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ABSTRACT. In the present study, the effects of 0.3 mg/kg and 1.0 mg/kg of methylphenidate on the overt behavior and academic functioning of 12 children with an established diagnosis of attention deficit disorder with hyperactivity were evaluated. A double-blind, placebo-control, within-subject (crossover) design was used, in which each child was tested four times in each drug condition. Drug conditions were alternated on a bidaily basis and each child received two different drug conditions each day. The academic tasks were designed for evaluation of the relationship between task complexity and dose. Whereas overt behavior improved with increasing dose, academic functioning was improved with methylphenidate, but did not vary with either dose or task complexity. Also, investigated were potential carryover effects of a morning dose of methylphenidate on performance in the afternoon. Behavioral and academic improvements produced by a dose of 0.3 mg/kg in the morning were no longer evident in the afternoon, but a morning dose of 1.0 mg/kg produced behavioral improvements that were clinically and statistically discernible in the afternoon, although the academic improvements had dissipated. *Pediatrics* 1989;84:648–657; *methylphenidate, attention deficit disorder, dose response, time response.*

ABBREVIATIONS. DSM-III, *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed; WRAT-R, *Wide Range Achievement Test*, revised edition; PICS, Parent Interview for Child Symptoms; ANOVA, analysis of variance.

Psychostimulant medication is the most widely used treatment for hyperactive children.[1,2] Although the effect of medication on the overt behavior of these children is well documented, the concomitant effects on cognition and academic performance are less clear and may be dose related. In their landmark study, Sprague and Sleator[3] described differential dose response effects of methylphenidate on behavior and cognitive performance in hyperactive children. These investigators found that performance of a cognitive task was best at a dose of 0.3 mg/kg but deteriorated to placebo-level performance at a dose of 1.0 mg/kg. Overt behavior was the most improved at the 1.0 mg/kg dose. Sprague and Sleator[3] postulated that cognitive and behavioral changes have different dose response relationships, and that high doses of stimulant medication may impair learning and academic performance. If substantiated, this hypothesis would have major implications for clinical practice because dose is typically titrated against parent or teacher reports of child behavior. Because the emphasis in determining dose levels is on reduction of overt activity and other disruptive behavior, many children are likely to receive doses that may be detrimental to cognition and academic performance.

The monotonic relation between dose and overt behavior has been convincingly demonstrated in numerous studies,[4–9] but, contrary to the general belief expressed in the literature,[10] the conclusion that doses approximating 1.0 mg/kg impair cognitive and academic performance may be premature. Several investigators have described linear dose response patterns with a range of academic and cognitive tasks using doses as large as 0.6 mg/kg,[7,11–13] although others have found cognitive performance to be improved by low doses (eg, 0.3 mg/kg) but not by moderate or high doses (eg, 0.6 to 1.0 mg/kg).[14–16]

Interpretation of the discrepant findings is confounded by a number of methodologic problems, including the omission of placebo-control or dou-

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ble-blind conditions,[17] the failure to control for order effects in medication conditions,[8,9] and the use of different prescription regimes in terms of fixed dose vs milligrams per kilogram dose or individual titration, as well as in terms of the number of doses per day. Also, most investigators have tested subjects only once at each drug condition, although Pelham and Hoza[18] challenged the underlying assumption that data generated from a single testing session yield stable estimates of drug effects. These investigators proposed that rapid and random alternation of drug conditions on a daily or bidaily basis, with testing conducted several times at each drug condition, is a more accurate way of determining drug and dose effects. Unfortunately, many of these methodologic limitations are evident in the few studies in which doses of 1.0 mg/kg have been included.[8,9,17,19] Finally, although dose response effects have been investigated with a wide range of tasks and measures, it is noteworthy that dose-related decrements in performance were often found to occur with the most difficult or complex version of a task,[3] and on "high-level" tasks in terms of their cognitive demands.[16]

Despite the concern that high doses may impair academic skills and achievement, it is surprising that the effects of such doses on performance of academic tasks have not been investigated. In previous studies, the effects of low and moderate doses (eg, 0.3 to 0.6 mg/kg) on children's productivity and accuracy in their regular classroom assignments have been evaluated,[5–7] as have the effects on experimenter-generated worksheets tailored to the child's ability.[13] The effects of high doses and of task complexity on academic performance have not been investigated. The present study was designed to extend existing dose response functions for academic performance by assessment of the effects of 1.0 mg/kg of methylphenidate, in addition to those of 0.3 mg/kg of methylphenidate, on performance of academic tasks in which complexity was manipulated. The overt behavior of the children while performing these tasks was evaluated to compare the concurrent dose response curves for behavior and academic performance.

