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.

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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 PBS for 1 minute. Cells were washed in PBS after 3.7 percent formaldehyde and after acetone. To preserve the ultrastructure, cells were then washed in PBS. We believe we are staining receptor-bound nucleotides, since soluble nucleotides would be removed by PBS washing.
14. Staining intensity of cytoplasmic cyclic AMP dramatically increased if cells had been incubated with 10-6 M cyclic AMP to saturate receptor sites.
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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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