Med. (Chicago) 49, 71 (1978), in Attention and Cognitive Development, G. A. Hale and M. Lewis, Eds. (Plenum, New York, 1979) have suggested that the response to stimulant medication on the paired-associate learning test may have diagnostic significance, but we acknowledged that, because of the limited literature on the effects of stimulants on children, there is no direct evidence for this. If normal children were shown to have a similar adverse response pattern to stimulants as normal adults on this test, then its diagnostic significance would be established, or if normal adults were shown to have the same favorable response to stimulants as hyperactive children, then its diagnostic significance would be discounted.

1 December 1980
Food dyes and impairment of performance in hyperactive children
HB Ferguson, JL Rapoport and H Weingartner

Science 211 (4480), 410-411.
DOI: 10.1126/science.7221548