The second purpose of the study was to investigate the usefulness of a rapidly alternating treatment design in which drug conditions were alternated on a twice daily basis. This design is predicated on the assumption that the behavioral and plasma half-life of methylphenidate is relatively short and that its effects have essentially dissipated 4 hours after an acute administration.[20–22] It is an attractive design in that it affords an efficient method of assessing medication and dose response effects that are based on several assessments at each medication condition and allows data to be interpreted for individual participants,[18] but it carries the potential for the confounding effects of carryover. That is, the effects of the morning medication condition may last longer than 4 hours and persist into the afternoon, thereby obscuring the effects of the afternoon medication condition. Because the most likely situation in which carryover effects occur is when a high dose is changed to a low dose or placebo, in the present study the carryover effects of 1.0 mg/kg of methylphenidate administered in the morning on academic performance and behavior in the afternoon following a midday dose of either 0.3 mg/kg or placebo were evaluated. Possible carryover effects of a morning dose of 0.3 mg/kg on behavior and academic performance following either placebo or 1.0 mg/kg of methylphenidate given at midday were also evaluated.

MATERIALS AND METHODS

Participants

A total of 12 children (10 boys and 2 girls) with an established *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed[23] (DSM-III), diagnosis of attention deficit disorder with hyperactivity participated in the study with the informed consent of their parents and assent from the child. Children were recruited for the project from child psychiatrists and pediatricians in the metropolitan Toronto area and from the psychiatric outpatient department at the Hospital for Sick Children in Toronto. Only those children with an established diagnosis of attention deficit disorder with hyperactivity and whose symptoms of inattentiveness, impulsiveness, and hyperactivity were considered by the referring physician to be of sufficient severity to warrant a trial with stimulant medication were eligible for the study. The participating children were between the ages of 6 and 11 years (mean ± SD = 8.4 ± 1.4 years) and were all of average intelligence (mean ± SD IQ 105 ± 14) as estimated by their Wechsler Intelligence Scale for Children—Revised (WISC-R) scores.[24] Of these, 4 children also met the DSM-III criteria for oppositional disorder, and 8 exhibited learning disabilities according to their school record and as indicated by scores less than the 25th percentile[25] on one or more of the subtests of the *Wide Range Achievement Test* (WRAT-R).[26] A total of 5 children had received stimulant medication previously, and the regular dose for the three children who were receiving medication at the time of referral was discontinued at least 48 hours prior to the study and was not reinstated until its completion.

A diagnosis of attention deficit disorder with hyperactivity was established from information derived from the referring physician, a semistructured interview with the child's parents conducted by a child psychiatrist using the Parent Interview for Child Symptoms (PICS, Schachar RJ, Wachsmuth R. 1984. Unpublished data), and from behavior ratings completed by the child's teacher. The PICS includes the child's developmental medical, and psychiatric history and contains 110 items designed to elicit parental descriptions of the child's current behavior in specific situations (eg, dinner time at home, play indoors and outdoors, behavior in a store). The absence or presence and severity of the behavioral symptoms as described by the parent are rated by the interviewer. The interview includes all of the details necessary to apply DMS-III diagnoses of attention deficit disorder with hyperactivity, conduct, oppositional, affective, anxiety, and psychosomatic disorders. Agreement between two psychiatrists rating the same interview (n = 20) was high for ratings of individual symptoms (κ = 0.95), and none of the disagreements resulted in different diagnoses being applied. Each child's classroom teacher rated the child's behavior using the Abbreviated Conners' Teacher Questionnaire,[27] the Rutter-B questionnaire,[28] and the SNAP questionnaire.[29]

A diagnosis of attention deficit disorder with hyperactivity was made if the child demonstrated at least three symptoms of inattentiveness, three of impulsiveness, and two of hyperactivity, with a history of these symptoms before 6 years of age based on the parental interview (PICS). Because attention deficit disorder with hyperactivity may be diagnosed on the basis of teacher report alone,[23] a diagnosis was also made if the child received a total score on the Rutter-B questionnaire of 9 or more (a score predictive of a clinical diagnosis of a psychiatric disorder[30]) and fulfilled any two of the following criteria: (1) had a score of 15 or more on the Abbreviated Conners' Teacher Questionnaire, which is a score predictive of a clinical diagnosis of hyperactivity;[31] (2) had at least four inattentive, four impulsive, and three overactive symptoms in the SNAP questionnaire, which are scores obtained by 5% of 10-year-old boys[28]; or (3) had a score of 5 or 6 on the Rutter-B hyperactivity factor, which is a score obtained by 3% of 10-year-old boys.[32]

Children with a full-scale WISC-R score of less than 80 with an exclusive diagnosis of emotional or conduct disorder, major neurologic, physical, or sensory impairment, and/or any contraindication for the use of methylphenidate (eg, presence of tics, seizures, or heart disease) were excluded from the study.

Experimental Design and Drug Administration

A multiple-blind, placebo-control, within-subject (ie, repeated measures) design was used in which each child was tested four times at each medication condition. Three medication conditions were used; placebo, low dose (0.3 mg/kg), and high dose (1.0 mg/kg). The order of medication condition was randomized with the restrictions that each child receive two different medication conditions each day (eg, high, low) and that the three conditions (placebo, low, high dose) occur with equal frequency in the morning and afternoon. The resulting six possible combinations are shown in Table 1.

The order of these six combinations was randomized for each child. An interval of 4 hours separated the morning and afternoon dose. The methylphenidate and placebo were packaged in colored gelatin capsules by the hospital pharmacist to avoid detection of dose and taste, placed in individual envelopes, and dispensed by the project staff 1 hour prior to each testing session.

Procedures

Children attended the research department with their parents for a half-day assessment session. While the parents were interviewed by a child psychiatrist (following the PICS protocol), the child was familiarized with the staff and testing procedures and practiced the tasks to be used during the medication trial. Consent was secured from the parents to obtain the child's scores on the WISC-R and WRAT; if these tests had not been administered within the last year, the WRAT and two subtests of the WISC-R (Vocabulary and Block Design) were administered.

A total of 12 test sessions were conducted with each child during a period of 6 days (ie, two test sessions per day). Children were tested individually, and test data were collected during the period 60 to 140 minutes after taking the capsule to ensure maximum medication effect.[20] The order of tasks was kept constant for all test sessions; the academic tasks, which took approximately 20 minutes, were commenced 110 minutes postingestion of the capsule, following two tasks that were designed to evaluate impulse control (results for these latter tasks are described in another paper.[33] The child's

TABLE 1. Combinations of Dose Conditions*

Time of Dose	Combination					
	1	2	3	4	5	6
Morning	P	P	L	L	H	H
Noon	H	L	H	P	L	P

* Abbreviations: P, placebo; L, low; H, high

behavior while completing the tasks was observed systematically.

Because the occurrence of side effects is possible with a dose of 1.0 mg/kg,[9] the children were monitored throughout the day for any adverse effects (eg, pallor, nausea, itchiness, decrease in appetite, stereotypic movements, tics) by a nurse. BP and pulse readings were taken immediately before each child received the capsule and again 1 hour later. Project staff maintained clinical logs of the child's mood, activity level, and play during each session, and, likewise, parents were asked to keep a diary of the child's mood, activity, and appetite during the rest of the day and bedtime behavior. At the end of the 6-day trial, the psychiatrist met with the child's parents to discuss results and a report was sent to the referring physician.

Tasks

Arithmetic Task. This task, which was developed specifically for the present study, consisted of three conditions of increasing complexity. In the first condition (very simple), the child was asked to check as many digits as possible in 1 minute (ie, no arithmetic operations were involved). In the second condition (simple), the child was asked to judge the oddness and evenness of digits, thus incorporating the cognitive operation of classification.[33] The child was asked to check as many odd (or even) digits as possible in 5 minutes. In the third condition (complex), an additional cognitive operation—one of transformation—was incorporated. The child was first asked to compute a simple addition or subtraction problem,[34] then judge the oddness on evenness of the answer that must be held in memory, and, finally, check the problem only if the answer was odd (or even). The task required visual recognition of the numbers 1 through 19, knowledge of the number facts of 20, and ability to judge oddness or evenness of digits. These skills are typically learned in grades 1 or 2; if the child was not familiar with the concept of odd and even numbers, he or she was taught and given additional practice to ensure competence.

Children were instructed to work on one column at a time, to check only the target items, to simply circle or scribble through any errors, completing as many problems as possible in 5 minutes. Each child was randomly assigned to the condition of oddness or evenness and retained that assignment for both the simple and complex conditions and for every test session. Equivalent versions were constructed for each test session. The total number of problems checked correctly and the total number of errors (ie, items omitted or incorrectly checked) were recorded at each session. To compare performance across the three conditions, scores for the very simple condition, which were based on 1-minute completion, were multiplied by 5 to estimate 5-minute scores.

Letter Search Tasks. In this task, which comprised two levels of difficulty, children were required to search a series of letter strings for those that contained the target stimuli. In the easiest condition the target stimulus consisted of a single letter, and in the more difficult condition it consisted of two adjacent letters in a specified order. The letter strings consisted of four letters that were perceptually confusable with the target stimuli that were present in 25% of the letter strings (ie, 40 targets). Exactly 2 minutes were allowed for each condition. The child was instructed to check only those letter strings containing the target stimulus and to work as fast as possible without making mistakes. The total number of letter strings correctly identified and the total number of errors (ie, omitted or incorrectly checked strings) were counted.

Behavioral Observations

Children were observed unobtrusively by trained research assistants (who were unaware of the medication condition) for a total of 8 minutes during the arithmetic task. Observations were conducted in 4-minute blocks consisting of 16 consecutive intervals. Each interval was divided into 10 seconds of observation followed by 5 seconds of recording. Thus, each child was observed for a total of 32 intervals at each test session, yielding a total of 128 intervals for each child at each medication condition. In each interval, the child's behavior was classified with reference to three dimensions: visual attention to task (on-task vs off-task), movement (still vs restless), and noise (quiet vs disruptive sounds). The proportion of intervals in which the child was coded as on-task, still, and quiet were computed for each session. Observers were trained to a criterion of 85% reliability, and the overall interobserver reliability calculated for 200 intervals was 93%.

Clinical Measures

Clinical measures included the assessment of treatment-emergent side effects (eg, stomach distress, pallor, mood swings, tics), pulse rate, and blood pressure readings. Pulse and blood pressure readings were taken in the sitting position immediately prior to medication and again 1 hour following administration of the oral dose.

Carryover Effects

Potential carryover effects of a morning dose of 1.0 mg/kg or 0.3 mg/kg on placebo-level performance in the afternoon were evaluated by comparing performance at all four placebo sessions conditional on the antecedent or consequent medication conditions. Thus session A constituted placebo performance in the afternoon if there had been a preceding high dose in the morning; session B constituted afternoon placebo performance if there had been a preceding low dose in the morning; session C constituted morning placebo performance when followed by high dose in the afternoon; session D constituted morning placebo performance when followed by low dose. The order of the four sessions was randomized across children. If carryover effects existed, then either session A or B or both would differ from sessions C and D.

Potential carryover effects from a morning dose of 1.0 mg/kg on the afternoon performance at low dose (0.3 mg/kg) and from a morning dose of 0.3 mg/kg on afternoon performance at high dosage (1.0 mg/kg) were evaluated in a similar manner in separate comparisons of all four low-dose sessions and all four high-dose sessions, respectively.

RESULTS

Arithmetic Task

Scores were based on the average score obtained by each child at the four test times at each dose condition (placebo, 0.3 mg/kg, and 1.0 mg/kg). Means and standard deviations of total correct and total errors for the three conditions of complexity at each dose condition are shown in Table 2. Square root transformations were conducted on the total correct scores to equate the variances across the three complexity conditions. A two-way analysis of variance (ANOVA) with repeated measures across dose (three levels) and complexity (three levels) was conducted on the transformed total correct scores. Significant main effects were found for dose (F (2, 22) = 15.16, $P < .001$), and for complexity (F (4, 44) = 119, $P < .0000$), but the interaction between dose and task complexity was not significant. According to a Newman-Keuls post hoc analysis,[35] the mean correct scores in both medication conditions were significantly greater than those at placebo ($P < .05$), but there was no difference between mean scores obtained at 0.3 mg/kg and 1.0 mg/kg. As shown in Table 2, children completed correctly twice as many digits on the very simple condition compared with the simple condition ($P < .05$), and six times as many problems on the simple condition compared with the complex one ($P < .05$).

Error data were analyzed with a 3 (dose) × 2 (complexity) ANOVA with repeated measures; no errors were possible on the very simple condition. The overall effect for complexity was significant (F (1, 11) = 4.85, $P < .05$), signifying that more errors were made in the simple than in the complex condition. Neither the main effect for dose nor the interaction between dose and complexity were significant.

Letter Search Task

Data for total correct and total errors were analyzed separately with a 3 (dose) × 2 (difficulty level)

TABLE 2. Academic Tasks and Overt Behavior at Each Treatment Condition*

Measure	Placebo	Methylphenidate	
		0.3 mg/kg	1.0 mg/kg
Arithmetic task			
Total correct			
Very simple	383.3 (191.9)	422.5 (171.4)	428.3 (188.0)
Simple	186.6 (76.1)	207.8 (65.9)	210.8 (74.6)
Complex	28.2 (22.3)	35.7 (22.8)	36.4 (21.1)
Total errors			
Simple	3.9 (3.6)	2.7 (2.2)	2.6 (2.9)
Complex	2.5 (4.2)	1.1 (0.8)	1.5 (1.1)
Letter task			
Total correct			
Easy	26.6 (12.8)	29.8 (11.3)	29.8 (13.4)
Hard	22.3 (9.6)	24.3 (8.1)	26.0 (9.6)
Total errors			
Easy	1.4 (0.9)	1.7 (1.0)	1.3 (1.2)
Hard	2.0 (1.4)	2.5 (2.3)	1.5 (1.4)
Overt behavior (%)			
On task	88 (14.5)	96 (5.3)	99 (1.3)
Still	38 (16.5)	54 (18.4)	67 (18.3)
Quiet	65 (21.8)	76 (20.7)	85 (15.4)

* Values are given as means ± SD.

ANOVA with repeated measures. There was a significant main effect for dose on total correct (F (2, 22) = 9.17, $P < .001$), and according to post hoc Newman-Keuls, performance in both medication conditions was better than placebo performance ($P < .05$) but there was no difference between performance at low or high dose (Table 1). The significant overall effect for difficulty level (F (1, 11) = 11.96, $P < .005$) indicated that more target letter strings were correctly identified in the easy version than in the more difficult version. The interaction between dose and difficulty was not significant. Analysis of the error data yielded no significant findings.

Overt Behavior

Univariate ANOVAs for repeated measures across dose were conducted separately for percentage of intervals the child was visually on-task, still, and quiet. Significant main effects for dose were found for on-task behavior (F (2, 22) = 6.10, $P < .03$), stillness (F (2, 22) = 32.73, $P < .0000$), and quietness (F (2, 22) = 13.75, $P < .0001$). By post hoc Newman-Keuls comparisons, stillness and quietness were significantly improved at a 0.3-mg/kg dose compared with placebo ($P < .05$) and both behaviors were further improved by the dose of 1.0 mg/kg compared with 0.3 mg/kg. On-task behavior was significantly better at both 1.0 mg/kg and 0.3 mg/kg than at placebo, but no advantage was gained by the high dose.

Clinical Measures

The mean pulse and blood pressure readings (systolic and diastolic) prior to medication and 1 hour after medication are shown in Table 3. A two-way ANOVA with repeated measures across dose (three levels) and time (pre- and 1-hour postingestion) was conducted separately for pulse and systolic and diastolic blood pressure. A significant dose by time interaction (F (2, 22) = 8.13, $P < .002$) was shown in analysis of pulse readings, but the main effects for dose and time were not significant. According to post hoc Newman Keuls analysis, there was a significant increase in pulse readings 1 hour following administration of the 1.0 mg/kg dose compared with placebo or 0.3 mg/kg ($P < .05$). The two-factor ANOVA conducted on systolic blood pressure also yielded a significant interaction between dose and time (F (2, 22) = 7.81, $P < .003$), but no main effects for dose or time. By post hoc analysis, at 1 hour postingestion, systolic blood pressure increased significantly at 1.0 mg/kg compared with 0.3 mg/kg or placebo ($P < .05$). Significant changes were also found in diastolic blood pressure, although the main effect for dose was not statistically significant, the main effect for time (F (1, 11) = 6.11, $P < .03$) and the interaction between time and dose (F (2, 22) = 4.22, $P < .03$) were both significant, indicating that diastolic pressure was significantly higher at 1.0 mg/kg than at 0.3 mg/kg or placebo ($P < .05$).

No side effects of sufficient severity to warrant discontinuation of the medication trial developed in any of the children. One child exhibited mild facial tics during two of the four sessions at the 1.0-mg/kg dose, but the tics disappeared within 24 hours and have not reoccurred although the child has been receiving a dose of 0.6 mg/kg twice daily. At the high dose, one child demonstrated marked irritability on one occasion, three were described as "somber," two complained of mild stomach distress, and six exhibited decreased appetite. Fewer side effects were reported at low dosage: three children were "somber," one complained of stomach distress, and one showed decreased appetite.

Carryover Effects

A one-way ANOVA with repeated measures across session (four levels) was conducted separately for the percentage of still and total correct in the complex arithmetic task. The mean values for percentage still and total correct at each of the four placebo sessions (A, B, C, D), and each of the

TABLE 3. Pulse and Blood Pressure Readings Pre- and 1 Hour Postmedication for Each Treatment Condition*

Measure	Placebo	Methylphenidate	
		0.3 mg/kg	1.0 mg/kg
Pulse rate (beats/min)			
Preingestion	92.1 (11.9)	93.0 (11.2)	92.0 (10.8)
Postingestion	91.9 (12.0)	91.4 (11.0)	96.3 (12.3)
Systolic (mm Hg)			
Preingestion	102.5 (8.8)	100.8 (7.7)	100.1 (7.7)
Postingestion	100.7 (8.9)	100.8 (7.5)	104.4 (9.8)
Diastolic (mm Hg)			
Preingestion	63.9 (4.5)	63.5 (3.8)	63.7 (4.9)
Postingestion	63.8 (4.8)	64.1 (3.7)	66.6 (5.7)

* Values are given as means ± SD.

TABLE 4. Mathematics Scores and Activity Scores for Each Session in Each Drug Condition, Used in Analysis of Carryover Effects*

Session	Treatment		Mathematics (Complex) Total Correct Score	% Still
	AM	PM		
Placebo				
A	H	P	37.4 (31.5)†	52.0 (27.8)‡
B	L	P	28.3 (19.5)	35.5 (24.1)
C	P	H	24.3 (20.4)	31.4 (17.0)
D	P	L	25.2 (20.6)	30.9 (12.2)
0.3 mg/kg				
A	H	L	36.2 (21.6)	58.3 (23.8)
B	P	L	34.1 (25.7)	47.7 (24.4)
C	L	H	38.2 (32.0)	53.8 (21.1)
D	L	P	33.4 (23.7)	53.2 (28.3)
1.0 mg/kg				
A	L	H	39.0 (25.0)	66.3 (21.1)
B	P	H	32.8 (21.0)	63.6 (18.4)
C	H	L	34.5 (20.1)	64.3 (24.5)
D	H	P	37.3 (27.0)	69.5 (26.0)

* Abbreviations: H, high; L, low; P, placebo.
† $P < .06$, A > B, C, D.
‡ $P < .01$, A > B, C, D.

four 0.3-mg/kg and 1.0-mg/kg sessions are presented in Table 4. The main effect of session for stillness was significant ($F(3, 33)) = 4.48$, $P < .01$), and, according to post hoc Newman-Keuls analysis, the children's stillness in session A (ie, afternoon placebo session preceded by morning high dosage) was significantly greater than that in any other placebo session ($P < .05$), but there were no differences in behavior between sessions B, C, or D. The main effect of session for total correct arithmetic answers was marginally significant (F (3, 33) = 2.75, $P < .06$), with mean scores in session A being higher than at other placebo sessions. There was no evidence of any other carryover effects (ie, from a morning dose of 1.0 mg/kg on the afternoon performance at low dose or from a morning dose of 0.3 mg/kg on afternoon performance at high dose).

DISCUSSION

It was demonstrated in results from the present study that methylphenidate enhances academic functioning by increasing accurate productivity on academic tasks, as well as improving overt behavior. All 12 children were able to complete substantially more work at all levels of the arithmetic task and the letter task without sacrificing accuracy following treatment with methylphenidate. Because most children decreased their error rates from placebo to medication conditions (although the difference was not significant), the stimulant-induced increase in the total correct score reflects a true improvement in academic functioning rather than a less interesting increase in the amount of work completed with a corresponding but proportionate increase in error rates. These improvements were observed in tasks designed to provide assessment of relatively complex skills comparable with those required for school work: in the complex level of the arithmetic task rapid and flexible switching between addition and subtraction were required, followed by rapid classification of the answer that was held in memory.

Stimulant-induced improvements in academic performance were discernible clinically as well as statistically; the majority of children (10 of 12 children) showed more than a 25% increase in the number of problems completed correctly compared with placebo-level performance. Also, changes in performance, which included a shift from using fingers or loud verbalization during computation to quiet verbal or silent mental computation were associated with changes from a placebo to a medicated state. The pattern of improvement in the complex version of the arithmetic task suggests greater efficacy in shifting mental set and in completing consecutive cognitive operations.

The beneficial effects on academic performance did not vary with dosage or task complexity. These academic task results are not entirely consistent with the conclusion of Sprague and Sleator[3] that for most children, cognitive performance (particularly with difficult versions of tasks) is maximized at a dosage of 0.3 mg/kg and is impaired by dosages of 1.0 mg/kg or higher. The present study indicated that a dose of 1.0 mg/kg resulted in a leveling of academic performance rather than a decline and that methylphenidate produced similar improvements in both simple and complex versions of the tasks. These results suggest that the continued improvement in academic productivity as a function of increasing dosage reported by some investigators using doses of as much as 0.6 mg/kg[5–7] may be attenuated as the dose approximates 1.0 mg/kg. We cannot, however, rule out the possibility that inclusion of an intermediate dose of 0.6 mg/kg might have resulted in improved performance relative to that obtained at 0.3 mg/kg or at 1.0 mg/kg.

One possibility of the apparent leveling in performance at higher dosages is that the finding may be an artifact resulting from a situation in which the high dosage improved the performance of some children relative to the dosage but actually impaired that of others. Inspection of the data from the present study ruled out such an explanation; seven children showed similar levels of performance at 0.3 mg/kg and 1.0 mg/kg, whereas three showed their greatest improvement at 1.0 mg/kg, and only two showed the best performance at 0.3 mg/kg, with a decline at 1.0 mg/kg. Alternatively, the lev-

eling of performance at 1.0 mg/kg may reflect an underlying decline in cognitive processing that was either masked by the marked behavioral improvements or that was only minimally addressed by the current tasks.

As expected, the children's overt behavior (ie, being on-task, still, and quiet), improved as a function of increasing doses. Despite these continued improvements in overt behavior with increasing dose, parallel improvements were not obtained in academic performance at the high dosage. These findings are provocative in that the separation of dose response functions for overt behavior and academic performance at the high dosage may reflect an underlying decline in cognitive functioning at a dosage of 1.0 mg/kg that was partly attenuated by the benefits accrued from the behavioral improvements. In other words, the high dose enabled the children to sit still and be quiet, thereby facilitating their cognitive functioning to some extent, but these behavioral improvements may have been insufficient to ameliorate a loss in speed or flexibility that may have been induced by the dosage. Further studies using complex tasks that tap other cognitive processes (eg, drawing analogies, inferring and integrating information) are needed to clarify this issue.

In the present study, an increase in pulse and blood pressure was observed for most children (n = 9) 1 hour following the ingestion of a 1.0-mg/kg dose of methylphenidate. Similar changes with a dose of 1.0 mg/kg were reported 2 hours postingestion by Winsberg and colleagues.[9] The increases observed in both studies were small and clinically unimportant, and the measures reverted to pretreatment levels when medication was discontinued and placebo was administered. In contrast to the findings of Winsberg and colleagues,[9] no severe side effects developed in any of the children participating in the present study following the 1.0-mg/kg dose, and certainly none that necessitated termination of their participation in the study. In the current study, the children received a dose of 1.0 mg/kg only once a day for 4 days that were not necessarily consecutive, whereas in the Winsberg study, children received the 1.0-mg/kg dose twice daily for 7 consecutive days. Because the use of 1.0 mg/kg in the present design was associated with only a few, mild side effects, researchers who wish to investigate dose response relationships with as much as 1.0 mg/kg are advised to consider a similar design in which this dose is administered only once a day on nonconsecutive days.

Consistent with the findings of Solanto and Conners,[8] the behavioral improvements produced by a dose of 1.0 mg/kg of methylphenidate were sustained for longer than 4 hours, but those produced by a dose of 0.3 mg/kg had essentially dissipated by the end of the testing session (ie, 3 hours postingestion). When children received a dose of 1.0 mg/kg of methylphenidate in the morning and then received placebo 4 hours later, their overt behavior in the afternoon session was so markedly improved compared with other placebo sessions that the project staff, who were unaware of the medication state, frequently guessed that the children were in a medicated state in both the afternoon and morning session. Inspection of the data for that afternoon placebo session confirmed the impression that the children's behavior was similar to that observed at low dosage. This carryover effect occurred unequivocally in 7 of the 12 children and was evident to a lesser extent in an additional 2. Surprisingly, there was no evidence of additive effects of the morning high dose on the effects produced by an afternoon dose of 0.3 mg/kg.

The finding of prolonged beneficial effects of the high dosage on academic performance was equivocal. The carryover effect was only marginally significant and this effect was evident in only 5 children of the 12 children. Of relevance here is the finding by Solanto and Conner[8] of a differential time course for methylphenidate on behavior and cognition that was dose related. A dose of 0.3 mg/kg produced behavioral and cognitive benefits (in terms of reduced activity and faster reaction times with improvements in accuracy) that were clearly evident 1 to 2 hours postingestion but no longer discernible 4 hours postingestion. In contrast, behavioral improvements were produced by a dose of 1.0 mg/kg that were still clearly evident 6 hours later, but the cognitive benefits had dissipated within 3 hours. Results of the present study suggest that for most children, stimulant-induced academic benefits may also dissipate within 3 to 4 hours.

The differential time course of action of 1.0 mg/kg of methylphenidate on academic and cognitive performance has implications for experimental design and clinical practice. From a design perspective, the carryover effects for behavior argue against alternating doses on a twice daily basis, because these persistent effects may serve to attenuate drug and dose effects by artificially inflating the afternoon performance. In the present study, however, methylphenidate was so effective in improving behavior compared with placebo performance that the difference could still be detected even when behavior was compared with inflated behavior estimates with placebo. The possibility is seen by the use of this design in the present study that the absence of a linear relationship between increasing dose and academic performance may be attributable to car-

ryover effects, which would have served to inflate scores at placebo and low doses. Although this explanation was not supported by either the group comparison or by evaluation of data for each child, this design incorporates the potential for such a confound.

From a therapeutic perspective, the carryover effects associated with a dose of 1.0 mg/kg are also problematic. Because a dose of 1.0 mg/kg not only maximized behavior but also produced long-lasting behavioral improvements, it would be tempting to recommend a dosage of 1.0 mg/kg once a day for most children. It is important to note that in this study we did not investigate the effects of consecutive daily doses of 1.0 mg/kg; the effects of such a regimen may differ from those described in this study. Notwithstanding the concern about side effects that are typically associated with a dose of 1.0 mg/kg, if the concomitant cognitive and academic improvements dissipate within 3 to 4 hours, then the child will not gain optimum benefit from a treatment regimen of 1.0 mg/kg per day. Of greater concern is the possibility that high doses impair cognitive performance. Although such effects have yet to be convincingly demonstrated, any decline in cognitive and academic performance might be obscured by the often dramatic and long-lasting behavioral improvements associated with high dosages. Finally, in attempting to determine an optimal dose for each child, it is essential that the physician consider the dose response and time course of action across academic and cognitive domains as well as the behavioral domain. Academic tasks such as those used in the present study are inexpensive, may be quickly administered and scored, and provide valuable information concerning the academic response of the child to medication.

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NATIONAL DAY OF PRAYER

A national day of prayer has been recognized as a part of our country's heritage since it was declared by the Continental Congress in 1775. . . . Officially it is the first Thursday of every May; this year it falls on May 5.

We could trust the spirit of President Abraham Lincoln who, in despair, said, "I have been driven many times upon my knees by the overwhelming conviction that I had nowhere else to go."

This is the anxiety felt by 13-million American children who are "Poorest in a Land of Plenty," title given a film produced by the National Council of Churces, to be introduced on Mother's Day, May 14 (NBC, 1 pm). The NCC's statistics show that "One out of every five children in America is poor; among 20 industrialized nations the USA has the third highest infant mortality rate; among industrialized nations only the USA and South Africa fail to provide comprehensive health care for children and pregnant women.

Submitted by Lewis A. Barness, MD

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Dose-Response Effects of Methylphenidate on Academic Performance and Overt Behavior in Hyperactive Children

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